Actelion Pharmaceuticals Ltd
(a Janssen Pharmaceutical Company of
Johnson & Johnson)*

Macitentan / ACT-064992

Chronic Thromboembolic Pulmonary Hypertension

Protocol AC-055E202

MERIT-2: Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension (Open-Label)

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

Study Phase:	2
EudraCT Number:	2013-003457-25
Status and version:	Final Version 4
Date:	22 June 2021
EDMS number:	EDMS-RIM-263288, 3.0

*Actelion Pharmaceuticals Ltd ("Actelion") is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Actelion studies may vary, such as, but not limited to Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

SPONSOR CONTACT DETAILS

SPONSOR	ACTELION Pharmaceuticals Ltd* Gewerbestrasse 16 CH-4123 Allschwil Switzerland
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File
MEDICAL HOTLINE	Site-specific toll telephone numbers and toll-free numbers for the Medical Hotline can be found in the Investigator Site File.

* Actelion Pharmaceuticals Ltd. ("Actelion") is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study.

CONTRACT RESEARCH ORGANIZATIONS INFORMATION

CENTRAL LABORATORY	Eurofins Global Central Laboratory Bergschot 71 4817 PA Breda The Netherlands
Contact person	Please refer to the Central Laboratory Manual.
CENTRAL STUDY DRUG RE-SUPPLY	Almac Clinical Technologies 20 Seagoe Industrial Estate Craigavon BT63 5UA United Kingdom
Contact person	Please refer to the Investigator Site File.
CENTRAL STUDY DRUG RE-SUPPLY	WDC Beerse Turnhoutseweg 30 Beerse 2340 Belgium
Contact person	Please refer to the Investigator Site File.
A list of site-specific contact details for Clinical Research Organizations (CROs) can be found in the Investigator Site File.	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document	Date
Amendment 3, Version 4	22-Jun-2021
Amendment 2, Version 3	28-Sep-2020
Amendment 1, Version 2	15-Jul-2020
Original Protocol, Version 1	29-Oct-2013

Amendment 3 (22-Jun-2021)

Overall Rationale for the Amendment: The reason for the amendment is to clarify how to manage the roll-over of MERIT-2 patients into a continued access program (post-trial access program or other open-label extension study). In addition, the forbidden concomitant medications section was updated to clarify that macitentan 10 mg is not considered as an investigational treatment.

A Protocol Amendment Summary of Changes Table for the current amendment is provided below and the updates are indicated in bold text.

Section Number and Name	Description of Change	Brief Rationale
Signature For Actelion Pharmaceuticals Ltd; Investigator Signature Page	Signature pages were deleted and replaced with 'Investigator Agreement' at the end of the document.	To align with Janssen TransCelerate protocol template.
Protocol Synopsis AC-055E202 (Concomitant medications); 5.2.3 Forbidden concomitant medications	List of forbidden concomitant medications was updated with 'Another investigational drug **(other than macitentan 10 mg)'**.	The list of forbidden medications was updated to clarify that macitentan 10 mg is not considered to be a forbidden investigational drug, to allow seamless transition of patients to a continued access program.
Protocol Synopsis AC-055E202 (Study Periods); Table 1 (Visit and assessment schedule); 3.1 Study design; Figure 1 (Study design); 8.1.5 EOT visit; 8.2 Safety follow-up period	It was clarified that for patients who are entering a continued access program, the enrollment into the continued access program (post-trial access program or other open-label study) must occur on the day of the last visit of the MERIT-2 study (end-of-study [EOS], which corresponds to end-of-treatment [EOT] in this case).	The purpose of the 30 day safety follow-up period is to monitor the subjects after intake of their last dose of study treatment for potential safety issues. For subjects who seamlessly transition to a continued access program with the same treatment, the safety follow-up period is not applicable since these subjects do not stop treatment. Therefore, for subjects who enter a continued access program, their EOT visit will be the EOS visit at the same time.
10.1.4 Reporting of adverse events; 10.2.2.2 During treatment and follow-up periods; 10.3.1 Reporting of pregnancy	Text corresponding to reporting of adverse event (AE), serious adverse event (SAE) and pregnancy up to 30 days after study drug distinuation was revised as: '**(up to EOS for participants who enter a continued access program on the same day as the EOS visit, see Section**	

Section Number and Name	Description of Change	Brief Rationale
	8.2.1)'.	
Protocol Synopsis AC-055E202 (Study periods); 8.1.5 EOT visit	EOT visit definition was updated as follows: **'End of treatment (EOT): The end of all study treatment for an individual participant.'**	It is clarified in the safety reporting requirements that for participants who enter a post-trial access program or another open label trial, safety information is to be reported up to EOS visit in this study.
Protocol Synopsis AC-055E202 (Study periods); 8.2.1 EOS visit	Following content was added to define EOS for individual participants: **For an individual participant, EOS visit is defined as follows:** − **For participants that complete treatment, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake.** − **For participants that prematurely discontinue study treatment, EOS visit is defined as the safety follow up visit 30–35 days after last study treatment intake.** − **For participants who complete treatment and who are entering a continued access program (post-trial access or other open-label extension study) the EOS visit is defined as the EOT visit.**	
9 Study Completion	End of current OL study was redefined as 'EOS visit'.	For consistency.
9.2 End of the trial	End of trial was redefined as: 'The end of the trial is reached when all the subjects have **either** completed their EOS visit, **died or are lost to follow-up**.'	For clarification.
9.4 Medical care of subjects after End-of-Study	Following statement was added: '**Local regulations on continued access will always take precedence.**'	For clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes have been made.	Minor errors were noted.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CL	Confidence limits
CRO	Clinical Research Organization
CRP	C-reactive protein
CS	Clinically significant
CTEPH	Chronic thromboembolic pulmonary hypertension
CV	Curriculum vitae
CYP	Cytochrome P-450
DB	Double-blind
DBP	Diastolic blood pressure
DoA	Delegation of authority
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
ET	Endothelin
ET_A	Endothelin receptor A
ET_B	Endothelin receptor B
FAS	Full Analysis Set
FC	Functional class
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ILSB	International Liver Safety Board
IMP	Investigational Medicinal Product

INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator Site File
IXRS	Interactive voice/web recognition system
LT	Liver test
MedDRA	Medical Dictionary for Regulatory Activities
MERIT	Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension
NCS	Not clinically significant
OL	Open-label
OLAS	Open-Label Analysis Set
OLSS	Open-Label Safety Set
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PQC	Product quality complaint
PVR	Pulmonary vascular resistance
RAS	Restricted Analysis Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Steering committee
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of the normal range
WHO	World Health Organization

PROTOCOL SYNOPSIS AC-055E202

TITLE	Long term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH)					
ACRONYM	MERIT-2: **M**acitentan in th**E** t**R**eatment of **I**noperable chronic **T**hromboembolic pulmonary hypertension (**O**pen-**L**abel)					
OBJECTIVES	**Safety objective**: • To evaluate the long-term safety and tolerability of macitentan 10 mg in subjects with inoperable CTEPH. **Efficacy objective**: • To evaluate the long term effects of macitentan 10 mg on exercise capacity and functional class (FC).					
DESIGN	Multicenter, open-label (OL) extension, single-arm, Phase 2 study					
STUDY PLANNED DURATION	**First subject First visit**	Q3 2014	**Last subject First visit**	Q4 2015	**Last subject Last visit**	Open
SITES / COUNTRIES	Approximately 60 centers in approximately 15 countries (planned).					
SUBJECTS / GROUPS	Up to 78 subjects in 1 group treated with macitentan 10 mg.					
INCLUSION CRITERIA	1. Written informed consent to participate in the study obtained from the subject, according to local regulations, prior to initiation of any study mandated procedure. 2. Subject with CTEPH having completed the double-blind (DB) AC-055E201 / MERIT-1 study as scheduled (i.e., who remained in the DB study up to Week 24). 3. Females of childbearing potential must have a negative pre-treatment serum pregnancy test, be advised on appropriate methods of contraception, and agree to use 2 reliable methods of contraception concurrently during study treatment and for at least 30 days after study treatment discontinuation					

EXCLUSION CRITERIA	1. Permanent discontinuation of DB study treatment due to an hepatic adverse event or liver aminotransferase abnormalities. 2. Hemoglobin < 100g/L. 3. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN). 4. Systolic blood pressure (SBP) < 90 mmHg. 5. Treatment with strong cytochrome P-450 3A4 (CYP3A4) inducers such as rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's wort. 6. Treatment with another endothelin receptor antagonist (ERA [e.g., bosentan, ambrisentan]). 7. Any known factor (e.g., drug or substance abuse) or disease (e.g., unstable psychiatric illness) that, in the opinion of the investigator, 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 to any of the study drug excipients. 9. Females who are pregnant or plan to become pregnant during the study, or are lactating.
CONCOMITANT MEDICATIONS	**Prohibited** • Strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifabutin, rifapentin, St. John's wort). • Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine) until study intervention discontinuation.

	* If patients are currently stable on a strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir), moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine), the patient may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment. • Another ERA (e.g., bosentan, ambrisentan). • Another investigational drug **(other than macitentan 10 mg)**
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, i.e., until whichever of the following occurs first: • Commercial availability of macitentan in this indication in the subject's country, • Actelion decides to stop this study (AC-055E202 / MERIT-2 OL extension), • The subject or the investigator decides to discontinue the study drug. **End of treatment (EOT):** The end of all study treatment for an individual participant. **Safety follow-up: F**or an individual subject, the end of this OL study corresponds to the 30-day safety follow-up, which should be performed 30 days after the permanent discontinuation of study drug. For patients who are entering a continued access program, the enrollment into the continued access program (post-trial access program or other open-label study) must occur on the day of the last visit of the MERIT-2 study (EOS, which corresponds to EOT in this case). **End of Study (EOS):** For an individual participant, EOS visit is defined as follows:

	• For participants that complete treatment, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake. • For participants that prematurely discontinue study treatment, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake. • For participants who complete treatment and who are entering a continued access program (post-trial access or other open-label extension study) the EOS visit is defined as the EOT visit.
INVESTIGATIONAL DRUG	Macitentan 10 mg, oral tablet, to be taken once daily.
COMPARATOR DRUG	Not applicable
EFFICACY ENDPOINTS	Exploratory: • Change from baseline to each scheduled time point in exercise capacity, as measured by the 6-minute walk distance (6MWD) • Change from baseline to each scheduled time point in Borg dyspnea index collected at the end of the 6-minute walk test • Proportion of subjects with worsening of WHO FC from baseline to each scheduled time point.
TOLERABILITY / SAFETY ENDPOINTS	• Treatment-emergent adverse events (AEs) up to 30 days after study drug discontinuation. • AEs leading to premature discontinuation of study drug. • Treatment-emergent serious adverse events up to 30 days after study drug discontinuation. • Treatment-emergent marked laboratory abnormalities up to 30 days after study drug discontinuation. • Change in vital signs (arterial blood pressure [BP], heart rate [HR]) and body weight from baseline to all assessed time points during the study.
STATISTICAL METHODOLOGY	This study will not be analyzed individually, but in combination with data from the DB AC-055E201 / MERIT-1 study. **Sample Size**

	The sample size for the OL extension study will be up to 78 randomized subjects from the DB study (AC-055E201 / MERIT-1), who are eligible for and consent to enter the OL extension. **Analysis sets** The Full Analysis Set (FAS), used for analysis in the DB study only, and reported here for completeness, comprises subjects from the DB AC-055E201 / MERIT-1 study who were randomized to either placebo or macitentan 10 mg. The OL analysis set (OLAS), comprises all data from subjects who enrolled into the OL extension study, from the time they enter the OL extension study. The restricted analysis set (RAS), comprises all data from subjects enrolled in the OL extension study who received macitentan 10 mg during the AC-055E201 / MERIT-1, from the time they enter the DB study. The OL Safety Set (OLSS), comprises all core and OL study subject data from subjects exposed to macitentan at least once, during either the DB or OL extension study for the period they are exposed to macitentan 10 mg.
STATISTICAL METHODOLOGY cont.	**Statistical Methods** Analysis of the exploratory efficacy endpoint variables will be conducted on the OLAS and RAS: **1.** On the OLAS, as change from baseline of the OL extension study, by randomized treatment group in the DB core study, **2.** On the RAS, as change from baseline of the DB core study (single arm) For the analysis of the exploratory endpoint variables in the OL extension no imputation of data will be performed. However, in order to maximize the use of collected data and to analyze the data at relevant time points, a time-windowing approach will be employed to include data from all study assessments up to EOS. The following analyses will be performed on all available data: • A repeated measures analysis of the change from baseline in 6MWD.

	• A repeated measures analysis of the change from baseline in Borg dyspnea index. An analysis using shift tables to display change from baseline to all window-based time points in WHO FC on the dichotomized yes/no worsening variable. **Safety and tolerability endpoints** The statistical evaluation of the safety and tolerability endpoint variables will be performed on the OLSS, summarizing values and changes at each study visit time point from baseline of the DB study for subjects originally randomized to macitentan in the DB core study and as changes from baseline of the OL study for subjects originally randomized to placebo in the DB study. **Statistical inference** No multiplicity adjustments will be made on exploratory efficacy endpoints. Any two-sided p-value ≤ 0.05 will be identified as statistically significant but will be considered as exploratory result.
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. • An independent International Liver Safety Board (ILSB; an external expert committee of hepatologists) provides ongoing assessment and advice regarding any serious hepatic events that may require further evaluation during the study. • A Publication Committee is involved in the preparation of potential manuscript(s) and will be consulted for authorship criteria (if applicable).

Table 1 Visit and assessment schedule

PERIODS	Name	TREATMENT						FOLLOW-UP
	Duration	Open						30 days
VISITS	Number	1	2	Monthly lab. & Safety Monitoring[j]	3, 4, 5….		U1, 2, 3…	
	Name	Enrollment[d]	Month 1		Month 6, Month 12, Month 18…	End-of-Treatment	Unscheduled	Safety Follow-up / EOS[k]
	Time	Day 1	Month 1 (± 1 week)	Month 2 & every month thereafter (± 1 week)	Month 6 & every 6 months thereafter (± 2 weeks)	Within 7d after study drug disc.	Any time[f]	30-33 days after study drug disc.
Informed consent		X						
Concomitant medications		X	X	X	X	X	X	X
Physical examination		X	X		X	X	X	X
Vital signs (BP – HR), weight		X	X		X	X	X	X
WHO FC/6MWT/Borg dyspnea index		X			X	X	X	
Complete laboratory tests[a]		X[b]	X		X	X	X	X
LTs				X				
Hemoglobin[c]				X				
Serum pregnancy test[e]		X	X	X	X	X	X	X
Study drug dispensing/return[g]		X	X	X	X	X	X	
AEs[h]		X	X	X	X	X	X	X
SAEs[i]		X	X	X	X	X	X	X

6MWT = 6-minute walk test; AEs = adverse events; BP = blood pressure; EOS = End-of-Study; FC = functional class; HR = heart rate; LTs = liver tests; SAEs = serious adverse events.

a. Complete laboratory tests: hematology and blood chemistry. All blood samples will be sent to the central laboratory for analysis.
b. 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.
c. Hemoglobin concentration will be measured every month during the first 6 months, and every 3 months thereafter up to the EOT visit.
d. For subjects who remain in the DB MERIT-1 study up to Week 24, the Enrollment visit is combined with the MERIT-1 Visit 5 / Week 24. Tests are not to be repeated if performed for the MERIT-1 Visit 5 / Week 24 on the day of this Enrollment visit.
e. Females of childbearing potential only.
f. Unscheduled visits can be performed at any time during the study, according to investigator's discretion. Any study specific procedure/assessment can be performed at an unscheduled visit; corresponding data will be collected in the electronic case report form.

g. Study drug dispensing according to investigational site practice (e.g., every 6 months, or every month).
h. AE reporting: all AEs occurring from study drug initiation and up to 30 days after study drug discontinuation.
i. SAE reporting: all SAEs occurring from signature of informed consent and up to 30 days after study drug discontinuation.
j. If the monthly laboratory samples are not collected at the site, the safety monitoring (assessments of AEs, SAEs, concomitant medications and methods of contraception) should be done via a telephone call that must be documented in the subject's file.
k. For participants who transition to a continued access program (post-trial access program or other open-label extension study), the EOT visit is defined as the EOS.

CORE PROTOCOL

1 BACKGROUND

1.1 Indication

Chronic thromboembolic pulmonary hypertension (CTEPH), one of the leading causes of severe pulmonary hypertension (PH), develops from the obstruction of pulmonary artery branches following episodes of pulmonary embolism (PE) with incomplete thrombus resolution, formation of fibrosis and remodeling of pulmonary blood vessels. Consequently, pulmonary vascular resistance (PVR) is increased, leading to PH and progressive right heart failure [Jenkins 2012]. CTEPH belongs to the World Health Organization (WHO) Group 4 [Simonneau 2009].
There are no specific signs or symptoms for CTEPH. Patients generally present with progressive dyspnea on exertion, edema and/or signs of right heart dysfunction including fatigue, chest pain and syncope [Pepke-Zaba 2011].

The incidence of CTEPH is not precisely known although estimates have ranged from 0.5% to 3.8% of patients after an acute PE, and in up to 10% of those with a history of recurrent PE [Haythe 2012].

CTEPH should be considered in all patients with unexplained PH. When left untreated, CTEPH is responsible for significant morbidity and mortality. Historically, 3-year mortality has been reported to be as high as 90% in patients with a mean pulmonary artery pressure of > 50 mmHg [Jenkins 2012].

All patients with suspected CTEPH should be referred to an expert center for a proper diagnostic evaluation to exclude or confirm the diagnosis. There are a number of modalities available to diagnose CTEPH. Ventilation–perfusion lung scanning is one of the most important diagnostic tests to help distinguish CTEPH from other forms of pulmonary arterial hypertension (PAH). Pulmonary arteriography is essential to determine whether or not a patient is a candidate for surgical intervention. Furthermore, hemodynamic evaluation by right heart catheterization provides vital prognostic information [Haythe 2012].

Pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH and represents a potentially curative option in eligible patients [Jamieson 2003]. However, many patients with CTEPH are considered non-operable due to predominantly distal thromboembolic pathology, or concomitant small-vessel arteriopathy. Therefore, there is a high need for medical treatments for CTEPH patients who are inoperable.

To date, none of the pharmacologic therapies approved for PAH (WHO Group 1) have demonstrated a clear benefit in randomized controlled trials in CTEPH. However, in a recently completed Phase 3 clinical trial in CTEPH patients who were deemed to be inoperable or who had persistent or recurrent PH after undergoing PEA, riociguat (a guanylate cyclase stimulator) demonstrated a significant improvement in exercise capacity and PVR [Ghofrani 2013a]. This new drug also significantly improved the exercise

capacity in a recently completed Phase 3 clinical trial in PAH patients [Ghofrani 2013b]. Riociguat has gained regulatory approval for the treatment of CTEPH in several countries, including the United States (US), Canada, Japan and European Union (EU). To date, riociguat is not approved world-wide.

1.2 Macitentan

Macitentan (ACT-064992) is an orally active, non-peptide, potent dual endothelin (ET) ET_A and ET_B receptor antagonist (ERA) in clinical development. ERAs are being developed for a variety of diseases associated with the deleterious effects of ET, particularly in the pulmonary and cardiovascular fields.

A summary of available macitentan preclinical and clinical data relevant to this study can be found in the AC-055E201 / MERIT-1 protocol. For more detailed information, please see the most recent version of the Investigator's Brochure (IB) [Macitentan IB].

1.2.1 Macitentan – Summary of risks and safety measures

Nonclinical 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 methods of contraception for female subjects of childbearing potential.

Macitentan was well tolerated in the completed Phase 1, 2, and 3 studies. A total of 863 patients received macitentan treatment and 370 patients received placebo in randomized, double-blind (DB), placebo-controlled, Phase 2 and 3 studies for a period of up to 188 weeks. This represents a total of 1120 patient-years exposure to macitentan treatment, and 484 patient-years exposure to placebo treatment.

In 3 placebo-controlled studies with macitentan, no significant imbalance in liver test (LT) elevations was observed across macitentan treatment groups (< 3 mg, 3 mg, 10 mg) and placebo. The proportions of patients with alanine aminotransferase (ALT) and/or aspartate amino transferase (AST) elevations > 3 × the upper limit of normal range (ULN) were similar across the treatment groups, but a higher percentage of patients treated with macitentan 10 mg had ALT > 3 × ULN compared to placebo. However, there were no patients in the studies who met the Hy's Law criteria (i.e., ALT/AST > 3 × ULN and total bilirubin > 2 × ULN), and who had no associated increase in alkaline phosphatase (AP) in the absence of alternative explanations which were possibly or likely the cause of the elevations. Subjects with serum AST and/or ALT > 3 × ULN will be excluded from the proposed clinical trial, and LTs will be assessed every month during the treatment period and 30 days after study drug discontinuation. The protocol also includes clear instructions regarding re-tests and criteria for treatment discontinuation in the case of clinically relevant elevations of aminotransferases.

Treatment with ERAs has been associated with increased incidence of edema, anemia and/or decreased hemoglobin [Abman 2009; O'Callaghan 2011]. Treatment with

macitentan was associated with a dose-related reduction in hemoglobin levels, which was established within the first 3 months of treatment. Decreased hemoglobin levels tended to show recovery towards baseline after discontinuation of treatment. Higher incidences of anemia adverse events (AEs) were reported in a dose-related fashion in the patients treated with macitentan in comparison to those treated with placebo. Anemia required transfusion in some patients treated with macitentan. Patients with hemoglobin $<$ 100 g/L will be excluded from the proposed clinical trial. During the treatment period, hemoglobin levels will be assessed every month during the first 6 months, and every 3 months thereafter; it will be assessed again 30 days after study drug discontinuation. The protocol also includes clear instructions regarding re-tests and criteria for treatment discontinuation in the case of clinically relevant anemia.

The incidences of edema AEs were similar in the macitentan and placebo groups, although subgroup analyses indicated fluctuations in the incidence of edema, with no clear pattern according to treatment (macitentan vs placebo) or macitentan dose. Edema serious adverse events (SAEs) were uncommon with macitentan treatment and only 3 patients (2 on placebo and 1 on macitentan 10 mg) discontinued treatment due to an edema AE. Overall, there is no indication that edema represents a significant safety concern with macitentan therapy.

Due to the vasodilatory effects of macitentan, effects on blood pressure (BP) might occur. In the DB PAH population, there was a slightly higher incidence of AEs denoting hypotension, relative to placebo on macitentan. However, hypotension SAEs were reported less frequently on macitentan than on placebo, and only one macitentan-treated patient discontinued due to this AE. Hypotension AEs were predominantly reported for female patients and there was no indication of an increased incidence in other potentially vulnerable subgroups, such as the elderly, or patients with renal function impairment at baseline. Patients with systolic blood pressure (SBP) < 90 mmHg will be excluded from the proposed study.

Reductions from baseline in leukocyte and platelet counts may be observed with macitentan. In the AC-055-302 / 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 AC-055-302 / SERAPHIN study (macitentan in PAH), menstrual disorder AEs (mainly menorrhagia, metrorrhagia, dysfunctional bleed) and ovarian cysts were reported at a low incidence overall, but more frequently on macitentan than placebo, in females of childbearing potential. 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.

In clinical trials, a higher reporting rate of upper respiratory tract infections but also bronchitis was seen with macitentan vs placebo. It is likely that many such events may represent symptoms of congestion due to local vasodilatation (e.g. rhinitis), rather than actual infection. For the clinically more relevant lower respiratory tract infections, especially pneumonia, there was no relevant difference between macitentan and placebo. In addition, there was a higher incidence of urinary tract infections and gastroenteritis in the patients who received macitentan treatment compared to those who received placebo. However, given that there was no imbalance in the incidence of these events that were reported as SAEs or that led to discontinuation of treatment, coupled with the fact that there was no increase in the reporting rate over time, these AEs were considered to be of limited clinical relevance.

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 subjects with CTEPH.

1.3 Purpose and rationale of the study

The purpose of this study is to gather additional experience with macitentan 10 mg in subjects with inoperable CTEPH beyond the 24 weeks of treatment in the DB AC-055E201 / MERIT-1 study.

The rationale of this study relies on the fact that the long term safety of macitentan in this population is not known. It is also unknown whether the efficacy of macitentan (if any) reaches a plateau at 24 weeks (end of the DB study) or would still increase over a longer treatment period.

In addition, the opportunity will be given to subjects who were on placebo in the DB AC-055E201 / MERIT-1 study to receive macitentan 10 mg and benefit from a potentially active treatment.

2 STUDY OBJECTIVES

Safety objective:

- To evaluate the long-term safety and tolerability of macitentan 10 mg in subjects with inoperable CTEPH.

Efficacy objective:

- To evaluate the long term effects of macitentan 10 mg on exercise capacity and functional class (FC).

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This study is a multi-center, single-arm, open-label (OL), Phase 2 extension study to assess the long-term safety, tolerability and efficacy of macitentan in subjects with inoperable CTEPH.

The study will be conducted in approximately 60 centers in approximately 15 countries. Up to 78 subjects (males or females) from the DB AC 055E201 / MERIT-1 study will be enrolled in this OL study. Subjects will be rolled over from the AC-055E201 / MERIT-1 study to this OL study without knowledge of their previous study drug (macitentan 10 mg or placebo).

Subjects who complete the 24 weeks of the DB MERIT-1 study as scheduled can be enrolled in the MERIT-2 OL extension study.

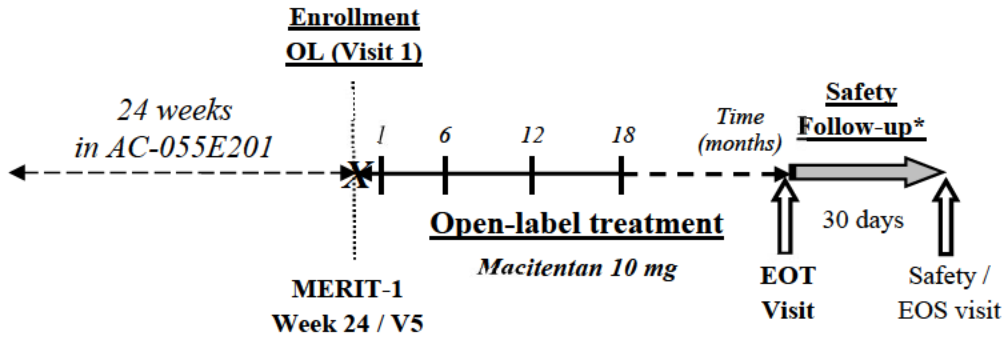
After the Enrollment visit, subjects will come to the site at Month 1 (Visit 2), Month 6 (Visit 3), and every 6 months thereafter (Visits 4, 5, 6…), up to the EOT visit [see Figure 1]. In addition, subjects will perform monthly laboratory and safety monitoring.

For each subject, the OL treatment duration 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) Actelion decides to stop this AC-055E202 / MERIT-2 OL extension study (e.g., if results of the AC-055E201 / MERIT-1 study 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.

Unscheduled visits may also take place anytime during the study.

A post-treatment Safety follow-up period (30 days) will follow the permanent study drug discontinuation. At the end of this Safety follow-up period, the Safety follow-up / End-of-Study (EOS) visit will be performed [see Figure 1]; this corresponds to the end of the OL study for an individual subject. For patients who are entering a continued access program, the enrollment into the continued access program (post-trial access program or other open-label study) must occur on the day of the last visit of the MERIT-2 study (EOS, which corresponds to EOT in this case).

Figure 1 Study design



EOS= End of Study; EOT = End of Treatment; OL = Open-label

*For patients who are entering a continued access program, the enrollment into the continued access program (post-trial access program or other open-label study) must occur on the day of the last visit of the MERIT-2 study (EOS, which corresponds to EOT visit in this case).

3.2 Study committees

- The same **Steering Committee (SC)** as the one involved in the AC-055E201 / MERIT-1 study was involved in the study design and will provide guidance on the conduct of the study.
- An independent **International Liver Safety Board** (**ILSB**): an external expert committee of hepatologists will provide ongoing assessment and advice regarding any serious hepatic events that may require further evaluation during the study.
- The same **Publication Committee** as the one involved in the AC-055E201 / MERIT-1 study will contribute to the preparation of potential manuscript(s) and will be consulted for authorship criteria (if applicable). This committee is composed of two SC members and one representative from Actelion.

4 SUBJECT POPULATION

4.1 Subject population description and rationale

The subject population will consist of male and female subjects with inoperable CTEPH who have completed the DB AC-055E201 / MERIT-1 study as scheduled. Subjects will be rolled over from the DB study to this OL study without knowledge of their previous study treatment (macitentan 10 mg or placebo).

The selection of subjects who complete the 24-week DB study period allows the inclusion only of those subjects who are sufficiently stable on study drug and/or on concomitant PAH

specific medications such as PDE-5 inhibitors and hence can potentially benefit from further treatment. It should be noted that subjects who experience a disease progression during the DB study (see AC-055E201 / MERIT-1 study protocol section 6.1.3) can be treated with the available standard of care. If they continue into the study up to the 24-week visit they are allowed to enter this OL extension, if they still fulfill the selection criteria.

4.2 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Written informed consent to participate in the study obtained from the subject, according to local regulations, prior to initiation of any study mandated procedure.

2. Subject with CTEPH having completed the DB AC-055E201 / MERIT-1 study as scheduled (i.e., who remained in the DB study up to Week 24).

3. Females of childbearing potential must have a negative pre-treatment serum pregnancy test, be advised on appropriate methods of contraception, and agree to use 2 reliable methods of contraception concurrently during study treatment and for at least 30 days after study treatment discontinuation.

- 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 have been taken for at least 1 month prior to randomization.
    - If the Essure procedure is chosen as a contraceptive method, a hysteron-salpingogram 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 these contraceptive methods must be used in combination with a spermicide.
- True abstinence from intercourse with a male partner is considered an acceptable method of contraception for this study (not requiring a second reliable of method of contraception) only when this is in line with the preferred lifestyle of the subject (e.g., homosexual females and females in religious order, nuns for example).

  Note 1: 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.

  Note 2: A female is considered to be of 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.

4.3 Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria:

1. Permanent discontinuation of DB study treatment due to an hepatic adverse event or liver aminotransferase abnormalities.
2. Hemoglobin < 100g/L.
3. Serum AST and/or ALT > 3 × ULN.
4. SBP < 90 mmHg.
5. Treatment with strong cytochrome P-450 3A4 (CYP3A4) inducers such as rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's wort.
6. Treatment with another ERA (e.g., bosentan, ambrisentan).
7. Any known factor (e.g., drug or substance abuse) or disease (e.g., unstable psychiatric illness) that, in the opinion of the investigator, 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 study drug excipients.
9. Females who are pregnant or plan to become pregnant during the study, or are lactating.

5 TREATMENTS

5.1 Study treatments

5.1.1 Study drugs

All subjects will receive macitentan 10 mg during the course of the study.

5.1.2 Dose rationale

In the completed AC-055-302 / SERAPHIN study, two doses of macitentan, 3 mg and 10 mg, demonstrated efficacy in PAH patients by improving clinical outcomes, functional status and exercise capacity. A dose-response was identified with the greatest efficacy demonstrated in the 10 mg dose group. Macitentan 10 mg in this patient population was well tolerated. For detailed information see the MERIT-1 protocol (section 1.2.2.4 and section 1.3) and macitentan IB [Macitentan IB].

Therefore, macitentan 10 mg was selected as the target dose for the MERIT-1 study. The same dose will be used in the MERIT-2 OL extension study to assess its longer term safety

in this population and to assess whether the effect observed with this dose in the MERIT-1 study, if any, reached the plateau or would still increase over time, and whether the achieved effect would be maintained over a long treatment period.

5.1.3 Investigational drug

Macitentan 10 mg will be provided as film-coated tablets debossed with '10' on either one or both sides.

If the subject is eligible, the first intake of study drug will take place at site, during the Enrollment visit, after successful completion of all assessments.

Thereafter, one tablet should be administered orally every morning irrespective of food intake. On the day of study visits, the morning dose of the study medication should be withheld until all visit assessments have been performed. The tablet should be taken from the bottle(s) that is(are) being dispensed during the visit.

5.1.4 Treatment assignment

All eligible subjects will receive macitentan 10 mg.

At Visit 1 (Enrollment visit), after completion of all assessments, and if the subject is eligible, the investigator/delegate will contact the Interactive Voice / Web Recognition System (IXRS), which will allocate medication bottles to the subject.

All study drug bottle numbers must be assigned through the IXRS.

5.1.5 Blinding

Not applicable.

5.1.6 Study drug supply

Actelion will supply all study drug to the site according to local regulations.

All drug supplies are to be used only in accordance with this protocol, and not for any other purpose.

5.1.6.1 Study drug packaging and labeling

The labeling and packaging of macitentan is conducted according to Good Manufacturing Practice, Good Clinical Practice (GCP), and any applicable laws and regulations of each country.

5.1.6.1.1 Study drug packaging

Study drug is provided as tablets and supplied in childproof bottles containing 36 tablets each.

5.1.6.1.2 Study drug labeling

Each medication bottle has 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 Investigational Medicinal Product (IMP) Label Dispensing Log.

5.1.6.2 Study drug distribution and storage

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 subjects enrolled in the study and in accordance with the protocol.

5.1.6.2.1 Study drug distribution

The study centers will be supplied with study drug according to the center's needs, depending on the number of subjects enrolled in the AC-055E201 / MERIT-1 study. Each center will have an individual stock of study drug, which will be timely re-supplied as soon as a predefined minimum level of study drug has been reached.

At each visit the medication bottle numbers will be allocated to the subjects through IXRS. Subjects will receive 1 medication bottle (childproof bottles containing 36 tablets each) at Enrollment (Visit 1), 5 medication bottles at Month 1 (Visit 2), and 6 medication bottles every 6 months thereafter (Visits 3, 4, 5…) up to the EOT visit.

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

Once a subject has been enrolled and the 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 distributed, the subject must be educated on the proper storage conditions at home. Study drug dispensing must be performed only upon written confirmation by an authorized study physician listed on the delegation of authority (DoA) form.

5.1.6.2.2 Study drug storage

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 DoA. Study drug must be kept in an appropriate secure area and stored according to the conditions specified on the label.

A temperature log must be maintained and temperature control must occur at least on a weekly basis at the site. 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 routinely used at site is acceptable 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), within 24 h of the excursion. The monitor must 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 IMP is kept segregated at the investigational site and returned to Actelion following internal drug return processes. New study drug supplies will be provided to the clinical investigator site.

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

5.1.6.3 Study drug return and destruction

The site must record the number of study drug received, dispensed, used, lost, returned during the study.

On an ongoing basis and/or on termination of the study, the monitor will collect used and unused subject bottles, and document the collection in the appropriate form before sending the bottles to the warehouse, where Actelion or its deputy will check drug reconciliation. In certain circumstances, used and unused drug containers may be destroyed at the site once drug accountability is finalized and has been checked by Actelion or its deputy, and written permission for destruction has been obtained from Actelion.

5.1.7 Compliance with study treatment

An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. An IMP dispensing and accountability log is to be completed on an ongoing basis, preferably on the visit day, for each subject. Subjects are instructed to return used and unused study drug (including empty bottles) at each visit. Study drug accountability must be performed on an ongoing basis by the study staff on the day of the visit and before providing further study treatment, in order to ensure that the subject is compliant with study requirements. Study drug accountability is also to be recorded in the electronic case report form (eCRF) and checked by the monitor during site visits.

Prior to each new dispensation, the visit compliance must be evaluated by the site staff, based on drug accountability, as per formula below:

Compliance = [(number of tablets provided to subject − number of tablets returned) / Total number of tablets that should have been taken during the period] × 100

The site staff must discuss any compliance issue with the subject and re-educate them on correct administration of study drug. Details of such discussion must be documented in the subject's file.

If the compliance with study drug intake is < 80% or > 120%, permanent discontinuation of study drug may be considered after consultation with Actelion.

5.1.8 Study drug interruption and premature discontinuation of study drug

The investigator should temporarily interrupt or permanently discontinue treatment with the study drug for a given subject if, on balance, he/she believes that continued administration would be contrary to the best interests of the subject, or if the subject is not compliant with study requirements (e.g., low compliance with study drug intake or visit attendance).

5.1.8.1 Study drug interruption

Study drug interruption should be avoided as much as possible.

If study drug intake is interrupted by the subject for any reason, she/he must immediately inform the investigator.

Interruptions of study drug must not last longer than 2 consecutive weeks. Longer interruptions must lead to permanent discontinuation of study drug.

All study drug interruptions as well as the reasons for interruptions must be recorded in the eCRF.

5.1.8.2 Premature discontinuation of study drug

Premature discontinuation of study drug may occur independently from study withdrawal. The subject may discontinue not only from study treatment but also from the study [withdrawal from study see Section 9.1].

The reason for premature discontinuation from study drug, the decision owner (as applicable), and whether subject decision to discontinue study treatment does or does not include study withdrawal must be documented in the eCRF. Reasons for premature discontinuation are mutually exclusive and only the primary reason for premature discontinuation must be recorded in the eCRF.

Study drug must be discontinued if any of the specific discontinuation criteria described in Section 5.1.8.3 is met.

Permanent discontinuation of study drug leads to the EOT visit and subsequently to the 30-day Safety follow-up period.

The premature EOT must be registered in the IXRS in a timely manner to avoid any automatic study drug re-supply. The date entered into the system must be the date of the last study drug intake.

5.1.8.3 Study-specific criteria for study drug interruption / permanent discontinuation of study drug

A) Pregnancy

If a female subject becomes pregnant while on study drug, study drug **must** be discontinued immediately, and a Pregnancy Form must be completed [see Section 10.3].

B) Liver aminotransferases abnormalities

Interruption of study drug

Study drug **must** be interrupted in the following cases:

- Aminotransferases (i.e., ALT and/or AST) > 3 and ≤ 8 × ULN

In such a case, a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and AP must be performed within one week. If AST and/or ALT elevation is confirmed, aminotransferases, total and direct bilirubin, and AP levels must be monitored weekly until values return to pre-treatment levels or within normal ranges. If the aminotransferase values return to pre-treatment levels or within normal ranges, reintroduction of study treatment can be considered. Interruptions must be for less than 2 consecutive weeks; longer interruptions must lead to permanent discontinuation of study drug.

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.

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).

Permanent discontinuation of study drug

Study drug **must** be stopped and its reintroduction is not to be considered in the following cases:

- Aminotransferases > 8 × ULN
- 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)

- Aminotransferases ≥ 3 × ULN and associated increase in total bilirubin ≥ 2 × ULN

In such cases, aminotransferases, total and direct bilirubin, and AP levels must be monitored weekly after study drug discontinuation until values return to pre-treatment levels or within 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.

All liver aminotransferases abnormalities leading to study drug interruption or discontinuation must be recorded as AEs [see Section 10].

An independent ILSB (an external expert committee of hepatologists) provides ongoing assessment and advice regarding any serious hepatic events that may require further evaluation during the study.

C) Hemoglobin abnormalities

In case of hemoglobin decrease from baseline* of > 20 g/L, a re-test must be performed within 10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

- Red blood cell cellular indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), peripheral blood smear, reticulocyte count, iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation), lactate dehydrogenase, indirect bilirubin.

  If hemoglobin decrease remains >20 g/L below baseline value at subsequent visits, further retests are to be performed as per investigator's judgement.

Study drug should be temporarily interrupted if clinically mandated based on the investigator's judgment, or in any of the following situations:

- A decrease in hemoglobin to < 80 g/L (< 4.9 mmol/L)
- A decrease in hemoglobin from baseline* of > 50 g/L
- The need for transfusion.

Reintroduction of study medication may be considered if hemoglobin recovery, defined as a return of hemoglobin above the lower limit of the normal range or to baseline is achieved.

Interruption of study medication must not last longer than 2 consecutive weeks; longer interruption must lead to permanent discontinuation of study drug.

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

D) Start of an ERA / strong CYP3A4 inducer / strong CYP3A4 inhibitors / moderate dual CYP3A4/CYP2C9 inhibitors / combination of moderate CYP3A4 and moderate CYP2C9 inhibitors / investigational drug

Study drug must be permanently discontinued if an ERA and/or a strong CYP3A4 inducer and/or strong CYP3A4 inhibitors and/or moderate dual CYP3A4/CYP2C9 inhibitors and/or coadministration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors and/or another investigational drug is started during treatment period.

5.2 Concomitant medications

5.2.1 Definition

A concomitant medication is any medication that started, stopped, or was ongoing between Enrollment (first dose of OL study drug) and last subject's visit.

5.2.2 Reporting of concomitant medications in the eCRF

Concomitant medications will be reviewed at each visit.

All concomitant medications taken from Enrollment (Visit 1) up to EOS visit are to be recorded in eCRF (and subject's file). This includes prescription, over the counter, herbal, recreational drugs and dietary supplements. Generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dosage, and indication will be collected.

5.2.3 Forbidden concomitant medications

- Strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbital, rifampin / rifampicin, rifabutin, rifapentin, St. John's wort)
- Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine) until study intervention discontinuation. For other examples of CYP inhibitors, refer to the FDA website [Food and Drug Administration 2020].

  * If patients are currently stable on a strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir), moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine), the patient may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment.
- Another ERA
- Another investigational drug **(other than macitentan 10 mg)**

6 STUDY ENDPOINTS

6.1 Exploratory efficacy endpoints

Exploratory endpoints:

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

6.2 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 [as detailed in Appendix 4] up to 30 days after study drug discontinuation.
- Change in vital signs (BP [i.e., DBP and SBP], HR) and body weight from baseline to all assessed time points during the study.

7 STUDY ASSESSMENTS

All study assessments are to be performed by a qualified study staff member: medical, nursing, or specialist technical staff.

The following order of assessments is recommended:

- Vital signs and physical exam
- WHO FC
- 6MWT
- Borg dyspnea index

7.1 Baseline parameters

7.1.1 Baseline demographics and disease characteristics

Baseline demographic, height, and disease characteristics of interest for this OL study will be taken from the AC-055E201 / MERIT-1 database.

7.2 Efficacy assessments

7.2.1 Six-minute walk test and Borg dyspnea index

7.2.1.1 6MWT

The 6MWT is performed at Enrollment (Visit 1), each 6-monthly visit (Visits 3, 4, 5…), and EOT visit. 6MWT must be performed before the Borg dyspnea index evaluation.

It is a non-encouraged test that measures the distance walked in 6 min.

Detailed guidelines on correct execution of these tests, the 'Actelion guidelines for 6MWT', are provided in Appendix 1.

Site team members conducting the 6MWT must be trained on these 6MWT guidelines. A training log must be collected upon completion of the training. Note: for site team members conducting 6MWTs in both the MERIT-1 and MERIT-2 studies, training performed for MERIT-1 does not need to repeated for MERIT-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 Actelion, and formal approval must be obtained from Actelion before performing any study-specific 6MWT.

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-055E201 / MERIT-1 study should be used.

Note: If oxygen supplementation is needed during the 6MWT at Enrollment, then oxygen should be delivered using the same method and the same flow during all study 6MWTs by that subject. If the flow must be increased during subsequent visits (e.g., due to worsening), this should be indicated in the source notes (as well as in the Concomitant Medication forms of the eCRF).

The data related to 6MWT will be recorded in the eCRF.

7.2.1.2 Borg dyspnea index

The Borg dyspnea index is evaluated after each 6MWT. It rates dyspnea on a scale from '0' to '10' [Appendix 2]. Borg dyspnea index will be collected in the eCRF.

7.2.2 WHO functional class

The WHO FC [Appendix 3] is assessed at Enrollment (Visit 1), each 6-monthly visit (Visits 3, 4, 5…), and EOT visit. When applicable, WHO FC should be performed before the 6MWT. The WHO FC will be collected in the eCRF.

7.3 Safety and tolerability assessments

The definitions, reporting and follow-up of AEs, SAEs and potential pregnancies are described in Section 10.

7.3.1 Vital signs

Vital signs (SBP, diastolic BP [DBP], HR) will be measured at Enrollment (Visit 1), Month 1 (Visit 2), each 6-monthly visit (Visits 3, 4, 5…), EOT visit, and Safety follow-up / EOS visit. Data will be recorded in the eCRF.

When applicable, vital signs should be performed before the 6MWT. SBP, DBP and pulse rate will be measured with the subject either in a supine or sitting position after having rested for at least 5 min. The right or left arm may be used. However, the same position and arm should be used throughout the trial for an individual subject.

7.3.2 Weight

Body weight will be measured at Enrollment (Visit 1), Month 1 (Visit 2), each 6-monthly visit (Visits 3, 4, 5…), EOT visit, and Safety follow-up / EOS visit. Data will be recorded in the eCRF.

Weight should be measured without shoes. The same scale should be used for each weight measurement.

7.3.3 Physical examination

Physical examination is to be performed at Enrollment (Visit 1), Month 1 (Visit 2), each 6-monthly visit (Visits 3, 4, 5…), EOT visit, and Safety follow-up / EOS visit. Data will be recorded in the eCRF.

Physical examination will be recorded by body system in the eCRF as normal or abnormal. If an abnormality is detected, it must be specified in the eCRF, describing the signs related to the abnormality (e.g., systolic murmur) not the diagnosis (e.g., mitral valve insufficiency).

Clinically relevant findings meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded as an AE in the eCRF.

7.3.4 Laboratory assessments

7.3.4.1 Type of laboratory

A **central** laboratory (see separate Laboratory Manual for contact details) will be used for the analysis of all laboratory tests described in the protocol.

Central laboratory data will be automatically transferred from the central laboratory database to the Actelion clinical database.

Blood samples will be **collected at site and sent for analysis to the central laboratory,** except at Visit 1 / Enrollment where an additional blood sample will be analysed by the

local laboratory (on top of the sample sent to the central laboratory) to check the eligibility of the subject on the day of Enrollment.

Under specific circumstances (e.g., subject lives far away from the site and cannot return every month), laboratory samples could be drawn in a local laboratory close to where the subject lives, and analyzed at central laboratory (*Note: a local phlebotomy service set-up may be used*). In that event, the local laboratory must be provided with the central laboratory kits, which must be used for blood collection. The blood samples collected locally will be shipped by the local laboratory to the central laboratory for analysis. Such a local laboratory shall be identified as soon as possible, but no later than upon enrollment of the subject in the study.

In case a central laboratory sample is lost, deteriorates, or is not analyzable for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was drawn within the same time-window and the local laboratory results are available.

In the exceptional event (e.g., subject is hospitalized in a different hospital from the site or in case of an emergency) where a local laboratory is utilized for the collection **and** analysis of blood samples, the local laboratory results of parameters required by the protocol (with the corresponding normal ranges) will be entered into the clinical database via dedicated eCRF pages [see Section 7.3.4.2].

For these local laboratories, the investigator/delegate will provide Actelion with the name, professional degree and curriculum vitae (CV) of the laboratory director, a copy of the laboratory's certification, and the normal ranges for each laboratory test that is evaluated in the study. These laboratory references must be updated whenever necessary.

Further details regarding blood sampling procedures, collection and shipment of samples and reporting of results are described in the Central Laboratory Manual.

Central laboratory reports will be communicated to the investigator [see separate Laboratory Manual]. All laboratory reports (from central and local laboratories, if applicable) 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 5 days) after receipt/acknowledgement, and filed with the source documentation.

Note: Alert reports from the central laboratory must be reviewed, signed and dated by the investigator or designated physician within 24 h of receipt. The person reviewing the laboratory report must indicate whether the abnormal values are considered clinically significant (CS) or not clinically significant (NCS); if CS an AE must be reported in the eCRF.

In case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion and the concerned site. Alert flags that will trigger such notifications are displayed in Appendix 5.

Central laboratory normal ranges are provided in Appendix 6.

Any clinically relevant laboratory abnormalities (including ALT/AST abnormalities > 3 × ULN) occurring after study drug initiation, which meet the definition of an AE must be reported by the investigator as an AE and/or SAE, as appropriate [see Section 10]. In such a case, repeated assessments are mandatory until they return to normal range or baseline value, stabilize, or until the change is no longer clinically relevant.

7.3.4.2 Data to be collected in eCRF if a local laboratory is used to analyze a blood sample

As a minimum, the following local laboratory parameters/results (i.e., results from samples drawn and analyzed locally) will be collected in the eCRF (together with the normal ranges):

- Any ALT, AST, AP, and total and direct bilirubin result related to the detection, confirmation and/or monitoring of ALT and/or AST elevations of > 3 × ULN.
- Any hematology work-up related to the detection, confirmation and/or monitoring of hemoglobin decrease from baseline of > 20 g/L, a value of hemoglobin < 100 g/L, or a hemoglobin decrease requiring transfusion.
- Any local laboratory test documenting the result of a parameter requested per protocol (e.g., in case no sample was sent to central laboratory at a planned visit because the patient was hospitalized at another hospital, or in case sample sent to central laboratory was hemolyzed).
- Any local laboratory result related to the documentation or follow-up of an AE or an SAE, including clinically relevant abnormal laboratory results and their follow-up.

In the event that several local laboratory samples have been drawn 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).

7.3.4.3 Laboratory parameters

At Enrollment/Visit 1, about 25–30 mL will be collected (half of this will be sent to the central laboratory for analysis, the rest will be analyzed locally to check the eligibility). At each of the following visit, about 15 mL will be collected. The total amount of blood collected per year is approximately 200 mL.

<u>Hematology</u>

Hematology tests will be performed at Enrollment (Visit 1), Month 1 (Visit 2), each 6-monthly visit (Visits 3, 4, 5…), EOT visit, and Safety follow-up visit.

These tests include:

- Hemoglobin*
- Hematocrit
- Erythrocyte count
- Leucocyte count with differential
- Platelet count
- Coagulation tests (partial thromboplastin time, International Normalized Ratio [INR]).

* In addition, hemoglobin will be measured every month during the first 6 months, and every 3 months thereafter up to EOT visit.

Rules for study drug interruption and laboratory re-tests in case of hemoglobin abnormality are provided in Section 5.1.8.3.

Blood chemistry

Blood chemistry tests will be performed at Enrollment (Visit 1), Month 1 (Visit 2), each 6-monthly visit (Visits 3, 4, 5…), EOT visit, and Safety follow-up visit.

These tests include measurement of:

- LTs*: liver aminotransferases (ALT and AST), AP, total and direct bilirubin
- Creatinine
- Blood urea nitrogen (BUN)
- Uric acid
- Glucose
- Sodium
- Potassium
- Magnesium
- Calcium
- Albumin
- C-reactive protein (CRP).

* In addition, LTs will be measured every month up to EOT visit.

Rules for study drug interruption / permanent discontinuation and laboratory re-tests in case of ALT and/or AST elevation are provided in Section 5.1.8.3.

On a case-by-case basis, if an abnormal ALT/AST value was observed, Actelion could request the analysis of additional parameters (e.g., acetaminophen concentration to rule out an acetaminophen-related liver toxicity). This additional analysis would be done on already collected samples.

Pregnancy test

For females of childbearing potential [Section 4.2], a serum pregnancy test must be performed at Enrollment (Visit 1) and every month (+/- 1 week) thereafter up to at least 30

days after study drug discontinuation. In addition, a serum pregnancy test must be performed at anytime if pregnancy is suspected during the study.

In the event of pregnancy, a Pregnancy Form must be completed [see Section 10.3].

For females of childbearing potential, each month, the study personnel must verify whether the methods of contraception are in accordance with the protocol [Section 4.2] and correctly used by the subject. Documentation that the discussion with the subject took place must be available in the subject's source notes. Methods of contraception will be collected in the eCRF.

8 SCHEDULE OF VISITS

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

8.1 Treatment period

8.1.1 Enrollment visit (Visit 1)

It is the responsibility of the investigator to obtain written informed consent from each subject (during the Enrollment visit at the latest) after adequate face-to-face explanation of the methods, objectives and potential hazards of the study, and prior to any study-specific assessment. After discussing the study with the investigator and after agreeing to study participation by signing the Informed Consent Form (ICF), subjects will be assigned medication bottles by the IXRS provider. The same subject number as the one assigned in the MERIT-1 study will identify the subject throughout the OL study.

This Enrollment visit will be combined with the Week 24 visit (i.e., Visit 5/Week 24) of the DB AC-055E201 / MERIT-1 study [see Figure 1].

This visit includes:

- Recording of concomitant medications
- Recording of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs and weight
- Assessment of WHO FC
- 6MWT
- Completion of Borg dyspnea index, after the 6MWT
- Complete laboratory tests including: hematology, blood chemistry, and serum pregnancy test (for females of childbearing potential only)
- After completion of all Enrollment assessments/procedures and verification of all entry criteria: dispensing of 1 medication bottle for the next month.
- Recording of AEs and SAEs:

- All SAEs (except for those already reported in the AC-055E201 / MERIT-1 study) occurring from signature of the consent form to first OL drug administration must be recorded in the OL eCRF and on an SAE form.
- All AEs occurring from the initiation of the OL study drug must be recorded in the OL eCRF.

Note 1: Tests are not to be repeated if performed for the AC-055E201 / MERIT-1 study on the day of this Enrollment visit.

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.

The investigator will check all the inclusion/exclusion criteria and decide on the subject's eligibility for the study. It must be verifiable in the source documents that the subject meets each of the inclusion criteria and none of the exclusion criteria.

The first tablet of study drug must be taken at site once all study assessments are performed. The site staff must inform the subject to then take one tablet every morning, irrespective of food intake. Subjects must be instructed not to take the study drug in the morning of the next visit day and to return the study drug bottle (even empty) and unused medication at the next visit.

8.1.2 Month 1 visit (Visit 2)

This visit is scheduled one month (± 1 week) from the day of Enrollment, and includes:

- Recording of concomitant medications
- Recording of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs and weight
- Complete laboratory tests including: hematology, blood chemistry, and serum pregnancy test (for females of childbearing potential only)
- Recording of AEs and SAEs
- Return of study drug bottle and unused medication
- Dispensing of 5 medication bottles (macitentan) for 5 months. Alternatively, if the subject comes to the investigational site every month for the monthly laboratory and safety monitoring, it is possible to dispense (and return) one medication bottle on a monthly basis.

Subjects must be instructed not to take the study drug in the morning of the next visit day and to return the study drug bottles (even empty) and unused medication at the next visit. Study drug must be taken from the bottle(s) that is(are) being dispensed.

8.1.3 Monthly laboratory and safety monitoring (Months 2, 3, 4, 5, 7, 8, 9….)

These monthly visits will occur between regular visits, every month (± 1 week) from the day of Enrollment, and include:

- Recording of concomitant medications
- Recording of methods of contraception (for females of childbearing potential only)
- Laboratory tests including:
  - LTs
  - Serum pregnancy test (for females of childbearing potential only)
  - Hemoglobin, if applicable (i.e., each month during the first 6 months, and every 3 months thereafter)
- Recording of AEs and SAEs
- If the subject comes to the investigational site every month for the monthly laboratory tests, it is possible to dispense (and return) one medication bottle on a monthly basis.

Note: Since one bottle contains 36 tablets, in case of monthly dispensing of study drug, the interval between 2 consecutive visits should not exceed 36 days in total.

In the specific cases where the monthly laboratory samples are not collected at the site [see Section 7.3.4.1], the safety monitoring (assessments of AEs, SAEs, concomitant medications and methods of contraception) should be done via a telephone call that must be documented in the subject's file.

8.1.4 Visits at 6-monthly intervals (Visits 3, 4 etc.)

These 6-monthly visits are scheduled every 6 months ± 2 weeks, from the day of Enrollment, and include:

- Recording of concomitant medications
- Recording of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs and weight
- Assessment of WHO FC
- 6MWT
- Completion of Borg dyspnea index, after the 6MWT
- Complete laboratory tests including: hematology, blood chemistry, and serum pregnancy test (for females of childbearing potential only)
- Recording of AEs and SAEs
- Return of study drug bottles and unused medication

- Dispensing of 6 medication bottles (macitentan) for 6 months. Alternatively, if the subject comes to the investigational site every month for the monthly laboratory tests, it is possible to dispense (and return) one medication bottle on a monthly basis.

Subjects must be instructed not to take the study drug in the morning of the next visit day and to return the study drug bottles (even empty) and unused medication at the next visit. Study drug must be taken from the bottle(s) that is(are) being dispensed.

8.1.5 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 Actelion decides to stop the study; see Section 3.1).

End of treatment (EOT): The end of all study treatment for an individual participant.

At the end of the OL study, the EOT visit is scheduled for all subjects still participating in this OL study. For subjects entering a continued access program, the EOT visit is defined as the EOS visit.

Subjects prematurely discontinuing macitentan treatment must also undergo the EOT visit.

Permanent study drug discontinuation must be reported in the IXRS in a timely manner to avoid any automatic study drug re-supply. Date entered into the system must 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.

This visit includes:

- Recording of concomitant medications
- Recording of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs and weight
- Assessment of WHO FC
- 6MWT
- Completion of Borg dyspnea index, after the 6MWT
- Complete laboratory tests including: hematology, blood chemistry and serum pregnancy test (for females of childbearing potential only)
- Recording of AEs and SAEs
- Return of study drug bottles and unused medication

- Schedule an appointment for the safety follow-up visit 30 days after last intake of study drug.

8.2 Safety follow-up period

For each subject, a post-treatment Safety follow-up period (30 days) will follow the permanent study drug discontinuation. For patients who are entering a continued access program, the enrollment into the continued access program (post-trial access program or other open-label study) must occur on the day of the last visit of the MERIT-2 study (EOS, which corresponds to EOT visit in this case).

8.2.1 EOS visit

For an individual participant, EOS visit is defined as follows:

- For participants that complete treatment, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake.
- For participants that prematurely discontinue study treatment, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake.
- For participants who complete treatment and who are entering a continued access program (post-trial access or other open-label extension study) the EOS visit is defined as the EOT visit.

All attempts should be made to perform the Safety follow-up / EOS Visit 30 days after the permanent discontinuation of study drug; a window of + 3 days is acceptable.

This visit includes:

- Recording of concomitant medications
- Recording of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs and weight
- Complete laboratory tests including: hematology, blood chemistry, and serum pregnancy test (for females of childbearing potential only)
- Reporting of any AEs and SAEs occurring up to 30 days after study drug discontinuation in the eCRF and on an SAE form (if applicable)

8.3 Unscheduled visits

An unscheduled site visit may be performed at any time during the study (between scheduled visits), as necessary, based on investigator discretion. These visits include (but are not limited to) those performed due to safety (e.g., occurrence of an adverse event, laboratory abnormalities) and/or CTEPH related (e.g., disease progression) issues.

The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF. If any of the

laboratory parameters listed in Section 7.3.4.3 need to be analyzed, this must be done at the central laboratory (except in case of emergency). If it has been done at a local laboratory, results must be recorded in the eCRF [see Section 7.3.4.2].

During such visits, any of the following assessments may be performed:

- Assessment of concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs and/or body weight
- WHO FC
- 6MWT
- Borg dyspnea index, after the 6MWT
- Complete laboratory tests including: hematology, blood chemistry, and serum pregnancy test (for females of childbearing potential only)
- Assessment of AEs and SAEs
- Return of study drug bottles and unused medication and dispensing of new bottle(s), if appropriate.

9 STUDY COMPLETION

All enrolled subjects who received study drug must be followed up to the EOS, whether or not they are prematurely discontinued from study treatment.

For an individual subject, the end of this OL study corresponds to EOS visit.

For all subjects, the reason for premature discontinuation from study and the decision owner (as applicable) must be documented in the eCRF.

9.1 Withdrawal from study

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn from the study if they state an intention to withdraw further participation in all components of the study, die, or are lost to follow-up for any other reason. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believe that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

A subject who prematurely discontinues study drug is not considered as withdrawn from the study and will be followed-up for Safety [as outlined in Section 8.2].

The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, e-mail address, person to be contacted in case the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject and document all attempts. The following methods must be used: at least three telephone calls must be placed to the last available telephone number, and one registered letter must be sent by post to the last available home address; this information will be collected in the eCRF. Additional methods may be acceptable if they are compliant with local rules/regulations, respecting the subject's right to privacy.

If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

9.2 End of the trial

The end of the trial is reached when all the subjects have either completed their EOS visit, died or are lost to follow-up.

9.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally or locally. In particular, if the results of the DB MERIT-1 study do not support further use of macitentan in CTEPH subjects, the MERIT-2 OL extension study will be discontinued.

Investigators can terminate the participation of their site in the study at any time.

If the study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Health Authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated 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 suspends or terminates the study without prior agreement from Actelion, the investigator must promptly inform Actelion and the IRB/IEC, and must provide Actelion and the IRB/IEC with a detailed written explanation of the termination or suspension.

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

Any suspension or premature termination of the study must be discussed with the SC.

9.4 Medical care of subjects after End-of-Study

After the last subject's visit, the investigator/delegate will explain to subjects which treatment(s)/medical care(s) would be necessary and available according to local regulations, whether the subject completed study treatment or not. Local regulations on continued access will always take precedence.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 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 (from study drug initiation until 30 days after study drug discontinuation) 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.
- 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, misuse and abuse of the study drug should be reported as AE. These events with the study medication should also be documented in the study drug log/accountability log of the eCRF (if possible).

For this study, any dose of study medication higher than the planned total daily dose in a single day will be considered an overdose. In the event of an overdose, standard supportive measures must be taken, as required.

10.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE forms 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 three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not influence daily activities, and usually does not 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 10.2.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be made on a case per case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

10.1.3 Relationship to study drug

Each adverse event 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 'suspect' (i.e., related) or 'not suspect' (i.e., not related).

10.1.4 Reporting of adverse events

All AEs occurring from initiation of the OL study drug and up to 30 days after study drug discontinuation (up to EOS for participants who enter a continued access program on the same day as the EOS visit, see Section 8.2.1) are defined as treatment-emergent AEs and must be recorded on specific AE forms 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.

10.1.5 Follow-up of adverse events

AEs still ongoing 30 days after study drug discontinuation must be followed up until they are no longer clinically significant.The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or product quality compliant (PQC) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.2 Definitions of serious adverse events

10.2.1 Serious adverse events

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

- Fatal
- 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.
- Requiring inpatient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but 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 following reasons for hospitalization are exempted from being reported:

- Hospitalizations for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalizations for pre-planned (i.e., planned prior to signing informed consent) standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris. However, complications that occur during hospitalization are AEs or SAEs (for example, if a complication prolongs hospitalization).

10.2.1.1 Serious adverse events associated with study design or protocol mandated procedures

An SAE is defined as related to study design or protocol mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated invasive procedures. Examples include discontinuation of a subject's

previous treatment during a washout period leading to exacerbation of underlying disease or a complication of an invasive procedure specifically required by the protocol.

10.2.2 Reporting of serious adverse events

10.2.2.1 Prior to start of OL treatment period

All SAEs (except for those already reported in the AC-055E201 / MERIT-1 study), as well as PQCs, occurring from signature of the ICF to first drug administration in the OL must be reported in the eCRF and on an SAE form of the MERIT-2 OL extension study (i.e., AC-055E202).

Note: All SAEs occurring between DB study drug initiation and up to 30 days after study drug (DB) discontinuation, or until initiation of study drug in the OL study (whichever occurs first) are to be reported on SAE forms and also on AE forms in the AC-055E201 / MERIT-1 eCRF.

10.2.2.2 During treatment and follow-up periods

All SAEs, regardless of causal relationship, as well as PQCs, occurring from the initiation of the OL study drug and up to 30 days after study drug discontinuation (up to EOS for participants who enter a continued access program on the same day as the EOS visit, see Section 8.2.1) must be reported on an SAE form and also on AE forms in the eCRF.Follow-up of serious adverse events
Serious adverse events 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.

10.2.3 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to the Sponsor within 24 h of the investigator's knowledge of the event, **only** if considered causally related to previous exposure to the study medication by the investigator.

10.2.4 Reporting procedures

All SAEs must be recorded on an SAE form, whether or not this event is considered by the investigator to be related to study drug.

All SAEs must be reported by the investigator to the Sponsor within 24 h of the investigator's first knowledge of the event. The reporting of the initial SAE should not be delayed if some information is unavailable at time of reporting.

The principal investigator or designee must complete the SAE form in English, and must assess the causal 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 event, especially causality, has been made by a physician. The completed SAE form must be sent to the Sponsor (see contact details provided on the SAE form).

Upon request, the detailed description of the event provided in the SAE form can be supplemented by copies of additional source documents that may include (but are not limited to): copies of autopsy reports, and hospital discharge summaries, as applicable.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

Once an SAE form is sent, 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 sent again to the Sponsor. Follow-up information about a previously reported SAE must also be reported within 24 h of the investigator's first knowledge of the new information.

Sponsor will confirm receipt of the initial SAE report, or any update provided thereafter, by sending an acknowledgement of receipt. If an acknowledgment of receipt is not received within 2–3 working days, the site should contact the monitor to clarify if the SAE form was received by Sponsor.

The Sponsor may contact the investigator to obtain further information. The principal investigator or designee should respond as soon as possible. The response should be filed at site with the appropriate SAE form.

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), follow-up information 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 the Sponsor to Health Authorities, ECs/IRBs and investigators, as appropriate. Either the Sponsor or the investigators will submit the reports to the ECs/IRBs, as required by local regulations.

The reference safety document to assess whether or not a SUSAR should be reported by the Sponsor to Health Authorities, ECs/IRBs and investigators is section 6 of the Investigator's Brochure [Macitentan IB].

10.3 Pregnancy

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 a woman becomes pregnant while on study drug, study drug must be discontinued immediately. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

10.3.1 Reporting of pregnancy

Any pregnancy occurring in female participants or partners of male participants during study drug administration and up to 30 days following study drug discontinuation (up to EOS for participants who enter a continued access program on the same day as the EOS visit, see Section 8.2.1) must be reported within 24 h of the investigator's knowledge of the event.

Pregnancies must be reported on the Pregnancy Notification form, which is sent to the Sponsor (see contact details provided on the respective Pregnancy form), and entered in the eCRF. All reporting requirements and timelines specified in Section 10.2.4 also apply to the reporting of a pregnancy.

10.3.2 Follow-up of pregnancy

Any pregnancies in female paticipants or partners of male participants must be followed to its conclusion and its outcome must be reported to the Sponsor on the End of Pregnancy - Collection Form B and on the Product Exposure During Pregnancy - Collection Form A.

Any AE and SAE associated with the pregnancy (including outcome e.g., spontaneous/therapeutic abortion) occurring up to 30 days after study drug discontinuation must be reported on separate AE pages in the eCRF. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 10.2.4.

10.4 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, vital signs, and project-specific labs/examinations as required) is monitored and reviewed on a continuous basis by the Actelion Clinical team (in charge of ensuring subjects' safety as well as data quality) by periodically monitoring clinical studies activities from protocol conception to database closure.

10.5 Product quality complaint handling

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide

to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

10.5.1 Procedures

All initial PQCs must be reported to the Sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the Sponsor.

10.5.2 Contacting sponsor regarding product quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.6 Special reporting situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding.

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated CROs supervised by Actelion.

A Statistical Analysis Plan (SAP) will be written and finalized before database closure and will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

Individual subject listings will be provided for efficacy, and safety endpoints, as well as for baseline and other subject characteristics. Each listing will be broken down by treatment group, site, subject number, and assessment date, where appropriate.

11.1 Variables

This OL extension study will only contain analyses related to exploratory efficacy and safety endpoints.

For the analysis of exploratory endpoints, baseline will be defined in one of two ways, depending on the analysis:

1) As the last value obtained up to and including the day of first administration of randomized study drug in the DB AC-055E201 / MERIT-1 study or,

2) As the last value obtained up to and including the day of first administration of macitentan 10 mg study drug during this study, the AC-055E202 / MERIT-2 OL extension study.

Exploratory endpoint variables will be calculated in reference to their baseline values at each scheduled time point in either AC-055E201 / MERIT-1 or AC-055E202 / MERIT-2 OL extension depending on the analysis.

11.1.1 Time windows

In order to minimize missing data and to analyze the data at the relevant planned (scheduled) visits, all recorded assessments up to EOS are re-assigned to the most appropriate time point according to the best fitting time-window for that assessment. Any unscheduled assessment (including endpoint variable, EOT and EOS assessments) will also be mapped to a time-window. The windows are based on the number of days since baseline corresponding to the date of assessment recording.

Should more than one assessment fall within the same time window, then the closest value to the planned time point will be assigned to the said time point for use in data summaries and analyses. In case of values that are equidistant to the planned time point, the last assessment will be considered for the analyses. If more than one value falls on the same day then the worst value will be used (e.g. for 6MWD the smallest value will be used).

For 6MWD and Borg dyspnea index, the date of 6MWT will be used to perform the mapping.

11.1.2 Exploratory variables

11.1.2.1 Six-minute walk distance (6MWD)

Absolute change in meters from baseline to time point in the 6MWD defined as:

$$(6MWD(m) at\ time\ point\ -6MWD(m)\ at\ baseline)$$

is the variable for the analysis of the exploratory endpoint, change from baseline to each scheduled time point in exercise capacity, as measured by the 6MWT.

11.1.2.2 Borg dyspnea index

Absolute change from baseline to time point in Borg dyspnea index defined as:

$$(Borg\ dyspnea\ index\ at\ time\ point\ -Borg\ dyspnea\ index\ at\ baseline)$$

is the variable for the analysis of the exploratory endpoint, change from baseline to each scheduled time point in Borg dyspnea index collected at the end of the 6MWT.

For Borg dyspnea index, the baseline value is the value reported at the same assessment as baseline 6MWD.

11.1.2.3 WHO Functional Class (WHO FC)

Occurrence of worsening in WHO FC level at time point as compared to baseline is considered and the following dichotomous variable is defined:

$$X_i = \begin{cases} 1\ if\ (Difference\ between\ time\ point\ and\ baseline\ in\ WHO\ FC) > 0 \\ 0\ if\ (Difference\ between\ time\ point\ and\ baseline\ WHO\ FC\ ) \leq 0 \end{cases}$$

The proportion of subjects experiencing any increase in WHO FC level at time point as compared to baseline, defined as the proportion of subjects who have occurrence of worsening ($X_i = 1$) is the variable for the analysis of the exploratory endpoint, proportion of subjects with worsening of WHO FC from baseline to each scheduled time point.

11.1.3 Safety variables(s)

A treatment-emergent AE is any AE temporally associated with the use of a study drug (from study drug initiation until 30 days after study drug discontinuation).

Baseline will be defined as the last value obtained up to and including the day of first administration of macitentan 10 mg during the DB or OL period.

Safety and tolerability endpoints will be analyzed for the combination of DB and OL periods from first administration of macitentan 10 mg in the DB or OL period for subjects who received at least one dose of macitentan 10 mg during the OL extension study.

- 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 [as detailed in Appendix 4] up to 30 days after study drug discontinuation.
- Change in vital signs (BP [i.e., DBP and SBP], HR) and body weight from baseline to all assessed time points during the study.

11.2 Analysis Sets

11.2.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS), used for analysis in the DB study only, and reported here for completeness, comprises subjects from the DB AC-055E201 / MERIT-1 study who were randomized to either placebo or macitentan 10 mg.

11.2.2 Open-Label Analysis Set (OLAS)

The OL analysis set (OLAS), comprises all data from subjects who enrolled into the OL extension study, from the time they enter the OL extension study (Table 2).

11.2.3 Restricted Analysis Set (RAS)

The restricted analysis set (RAS), comprises all data from subjects enrolled in the OL extension study who received macitentan 10 mg during the AC-055E201 / MERIT-1, from the time they enter the DB study (Table 2).

11.2.4 Open-Label Safety Set (OLSS)

OL Safety Set (OLSS), comprises all DB and OL study subject data from subjects enrolled in OL extension study and who received macitentan 10 mg at least once, during either the DB or OL extension study for the period they are exposed to macitentan 10 mg (Table 2).

11.2.5 Role of the different analysis sets

The analyses of the exploratory efficacy endpoints will be performed on the OLAS and RAS:

1. On the OLAS, as change from baseline of the OL extension study, by randomized treatment group in AC-055E201 / MERIT-1,
2. On the RAS, as change from baseline of the DB core study in macitentan 10 mg only.

The OLSS will be used for the analyses of the safety variables. Listings will be prepared on the RAS, OLAS, and OLSS as appropriate. Subject disposition will be summarized for the OLAS. No per protocol analyses will be conducted.

Table 2 Use of analysis sets for analysis of efficacy and safety variables

	Analysis Sets		
Variable	**OLAS**	**RAS**	**OLSS**
Efficacy			
6MWD	X	X	
Borg dyspnea index	X	X	
WHO FC	X	X	
Safety			
AEs			X
SAEs			X
Marked laboratory abnormalities			X
Vital signs			X
Subject Disposition	X		
Demographics	X		
Exposure	X		

6MWD = 6-minute walk distance; AEs = adverse events; FC = functional class; OLAS = Open-Label Analysis Set; OLSS = Open-Label Safety Set; RAS = Restricted Analysis Set; WHO = World Health Organization.

11.2.6 Randomization and stratification

The sample size for the OL extension study will be up to 78 randomized (1:1 to placebo:macitentan 10 mg) subjects from the AC-055E201 / MERIT-1 DB study, who are eligible for and consent to enter the OL extension.

Randomization in the AC-055E201 / MERIT-1 DB study was not stratified.

11.3 Description of statistical analyses

11.3.1 General considerations

- Unblinding of study drug code will occur only after AC-055E201 / MERIT-1 study database closure in accordance with Actelion standard operating procedures (SOPs).
- Analyses will be conducted only on subject data from subjects who enroll in the OL study and are exposed to macitentan 10 mg at least once, during either the DB or OL extension studies.
- For the analysis of the exploratory endpoints on the OLAS where comparisons between original randomized groups are made, the experiment-wise significance level will be controlled at the two-sided $\alpha = 0.05$ level and two-sided 95% confidence intervals will be provided. Any two-sided p-value ≤ 0.05 will be identified as

statistically significant but will be considered as exploratory result. No multiplicity adjustment will be made.

- Given the small sample size in this study only the following model covariates may be considered for inclusion in the analysis of the exploratory endpoints: randomized treatment, time or visit, and baseline value related to the outcome variable of interest.
- AEs will be coded using the same version of the MedDRA dictionary used in the AC-055E201 / MERIT-1 study. Concomitant Medications will be coded using the same versions of the WHO drug code and the Anatomic Therapeutic Chemical class code dictionaries as used in the AC-055E201 / MERIT-1 study.
- All important protocol deviations related to study inclusion or exclusion criteria, conduct of the study, patient management, or patient assessment will be described in the final report. Subject listings for protocol deviations will be presented broken down by center.
- SAS version 9.2 or higher will be used for all statistical analysis.
- All analysis variables will be listed and presented in tables; variables to be presented in figures will be specified in the SAP.
- Data will be listed and summarized by appropriate descriptive statistics (tables or figures), typically including:
  - Number of non-missing observations, number of missing observations, mean, standard deviation, minimum, Q1, median, Q3 and maximum for continuous variables
  - Number of events, number of censored observations , number of subjects at risk, and Kaplan-Meier estimates of the survival function for time-to-event variables
  - Number of non-missing observations, number of missing observations and frequency with percentage per category (percentages based on the sum of number of non-missing observations and total number of observations) for categorical variables.

Absolute changes from baseline are defined as: post-baseline value minus baseline value, such that a positive sign indicates an increase as compared to baseline.

11.3.2 Analysis of subject disposition and study completion/withdrawal

A study flowchart will be used to show the disposition of study subjects throughout the progression of the study. It will display the numbers of patients randomized into the AC-055E201 / MERIT-1 study divided into the placebo and macitentan 10 mg treatment groups to which they were randomized. The number of subjects by treatment group entering into the AC-055E202 / MERIT-2 OL extension study along with the number of subjects continuing and discontinuing treatment and follow-up during the OL extension

study, along with reasons for discontinuations will be displayed. The final row of the flowchart will result in the number of subjects completing the OL extension study in each treatment group.

The items in the flowchart will be supported by tables and listings related to each level and will be presented by randomized treatment group:

- Summary of patient recruitment by country and center in the OLAS
- Summary of reasons for premature study discontinuation in the OLAS
- Summary of reasons for treatment discontinuation in the OLAS.

The number and percent of patients included in and excluded from each analysis set, based on the set definitions in Section 11.2 will be summarized in tables and listings, and will be supported by a summary table of major protocol deviations. Major protocol deviations will be displayed by region.

11.3.3 Analysis of the exploratory variables

Analysis of the exploratory efficacy variables will be conducted on both the OLAS and RAS analysis sets.

11.3.3.1 6MWD and Borg dyspnea index

The change from baseline to window-based time points for 6MWD and Borg dyspnea index will be displayed using descriptive statistics for continuous variables as described in Section 11.3.1 along with 95% two-sided confidence limits (CL) of means and medians.

For the analyses based on the OLAS, comparing by randomized groups, a repeated measures analysis will be performed using mixed model techniques, allowing for estimation of the adjusted overall treatment effect and treatment effect at each visit. The dependent variable of the model will be the change from baseline. Study visit, treatment, treatment by visit interaction and baseline value will be included as fixed effects in the model, while patient will be included as random effect.

The results will be displayed in a summary table showing: the p-value for the treatment by visit interaction, the adjusted means and 95% CL for each treatment and visit, as well as the adjusted differences to placebo with 95% CL at each visit. If the treatment by visit interaction is not significant at the 0.05 level then the model will be re-run without including the interaction term and the overall treatment effects will be displayed in the summary table.

11.3.3.2 WHO FC

The change from baseline to window-based time points for proportion of patients worsening will be displayed using descriptive statistics for categorical variables as described in Section 11.3.1.

For the analyses based on the OLAS, comparing by randomized groups, changes from baseline to all window-based time points in WHO FC will be analyzed comparing the proportion of patients worsening in the two treatment groups by means of the Fisher's exact test. A shift table will display the change in WHO FC from baseline to each window-based time point. In addition, the relative risk will be displayed with its 95% CL.

11.3.4 Exposure to study drug

Analysis of exposure to study drug will be conducted on the OLAS during the OL period. Exposure will be described in terms of duration and dose. The duration of exposure is defined as the time elapsing between study drug initiation and discontinuation, inclusive. The duration of exposure, mean daily dose and compliance will be tabulated using the usual location and scale summary statistics by randomized treatment group.

The mean daily dose per subject is defined as the ratio between the total study drug dose taken during the treatment period and the total exposure time. Compliance, in percent, is defined as percent of doses taken divided by expected number of doses during follow-up.

11.3.5 Demographic and baseline characteristics

Summaries for demographic and baseline characteristics will be performed on the OLAS. The variables age, sex, race, height, weight, BMI, geographical location, and baseline disease characteristics corresponding to the endpoint variables will be summarized per treatment group and overall.

11.3.6 Analysis of the safety variables

The OLSS will be used to perform all safety analyses.

All safety data will be included in listings, with flags for quantitative abnormalities.

11.3.6.1 Adverse Events

The number and percentage of subjects experiencing treatment-emergent AEs and SAEs at least once from baseline up to 30 days following study drug discontinuation will be tabulated by randomized treatment group and by:

- System organ class (SOC) and individual preferred term within each SOC, in descending order of incidence within the macitentan 10 mg treatment group
- Proportion of subjects with events coded with the same preferred term, in descending order of incidence in the macitentan 10 mg treatment group

Furthermore, treatment-emergent AEs and SAEs occurring up to 30 days after study drug discontinuation will be tabulated as described above by severity and relationship to study drug.

AEs leading to premature discontinuation of study drug and death will also be summarized as described above.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for SAEs, for AEs leading to premature discontinuation of study drug, and for AEs leading to death.

11.3.6.2 Laboratory Parameters

Descriptive summary statistics by visit and study treatment will be provided for observed values and absolute changes, from baseline up to EOT plus 30 days, in both hematology and blood chemistry laboratory tests. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT plus 30 days will be assigned to the most appropriate visit time point according to the best fitting time-window for that assessment.

Actelion internal guidelines will be used for the definitions of marked abnormalities and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory variables are transformed to standard units. All laboratory data transferred are taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

Marked laboratory abnormalities will be summarized for each laboratory parameter providing their incidence and frequency. The summary will be conducted by treatment group for the OL period only. Absolute values and changes of laboratory parameter values during the course of the study from baseline up to EOT plus 30 days will be summarized using the usual location and scale summary statistics by treatment group.

11.3.6.3 Vital signs and body weight

Similarly to laboratory parameters, descriptive summary statistics by visit and study treatment will be provided for observed values and absolute changes, from baseline up to EOT plus 30 days, both for vital signs and body weight. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT plus 30 days will be assigned to the most appropriate visit time point according to the best fitting time-window for that assessment.

11.4 Sample size

The sample size for the OL extension study will be up to 78 randomized subjects from the DB study (AC-055E201 / MERIT-1), who are eligible for and consent to enter the OL extension.

12 DATA HANDLING

12.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

CRF data will be captured via electronic data capture (EDC) using the Rave system provided by Medidata Solutions, Inc., a web-based tool.

Site team members who obtained access to the eCRF in the AC-055E201/ MERIT-1 study will use the same account to access to the eCRF of the OL study.

The investigator and site staff will be trained to enter and edit the data via a secure network, with secure access features (username, password and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to 21 CFR Part 11).

Subject Enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through IXRS and eCRF.

For each subject enrolled, regardless of study drug initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study or in case of premature treatment discontinuation, then the reason must be noted on the eCRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents submitted to Actelion, subjects must be identified only by study-specific subject number, and never by name, initials, or hospital subject number. The investigator/delegate must keep a subject identification code list, at the site, showing the study-specific subject number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

12.3 Database management and quality control

Electronic CRFs will be used for all subjects. The investigator will have access to the site eCRF data throughout the study. The eCRF must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be prompted by logical checks/error messages built into the web-based data entry screening 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 Actelion to look for unexpected patterns in data and study monitoring. In the case that problematic data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF, so that the investigator/delegate can respond and clarify directly onto the eCRF.

The investigator/delegate 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 Health Authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

Laboratory samples will be processed through a central laboratory and the results will be sent electronically to Actelion. If local laboratory data is obtained, it must be entered in the eCRF by the site, as defined in Section 7.3.4.2.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate SOP. At the end of the trial, the investigator will receive the eCRF of the subjects of her/his site (including all data changes made) on a CD-ROM or as a paper copy.

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted.

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

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an IRB/IEC. 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 study, the documents reviewed, and the date of approval.

A list of members participating in the meeting must be provided, including the names, qualifications and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation. If a study staff member was present during a meeting, it must be clear that this person did not vote.

Modifications made to the protocol after receipt of the approval must also be submitted as amendments by the investigator to the IRB/IEC in accordance with local procedures and regulations [see Section 13.6].

In cases where an investigator is moving to a new site location, or a new principal investigator is taking over a study site, 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 IRB/IEC requirements, the updated information will be submitted for approval/notification, as appropriate.

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent from each individual participating in this study and/or legal representative, according to ICH-GCP guidelines and local regulations. The investigator/delegate must explain to 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 should be given ample time review the information provided by the investigator/delegate.

When the results of the DB AC-055E201 / MERIT-1 study become available, the investigator/delegate should inform the subjects about these results. Details of such discussion must be documented in the subject's file

The ICF will be provided in the local language(s) of the country.

Site staff authorized to participate in the consent process and/or to obtain consent from the subject and/or legal representative will be listed on the Actelion DoA form. A study physician must always be involved in the consent process.

The subject and/or legal representative must personally sign and date (including the time, if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be personally signed and dated (including the time, if appropriate by the authorized site staff listed on Actelion DoA form.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation (alternatively, 2 originals may be signed [one original given to the subject, one filed at site]; it must be clearly documented at site which procedure is being followed).

The informed consent process must be fully documented in the subject's medical records, including study reference, subject number, date/time (if applicable) of when the subject was first introduced to the Actelion clinical study, date/time (if applicable) of consent, who participated in the consent discussion, who consented on behalf of the subject and any additional person present during the consent process (e.g., subject family member), and a copy of the signed ICF given to the subject / legal representative.

If the signing of informed consent and performance of the first study-specific procedures or assessments take place on the same day, it must be clearly stated in the source documents that the subject has given fully informed consent prior to the first study-specific procedures or assessments.

If the site would like to recruit a subject who would be considered as vulnerable (e.g., subject cannot read, does not speak or understand the ICF language), additional measures

must be implemented in order to ensure subject rights are respected and the consent obtained is legally valid. Actelion, the regulatory authorities (if applicable) and the IRB/IEC must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IRB/IEC, according to procedures.

13.4 Compensation to subjects and investigators

Actelion provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site 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.

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the approved version of the protocol and must not implement any violation/deviation/change from the protocol, except when the change involves only logistical or administrative aspects (e.g., change in telephone number), or in case it would be necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative, in a timely manner. The investigator/delegate must document and explain any violation/deviation/change from the approved protocol. Protocol violation/deviation/change must also be submitted to IRB/IEC and to the regulatory authority(ies), according to their requirements.

13.6 Protocol amendment

Any change to the protocol can only be made through a written protocol amendment approved by Actelion. A protocol amendment must be submitted to IRB/IEC, and regulatory authority(ies), according to their requirements.

Approval must be obtained before any change can be implemented, except when the change involves only logistical or administrative aspects (e.g., change in telephone number), or in case it would be necessary to eliminate an immediate hazard to the subject; in this case. IRB/IEC and regulatory authority(ies) must be notified as soon as possible, according to their requirements, but not later than 15 calendar days.

13.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records

are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring and available when needed.

These records are to be classified into two different categories of documents: investigator's file, and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (e.g., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. 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.

Documentation of study assessment, even data that are not reported in the eCRF, must be available in the subject's medical records, including the study-specific procedures/assessments prior to enrollment.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the monitor has been provided personal access to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but the validation of the system cannot be confirmed, or if the monitor could not be provided with access to the system, the site is requested to print the complete set of source data needed for verification by the monitor. The print-outs must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies containing the same information as the original subject's data. The printouts will be considered as the official clinical study records.

In order to verify that the process the site uses to prepare certified copies is reliable, the monitor must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The monitor does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Actelion's instructions. If the monitor is not able to observe this process, then the site's certified copies cannot be relied upon, and therefore the site cannot be used for the clinical study. The printouts should be filed either with the subject medical records or with the subject's CRF.

13.8 Monitoring

The monitor will contact and visit the investigational site regularly, and on request must be permitted access to trial facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the eCRFs and other protocol-related documents. 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 eCRFs will be performed according to the study-specific monitoring plan.

The required site personnel must be available during monitoring visits and must allow adequate time to meet with the monitor to discuss study related issues. An initiation visit will be performed after the required essential documents are received at Actelion and before the first subject is included in the study. Monitoring visits will be conducted regularly; frequency will be based on subject recruitment rate and critical data collection times. A close-out visit will be performed for any initiated site.

The investigator agrees 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 site, the investigator is responsible for contacting that hospital in order to document the SAE.

13.9 Audit

Actelion's Global Quality Management representative may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, applicable regulations, and Actelion's requirements (e.g., SOPs). Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a convenient time for the audit.

The investigator and staff must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

13.10 Inspections

Health Authorities and/or IRB/IEC may also wish to conduct an inspection of Actelion's clinical study (during the study or after its completion).

Should an inspection be requested by a Health Authority and/or IRB/IEC, the investigator must inform Actelion immediately, (usually via the monitor), that such a request has been made.

The investigator and staff must cooperate with inspector(s) and allow access to all study documentation (e.g. subject records) and study facilities.

13.11 Reporting of study results and publication

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

The Coordinating Investigator and the SC will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion prior to publication.

Janssen Pharmaceutical Companies (Actelion) will post results from Phase 1–4 clinical studies on external registries as required by law, and from interventional studies in patients for marketed products. In accordance with Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. For observational studies, the first publication will include data in their entirety and not as individual site data. Study results can be submitted for presentation at a congress before publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; and
- Drafting of the publication or critical review for important intellectual content; and
- Providing final approval of the version to be published.

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

Any study-related publication written independently by investigators must be submitted to Actelion for review at least 30 days prior to submission for publication or presentation. Upon review, Actelion may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

14 REFERENCES

[Abman 2009] Abman SH. Role of endothelin receptor antagonists in the treatment of pulmonary arterial hypertension. Annu Rev Med. 2009;60:13-23

[ATS Guidelines 2002] American Thoracic Society (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–117.

[Food and Drug Administration 2020]. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (Table 2-2). https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 09 July 2020.

[Ghofrani 2013a] Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013;369(4):319-329.

[Ghofrani 2013b] Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369(4):330-340.

[Haythe 2012] Haythe J. Chronic thromboembolic pulmonary hypertension: A review of current practice Progress in Cardiovascular Diseases 55 (2012) 134–143.

[Jamieson 2003] Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg 2003;76:1457– 1462.

[Jenkins 2012] Jenkins D, Mayer E, Screaton N, Madani M. State-of-the-art chronic thromboembolic pulmonary hypertension diagnosis and management. Eur Respir Rev 2012; 21: 123, 32–39.

[Macitentan IB] Investigator's Brochure: JNJ-67896062 Opsumit® (Macitentan), Edition 18. Actelion Pharmaceuticals Ltd, December 2020.

[O'Callaghan 2011] O'Callaghan DS, Savale L, Montani D, et al. Treatment of pulmonary arterial hypertension with targeted therapies. Nat Rev Cardiol. 2011;8(9):526-38.

[Pepke-Zaba 2011] Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011; 124: 1973–1981.

[Simonneau 2009] Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:Suppl:S43-S54.

15 APPENDICES

Appendix 1 Sponsor Guidelines for 6MWT

6-Minute Walk Test (6MWT)

General instructions

The American Thoracic Society published an official statement on the 6MWT in 2002 **[**ATS Guidelines 2002**]**. Only a brief summary of these guidelines is included here.

- **The 6MWT should be performed** indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The use of a 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.
- **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 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.
- If **oxygen** supplementation is needed during the 6MWT at Enrollment, then during all study 6MWTs by that subject oxygen should be delivered in the same way with the same flow (if possible). If the flow must be increased during subsequent visits (e.g., due to worsening), this should be indicated in the source notes.

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

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 h of beginning the test.
- The subject should sit at rest for at least 10 min 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 a 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 2]. 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 2 Borg Dyspnea Index (Perceived Breathlessness / Borg Scale)

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 3 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 or 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 4 Laboratory Abnormalities

Laboratory abnormalities according to the most updated version of CTCAE.

A marked abnormality is defined based on the following list (SI units).

Parameter	LL	LLL	HH	HHH	HHHH
Hemoglobin (g/L)	< 100	< 80	Increase in (> 20 g/L above ULN) or above baseline if baseline is above ULN	Increase in (> 40 g/L above ULN) or above baseline if baseline is above ULN	
Hematocrit	< 28% for females < 32% for males	< 20%	> 60% in men > 55% in women	> 65%	
Platelet count (10^9 /L)	< 75	< 25	> 600	> 999	
Leucocytes (× 10e9 /L)	< 3.0	<2.0	> 20.0	> 100.0	
Neutrophils (10^9 /L)	< 1.5	<1.0	NA	NA	
Eosinophils			> 5.0 × 10e9 or > 5%	NA	
Lymphocyte (10^9 /L)	< 0.8	< 0.5	> 4.0	> 20.0	
AST (U/L)	NA	NA	> 3 ULN	> 5 ULN	> 8 ULN
ALT (U/L)	NA	NA	> 3 ULN	> 5 ULN	> 8 ULN
AP	NA	NA	> 2.5 ULN	> 5 ULN	
Total bilirubin (umol/L)	NA	NA	> 2 ULN	> 5 ULN	

Parameter	LL	LLL	HH	HHH	HHHH
INR			> 1.5 × ULN or >1.5 times above baseline if on anticoagulation	> 2.5 × ULN or > 2.5 times above baseline if on anticoagulation	
Creatinine (umol/L)	NA	NA	> 1.5 ULN or 1.5 × baseline	> 3 ULN or > 3× baseline	
Glucose (mmol / L)	< 3.0	< 2.2	> 8.9	> 13.9	
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1	
Sodium (mmol/L)		< 130	> 150	> 155	
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0	
Magnesium (mmol/L)	< 0.5	< 0.4	-	> 1.23	
Uric acid (mmol/L)	-	-	> 0.59	> 0.72	
Albumin (g/L)	< 30	< 20	-	-	
BUN	-	-	> 2.5 ULN	> 5 ULN	

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CTCAE = common terminology criteria for adverse events; LL / HH = marked abnormalities; LLL / HHH / HHHH = alert values; INR = international normalized ratio; NA = not applicable; SI = international system of unit; ULN = upper limit of the normal range.

Appendix 5 Central Laboratory Alert Flags

- On top of the flags described below, at a minimum, results above the upper limit or below the lower limit of the reference range for normal subjects will be flagged.
- **Exclusionary Alert Value – At Enrollment (V1):** The result is outside the study-specific defined limit for inclusion in the study.

  Hemoglobin < 100 g/L
  AST > 3 × ULN
  ALT > 3 × ULN
  Serum pregnancy test positive

- **Total Bilirubin flag Alert Value – All visits except Enrollment (V1):** In combination with ALT and/or AST > 3 x ULN, study medication should be stopped.

  Total bilirubin ≥ 2 x ULN

- **Interruption or permanent discontinuation of study medication – All visits except Enrollment (V1):** Please refer to the study protocol; study medication must be interrupted or stopped (see protocol Section 5.1.8.3).

  AST > 8 × ULN
  ALT > 8 × ULN
  Serum pregnancy test positive
  Hemoglobin < 80 g/L
  Hemoglobin > 50 g/L decrease from baseline in MERIT-1

- **Repeat Alert value – All visits except Enrollment (V1):** Repeat testing is needed (+ interrupt study medication in case of ALT and/or AST > 3 × ULN) (see protocol Section 5.1.8.3).
  AST > 3 × ULN
  ALT > 3 × ULN
  Hemoglobin > 20 g/L decrease from baseline in MERIT-1

Appendix 6 Central Laboratory Normal 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	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	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	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	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		
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	13	y	999	y	M/F	20	44	%	1	20	44	%		
Monocytes (%)	Hematology	7	y	999	y	M/F	3	10	%	1	3	10	%		

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
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	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	13	y	999	y	M/F	0.0	0.7	x10E3/uL	1	0.0	0.7	x10E9/L		
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	15	y	999	y	M/F	150	350	x10E3/uL	1	150	350	x10E9/L		
Reticulocytes (%)	Hematology	18	y	999	y	M/F	0.7	2.5	%	1	0.7	2.5	%		
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		
Sodium	Chemistry	0	y	999	y	M/F	135	148	mmol/L	1	135	148	mmol/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
Potassium	Chemistry	0	y	999	y	M/F	3.5	5.3	mmol/L	1	3.5	5.3	mmol/L		
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	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	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
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

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
ALT	Chemistry	19	y	999	y	M/F	0	45	U/L	1	0	45	U/L	4	4
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	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)	Immuno-chemistry	0	y	999	y	F	0	9	mIU/mL	1	0	9	IU/L	2	2

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; MCH = mean cell hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean cell volume; SI = international system of unit; TIBC = total iron binding capacity

Appendix 7 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 2 (28-Sep-2020)

Overall Rationale for the Amendment: The main reason for the amendment is to update the description of the investigational medicinal product used in this study from debossed on one side to debossed on either one or both sides. The regulatory status of riociguat for treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and the investigational drug storage conditions have been updated. Procedural changes for safety reporting process have been included following integration of safety reporting/procedures between Actelion and Janssen.

The updates are indicated in bold text and strike-through for the deleted text in the following table.

Section Number and Name	Description of Change	Brief Rationale
Contract Research Organizations Information	Additional details of Central Study Drug Re-supply was included.	To update the information of Central Study Drug Re-Supply.
SYNOPSIS, Study Committees, 3.2 Study Committees	Modified the statement: A Publication Committee is involved in the preparation of potential manuscript(s) and will be consulted for authorship criteria **(if applicable)**.	To allow the Publication Committee to prepare a manuscript or publication if required.
1.1 Indication	Information regarding recent updates about riociguat's approval for CTEPH treatment in various countries is included as follows: "**Riociguat has gained regulatory approval for the treatment of CTEPH in several countries, including the United States (US), Canada, Japan and European Union (EU). To date, riociguat is not approved world-wide.**	To include the approval and clinical use of riociguat for CTEPH treatment.
5.1.3 Investigational drug	The original statement from Version 1 is revised to: "Macitentan 10 mg will be provided as film-coated tablets debossed with '10' on **either** one **or both** sides**."**	To update the description related to appearance of investigational product from new batches.
5.1.6.2.2 Study drug storage	A revised statement regarding study drug storage is included: ~~• Opened bottles of study drug must be~~	The text is changed to make the label as a primary reference

Section Number and Name	Description of Change	Brief Rationale
	~~stored at room temperature, below 30 °C (86 °F), and must be protected from moisture. Unopened, sealed study medication bottles can be stored either at room temperature, below 30 °C [86 °F], or in refrigerators at a temperature of at least 2 °C (36 °F).~~ • **Study drug must be kept in an appropriate secure area and stored according to the conditions specified on the label.** • ~~If the temperature at a subject's home exceeds 30 °C (86 ºF) the subject must 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 or unsealed bottles must not be stored in the refrigerator.~~	source for storage conditions requirement and remove the details from the protocol.
5.1.8.3 Study-specific criteria for study drug interruption / permanent discontinuation of study drug	**B) Liver aminotransferases abnormalities** Following statement is deleted: ~~In order to ensure the proper and comprehensive evaluation of cases of ALT and/or AST increase > 3 X ULN, additional subject data will be collected in the hepatic event questionnaire of the eCRF.~~	To delete information as the data collection form is not available or required.
	C) Hemoglobin abnormalities Added the statement: **If hemoglobin decrease remains >20 g/L below baseline value at subsequent visits, further retests are to be performed as per investigator's judgement.**	Added the text to clarify retests if hemoglobin decrease remains >20g/L below baseline
SYNOPSIS, Study Committees, 3.2 Study Committees, 5.1.8.3 Study-specific criteria for study drug interruption / permanent discontinuation of study drug	Added the text: An independent ILSB (an external expert committee of hepatologists) provides ongoing assessment and advice regarding any **serious** hepatic events that may require further evaluation during the study.	The ILSB provides ongoing assessments and advice regarding only serious hepatic events.
10.1.1 Definition of adverse events	Additional information on reporting of AEs associated with overdose, misuse and abuse of study drug was added.	To provide clarity about reporting of such AEs.
10.1.5 Follow-up of adverse events	New paragraph added: **The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature**	Additional information regarding conduct of supplemental measurements and

Section Number and Name	Description of Change	Brief Rationale
	and causality of the AE, SAE, or product quality compliant (PQC) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.	evaluations was added.
10.2.2.1 Prior to start of OL treatment period; 10.2.2.2 During treatment and follow-up periods	Inclusion of PQCs as reportable events in addition to SAEs	PQCs included to comply with internal procedures.
10.2.4 After the 30-day follow-up period; 10.2.5 Reporting procedures	The 'Actelion Global Drug Safety department' is updated to 'Sponsor'. Updated the Reporting procedure for serious adverse events (SAEs).	Text updated due to Actelion and Janssen safety process integration.
10.2.5 Reporting procedures	Waiving of SAEs related to the underlying disease was removed.	Disease-relatedness removed due to Actelion and Janssen safety process integration.
10.3.1 Reporting of pregnancy	Reporting of pregnancy in partners of male participants included. Removal of the use of Actelion and change in the name of the Pregnancy form.	To provide more clarification on the reporting procedure and to capture reproduction-related information in case pregnancy of all study participants to comply with internal procedures due to Actelion and Janssen safety process integration. Change in pregnancy forms due to Actelion and Janssen safety process integration.
10.3.2 Follow-up of pregnancy	Name of pregnancy forms were added and text modified.	
10.5 Product quality complaint handling	A new section on PQC handling and reporting was added.	PQC handling section added to comply with internal procedures due to Actelion and Janssen safety process

Section Number and Name	Description of Change	Brief Rationale
		integration.
10.6 Special reporting situations	A new section on special reporting situations was added.	To define special reporting situations to comply with internal procedures due to Actelion and Janssen safety process integration.
12.3 Database management and quality control	The eCRF must be kept current to reflect subject status at any time point during the course of the study ~~(i.e., the data should be entered in the system within 10 days of the subject's visit/assessment completion).~~	To follow Janssen Guidelines.
13.11 Reporting of study results and publication	Statement regarding Actelion's policy for study data disclosure was revised as: '**Janssen Pharmaceutical Companies (Actelion) will post results from Phase 1-4 clinical studies on external registries as required by law and from interventional studies in patients for marketed products**.'	To follow Janssen's policy on scientific publications.
	Deleted reference to Actelion's Policy on Scientific Publications	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted and updates were made.

Amendment 1 (15 July 2020)

Overall Rationale for the Amendment: The purpose of this amendment is to update the study specific criteria for drug interruption / permanent discontinuation and forbidden concomitant medication sections to prohibit strong CYP3A4 inhibitors, moderate dual CYP3A4 / CYP2C9 inhibitors, and concomitant administration of moderate CYP3A4 and CYP2C9 inhibitors.

Inclusions are presented below in **bold**.

Section number and Name	Description of Change	Brief Rationale
Sponsor Contact Details, Actelion Contributors to the Protocol, Signature	Details of Clinical Trial Physician, Trial Statistician, and Drug Safety Physician are updated.	To update the information of study responsible physician

Page for Actelion Pharmaceuticals Ltd		and protocol contributors.
	Signatories are updated.	To update the information of new signatories.
Synopsis (concomitant medications); and Section 5.2.3 Forbidden concomitant medication.	Additional restriction included for CYP3A4 and CYP2C9 inhibitors. • **Strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g. miconazole, piperine) until study intervention discontinuation.** *** If patients are currently stable on a strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir), moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g. miconazole, piperine), the patient may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment**	To add strong CYP3A4 inhibitors or moderate dual CYP3A4/CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors to the list of forbidden concomintant medications.
Section 5.1.8.3 Study specific criteria for study drug interruption / permanent discontinuation of study drug;	Start of an ERA / strong CYP3A4 inducer / **strong CYP3A4 inhibitors / moderate dual CYP3A4/CYP2C9 inhibitors / combination of moderate CYP3A4 and moderate CYP2C9 inhibitors** / investigational drug – Study drug must be permanently discontinued if an ERA and/or a strong CYP3A4 inducer and/or **strong CYP3A4 inhibitors and/or moderate dual CYP3A4/CYP2C9 inhibitors and/or coadministration of a combination**	To add strong CYP3A4 inhibitors or moderate dual CYP3A4/CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors to the list of forbidden

	of moderate CYP3A4 and moderate CYP2C9 inhibitors and/or another investigational drug is started during treatment period.	concomintant medications.
Section 5.2.3 Forbidden concomintant medication; and 14 References	A new reference was added to Section 5.2.3 and to the reference list.	To provide investigators with some examples of CYP3A4 and CYP2C9 inhibitors

INVESTIGATOR AGREEMENT

Macitentan / ACT-064992 EDMS-RIM-263288, 3.0
Chronic thromboembolic pulmonary hypertension
Protocol AC-055E202, MERIT-2
Amendment 3, Version 4, 22 June 2021, page 90/90

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceuticals Ltd and Janssen Research & Development, a

Signature: PPD Date: PPD

Note: If the addr uring the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S.

Actelion Pharmaceuticals Ltd
Janssen Research & Development*

Clinical Protocol

COVID-19 Appendix

Protocol Title

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

MERIT-2

Macitentan in thE tReatment of Inoperable chronic Thromboemolic pulmonary hypertension (Open-Label)

Protocol AC-055E202; Phase 2

JNJ-67896062 /ACT-064992 (macitentan)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Actelion Pharmaceuticals Ltd., Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; Janssen Research & Development, LLC; or Actelion Pharmaceuticals Ltd. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT Number: 2013-003457-25

Status: Approved
Date: 21 June 2021
Prepared by: Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-265560, 3.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL AC-055E202

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

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

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

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

GUIDANCE SPECIFIC TO THIS PROTOCOL

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of participant care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

    - Remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent). The following assessments should be made and documented in the eCRF and source documents:

        - Follow-up on ongoing AEs, recording of new AEs
        - Changes in concomitant mediations
        - Study intervention compliance
        - Contraceptive method and results from urine pregnancy test, as applicable

      Details regarding these contacts (date, time, contact person) must be properly documented in source records including a detailed content of the discussion points (eg, responses from subject and/or results of physical evaluation [as applicable] performed by the trained site staff or treating physician).

    - Procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at home administration (including the potential for self-administration of study intervention). The subject will be asked to return empty study medication bottles/unused tablets at their next on-site visit. Intervention compliance will meanwhile be assessed via visit phone calls.
    - Laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy tests), home testing may be employed. Safety laboratory testing should include LTs (LTs: liver aminotransferases [ALT and AST], AP, total and direct bilirubin) and hemoglobin (per protocol Table 1 [Visit and assessment schedule]) at a minimum.
    - The investigator must review all safety assessments to confirm the participant can pursue his/her study intervention. If the safety assessments cannot be performed and reviewed by the investigator in a timely manner, the investigator may decide to interrupt or discontinue permanently study intervention, if it is in the best interest of the participant.

Once restrictions are lifted, the subject should return to the site as soon as possible to perform all safety and efficacy assessments that have been missed. If assessments are done at a time other than a scheduled visit, an unscheduled visit should be created in the eCRF to record the results:

- Missed or out of window assessments/visits will be captured in the case report form (CRF) for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF. Other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs and / or other study systems, if applicable. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

Guidance on consenting and monitoring:

- Before implementing any of the above mitigations for an individual subject, the subject must provide consent for the mitigation action. If allowed by local HA/IRB/EC, verbal consent, based on the local regulations, is acceptable and must be documented in the subject source notes. Documentation of verbal consent must include: who consented, when they were consented, what they were told at the time, how they consented (eg, telephone, etc.), who captured the oral/verbal consent (including signature of the investigator or staff member who captured the consent), and an identification of impartial witness who was present at the time of consent as well as how the impartial witness was selected.
- Site monitoring will, in general, be limited to remote monitoring until further notice; however, certain regions and countries may continue to have on-site monitoring at this time, as allowed per country COVID-19 guidance/travel restrictions. The Site Manager will be in contact with the study site to schedule the next remote or on-site monitoring visit.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

- Study participants can undergo a COVID-19 vaccination procedure in compliance with applicable local governmental regulations.
- No pharmacokinetic interaction between the study intervention and currently available COVID-19 vaccines are expected. In addition, based on the mechanism of action of the study intervention and COVID-19 vaccines, no relevant interaction is expected.
- Any COVID-19 vaccine administered to a study participant is considered a concomitant medication and should be reported on the electronic case report form (eCRF).
- For serious adverse events (SAEs) reported after COVID-19 vaccination, the investigator should provide narrative details on the SAE form to allow adequate assessment of causal relationship between the reported SAE and vaccination. This is particularly relevant in cases where the reported SAE is an expected event with the study intervention and the COVID-19 vaccine. If the event is serious and considered to be related to both the COVID-19 vaccine and the study intervention, it is a serious adverse reaction and expectedness must be assessed. Suspected unexpected serious adverse reaction (SUSAR) reporting will be performed if the serious adverse reaction is unexpected per applicable reference safety document.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
ACT-064992 (macitentan)
Clinical Protocol AC-055E202

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

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

Signature: PPD Date: PPD

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 5
Status: Approved, Date: 21 June 2021