Macitentan / ACT-064992

Macitentan in Fontan-palliated subjects

Protocol AC-055H301

RUBATO

Prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group study assessing the efficacy and safety of macitentan in Fontan-palliated adult and adolescent subjects

Study Phase:	3
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COORDINATING INVESTIGATOR

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SPONSOR SIGNATURE PAGE

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Treatment name / number

Macitentan / ACT-064992

Indication

Macitentan in Fontan-palliated subjects

Protocol number, study acronym, study title

AC-055H301, RUBATO, Prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group study assessing the efficacy and safety of macitentan in Fontan-palliated adult and adolescent subjects.

I approve this protocol.

Title	Name	Date	Signature
Clinical Trial Physician	Thierry Francis Briand	PPD	PPD
Clinical Trial Scientist	Michael Friberg		
Clinical Trial Statistician	Michela Efficace		

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INVESTIGATOR SIGNATURE PAGE

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AC-055H301, RUBATO, Prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group study assessing the efficacy and safety of macitentan in Fontan-palliated adult and adolescent subjects.

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

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Independent Ethics Committee or Institutional Review Board (IEC/IRB) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment, and I will re-consent the subjects (if applicable). I will allow direct access to source documents and study facilities to sponsor representative(s), particularly Clinical Research Associate(s) (CRA[s]) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor is/are being used only as described in this protocol. I will ensure that all subjects or legally designated representatives have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk-benefit balance for an individual subject. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to health authorities worldwide.

	Country	Site number	Town	Date	Signature
Principal Investigator					

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 9, Version 10	19 November 2020
Amendment 8, Version 9	15 July 2020
Amendment 7, Version 8	18 December 2019
Amendment 6, Version 7	19 November 2018
Amendment 5, Version 6	27 August 2018
Amendment 4, Version 5	20 February 2018
Amendment 3, Version 4	27 June 2017
Amendment 2, Version 3	26 April 2017
Amendment 1, Version 2	01 February 2017
Original Protocol, Version 1	24 August 2016

Amendment 9 (19 November 2020)

Overall Rationale for the Amendment: The purpose of this amendment is to make global safety updates, and align the protocol with Janssen processes as part of the Actelion and Janssen integration.

Study treatment supply and storage information was simplified as part of the Actelion and Janssen integration.

Furthermore, an appendix was added to facilitate evaluation of exclusion criterion 6.3.

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

Section number and Name	**Description of Change**	**Brief Rationale**
Synopsis; 3.1 Study design; 3.3 Study committees; 5.1.5 Blinding; 5.1.6.2 Unblinding for IDMC; 10. Statistical methods; 10.4 Interim analysis	Addition of statistical support group (SSG).	Updated for accuracy
5.1.3 Study treatment administration	Reference added to sections detailing the new IMP overdose definition.	Definition of overdose was added to provide more clarity.

Section number and Name	Description of Change	Brief Rationale
5.1.6.3 Unblinding for suspect unexpected serious adverse reactions; 5.1.11.2 Liver aminotransferase abnormalities; 7.2.4.1 Type of laboratory; 9.1.1 Definition of adverse event; 9.2.3 Follow-up of serious adverse events; 9.2.4 After the 30-day follow-up period; 9.2.5 Reporting procedures; 12.10 Audit.	"Actelion Global Drug Safety" and/or "Actelion" updated to "the sponsor"	Updated as part of Actelion Pharmaceuticals and Janssen pharmaceuticals integration.
5.1.7 Study treatment supply	Information about study treatment manufacturing sites is deleted.	Information removed to allow greater flexibility.
5.1.7.2.2 study treatment storage	Specific temperature range for study treatment storage removed. Highly detailed information regarding study treatment storage temperature regulations and deviation reporting requirements removed	Superfluous information removed for clarity.
5.1.11.1 Pregnancy; 7.2.4.1 Type of laboratory	"Pregnancy Form" updated to "Pregnancy Notification Form"	Updated to align with Janssen processes
7.2.7.1 Pharmacokinetic assessments	Additional local equivalent added as an alternative to the bioanalytical laboratory.	Updated in case samples are not able to be exported from their country of origin
7.2.3.6 VSFU; 8.2 Premature withdrawal from study	Addition of "including the use of locator agencies"	Included for clarity
9 Safety definitions and reporting requirements	Details of reporting requirements and SOPs added.	Updated to align with Janssen processes
9.1.5 Follow-up of adverse events	Details of investigator obligations to perform or arrange supplemental measurements and evaluations added.	Updated to align with Janssen processes
9.2.1 Definitions of serious adverse events	Inclusion of suspected transmission of any infectious agent via a medicinal product.	Included to align with Janssen processes.

Section number and Name	Description of Change	Brief Rationale
9.2.2 Reporting of serious adverse events	Inclusion of PQCs as a reporting requirement	Updated to align with Janssen processes
9.2.5 Reporting procedures	Reporting requirements for SUSARs was updated to provide additional information.	Text updated to align with Janssen processes.
9.3 Pregnancy	9.3.1 Reporting of pregnancy Updated to include partners of male subjects, and to clarify that the sponsor must be informed within 24-hours of site staff knowledge of the event. "Actelion Pregnancy Form" updated to "Pregnancy Notification Form" 9.3.2 Follow-up of pregnancy Additional information added regarding product exposure during pregnancy collection and end of pregnancy collection forms. Information regarding abnormal pregnancy outcomes to be considered as SAEs added.	The pregnancy reporting section was updated to reflect the standard Janssen wording and include monitoring of pregnant partners of male patients per Janssen safety reporting procedures as part of the ongoing integration of Actelion into the Janssen ecosystem
9.5 Product quality complaints	Section added.	Added to align with Janssen processes
9.6 Special reporting situations	Section added.	Added to align with Janssen processes
9.7 Contacting sponsor regarding product quality	Section added.	Added to align with Janssen processes
10.3.5.1 Peak VO_2 at other visits, VE/VEO_2, VO_2/HE, VO_2 at VAT, OUES and %predicted peak VO_2	'Reference with information about classification for VE/VCO_2 slope and peak VO_2 categorization was deleted.	Reference removed as it does not correspond to the population of this study.
13. References	Removal of the following reference: [Arena 2007] Arena R, Myers J, Abella J. Development of a Ventilatory Classification System in Patients With Heart Failure. Circulation. 2007;115:2410-7.	Removed as not required.

Section number and Name	Description of Change	Brief Rationale
Appendix 10 Child-Pugh Classification	Appendix Added.	Added as an aid to correctly evaluate exclusion criterion 6.3.

Abbreviations: IMP=investigational medicinal product; PQC=Product quality complaint; SUSAR= Suspected unexpected serious adverse reaction.

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AV	Atrioventricular
BMI	Body mass index
BP	Blood pressure
BR	Breathing reserve
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CHD	Congenital heart disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Confidence limit
CPET	Cardiopulmonary exercise testing
CRA	Clinical research associate
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical trial team
CYP3A4	Cytochrome P450 3A4
ECG	Electrocardiogram
ECHOC	Echocardiography
eCRF	electronic Case Report Form
EC-TCPC	Extra cardiac tunnel total cavopulmonary connection
EDC	Electronic data capture
EMA	European Medicines Agency
EOP	End-of-post-treatment observation period
EOS	End-of-Study

EOT	End-of-Treatment
EQ-5D-5L	Euro Quality of Life 5D(imensions)
ERA	Endothelin receptor antagonist
ET	Endothelin
FAS	Full Analysis Set
FC	Functional class
FDA	Food and Drug Administration (US)
FEV1	Forced expiratory volume over 1 second
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GQM	Global Quality Management
HF	Heart failure
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
ILSDRB	Independent liver safety data review board
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive response technology
ISAC	Independent statistical analysis center
ISF	Investigator site file
KM	Kaplan-Meier
LS	Least square
LT-TCPC	Lateral tunnel total cavopulmonary connection
LV	Left ventricle
M	Arithmetic mean
MAESTRO	**Ma**citentan in **E**isenmenger **S**yndrome **T**o **R**est**o**re exercise capacity

MedDRA™	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed Model Repeated Measures
MVV	Maximal voluntary ventilation
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
o.d.	Once daily
OL	Open-label (extension)
OS	Overall survival
OUES	Oxygen uptake efficiency slope
PA-Ac	Physical Activity measured by Accelerometer
PAH	Pulmonary arterial hypertension
PDE5i	Phosphodiesterase 5 inhibitor
PGA-S	Patient Global Assessment of Disease Severity
PGI-C	Patient Global Impression of Change
PH	Pulmonary hypertension
PI	Principal investigator
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PLE	Protein-losing enteropathy
PORTICO	PORtopulmonary Hypertension Treatment wIth maCitentan – a randOmized Clinical Trial
PPS	Per-Protocol Set
PQC	Product quality complaint
PTOP	Post-treatment observation period
PVR	Pulmonary vascular resistance
Q-Q	Quantile-quantile
QoL	Quality of life
QS	Quality System
RER	Respiratory exchange ratio
RSI	Reference safety information

RV	Right ventricle
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SCL	Study Closure
SCR	Screened Analysis Set
SD	Standard deviation
SERAPHIN	**S**tudy with **e**ndothelin **r**eceptor **a**ntagonist in **p**ulmonary arterial **h**ypertension to **i**mprove cli**n**ical outcome
S-FU	Safety follow-up
SI	International System of Units
SIV	Site initiation visit
SOC	System organ class
SpO_2	Peripheral oxygen saturation
SS	Safety Set
SSG	Statistical support group
SUSAR	Suspected unexpected serious adverse reaction
SVDV	Systemic ventricle diastolic volume
SVSV	Systemic ventricle systolic volume
TCPC	Total cavopulmonary connection
TEMPO	Treatment with endothelin receptor antagonist in fontan patients, a randomized, placebo-controlled, double-blind study measuring peak oxygen consumption
ULN	Upper limit of normal
VAS	Visual analogue scale
VAT	Ventilatory anaerobic threshold
VCO_2	Carbon dioxide production
VE	Minute ventilation
VHP	Voluntary Harmonization Procedure
VO_2	Oxygen uptake/consumption ($\dot{V}O_2$ is a flow = a ratio of a volume by unit of time)
VSFU	Vital Status Follow-Up

WHO	World Health Organization
WU	Wood unit

PROTOCOL SYNOPSIS AC-055H301

TITLE	Prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group study assessing the efficacy and safety of macitentan in Fontan-palliated adult and adolescent subjects.
ACRONYM	RUBATO P**R**ospective, m**U**lti-center, double-**B**lind, r**A**ndomized, placebo-con**T**rolled, parallel-group study assessing the efficacy and safety of macitentan in F**O**ntan-palliated adult and adolescent subjects.
OBJECTIVES	**Primary objective** To assess the effect of macitentan on exercise capacity (measured by peak oxygen uptake [VO_2]) in comparison with placebo in Fontan-palliated subjects. **Secondary objectives** To assess the effect of macitentan on long-term exercise capacity (measured by peak VO_2 over 52 weeks). To assess the effect of macitentan on daily Physical Activity measured by Accelerometer (PA-Ac). To evaluate the safety and tolerability of macitentan. **Other objectives** Other objectives are described in Section 2.3.
DESIGN	A prospective, adaptive, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study. The study contains an interim analysis (IA) for unblinded sample size adaptation, based on comparative interim results on the primary efficacy endpoint. This IA will be implemented through an Independent Data Monitoring Committee (IDMC), providing recommendations to the Sponsor Committee. Only the IDMC and the Independent Statistical Analysis Center (ISAC)/statistical Support Group (SSG) will be unblinded to the data.

PERIODS	**Screening period:** Lasts up to 30 days; starts with the signature of the informed consent (Visit 1) and ends with the subject's Randomization (Visit 2). **Treatment period:** Starts with the administration of the first dose of study treatment (Visit 2) and ends on the day of the last dose of study treatment, expected to be at 52 weeks. Subjects who prematurely and permanently discontinue study treatment before Week 52 (Visit 6) must have a premature End-of-Treatment (EOT) visit as soon as possible but not later than 7 days after the last dose of study drug. **Safety follow-up (S-FU) period:** After permanent study treatment discontinuation, subjects will be followed up for a minimum of 30 days (S-FU). Subjects eligible to enter the AC 055H302 open-label (OL) extension study may do so as soon as their eligibility has been confirmed, even prior to completion of the full S-FU period. The period ends with administration of first study drug in the OL extension study. **Post-treatment observation period (PTOP):** Those subjects who prematurely and permanently discontinue study treatment will enter the PTOP after their S-FU period is completed. The PTOP lasts until the planned study EOT (at most 52 weeks after Randomization) for each individual subject. This last visit of the PTOP is called End-of-PTOP (EOP). The PTOP consists of an abbreviated schedule of assessments at 90-day intervals. **End-of-Study (EOS):** EOS is reached by an individual subject: • when the S-FU period has been completed (for those subjects who do not discontinue study treatment prematurely), or

	• when the S-FU period and PTOP have been completed (for those subjects who discontinue study treatment prematurely), or • if subjects enter the AC-055H302 RUBATO open-label (OL) extension study, with first administration of OL study drug. For all subjects, EOS corresponds to the last visit performed in this AC-055H301 RUBATO double-blind study. Study Closure (SCL) will be announced by the sponsor when all subjects have reached their EOS in AC-055H301 RUBATO. **Vital Status Follow-up (VSFU):** A VSFU will be performed within 8 weeks after the SCL announcement to determine each vital status of all subjects randomized in AC-055H301 RUBATO, irrespective of whether the subject is included in the AC-055H302 OL extension study. **Study Closure (SCL):** The SCL applies to all randomized subjects and will occur: • when all subjects have had their individual VSFU, and • no later than 8 weeks after SCL announcement.
PLANNED DURATION	Approximately 34 months from first subject, first visit to last subject, last visit.
SITE(S) / COUNTRY(IES)	31 investigational sites in 11 countries (planned).
SUBJECTS / GROUPS	At least 134 adults and adolescents will be randomized in a 1:1 ratio to macitentan 10 mg or placebo. Randomization will be stratified by geographical region (America, Europe, Asia, Oceania). The sample size will be re-estimated at the time of the IA based on treatment effect and variability estimates for the primary efficacy endpoint (i.e., change from baseline to Week 16 in peak VO_2), following rules as described in the Statistical

	Analysis Plan (SAP). Only upwards adjustment of the pre-planned sample size is allowed. An upper bound of the sample-size adjustment is considered up to a 100% increase of the initially planned sample size (i.e., total sample size of 268 subjects).
INCLUSION CRITERIA	1. Written informed consent/assent from the subject and/or a legal representative prior to initiation of any study-mandated procedures. 2. Male or female ≥ 12 years old. 3. Fontan-palliated subjects with either intra-atrial lateral tunnel total cavopulmonary connection (LT-TCPC), or extra cardiac tunnel TCPC (EC-TCPC) surgery > 1 year before Screening. Either LT- or EC-TCPC can be primary or secondary to atrio-pulmonary connection. 4. New York Heart Association (NYHA) functional class (FC) II or III (assessed by the investigator using the Specific Activity Scale [Appendix 4]). 5. Ability to understand and comply with the instructions, and ability to physically perform the cardiopulmonary exercise testing (CPET). 6. Women of childbearing potential must: 6.1. Have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at the Randomization visit (Visit 2), and, 6.2. Agree to perform monthly pregnancy tests up to the end of the S-FU period, and, 6.3. Agree to use reliable contraception [Section 4.5.2] from at least 30 days prior to Visit 2 and up to at least 30 days after study drug discontinuation.
EXCLUSION CRITERIA	1. Pattern of Fontan circulation severity. Any of the following: 1.1. Known severely reduced single ventricle ejection fraction (< 30%) 1.2. Known Fontan circulation stenosis, affected area > 50% of the diameter 1.3. Known valvular defects (severe atrioventricular [AV] valve regurgitation, outflow obstruction) 1.4. Known pulmonary-venous pathway obstruction

	1.5. Peripheral oxygen saturation (SpO_2) of < 88% at rest at Screening 2. Deterioration of the Fontan-palliated condition. Any of the following events within 3 months prior to Screening: 2.1. Candidate on the active list for heart transplantation 2.2. Clinical worsening leading to medical interventions including reoperation of Fontan circulation (e.g., mechanical circulatory support, Fontan take-down, Fontan revision/conversion, AV valve repair/replacement). 2.3. Unscheduled hospitalization due to deterioration of the Fontan-palliated condition[1] 2.4. Signs and symptoms of heart failure[2] requiring change in diuretic therapy 2.5. Ventricular tachyarrhythmia or supraventricular tachyarrhythmia[3] 2.6. Peritoneal, pleural, mediastinal, or pericardial effusions 2.7. Thrombotic or hemorrhagic complications (including thromboembolism and hemoptysis) 2.8. Protein-losing enteropathy (serum albumin < 30 g/L and total protein < 50 g/L) 2.9. Plastic bronchitis/chyloptysis 2.10. Signs and symptoms requiring the addition of a new class of cardiovascular medication (e.g., nitrates, alpha-blockers, or endothelin receptor antagonists [ERAs]) 3. Limitations to CPET: 3.1. History of syncope during exercise 3.2. Symptomatic coronary artery disease at Screening.

[1] Only applicable as an event if hospitalization/intervention was unscheduled / not related to routine Fontan-related follow-up, and hospital stay was > 24 hours.

[2] Includes orthopnea, nocturnal dyspnea, pulmonary edema, or radiological signs. Persistent congestion with edema only qualifies if the peripheral edema is moderate-to-severe despite optimal diuretic therapy.

[3] Subjects are excluded for arrhythmia only if it requires hospitalization, or cardioversion, addition/increase in antiarrhythmic treatment, or invasive tests or treatment.

	3.3. Respiratory limitation with a breathing reserve of < 10% 3.4. Iron deficiency defined as ferritin < 10 µg/L at Screening 3.5. Iron supplementation, regardless of route of administration, unless already present at stable dose for more than 3 months prior to Screening 3.6. Body mass index (BMI)-for-age reference (z-scored) equivalent to BMI > 35 kg/m^2 (for adults) at Screening 3.7. Exercise training program for cardiopulmonary rehabilitation in the 3-month period prior to Screening 3.8. Myocardial infarction < 6 months before Screening 3.9. Pacemaker at Screening 4. Peak VO_2 < 15 mL/kg/min at Baseline. 5. Systolic blood pressure (BP) < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height) at rest or during CPET at Screening or at Baseline. 6. Criteria related to macitentan use: 6.1. Hemoglobin < 75% of the lower limit of normal assessed by central laboratory at Screening 6.2. Known or suspected pulmonary veno-occlusive disease 6.3. Known and documented severe hepatic impairment defined as Child-Pugh Score C [Appendix 10], based on measurement of total bilirubin, serum albumin, international normalized ratio or prothrombin time (except for patients under non-Vitamin K antagonists) and based also on presence/absence and severity of ascites and hepatic encephalopathy 6.4. Serum aspartate aminotransferase and/or alanine aminotransferase > 3 × upper limit of normal range assessed by central laboratory at Screening 6.5. Severe renal impairment (estimated creatinine clearance < 30 mL/min/1.73m^2) assessed by central laboratory at Screening

	6.6. Pregnancy, breastfeeding, or intention to become pregnant during the study, or women of childbearing potential not using a reliable method of contraception 6.7. Hypersensitivity to any active substance or excipient of any of the study drugs 6.8. Treatment with a strong cytochrome P450 3A4 (CYP3A4) inducer such as carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort, within 1 month prior to Randomization (Visit 2) 6.9. Treatment with a strong CYP3A4 inhibitor such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir, within 1 month prior to Randomization (Visit 2) 7. General exclusion criteria: 7.1. Any factor or condition likely to affect protocol compliance of the subject as judged by the investigator 7.2. Treatment with another investigational therapy in the 3-month period prior to Screening 7.3. Treatment with nitrates, alpha-blockers, or ERAs in the 3-month period prior to Screening 7.4. Introduction or change of dose of pulmonary hypertension-specific drugs (other than ERAs) in the 3-month period prior to Screening 7.5. Known drug or substance (e.g., alcohol) abuse, unstable psychiatric illness, or any other condition that, in the opinion of the investigator, may interfere with participation in the study 7.6. Any planned surgical intervention (e.g., organ transplant) during the study period, except minor interventions (e.g., tooth extraction) 8. Any known factor or disease that may interfere with treatment compliance or full participation in the study (e.g., chemotherapy treatment for cancer) or illness with an anticipated life expectancy of less than 12 months.

STUDY TREATMENTS	**Investigational treatment** Macitentan 10 mg, oral tablet, once daily, with or without food. **Comparator and/or placebo** Matching placebo oral tablet, once daily, with or without food.
ENDPOINTS	**Primary efficacy endpoint** The primary endpoint is the change in peak VO_2 from Baseline (Randomization/Visit 2) to Week 16 (Visit 4). **Secondary efficacy endpoints** • Change from Baseline (Visit 2) over 52 weeks in peak VO_2. • Change from Baseline (Visit 2) to Week 16 (Visit 4) in mean count per minute of daily PA-Ac. **Other efficacy endpoints** Other efficacy endpoints are described in Section 6.1.3. **Safety endpoints** • Treatment-emergent adverse events (AEs) and serious AEs up to 30 days after study treatment discontinuation or until initiation of study drug in the AC-055H302 OL extension study, whichever occurs first. • AEs leading to premature discontinuation of study treatment. • Change in vital signs (systolic and diastolic arterial BP and pulse rate), including SpO_2 and body weight from Baseline (Visit 2) to all assessed time points during the study. • Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation or until initiation of study drug in the AC-055H302 OL extension study, whichever occurs first. • Change in laboratory parameters from Baseline (Visit 2) to all assessed time points during the study. **Quality of life endpoints** Quality of life (QoL) endpoints are described in Section 6.3. **Pharmacoeconomic endpoints** Pharmacoeconomic endpoints are described in Section 6.3.

	Pharmacokinetic endpoints Pharmacokinetic (PK) endpoints are described in Section 6.3.
ASSESSMENTS	Refer to the schedule of assessments in Table 2 and Table 3.
STATISTICAL METHODOLOGY	All statistical analyses will be conducted by Actelion or by designated CROs supervised by Actelion, except for the IA, which will be conducted by the ISAC/SSG who will provide results to the IDMC. A Statistical Analysis Plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations. This study implements one IA for unblinded sample size re-estimation and the statistical methods are described below. **Analysis sets** Analyses for the primary, secondary and other efficacy endpoints will be carried out on the Full Analysis Set (FAS), which comprises all randomized subjects within the treatment group to which they were randomized. Additional sensitivity analyses of the primary endpoint will be conducted on the FAS, applying ranking, observed case approach without imputation, and on the Per-Protocol Set (PPS) to assess the robustness of the results of the primary statistical analysis. PPS includes all subjects from the FAS without protocol deviations, which would affect the main analysis of the primary variable. The Safety Set (SS) will be evaluated for safety endpoints in a descriptive manner. SS includes all subjects who received at least one dose of study treatment, based on the actual treatment received. The Pharmacokinetic Analysis Set (PKS) includes all randomized and treated subjects, for whom a PK blood sample at trough has been taken and who do not deviate from the protocol in a way that might affect the evaluation of the trough concentrations.

Primary variable
The primary endpoint for the study is the change in peak VO_2 from Baseline (Visit 2) to Week 16 (Visit 4).

Null and alternative hypotheses
The statistical hypotheses for the primary endpoint are formulated in terms of the arithmetic means (M) of the change in peak VO_2 in subjects treated with either placebo or macitentan 10 mg from Baseline (Visit 2) to Week 16 (Visit 4).

H_0: $M_{\text{macitentan 10 mg}} = M_{\text{placebo}}$ versus

H_A: $M_{\text{macitentan 10 mg}} \neq M_{\text{placebo}}$

The null hypothesis is tested as per primary endpoint at a two-sided Type I error of 1%. The study would be 'conclusive' at the two-sided 1% level; it could also be declared 'positive' at a significance level of 5% on the primary endpoint.

Primary statistical analysis
The null hypothesis will be tested by means of an analysis of covariance (ANCOVA) model on the change in peak VO_2. Model covariates will include randomized treatment, geographical region, and peak VO_2 at Baseline (Visit 2).

For the control of type-I error at final analysis, the primary efficacy endpoint will be tested by combining the p-values from the ANCOVA of first-stage (based on actual number of subjects available at the time of IA) and second-stage (based on the remaining number of subjects required to reach the total sample size after IA results), using the weighted inverse-normal combination method [Lehmacher 1999] with fixed weights proportional to the information available at the time of the IA.

At final analysis, the difference in the change in peak VO_2 from Baseline to Week 16 between macitentan 10 mg and placebo and corresponding p-value will be estimated at each stage separately (first-stage and second-stage) from the main ANCOVA model using a population-wise splitting of data approach. Final interpretation of the results will then be based on the final adjusted p-value, median unbiased estimator for the overall treatment effect and corresponding Repeated

	Confidence Intervals obtained by ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company). Absolute values at Baseline and at Week 16 as well as absolute change in peak VO_2 from Baseline to Week 16 will also be summarized using descriptive statistics. Missing values will be imputed as specified in the statistical section of this protocol and detailed in the SAP. Assumptions of normality of residuals and homogeneity of variance (assessment of ANCOVA model assumptions) will be investigated and graphically presented when applicable (e.g., Q-Q and residual plots). Sensitivity and supportive analyses include separate extended models on the FAS with factors of NYHA FC and geographical region. Subgroup analyses will be conducted for adolescent subjects, adult subjects, geographical region, US subjects, non-US subjects, and ventricular dominance: Left ventricle (LV) versus right ventricle (RV) / mixed. Treatment-by-subgroup variable interaction will be tested for heterogeneity. **Secondary efficacy endpoints** If the primary endpoint is statistically significant at alpha significance level of α=1% two sided in the final analysis, the secondary efficacy endpoints, i.e., change from Baseline over 52 weeks in peak VO_2 and change from Baseline to Week 16 in mean count per minute of daily PA-Ac, will be analyzed at the same alpha-level as the primary endpoint using a hierarchical testing procedure following the order specified in the secondary endpoints [Section 10.3.3]. The final analysis of the secondary efficacy endpoints will be conducted using the inverse normal combination method with pre-specified weights to combine first and second stage p-values, similar to the primary endpoint main analyses. The change from Baseline over 52 weeks in peak VO_2 will be evaluated on the FAS population by means of a mixed model repeated measures (MMRM). The model will include

	randomized treatment group, time (via a categorical variable for visit), treatment-by-time interaction, Baseline-by-time interaction, and peak VO_2 at Baseline as fixed effects. An unstructured variance-covariance matrix will be specified. The change from Baseline to Week 16 in mean count per minute of daily PA-Ac will be analyzed by means of an ANCOVA including treatment group and baseline mean count per minute of daily PA-Ac as covariates. Final interpretation of the results for the secondary endpoints will be similar to the primary endpoints and will be performed on the final adjusted p-value, median unbiased estimator for the overall treatment effect and corresponding 99% confidence intervals obtained by ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company). **Other efficacy endpoints** Other efficacy endpoints will be analyzed for exploratory purposes. Time-to-composite endpoint will be analyzed using a Kaplan-Meier approach and a Cox regression model. **Safety and tolerability endpoints** Safety and tolerability endpoints will be analyzed descriptively by actual treatment on the SS. As per treatment received, AE incidences will be summarized for the entire study period, from Screening to EOT plus 30 days. Incidences of treatment-emergent AEs will be displayed. Changes in laboratory parameters and vital signs will be presented from Baseline (Visit 2) to post-baseline visits and to worst and last post-baseline. Drop-out patterns, i.e., reasons for premature discontinuation by treatment group, will be investigated. **Quality of life endpoints** The QoL endpoints will be analyzed descriptively by randomized treatment group using the FAS. Continuous scales EQ-5D Visual Analogue Scale (VAS) will be summarized as absolute and changes from baseline values at each time point.

	Categorical scales (Patient Global Assessment of Disease Severity [PGA-S], Clinician Global Impression of Severity [CGI-S], Patient Global Impression of Change [PGI-C], Clinician Global Impression of Change [CGI-C] and Euro QoL 5D [EQ-5D-5L]) will be summarized as the proportion of patients within each response category at each time point. **Pharmacoeconomic endpoints** Those endpoints will be summarized descriptively by randomized treatment group using the FAS. **Pharmacokinetic endpoints** Trough concentrations of macitentan and its metabolite will be analyzed descriptively on the PKS. **Sample-size assumptions** The family-wise Type I error is set to 1%. The study sample size necessary for comparison of the primary endpoint, change in peak VO_2 from Baseline (Visit 2) to Week 16 (Visit 4), between subjects randomized in a 1:1 ratio to macitentan 10 mg or placebo is based on the following assumptions: ***Type-I and -II errors – Power*** • A two-sided Type I error of 1% and a Type II error of 20% (80% power). ***Effect and variability assumptions*** • Assumptions are based on previous studies in subjects with Fontan-palliated circulation (TEMPO study [Hebert 2013, Hebert 2014] with bosentan and other studies, e.g., with bosentan, sildenafil, or iloprost): – A difference equal to 2.4 mL/kg/min, and – A standard deviation of the difference of 4.0 mL/kg/min, and – A normal distribution for the primary endpoint. Based on the above assumptions, a total of 134 subjects, i.e., 67 per treatment group, are required to establish superiority of macitentan 10 mg over placebo with 80% power to correctly reject the null hypothesis, when it is false, in favor of the alternative hypothesis. This test is based on a two-sample t-test for independent samples with a two-sided significance level 0.01 and equal per-group variances.

	The sample size will be re-estimated in the IA, based on observed unblinded treatment effect and standard deviation, following rules as described in the SAP. The IA will be conducted approximately when the first 95 randomized subjects (i.e., 70% of pre-planned sample size) are randomized and have completed their Week 16 CPET assessment (i.e., Visit 4/Week 16), or withdrew from the study without a Week 16 CPET assessment. This sample size re-estimation allows the sample size to be potentially increased up to 268 subjects based on conditional power considerations for the primary efficacy endpoint [see Section 10.5.3]. The total sample size of the study shall not exceed 268 subjects and shall not be below the initial sample size of 134 subjects.
STUDY COMMITTEES	An independent data monitoring committee (IDMC) will review data at regular intervals according to the IDMC charter. The IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data. The IDMC will also interpret the results of the interim analysis planned for sample size re-estimation and provide the Sponsor Committee with the appropriate recommendation regarding the new target sample size.
STUDY EXTENSION	Subjects who complete the study will be offered to participate in an open-label extension study, AC-055H302 RUBATO OL under a separate protocol.

PROTOCOL

1 BACKGROUND

1.1 Indication

The Fontan procedure was introduced in 1968 to treat patients with tricuspid atresia. This surgical approach has subsequently been applied to a range of complex congenital heart malformations characterized by the presence of only one functional ventricular chamber, in patients in whom biventricular repair is not possible. The introduction of the Fontan surgical operations and their subsequent modifications brought expected survival into adulthood, although short-term (e.g., arrhythmia, thrombosis, etc.) and long-term complications (e.g., heart failure [HF], liver, and renal failure) are as yet unavoidable and life expectancy is reduced. Recent studies in the US have found Kaplan-Meier (KM) survival estimates for patients operated in the modern Fontan surgical era (from the 1990s onward) of about 96%, 90%, 80%, and 70% at 1, 10, 20 and 25 years post-Fontan operation, respectively [Pundi 2015, Dabal 2014, Khairy 2008].

After successfully completed surgeries, Fontan-palliated patients are affected by a number of complications associated with considerable morbidity and mortality. Their exercise capacity (measured by peak oxygen uptake [VO_2]) remains limited, with peak VO_2 ranging from 48% to 65% of predicted value, and their exercise capacity decreases with time. When exercise capacity of Fontan-palliated patients falls below about 45% to 50% of peak VO_2 predicted for age and sex [Goldberg 2014], there is an associated increased risk of hospitalization or death [Diller 2005, Diller 2010].

[Diller 2015] estimated that a 40-year old patient with Fontan physiology has a 5-year risk of death (18.0%; 95% confidence interval, 11.9% to 24.6%) comparable with that of a 75-year old person from the general UK population.

Currently, there are no medicinal products approved for use in the treatment of Fontan-palliated patients.

1.2 Study treatment

1.2.1 Macitentan

Macitentan (ACT-064992, Opsumit®) is an orally active, non-peptide, potent dual endothelin ET_A and ET_B receptor antagonist (ERA).

There are several publications [Derk 2015] on the efficacy and tolerability of endothelin (ET) receptor blockade in Fontan-palliated patients, after successful surgery. Among these studies, the placebo-controlled clinical study TEMPO [Hebert 2014], was conducted in Denmark and Sweden with bosentan in 75 Fontan-palliated patients. Sixty-nine patients (30 adolescents, 39 adults) completed this study, that showed that bosentan, administered

for 14 weeks, significantly increased peak VO_2 and exercise duration during cardiopulmonary exercise testing (CPET), as well as improved New York Heart Association (NYHA) functional class (FC), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) compared to placebo. No serious adverse effects were seen.

A recently published study further supports that ERAs might provide most pronounced hemodynamic (PVR decrease) and functional improvement (NYHA) in adults and adolescents.

This small prospective cohort study conducted without a control group by [Agnoletti 2017], was the first study that assessed the effects of ERAs (bosentan, macitentan) in patients with a Fontan circulation with increased pulmonary vascular resistance (PVR), using cardiac catheterization and CPET. These patients were reevaluated after 6 months. Pre- and post-treatment hemodynamic variables were assessed by cardiac catheterization. The main study inclusion was PVR $\geq$ 2 Wood units (WU)*m^2. Functional capacity was evaluated by CPET. The primary endpoint was to obtain a reduction of PVR, while the secondary endpoint was to obtain an improvement of functional capacity.

A cohort of 8 adult patients with a Fontan circulation was treated with macitentan. NYHA FC improved, PVR decreased and cardiac index increased, while CPET showed no significant functional improvement. For 8 adolescents on bosentan (local legislative authority and the ethic committee allowed macitentan use only in adult patients), NYHA FC improved, PVR decreased, cardiac index increased, and CPET showed significant functional improvement, with improvement in anaerobic threshold VO_2 and VO_2 max as well as oxygen pulse.

Systolic blood pressure diminished in all adolescents (all on bosentan) and adults (all on macitentan), significantly so only for adolescents. No significant differences were detected in diastolic blood pressure and oxygen saturation. Blood tests of hepatic and renal function were unchanged, no hepatic toxicity developed, and anemia never occurred.

For detailed information on macitentan, please see the most recent version of the macitentan Investigator's Brochure (IB). Detailed information on 'Special warnings and precautions' and 'General precautions' are provided in sections 1.7 and 1.8 of the IB [Macitentan IB].

1.2.2 Physico-chemical properties of macitentan

Please refer to the Macitentan IB.

1.3 Purpose and rationale of the study

The purpose of the AC-055H301 study is to assess the efficacy and safety of macitentan 10 mg once daily (o.d.) in Fontan-palliated adult and adolescent subjects. The main goal

of the study is to assess the benefit on exercise capacity as measured by the primary efficacy endpoint, namely the change from baseline of peak VO_2.

Prior randomized, placebo-controlled clinical studies performed with pulmonary hypertension (PH)-specific vasodilatory medications (other than macitentan) showed statistically significant benefits in Fontan-palliated adolescents and adults. The benefit was measured by exercise capacity, and these studies also showed satisfactory safety effects. The Hebert 2014 study was performed in adolescents and in adults, with bosentan (an ERA, like macitentan) administered for 14 weeks. The Shang 2013 study was performed in children only, with bosentan administered for 1 year and the children followed up for 2 years. The Phase 1/2 range-finding study [Goldberg 2015] administered a phosphodiesterase-5 inhibitor (udenafil) to adolescents. The Cedars 2016 cross-over study administered ambrisentan (another ERA) to adults only.

In Fontan-palliated patients, the trans-pulmonary gradient corresponds to PVR in patients with pulmonary arterial hypertension (PAH). High PVR index is associated with low 6-minute walk distance (6MWD) and survival in children with PAH (whether idiopathic PAH or PAH associated with congenital heart disease [CHD]) [Sajan 2011]. Therefore, macitentan, which is expected to have a beneficial effect on hemodynamics [Agnoletti 2017] as well as on vascular remodeling, may be beneficial in Fontan-palliated subjects through an effect that cannot be measured short-term, i.e., during the duration of the proposed Phase 3 study. Macitentan is specifically expected to provide short-to-medium-term benefit on exercise capacity (measured by peak VO_2), and potentially a longer-term effect on morbidity (effect on progressive HF).

The rationale for this study is to assess the efficacy, safety, and pharmacokinetics (PK) of macitentan in Fontan-palliated adolescents and adults.

1.4 Summary of known and potential risks and benefits

Macitentan is approved for the treatment of PAH based on data generated in the SERAPHIN study [Pulido 2013]. In addition, macitentan was investigated in another CHD indication (Eisenmenger Syndrome) in the MAESTRO study [Gatzoulis 2019]. Safety and tolerability are well documented in both indications.

Effects on blood pressure

This drug is a vasodilator. However, in the pivotal study in PAH, no difference in mean change from baseline in blood pressure (BP) was observed.

Effect on hemoglobin

In placebo-controlled Phase 2 and 3 studies, treatment with macitentan was associated with mild to moderate decreases in hemoglobin concentration, which stabilized after the first

few weeks of macitentan treatment. Few patients discontinued macitentan treatment due to anemia.

Effect on liver enzymes

Elevations of liver aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) have been associated with PAH and with other ERAs. In a long-term placebo-controlled trial in PAH [Pulido 2013], macitentan 10 mg was not associated with increased incidences of treatment-emergent elevations of AST and/or ALT versus placebo. Based on the cumulative review of the macitentan liver cases by an independent liver safety data review board (ILSDRB), there was no clear evidence of hepatotoxicity.

Effect on edema/fluid retention

Events of edema/fluid retention are frequent symptoms of PAH worsening and associated complications such as right ventricular failure. Such events were reported with similar incidences for macitentan and placebo patients in the pivotal placebo-controlled study in PAH [Pulido 2013]. Based on the observation of individual post-marketing cases where a causal relationship could not be excluded, and on other observations linked to the use of ERAs in various heart conditions, 'edema/fluid retention' was added to the undesirable effects section in the Prescribing Information of macitentan.

Hypersensitivity reactions

During post-marketing experience, hypersensitivity reactions (angioedema, pruritus, rash) have been reported.

Pregnancy

Macitentan must not be administered to a pregnant female because it may cause fetal harm. Women of childbearing potential will be included in the trial only if they do not intend to become pregnant during the study, are not breastfeeding, and agree to use reliable contraception [Section 4.5] from 30 days before start of treatment until one month after end of study drug treatment. Pregnancy tests will be performed monthly during treatment and 1 month after stopping treatment.

More comprehensive safety data is provided in the IB [Macitentan IB].

Benefit

It is expected that macitentan treatment in Fontan-palliated patients in NYHA FC II and III will positively impact exercise capacity and possibly delay disease progression.

It is the investigator's responsibility to monitor the risk-benefit ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual subject level, and to discontinue study treatment or the study if, on balance, he/she believes that continuation would be detrimental to the subjects' well-being.

2 STUDY OBJECTIVES

2.1 Primary objective

To assess the effect of macitentan on exercise capacity (measured by peak VO_2) in comparison with placebo in Fontan-palliated subjects.

2.2 Secondary objectives

- To assess the effect of macitentan on long-term exercise capacity (measured by peak VO_2 over 52 weeks).
- To assess the effect of macitentan on daily Physical Activity measured by Accelerometer (PA-Ac).
- To evaluate the safety and tolerability of macitentan.

2.3 Other objectives

- To assess the efficacy of macitentan on endpoints related to exercise capacity.
- To assess the effect of macitentan on NT-proBNP.
- To assess the effect of macitentan on clinical worsening.
- To assess the effect of macitentan on Quality of life (QoL).
- To assess the effect of macitentan on pharmacoeconomic endpoints.
- To assess the plasma concentration of macitentan and its metabolite at trough.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, adaptive, multi-center, double-blind, randomized, placebo-controlled, parallel-group Phase 3 study.

At least 134 subjects will be randomized in a 1:1 ratio to either macitentan or placebo. Randomization will be stratified by geographical region (America, Europe, Asia, Oceania). The study will be conducted in approximately 31 investigational sites in 11 countries.

Given the uncertainty about both the true treatment effect and variability of the primary efficacy endpoint variable, an interim analysis (IA) will be conducted for unblinded sample size re-estimation. This IA will be performed by an Independent Statistical Analysis

Center/Statistical Support Group (ISAC/SSG) [see Section 3.3] for the Independent Data Monitoring Committee (IDMC). Only the IDMC and the ISAC/SSG will be unblinded to the data. This sample size re-estimation allows the sample size to be potentially increased up to a total sample size of 268 subjects [see Section 10.5.3].

3.1.1 Study periods

The study comprises the following consecutive periods:

Screening period: Lasts up to 30 days; starts with the signature of the informed consent (Visit 1) and ends with the subject's Randomization (Visit 2).

Treatment period: Starts with the administration of the first dose of study treatment (Visit 2) and ends on the day of the last dose of study treatment, expected to be at 52 weeks.

Subjects who prematurely and permanently discontinue study treatment before Week 52 (Visit 6) must have a premature End-of-Treatment (EOT) visit as soon as possible but not later than 7 days after last dose of study drug.

Safety follow-up (S-FU) period:

After permanent study treatment discontinuation, subjects will be followed up for a minimum of 30 days (S-FU).

Subjects eligible to enter the AC 055H302 open-label (OL) extension study may do so as soon as their eligibility has been confirmed, even prior to completion of the full S-FU period. The period ends with administration of first study drug in the OL extension study.

Post-treatment observation period (PTOP):

Subjects who prematurely and permanently discontinue study treatment will enter the PTOP after their S-FU period is completed. The PTOP lasts until the planned study EOT (at most 52 weeks after Randomization) for each individual subject. This last visit of the PTOP is called End-of-PTOP (EOP). The PTOP consists of an abbreviated schedule of assessments at 90-day intervals.

End-of-Study (EOS):

EOS is reached by an individual subject:

- when the S-FU period has been completed (for those subjects who do not discontinue study treatment prematurely), or
- when the S-FU period and PTOP have been completed (for those subjects who discontinue study treatment prematurely), or

- if subjects enter the AC-055H302 RUBATO open-label (OL) extension study, with first administration of OL study drug.

For all subjects, EOS corresponds to the last visit performed in this AC-055H301 RUBATO double-blind study.

Study Closure (SCL) will be announced by the sponsor when all subjects have reached their EOS in AC-055H301 RUBATO.

Vital Status Follow-up (VSFU):

A VSFU will be performed within 8 weeks after the SCL announcement to determine each vital status of all subjects randomized in AC-055H301 RUBATO, irrespective of whether the subject is included in the AC-055H302 OL extension study [see Section 7.2.3.6].

Study Closure (SCL):

The SCL applies to all randomized subjects and will occur:

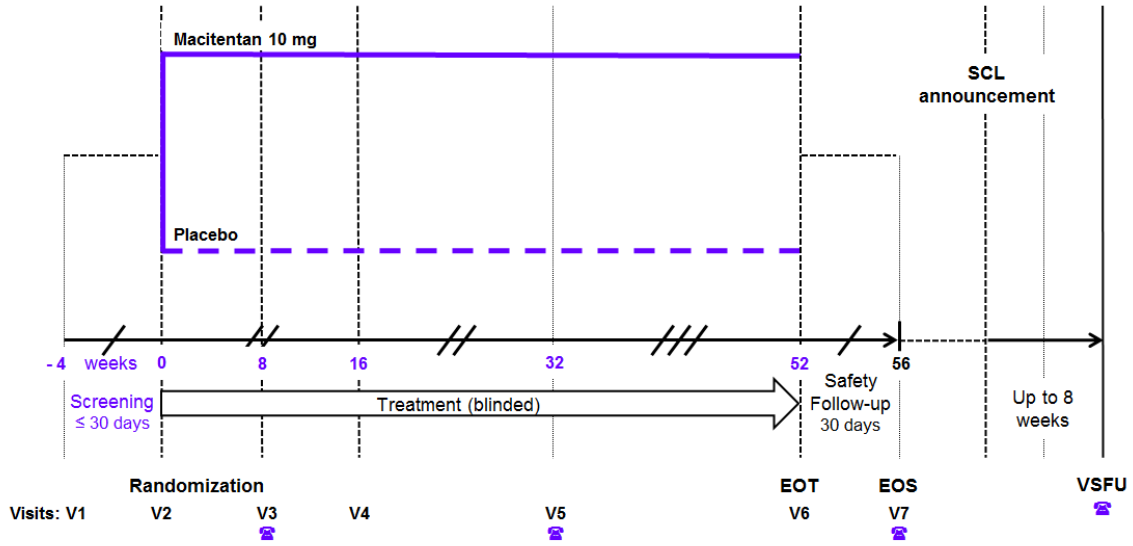
- when all subjects have had their individual VSFU, and
- no later than 8 weeks after SCL announcement.

The visit schedule and protocol-mandated procedures are performed according to the table of assessments [Table 2 and see Table 3 for subjects entering the PTOP], and are described in Section 7.

The overall study design is depicted in Figure 1. An example of premature discontinuation and PTOP is depicted in Figure 2.

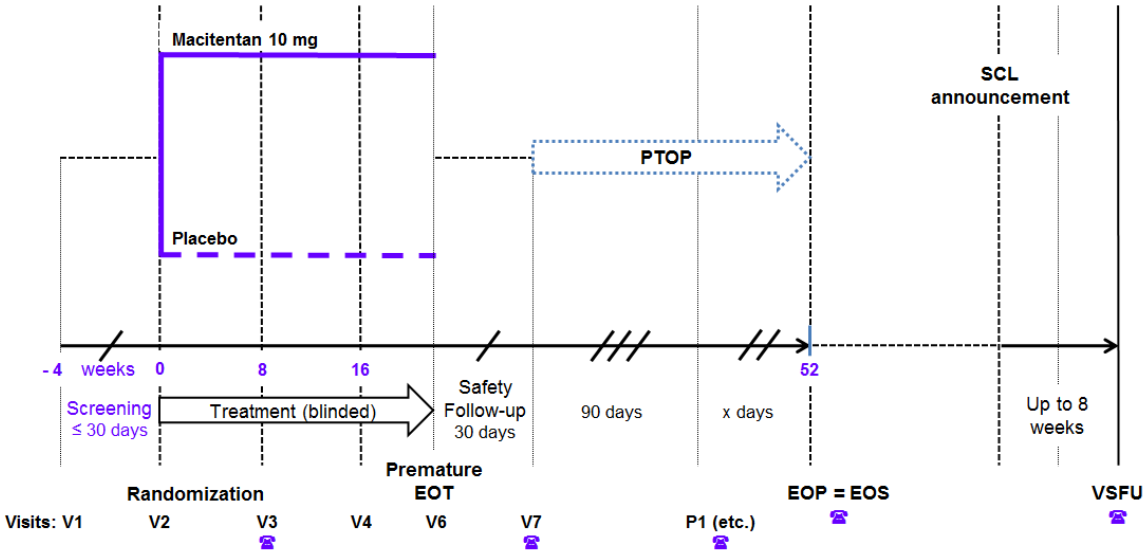
Figure 3 depicts the design for a subject who enters the AC-055H302 OL extension study at Week 52.

Figure 1 Study design



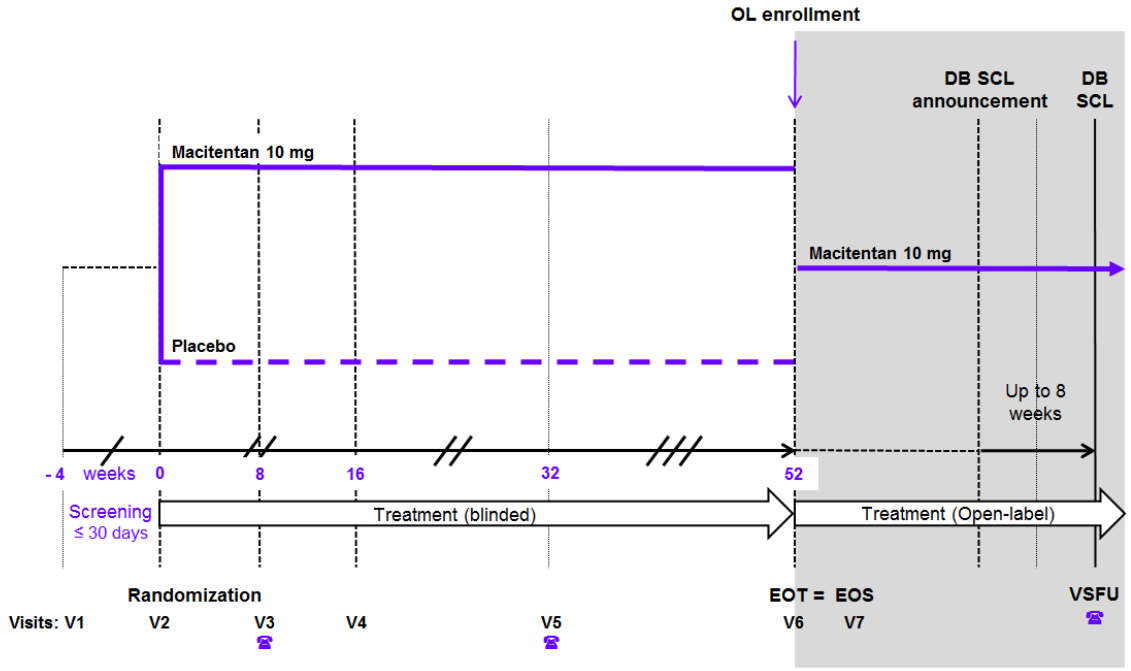
EOS = End-of-Study; EOT = End-of-Treatment; SCL = Study Closure; V = visit; VSFU = Vital Status Follow-Up; ☎= Telephone call (for visit).

Figure 2 PTOP (example of discontinuation after Visit 4)



EOS = End-of-Study; EOP = End-of-PTOP; EOT = End-of-Treatment; P = PTOP visit; PTOP = Post-treatment observation period; SCL = Study Closure; V = visit; VSFU = Vital Status Follow-Up; ☎= Telephone call (for visit).

Figure 3 OL extension study (entry at Visit 6)



DB = Double-blind; EOS = End-of-Study; EOT = End-of-Treatment; OL = Open-label (extension); SCL = Study Closure; V = visit; VSFU = Vital Status Follow-Up; ☎= Telephone call (for visit).

No S-FU will be performed in subjects entering the AC-055H302 RUBATO-OL extension study at individual subject's EOT/EOS for the AC-055H301 RUBATO study.

In instances where administration of AC-055H302 OL study drug does not immediately follow EOT in the AC-055H301 RUBATO study, the subject will enter the normal S-FU period until administration of the first dose of the OL study drug occurs.

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., Informed Consent Form [ICF] signed) and ends with the last visit of the last subject. This is expected to last approximately 34 months.

The subjects will be treated for 52 weeks. Subjects who prematurely and permanently discontinue study treatment will enter a PTOP, which lasts until 52 weeks after randomization to monitor the medical condition of those individual subjects after stopping macitentan. For an individual subject, the study is completed with the EOS visit either when the S-FU period has been completed (for those subjects who do not discontinue study treatment prematurely), or when the S-FU period and PTOP have been completed (for those subjects who discontinue study treatment prematurely), or if subjects enter the AC-055H302 RUBATO OL extension study, with first administration of OL study drug.

At the end of the trial, when all subjects have completed their EOS, a SCL announcement will be made which is followed by an 8 week period within which each vital status of all subjects randomized in AC-055H301 RUBATO will be collected, irrespective of whether the subject is included in the AC-055H302 OL extension study [VSFU, see Section 7.2.3.6], unless already known.

This information will be collected in the eCRF after study completion.

3.2 Study design rationale

The study will assess the efficacy, safety, and PK of treating Fontan-palliated subjects with macitentan compared to placebo.

As there are no approved medications for treatment of patients with Fontan circulation-associated reduced exercise capacity and / or progressive HF, a placebo-controlled study as add-on to standard of care is ethically appropriate.

As described in Section 1.2.1, evidence from a study conducted with an ERA (bosentan) in Fontan-palliated patients indicated a clinically and statistically significant beneficial impact on exercise capacity at Week 14 [Hebert 2014]. Considering past experience on time to maximal effect of macitentan on exercise capacity in patients with PAH (in the SERAPHIN study, 10 mg macitentan given o.d. improved the functional capacity of adult patients with PAH, as measured by the 6MWD test at 3 months [AC-055-302 SERAPHIN, *post-hoc* analysis, data on file] and at 6 months [Pulido 2013]), a time point of 16 weeks was chosen for assessing the primary endpoint.

A recent study administering bosentan in adolescents and macitentan in Fontan-palliated adults [Agnoletti 2017] further supports that ERAs might provide most pronounced hemodynamic (PVR decrease) and functional improvement (NYHA) in adults and adolescents.

Very limited evidence on long-term follow up of treatment of Fontan-palliated patients with PH-specific vasodilators is available. In the [Shang 2013] study, Fontan-palliated children were treated for 1 year and followed up for 2 years. Considering the recommendation of at least a yearly follow-up of Fontan-palliated patients, a 1-year study duration was defined. Additional assessments of peak VO_2 in this time frame will help to understand the dynamics of the impact on exercise capacity and possibly disease progression.

3.3 Study committees

An IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with the highest scientific and ethical standards. The IDMC will be fully operational prior to enrollment of the first subject into the study and is supported by an Independent Statistical Analysis Center/Statistical Support Group (ISAC/SSG). The composition and operation of the IDMC are described in the IDMC charter.

In addition, the IDMC will review the report of the IA provided by the ISAC/SSG and provide a recommendation to the Sponsor Committee on potential sample size adjustments following rules described in the IDMC charter.

An ILSDRB (an external expert committee of hepatologists) has been appointed to monitor all Actelion studies with macitentan, as well as post-marketing cases, and to provide ongoing assessment and advice regarding serious hepatic adverse events (AEs) of special interest during the study as per the ILSDRB charter.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll adolescent and adult male and female subjects aged 12 years and older, with either Lateral Tunnel Total Cavopulmonary Connection (LT-TCPC), or Extra Cardiac Tunnel Total Cavopulmonary Connection (EC-TCPC).

They must be in NYHA FC II or III (confirmed by the investigator with the Specific Activity Scale) [Appendix 4] and be able and willing to perform CPET (confirmed by the ability to reach a respiratory exchange ratio of 1.1, based on historical and/or baseline CPET).

Women of childbearing potential must not be pregnant, breastfeeding, or have the intention of becoming pregnant during the study and agree to use reliable contraception throughout the study.

Eligible subjects and/or legal representatives must be able and willing to give informed consent/assent for participation in the clinical study.

Treatment with ERAs is not permitted.

4.2 Rationale for the selection of the study population

LT-TCPC and EC-TCPC Fontan-palliated patients constitute the majority of present-day Fontan-palliated patients and are considered to constitute a homogeneous group in terms of prognosis. The medical need in Fontan-palliated patients with NYHA FC II and III is greater than in patients with milder disease (FC I), as higher FC is both an indicator of decreased exercise tolerance and progression of their HF. FC IV patients are considered too severe, heterogeneous, and are likely to be late failing-Fontan patients with overt clinical signs of HF and/or other signs of Fontan-related serious complications. Furthermore, the only true treatment of FC IV Fontan-palliated patients is heart transplantation. Failing-Fontan patients are not planned to be included in this study.

The LT-TCPC and EC-TCPC Fontan-palliated surviving patient population is a relatively young population in which medical need is high because their exercise capacity is significantly reduced. In this population, patients are expected to derive a significant beneficial effect on their exercise capacity and, potentially, disease progression can be delayed. Within this population, adolescents have the greatest need for improvement of their exercise capacity as they are at an age where their exercise intolerance progresses the most rapidly [Giardini 2008, Kempny 2012, Fernandes 2010].

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject:

1. Written informed consent/assent from the subject and/or a legal representative prior to initiation of any study-mandated procedures.
2. Male or female ≥ 12 years old.
3. Fontan-palliated subjects with either LT-TCPC, or EC-TCPC surgery > 1 year before Screening. LT-TCPC, or EC-TCPC surgery can be primary or secondary to atrio-pulmonary connection.
4. NYHA FC II or III (assessed by the investigator using the Specific Activity Scale [Appendix 4]).
5. Ability to understand and comply with the instructions, and ability to physically perform the CPET.
6. Women of childbearing potential must:

6.1. Have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at the Randomization visit (Visit 2), and,
6.2. Agree to perform monthly pregnancy tests up to the end of the S-FU period, and,
6.3. Agree to use reliable contraception [Section 4.5.2] from at least 30 days prior to Visit 2 and up to at least 30 days after study drug discontinuation.

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject:

1. Pattern of Fontan circulation severity. Any of the following:
   1.1. Known severely reduced single ventricle ejection fraction (< 30%)
   1.2. Known Fontan circulation stenosis, affected area > 50% of the diameter
   1.3. Known valvular defects (severe atrioventricular [AV] valve regurgitation, outflow obstruction)
   1.4. Known pulmonary-venous pathway obstruction
   1.5. Peripheral oxygen saturation (SpO_2) of < 88% at rest at Screening

2. Deterioration of the Fontan-palliated condition. Any of the following events within 3 months prior to Screening:
   2.1. Candidate on the active list for heart transplantation
   2.2. Clinical worsening leading to medical interventions including reoperation of Fontan circulation (e.g., mechanical circulatory support, Fontan take-down, Fontan revision/conversion, AV valve repair/replacement).
   2.3. Unscheduled hospitalization due to deterioration of the Fontan-palliated condition[1]
   2.4. Signs and symptoms of HF[2] requiring change in diuretic therapy
   2.5. Ventricular tachyarrhythmia or supraventricular tachyarrhythmia[3]
   2.6. Peritoneal, pleural, mediastinal, or pericardial effusions
   2.7. Thrombotic or hemorrhagic complications (including thromboembolism and hemoptysis)
   2.8. Protein losing enteropathy (PLE) (serum albumin < 30 g/L and total protein < 50 g/L)
   2.9. Plastic bronchitis/chyloptysis

[1] Only applicable as an event if hospitalization/intervention was unscheduled / not related to routine Fontan-related follow-up, and hospital stay was > 24 hours.
[2] Include orthopnea, nocturnal dyspnea, pulmonary edema, or radiological signs. Persistent congestion with edema only qualifies if the peripheral edema is moderate-to-severe despite optimal diuretic therapy.
[3] Subjects are excluded for arrhythmia only if it requires hospitalization, or cardioversion, addition/increase in antiarrhythmic treatment, or invasive tests or treatment.

2.10. Signs and symptoms requiring the addition of a new class of cardiovascular medication (e.g., nitrates, alpha-blockers, or ERAs)

3. Limitations to CPET:
   3.1. History of syncope during exercise
   3.2. Symptomatic coronary artery disease at Screening
   3.3. Respiratory limitation with a breathing reserve of < 10%
   3.4. Iron deficiency defined as ferritin < 10 µg/L at Screening
   3.5. Iron supplementation, regardless of route of administration, unless already present at stable dose for more than 3 months prior to Screening
   3.6. Body mass index (BMI)-for-age reference (z-scored) equivalent to BMI > 35 kg/m^2 (for adults) at Screening
   3.7. Exercise training program for cardiopulmonary rehabilitation in the 3-month period prior to Screening
   3.8. Myocardial infarction < 6 months before Screening
   3.9. Pacemaker at Screening

4. Peak VO_2 < 15 mL/kg/min at Baseline.

5. Systolic BP < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height) at rest or during CPET at Screening or at Baseline.

6. Criteria related to macitentan use:
   6.1. Hemoglobin < 75% of the lower limit of normal assessed by central laboratory at Screening
   6.2. Known or suspected pulmonary veno-occlusive disease
   6.3. Known and documented severe hepatic impairment defined as Child-Pugh Score C [Appendix 10], based on measurement of total bilirubin, serum albumin, international normalized ratio or prothrombin time (except for patients under non-Vitamin K antagonists) and based also on presence/absence and severity of ascites and hepatic encephalopathy
   6.4. Serum AST and/or ALT > 3 × upper limit of normal range assessed by central laboratory at Screening
   6.5. Severe renal impairment (estimated creatinine clearance < 30 mL/min/1.73m^2) assessed by central laboratory at Screening
   6.6. Pregnancy, breastfeeding, or intention to become pregnant during the study, or women of childbearing potential not using a reliable method of contraception
   6.7. Hypersensitivity to any active substance or excipient of any of the study drugs
   6.8. Treatment with a strong cytochrome P450 3A4 (CYP3A4) inducer such as carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort, within 1 month prior to Randomization (Visit 2)

6.9. Treatment with a strong CYP3A4 inhibitor such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir, within 1 month prior to Randomization (Visit 2)

7. General exclusion criteria:
   7.1. Any factor or condition likely to affect protocol compliance of the subject, as judged by the investigator
   7.2. Treatment with another investigational therapy in the 3-month period prior to Screening
   7.3. Treatment with nitrates, alpha-blockers, or ERAs in the 3-month period prior to Screening
   7.4. Introduction or change of dose of PH-specific drugs (other than ERAs) in the 3-month period prior to Screening
   7.5. Known drug or substance (e.g., alcohol) abuse, unstable psychiatric illness, or any other condition that, in the opinion of the investigator, may interfere with participation in the study
   7.6. Any planned surgical intervention (e.g., organ transplant) during the study period, except minor interventions (e.g., tooth extraction)

8. Any known factor or disease that may interfere with treatment compliance or full participation in the study (e.g., chemotherapy treatment for cancer) or illness with an anticipated life expectancy of less than 12 months.

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

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

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy,
- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3 definition]),
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis,
- Pre-pubescence (pre-pubescent females must have their childbearing potential status reassessed at each visit and recorded in the electronic Case Report Form [eCRF]).

To determine pre-pubescent status of female subjects who have not reached menarche, the subject will do a self-assessment in the presence of the investigator (or female counselor

when applicable) according to the Tanner stages described in Appendix 5. The onset of puberty is defined as reaching stage 2 on the Tanner scale.

The site study personnel will record the Tanner stage and the childbearing potential in the eCRF. Once childbearing potential is achieved, the Tanner stage will no longer be self-assessed. For abstinent subjects of childbearing potential, the study personnel will ask at each visit whether the subject currently is or might become sexually active. If confirmed the study personnel will counsel the female on the appropriate methods of contraception as applicable [see to Section 4.5.2].

The reason for not being of childbearing potential will be recorded in the eCRF.

4.5.2 Acceptable methods of contraception

Women of childbearing potential [see definition in Section 4.5.1] must use acceptable birth control from Screening up to at least 30 days after study treatment discontinuation. Reliable contraception must be started at least 30 days prior to Visit 2.

The methods of birth control used (including non-pharmacological methods) must be recorded in the eCRF.

To ensure compliance, the study personnel must remind women of childbearing potential at each visit to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

If subjects decide that they want to change the form of birth control being used, they need to talk with the treating physician to be sure that another acceptable form of birth control is chosen.

4.5.2.1 Countries having taken part in the VHP (Voluntary Harmonization Procedure), or countries with a restricted list of contraception methods

Study treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced. It must be ensured that a female counselor is available to discuss this topic, if requested.

In countries having taken part in the VHP, namely **Denmark, Germany and UK, one** of the following highly effective contraception methods is required:

- combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal

- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the women of childbearing potential trial subject and that the vasectomized partner has received medical assessment of the surgical success).

Other countries may have adopted the same restricted list of contraception methods. Please refer to your country-specific approval documents and approved local Informed Consent.

4.5.2.2 Countries not having taken part in the VHP (excluding France) or countries without a restricted list of contraception methods

In the Czech Republic, Poland and Ireland, study treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced. It must be ensured that a female counselor is available to discuss this topic, if requested.

True abstinence from intercourse with a male partner, only when this is in line with the preferred lifestyle of the subject, is considered an acceptable birth control method.

Other countries may have adopted the same approach regarding contraception methods. Please refer to your country-specific approval documents and approved local Informed Consent.

4.5.2.3 France

Study treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced. It must be ensured that a female counselor is available to discuss this topic, if requested.

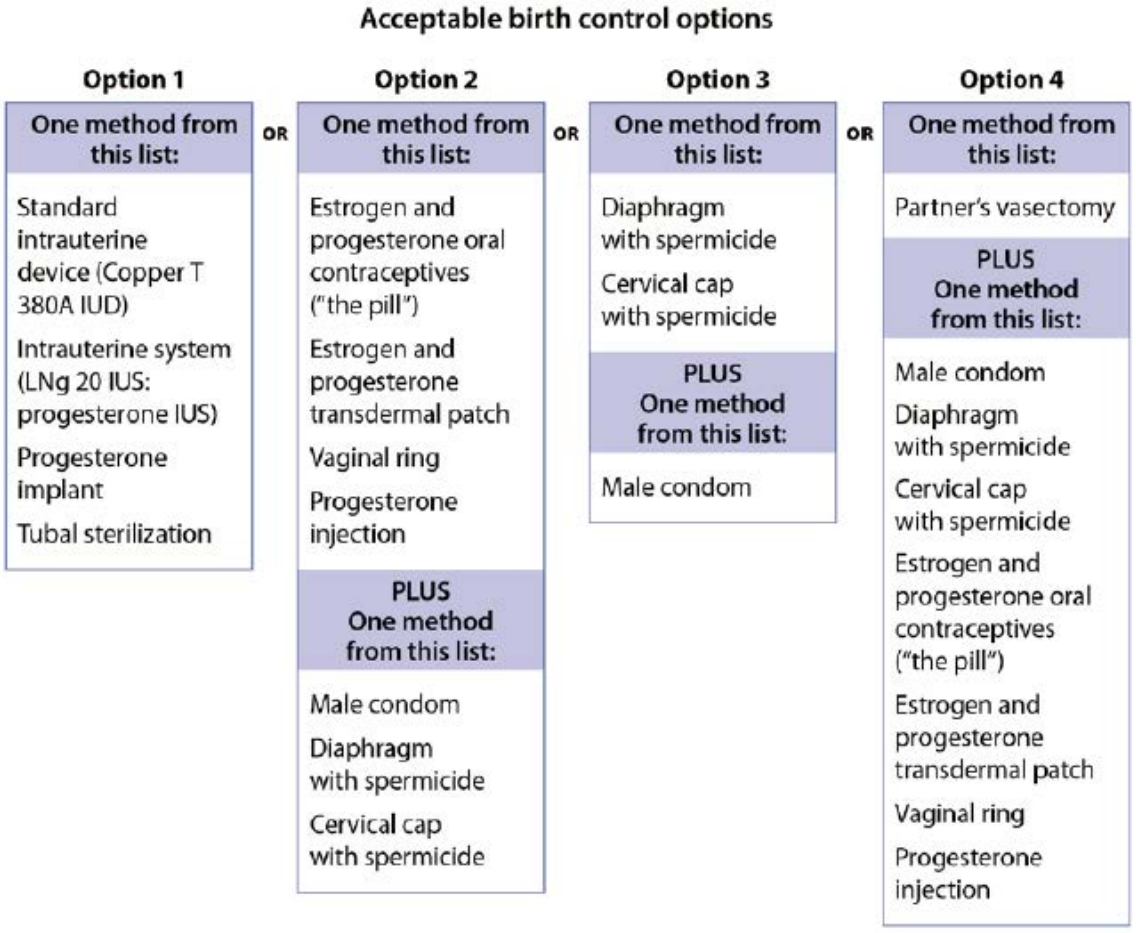
4.5.2.4 North America

Subjects may choose one highly effective form of contraception (intrauterine devices, contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods) [Figure 4]. If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method.

In addition to acceptable birth control methods identified in Figure 4, true abstinence from intercourse with a male partner, only when this is in line with the preferred lifestyle of the subject, is considered an acceptable birth control method.

The investigator must counsel subjects on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive measures.

Figure 4 Acceptable birth-control options



4.5.2.5 Asia and Oceania

Study treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced. It must be ensured that a female counselor is available to discuss this topic, if requested.

True abstinence from intercourse with a male partner, only when this is in line with the preferred lifestyle of the subject, is considered an acceptable birth control method.

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment: Description and rationale

Macitentan 10 mg will be provided as film-coated tablets debossed with '10' on one side, for o.d. oral administration with or without food.

Inactive ingredients of the macitentan tablet formulation are the following: lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate type A, polysorbate. The film coat contains titanium dioxide, talc, xanthan gum, polyvinyl alcohol, and soy lecithin.

The macitentan 10 mg o.d. dose selected for the proposed study is based on the formulation and the dose regimen approved for treatment of adult patients with PAH from World Health Organization (WHO) FC II and III. Treatment with another related ERA, bosentan, has shown efficacy and safety in Fontan-palliated adolescent and adults with the dose regimen approved for PAH [Hebert 2014] and dose adjusted on body weight [Shang 2013].

5.1.2 Comparator: Description and rationale

The treatment comparator will be matching placebo tablets, for o.d. oral administration with or without food.

As no approved medicinal treatment for patients with Fontan-palliation exists and the disease progression is rather slow, it is ethical to compare the investigational medicinal product to placebo as add on to standard of care.

5.1.3 Study treatment administration

If the subject is eligible, the first intake of study treatment will take place at site, during the Randomization visit (Visit 2), after successful completion of all Screening (Visit 1) and Randomization (Visit 2) assessments.

The subjects must be instructed not to take study treatment in the morning of study visit days.

On the days of study visits, the dose of the study treatment should be withheld until all assessments have been performed. Study treatment will then be administered from the newly dispensed batch.

If a dose is missed, it should not be taken as compensation the following day, but instead the subject should continue with the regular dosing. The interruption should be noted in the eCRF.

For this study, any dose of study treatment higher than the planned total daily dose in a single day will be considered an overdose [see Sections 9.1 and 9.6].

In the event of an overdose, standard supportive measures must be taken, as required.

Table 1 Dosing scheme

Treatment period	Duration	Study treatment	Dose regimen
Screening	Day −30 to Day −1	NA	NA
Treatment	Day 1 to Day 364/EOT	Placebo or macitentan	10 mg o.d.
Safety follow-up	30 days after EOT	NA	NA
PTOP*	Immediately after Safety follow-up	NA	NA

* PTOP is only entered if subject prematurely and permanently discontinues treatment with macitentan. Any treatment initiated during the PTOP is captured in the concomitant medications page in the eCRF.
eCRF = electronic Case Report Form; EOT = End-of-Treatment; NA = not applicable; o.d. = once daily; PTOP = post-treatment observation period.

5.1.4 Treatment assignment

After having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the interactive response technology (IRT) system at Visit 2 to randomize the subject. The IRT assigns a randomization number to the subject and assigns the treatment kit number, which matches the treatment arm assigned by the randomization list to the randomization number.

Subjects are assigned to the two treatment arms in a 1:1 ratio based on a permutated-block randomization stratified by the geographical region (America, Europe, Asia, Oceania) in order to balance treatment arms throughout the conduct of the trial.

The randomization list is generated by an independent Contract Research Organization (CRO), Almac Clinical Technologies, using SAS® v9.3.

5.1.5 Blinding

This study will be performed in a double-blind fashion. The investigator and study personnel, the subjects, the clinical research associates (CRAs), Actelion personnel, and

CRO personnel involved in the conduct of the study will remain blinded to the study treatment until study completion [see Section 8.1]. Actelion personnel responsible for clinical study supply distribution will need to be unblinded to ensure adequate supply of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file and they will not take part in any clinical trial team (CTT) meetings after study set-up has been completed.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential and accessible only to authorized persons, e.g., Global Quality Management (GQM), and the ISAC/SSG, who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.

5.1.6 Unblinding

5.1.6.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure, in accordance with Actelion Quality System (QS) documents.

5.1.6.2 Unblinding for IDMC

The ISAC/SSG not otherwise involved in the design, conduct and analysis of the study, will have access to the randomization code in order to prepare unblinded reports and IA results for review by the IDMC, as described in the IDMC charter. The randomization code will be made available only to the ISAC/SSG in accordance with Actelion's quality documents.

5.1.6.3 Unblinding for suspected unexpected serious adverse reactions

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, the sponsor will request the unblinding of the treatment assignment. The treatment assignment will not be communicated to site personnel or to the Actelion personnel. Unblinded SUSAR information will be provided to respective health authorities and independent ethics committees (IECs) or institutional review boards (IRBs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.4 Emergency procedure for unblinding

The investigator, study personnel and Actelion personnel must remain blinded to the subject's treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded treatment assignment through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible, and if it does not

interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended unblinding with Actelion personnel.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. In all cases, Actelion personnel must be informed as soon as possible before or after the unblinding.

A subject may stay on study treatment after unblinding provided the following conditions are met:

- The treating physician believes that the benefit/risk balance remains favorable.
- Unblinding was not due to an intentional overdose of study drug.

Unblinding will not be allowed for the sole purpose of entering the AC-055H302 OL extension.

The circumstances leading to unblinding must be documented in the Investigator Site File (ISF) and eCRF.

5.1.7 Study treatment supply

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

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

5.1.7.1 Study treatment packaging and labeling

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

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located. Each medication bottle has a booklet affixed, detailing all relevant information. The booklet contains a tear-off part specifying the study protocol number, the packaging batch number and the bottle number. When the study treatment is given 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.

5.1.7.2 Study treatment distribution and storage

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

5.1.7.2.1 Study treatment distribution

The study centers will be supplied with study treatment according to the centers' needs, depending on the rate of subject enrollment. Each center will have an individual stock of study treatment, which will be re-supplied continuously as soon as a predefined minimum level of study treatment has been reached.

5.1.7.2.2 Study treatment storage

Study treatment must be kept in a locked room or a locked cupboard in a restricted access room, which can be accessed only by the pharmacist, the investigator, or another duly designated person as specified on the delegation of authority form.

The subject must be educated on the proper study treatment storage conditions at home.

Bottles containing study treatment tablets must be stored according to conditions specified on the label. Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study treatment handling and storage.

5.1.7.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used and unused study treatment (including empty bottles) at each visit. The protocol-mandated study-treatment dispensing procedures may not be altered without prior written approval from Actelion. An accurate record of the date and amount of study treatment dispensed/returned to/by each subject must be available for inspection at any time.

Once a subject has been enrolled and study treatment assigned, the corresponding bottles/packs must not be used for another subject. If a subject has been dispensed a bottle/pack in error (one that has not been allocated yet to another subject), the IRT system helpdesk must immediately be contacted.

At the time study treatment is dispensed, the subject should be educated on the proper storage conditions at home [see Section 5.1.7.2.2].

5.1.7.4 Study treatment return and destruction

The protocol-mandated study treatment return procedures may not be altered without prior written approval from Actelion. On an ongoing basis (if required) or on termination of the study at site level, the CRA will collect used and unused treatment kits, which will be sent to the warehouse, where Actelion personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by Actelion personnel or the deputy, and written permission for destruction has been obtained from Actelion.

In case study treatment cannot be reconciled by the CRA before destruction, a note to file is written by the study team.

5.1.8 Study treatment accountability and compliance with study treatment

5.1.8.1 Study treatment accountability

The inventory of study treatment dispensed to and returned by the subject (i.e., study-treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. It is to be recorded by site personnel on the Study-Treatment Accountability and Compliance Log and in the eCRF and checked by the CRA during the monitoring visits and once each individual subject has terminated the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit (i.e., bottle) dispensed to the subject:

- Allocated bottle number (pre-populated in the eCRF)
- Dispensed bottles number
- Date dispensed / number of tablets dispensed
- Date returned / number of tablets returned

All study treatment supplies, including unused, partially used, or empty bottles must be retained at the site for review by the CRA.

If the subject forgets to bring the remaining study treatment to a study visit, he/she must be instructed to not take any tablets from the remaining study treatment bottle and to return it at the next visit.

5.1.8.2 Study treatment compliance

Study treatment compliance must be evaluated by the site staff prior to each new dispensation. It is based on study treatment accountability. Study treatment compliance will be calculated by site personnel at each visit when the IMP is returned and new IMP dispensed, using the below formula, and entered in the eCRF:

Compliance = [(number of tablets dispensed – number of tablets returned) / Total number of tablets that should have been taken since the last visit[*]] × 100.

[*] The number of tablets that should have been taken since the last visit is derived from the number of planned treatment days between the previous visit and the day before the current visit. It is defined as current visit date – previous visit date.

Between visits, compliance is expected to be between 80% and 120%. Compliance values outside of this range will be considered as a protocol deviation, which will be reported in the eCRF by the CRA. Permanent discontinuation of study treatment may be considered after consultation with Actelion.

5.1.9 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted.

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.11.

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

Interruptions of study treatment must be kept as short as possible. If treatment is stopped for more than 4 consecutive weeks, re-introduction is not permitted, and treatment must be permanently discontinued [see Section 5.1.10].

Study treatment interruptions as well as reasons for interruptions must be recorded in the eCRF.

5.1.10 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Actelion personnel. The main reason and whether discontinuation of study treatment is the decision of the subject (e.g., AE or lack of efficacy), the investigator (e.g., due to pre-specified study treatment discontinuation criteria, an AE or lack of efficacy), or Actelion (e.g., study termination) must be documented in the eCRF.

A subject has the right to prematurely discontinue study treatment at any time, without any justification, by withdrawal from study treatment only, or by withdrawal from any further participation in the study, including the VSFU (i.e., premature withdrawal from the study [see Section 8.2]). Although a subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continued administration would be contrary to the best interests of the subject.

Study-specific criteria for discontinuation of study treatment are described in Section 5.1.11.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until at least the S-FU visit and, if applicable, during the PTOP until Week 52, as well as for collection of vital status at SCL, provided that the subject's consent for this limited participation in the study has not been withdrawn.

The subject will be asked to return for an EOT visit within 7 days of last intake of study treatment and assessed for a S-FU visit 30 days after the last intake of study treatment. If

the subject enters the PTOP, the subject will be called on the telephone for follow-up visits as described in Table 3. The assessments that are performed at each visit are described in Table 3 [see Section 7.1]. Importantly, if discontinuation occurs prior to the Week 16 CPET assessment for the primary endpoint, it is requested that the subject returns to the site at Week 16 for a CPET evaluation.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 8.2 and 8.4, respectively.

5.1.11 Study-specific criteria for interruption / premature discontinuation of study treatment

Study treatment interruptions exceeding 4 consecutive weeks must lead to permanent discontinuation of study treatment.

5.1.11.1 Pregnancy

If a female subject becomes pregnant while on study treatment, study treatment must be interrupted immediately, and a Pregnancy Notification Form must be completed [see Section 9.3.1].

5.1.11.2 Liver aminotransferase abnormalities

Interruption of study treatment
Study treatment must be interrupted in the following cases:

- Aminotransferases (i.e., ALT and/or AST) ≥ 3 and < 8 × upper limit of normal (ULN)

A re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase (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, re-introduction of study treatment can be considered.

Re-introduction of study treatment after treatment interruption should only be considered if the potential benefits of study treatment 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 re-introduction, then again after a further 2 weeks and thereafter according to the recommendations above (e.g., at monthly intervals).

Permanent discontinuation of study treatment

Study treatment must be stopped, and its re-introduction is not to be considered in the following cases:

- Aminotransferases (ALT and/or AST) ≥ 8 × ULN
- Aminotransferases (ALT and/or AST) ≥ 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 (ALT and/or AST) ≥ 3 × ULN and associated increase in total bilirubin ≥ 2 × ULN

A re-test of aminotransferases (ALT and AST), total and direct bilirubin, and AP must be performed. Aminotransferases, total and direct bilirubin, and AP levels must be monitored weekly after study treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Other diagnoses (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus, alcoholic hepatitis, non-alcoholic steatohepatitis, autoimmune disease) and/or etiologies (e.g., hepatic toxicity of concomitant medication[s] or other substances) should be considered and ruled out by performing the appropriate tests.

All liver aminotransferases abnormalities leading to study treatment interruption or discontinuation must be recorded as AEs [see Section 9].

To ensure the proper and comprehensive evaluation of cases of ALT and/or AST increase > 3 × ULN, additional subject data may be collected in the hepatic event questionnaire distributed by the sponsor.

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

5.1.11.3 Hemoglobin abnormalities

If there is a case of hemoglobin < 100 g/L accompanied by a change from baseline[4] of ≥ 50 g/L during the treatment period (up to and including Visit 7), or a blood transfusion, a re-test must be performed within 10 days of the initial test showing the decrease, with additional laboratory evaluations that may include, but are not limited to, any of the following:

[4] Baseline hemoglobin refers to the last hemoglobin value obtained prior to first intake of study treatment.

- 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.

Study treatment must be temporarily interrupted if clinically mandated based on the investigator's judgment.

Any hemoglobin decrease equivalent to CTCAE version 4.03 grade 3 or higher (i.e., hemoglobin < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L) should result in interruption of study medication, unless an underlying blood loss event caused this decrease.

Re-introduction of study treatment may be considered by the investigator if hemoglobin recovery, defined as a return of hemoglobin above the lower limit of the normal range or to baseline, is achieved.

5.1.11.4 Drop in BP

BP is measured at each visit and at regular intervals during the conduct of CPET. Study treatment must be temporarily interrupted if systolic BP drops to < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height).

Re-introduction of study treatment after treatment interruption should only be considered if the potential benefits of study treatment outweigh the potential risks and when BP values are within pre-treatment levels or within normal ranges.

BP must then be checked within 3 days after re-introduction, then again after a further 2 weeks and thereafter according to the recommendations of the treating physician. These checks need not occur at the study site and results may be communicated to the site via phone.

5.1.11.5 Initiation of forbidden medication

Study treatment must be permanently discontinued if any forbidden medications are started during the treatment period.

However, if subjects are currently stable on a moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine), the subject may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment. However, the subject will not be eligible to enter the OL study unless the forbidden medication is discontinued 1 month prior to OL enrollment.

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to signing of informed consent.

A therapy that is study-concomitant is any treatment that is ongoing or initiated after signing of informed consent.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period.

5.2.2 Reporting of previous/concomitant therapy / auxiliary medicinal products in the eCRF

The use of all study-concomitant therapy (including contraceptives and traditional and alternative medicines, e.g., plant-, animal- or mineral-based medicines) will be recorded in the eCRF. Previous therapy must be recorded in the eCRF if discontinued less than 30 days prior to signing of the informed consent. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, frequency, and indication will be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

Allowed therapy consists of agents typically prescribed to manage conditions associated with Fontan palliation.

- Antiplatelet agents
- Anticoagulants (Vitamin K antagonist, new oral anticoagulants [oral non-vitamin K antagonist anticoagulants]), etc.)
- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Oral diuretics
- Antiarrhythmics
- Beta blockers
- PH-specific drugs except ERAs

5.2.4 Forbidden concomitant therapy

Forbidden therapy includes agents interfering with CPET, influencing drug exposure and/or affecting the primary endpoint.

- Therapies interfering with the CPET evaluation
  - Pacemakers
  - Nitrates

- Vasodilators
  - Alpha-blockers
  - ERAs other than macitentan
- CYP3A4 and drug-drug-interaction
  - Strong inducers of CYP3A4 (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort)
  - Strong inhibitors of CYP3A4 (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*. For other examples of CYP inhibitors, refer to the Food and Drug Administration website [FDA 2020].
- Iron supplementation, regardless of the route of administration, unless already present at stable dose for more than 3 months prior to Screening
- Any investigational therapy.

* If subjects are currently stable on a moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g. miconazole, piperine), the subject may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment. However, the subject will not be eligible to enter the OL study unless the forbidden medication is discontinued 1 month prior to OL enrollment.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the change in peak VO_2, from Baseline (Randomization/Visit 2) to Week 16 (Visit 4).

6.1.2 Secondary efficacy endpoints

- Change from Baseline (Visit 2) over 52 weeks in peak VO_2.
- Change from Baseline (Visit 2) to Week 16 (Visit 4) in mean count per minute of daily PA-Ac.

6.1.3 Other efficacy endpoints

- Endpoints related to exercise capacity from Baseline (Visit 2) to Week 16 (Visit 4), and Week 52 (Visit 6):

  - Change in peak VO_2 (other than to Week 16 [Visit 4])
  - Change in ventilatory efficiency (assessed as minute ventilation [VE] / carbon dioxide production [VCO_2] slope)
  - Change in VO_2 at ventilatory anaerobic threshold (VAT)
  - Change in oxygen uptake efficiency slope (OUES)
- Percent of Baseline (Visit 2) at Week 16 (Visit 4) in NT-proBNP.
- Percent of Baseline (Visit 2) in NT-proBNP over 52 weeks.
- Composite endpoint of event related to Fontan-palliated clinical worsening, time from Randomization (Visit 2) to first occurrence up to EOS of one or more of the following:
  - Unscheduled hospitalization for Fontan-palliated morbidity event[5]
  - Signs and symptoms of HF[6], requiring change in diuretic therapy
  - Clinical worsening leading to interventions related to the Fontan-palliated condition
  - Worsening to NYHA FC III, investigator assessed using the Specific Activity Scale [Appendix 4].
  - Signs and symptoms requiring the addition of a new class of cardiovascular medication (e.g., nitrates, alpha-blockers, or ERAs), or insertion of a pacemaker.
  - Failing-Fontan defined as one or more of the following:
    - Enlisted on the active list for heart transplantation or effective heart transplantation
    - Reoperation (e.g., mechanical circulatory support, Fontan take down, Fontan revision / conversion, AV valve repair/replacement)
    - Worsening to NYHA FC IV, investigator assessed using the Specific Activity Scale [Appendix 4].
    - PLE
    - Plastic bronchitis/chyloptysis
    - Peritoneal, pleural, mediastinal, or pericardial effusions
    - Severe hepatic impairment (as described in exclusion criterion 6.3)
    - Severe renal impairment (as described in exclusion criterion 6.5)
    - Death related to Failing-Fontan
- Events related to Fontan-palliated morbidity, time from Randomization (Visit 2) to first occurrence up to EOS of one or more of the following:

[5] Only applicable as an event if hospitalization / intervention was unscheduled/not related to routine Fontan related follow-up, and hospital stay was (≥ 24 hours).

[6] Note: Include orthopnea, nocturnal dyspnea, pulmonary edema, or radiological signs. Persistent congestion with edema only qualifies as a sign of heart failure if the peripheral edema is moderate-to-severe despite optimal diuretic therapy.

- Ventricular tachyarrhythmia or supraventricular tachyarrhythmia[7]
- Thrombotic or hemorrhagic complications (including thromboembolism and hemoptysis)

- Change from Baseline (Visit 2) to Week 16 (Visit 4) in daily mean time in minutes spent in sedentary, light, moderate, or vigorous PA-Ac.
- Change from Baseline (Visit 2) over 52 weeks in mean count per minute of daily PA-Ac.
- Change from Baseline (Visit 2) over 52 weeks in daily mean time in minutes spent in sedentary, light, moderate, or vigorous PA-Ac.

6.2 Safety endpoints

- Treatment-emergent AEs[8] and serious AEs (SAEs) up to 30 days after study treatment discontinuation, or until initiation of study drug in the AC-055H302 OL extension study, whichever occurs first.
- AEs leading to premature discontinuation of study treatment.
- Change in vital signs (systolic and diastolic arterial BP and pulse rate), including SpO_2 and body weight from Baseline (Visit 2) to all assessed time points during the study.
- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation, or until initiation of study drug in the AC-055H302 OL extension study, whichever occurs first.
- Change in laboratory parameters from Baseline (Visit 2) to all assessed time points during the study.

6.3 Quality of life endpoints

- Patient Global Assessment of Disease Severity (PGA-S) and Clinician Global Impression of Severity (CGI-S) at Baseline (Visit 2), Week 16 (Visit 4), and Week 52 (Visit 6).
- Patient Global Impression of Change (PGI-C) and Clinician Global Impression of Change (CGI-C) questionnaire at Week 16 (Visit 4) and Week 52 (Visit 6).
- Proportion of subjects in each level of each dimension of the Euro QoL 5D (EQ-5D-5L) questionnaire at Baseline (Visit 2), Week 16 (Visit 4), and Week 52 (Visit 6).
- Self-rated health status assessed by the EQ-5D Visual Analogue Scale (VAS) at Baseline (Visit 2), Week 16 (Visit 4), and Week 52 (Visit 6).

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[7] Arrhythmia qualifies as an event only if it requires hospitalization, cardioversion, addition/increase in antiarrhythmic treatment, or invasive tests or treatment.

[8] A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment start until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

6.4 Pharmacoeconomic endpoints

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

6.5 Pharmacokinetic endpoints

Trough (pre-dose) plasma concentrations of macitentan and its metabolite ACT-132577, at Week 4 (during the regular corresponding monthly blood draw) and Week 16 (Visit 4), or at EOT in the case of premature study drug discontinuation prior to Week 16.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 General information

The study visits are listed in Table 2 (and Table 3 for PTOP). For all visits, the subjects must be seen on the designated (calendar) day with an allowed visit window of ± 7 days. A visit may occur over more than one day. A follow-up safety visit (S-FU) must be performed at earliest 30 days, but not later than 35 days, after intake of the last dose of study treatment.

The assessments pertaining to a visit may be performed within the allowed time window.

In addition, unscheduled visits can occur at any time [Section 7.1.2].

In case of premature discontinuation of study treatment, the EOT visit must take place as soon as possible and no later than 7 days after the last dose of study treatment. Subjects who prematurely discontinue study treatment for any reason will not be replaced.

7.1.1 Screening/re-screening

Screening starts with the signature of the informed consent. The date on which the first screening assessment is performed corresponds to the date of the Screening visit.

It is the responsibility of the investigator/delegate to obtain written informed consent from each subject participating in this study after adequate face-to-face explanation of the objectives, methods, and potential hazards of the study. The subjects (and if applicable their legal representative) who agree to participate in the study and the investigator/delegate must sign the ICF (and if applicable assent form) prior to any study-related assessment or procedure.

Subjects who have signed informed consent and are in screening when the enrollment target has been met may still be randomized if they meet all the selection criteria.

It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication). In this case, re-consent is required if the initial consent signature is more than 30 days old or if a new informed consent version is available.

All screening assessments should be repeated at the time of re-screening. The PA-Ac is mandatory at re-screening.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator, and the results will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

Table 2 Visit and assessment schedule

PERIODS	Name	SCREENING	TREATMENT						FOLLOW-UP	
	Duration	30 days	52 Weeks						30 days	
VISITS[11]	Number	1	2	3	4	5	6	*U1, U2, …*	7	8
	Name	Screening	Randomization	Week 8 ☎	Week 16	Week 32 ☎	Week 52 / EOT	*Unscheduled visit*[5]	Safety FU[1] (S-FU) ☎	Vital Status FU (VSFU)[14] ☎
	Time	Within 30 days of Day 1	Day 1 (≥ 9 days after Screening)	Day 57 (± 7 days)	Day 113 (± 7 days)	Day 225 (± 7 days)	Day 365 (± 7 days) or within 7 days after premature discontinuation	*Any day between Day 1 and end of S-FU*	30-35 days after EOT	Within 8 weeks of sponsor's announced Study Closure
Informed consent		X								
Medical history		X								
Disease severity diagnosis[3]		X								
Concomitant therapy		X	X	X	X	X	X	*X*	X	
Physical examination		X	X[8]		X[8]		X	*X*		
Vital signs (BP, HR, weight, height, SpO_2)		X	X		X		X	*X*		
NYHA FC (using Specific Activity Scale)		X	X	X	X	X	X	*X*	X	
Echocardiography		X					X	*X*		
12-lead ECG[6]		X						*X*		
Laboratory tests*[7]		X	X	X[7]	X	X[7]	X	*X*	X[7]	
NT-proBNP			X		X		X	*X*		

Pregnancy test. contraception & reassessment of childbearing potential[9]	X	Monthly (28 ± 7 days)					*X*	X	
CPET (incl. ECG, spirometry)	X[13]	X		X		X	*X*		
Physical Activity measured by Accelerometer (PA-Ac)[12]	X			X		X			
PK sampling[10]				X		X[10]			
PGA-S/CGI-S		X		X		X	*X*		
PGI-C/CGI-C				X		X	*X*		
EQ-5D-5L questionnaire		X		X		X	*X*		
Study treatment dispensing/return[2]	–	X		X		X	*X*	–	
Worsening/morbidity event assessment	X	X	X	X	X	X	*X*	X	
SAEs/AEs[4]	X	X	X	X	X	X	*X*	X	
Vital Status									X

*Transferred electronically by an external service provider.

[1] Visit may be performed by telephone, as long as laboratory assessments are done with central lab kits.
[2] Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
[3] Disease severity diagnosis is based on exclusion criteria 1–2.
[4] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation, or until initiation of study drug in the OL study, whichever occurs first, must be reported.
[5] Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, based on the judgment of the investigator.
[6] ECG will be collected as part of CPET assessments except at Screening.
[7] Laboratory assessments **at Visit 1, 2, 4, and 6 are full panels**, while they are done for **aminotransferases and hemoglobin monthly (28 ± 7 days) until Week 24**. Subsequently, **aminotransferases and hemoglobin are done at Week 32, Week 40, Week 52, and at S-FU**. **Additional liver tests may be performed as clinically indicated, and as recommended per local label**.
[8] Physical examination is tailored to organs that are prompted by *ad hoc* anamnesis or are needed to be assessed to detect morbidity events (e.g., edema).
[9] Serum pregnancy test at Screening and monthly (28 ± 7 days) urine pregnancy tests afterwards. If urine tests are done at site, subjects will be re-assessed for contraceptive measures and childbearing potential (otherwise this is done at the next site visit). Results are checked via telephone calls from the site.
[10] PK sample **taken at Week 4 at the same time as regular monthly blood draw**; Sample at EOT is only taken if EOT is prior to Week 16.

[11] A visit may occur over more than one day.
[12] Daily PA-Ac will be collected during the screening period to establish the baseline in the 9 days following the visit. For subsequent visits (Week 16), data collection will start (following CPET) within the allowed time window of the corresponding visit and finish 9 days later. For Visit 6 (Week 52), data collection will be during the 9 days preceding the visit.
[13] A CPET test for training purposes is conducted during Screening. Results are collected in the eCRF.
[14] The VSFU does NOT need to be conducted if the subject's individual EOS was not more than 4 weeks prior to the sponsor's announcement of the Study Closure.
AE = adverse event; BP = blood pressure; CGI-C = Clinician Global Impression of Change; CGI-S = Clinician Global Impression of Severity; CPET = cardiopulmonary exercise testing; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End-of-Study; EOT = End-of-Treatment; EQ-5D-5L = Euro QoL 5D; FC = functional class; HR = heart rate; NYHA = New York Heart Association; OL = open-label; PA-Ac = Physical Activity measured by Accelerometer; PGI-C = Patient Global Impression of Change; PGA-S = Patient Global Assessment of Disease Severity; PK = pharmacokinetic; SAE = serious adverse event; S-FU = safety follow-up; SpO_2 = peripheral oxygen saturation, VSFU = Vital Status Follow-Up; ☎ = Telephone call (for visit).

Table 3 Visit and assessment schedule in PTOP

PERIODS	Name	POST-TREATMENT OBSERVATION PERIOD				FOLLOW-UP
VISITS	Number	P1, P2, …	16 P	*UP1, UP2, …*	EOP	8
	Name	Telephone call ☎	Week 16 P	*Unscheduled visit*	End-of-PTOP[5]	Vital Status FU (VSFU)[4] ☎
	Time	Every 90 (± 7 days) days after end of S-FU period	Day 113 (± 7 days)	*Any time*	Week 52	Within 8 weeks of sponsor's announced Study Closure
Concomitant therapy[1]		X	X	*X*		
CPET[2]			X	*X*		
EQ-5D-5L questionnaire[3]		X	X	*X*	X	
Worsening/morbidity event assessment		X	X	*X*		
Serious adverse events		X	X	*X*	X	
Vital Status						X

[1] Change in dose will not be collected.
[2] CPET during the PTOP is at the discretion of the treating physician but requested at Week 16 if not performed already during the treatment period.
[3] To administer the EQ-5D over the phone, use designated scripts.
[4] The VSFU does NOT need to be conducted if the subject's individual EOS was not more than 4 weeks prior to the sponsor announcement of the Study Closure.
[5] The EOP visit could be done as a telephone call unless the subject plans to enroll in the AC-055H302 OL.

CPET = cardiopulmonary exercise testing; EOP = End-of-PTOP; EOS = End-of-Study; EQ-5D-5L = Euro QoL 5D; PTOP = post-treatment observation period; S-FU = safety follow-up, VSFU = Vital Status Follow-Up; ☎= Telephone call (for visit).

7.2 Study assessments

The study assessments are listed in Table 2. The assessments that are mandatory during a visit are marked with an 'X'. Optional assessments (during unscheduled visits) are marked with an '*X*'.

An evaluation of how these assessments relate to standard of care is found in Appendix 6.

All study assessments are performed by qualified study personnel (medical, nursing, or specialist technical personnel) and are recorded in the eCRF, unless otherwise specified. If an assessment does not produce evaluable results, the treating physician may decide to repeat the assessment during the study visit, or at an unscheduled visit. Study assessments performed during unscheduled visits will also be recorded in the eCRF. When applicable, the following order of assessments is recommended:

1. Quality of life questionnaires (CGI-C, CGI-S, EQ-5D-5L, PGI-C, PGA-S)
2. Physical examination, vital signs and echocardiography
3. Electrocardiogram (ECG) / CPET
4. Blood sampling (including PK), pregnancy test.

If the principal investigator (PI) delegates any study procedure/assessment for a subject, e.g., CPET, echocardiography, blood sampling [see Section 7.2.4.1], to an external facility, he/she should inform Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. The supervision of any external facilities remains the responsibility of the PI.

Any incidental finding of an abnormality discovered by this external facility must be shared with the PI who is responsible for reporting the event (e.g., AE) in the eCRF as appropriate. Clinically relevant incidental findings will be followed up per local medical practice.

Calibration certificates / evidence of equipment maintenance or calibration for the below-listed equipment used to perform study assessments must be available prior to the screening of the first subject.

- Temperature measurement devices for study treatment storage area and freezer.
- CPET equipment (metabolic cart including ECG device, ergometer).

Evidence of equipment calibration must be present in the ISF.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected on all randomized subjects include: age, sex, race and ethnicity[12], body weight, height, NYHA FC (assessed using the Specific Activity Scale), as well as the reason why a woman is not considered to be of childbearing potential (if applicable). Relevant medical history / current medical conditions based on investigator's judgment (e.g., chronic and ongoing acute conditions, serious past conditions) present before and/or at the time of signing informed consent will be recorded on the medical history page. These include the original congenital heart defect leading to Fontan-palliation, concomitant procedures (e.g., Norwood, Glenn, fenestration), type of current TCPC (LT- or EC-TCPC), and whether TCPC is primary or secondary (conversion from another Fontan-palliated type), in addition to the date of Fontan surgery completion. Where possible, diagnoses and not symptoms will be recorded.

For subjects who failed screening, the following data will be recorded in the eCRF if available:

- Age, sex, race and ethnicity[14]
- Reason for screen failure;
  - subject not eligible as per inclusion/exclusion criteria,
  - subject withdrew consent,
  - other (specify), e.g., concomitant medication related to inclusion/exclusion criteria.

7.2.2 Efficacy assessments

7.2.2.1 Cardiopulmonary exercise testing

CPET will be conducted at study sites for Visits 1 (training CPET during Screening), 2 (Randomization), 4 (Week 16), and 6 (Week 52).

Furthermore, if a subject discontinues treatment prematurely, a CPET will be conducted within 7 days of EOT. If treatment is discontinued prior to Visit 4 (Week 16), and the subject enters the PTOP, it is requested that the subject returns for a CPET assessment at Week 16.

A CPET test will be conducted during the screening period. Results of the training CPET are captured in the eCRF.

Detailed guidelines on correct execution of the test, the Actelion CPET guidelines, are provided in Appendix 3. Additional information is provided in the central reading facility's

[12] For countries that do not allow the collection of race/ethnicity, ensure that 1) the ICF makes the collection of race possible in these countries; or 2) race/ethnicity will be collected in the eCRF only where it is allowed.

manual. Site staff conducting the tests must be trained on these CPET guidelines and a training log must be collected upon completion of the training. For each individual subject, the CPET should be conducted under the **same conditions throughout the study** (e.g., same device, about the same time of the day, etc.).

Variables that are assessed include VO_2, VCO_2, heart rate (HR), and VE.

Basic spirometry to determine breathing reserve will also be part of the CPET procedure. Spirometry testing will be performed according to recommendations from the American Thoracic Society / European Respiratory Society guidelines [Miller 2005a, Miller 2005b].

Breathing reserve (BR) is calculated from estimating maximal voluntary ventilation (MVV) by assessing the forced expiratory volume in one second (FEV1) × 40, as well as the peak VE using the following formula.

BR% = ([MVV - VE]/MVV) × 100

Peak VO_2 (highest volume of oxygen taken up per kg and minute) is assessed during CPET via metabolic cart (breath-by-breath analysis) and calculated as the highest value reached over a 30-second interval [Guazzi 2012, Guazzi 2016a, Guazzi 2016b].

The % predicted value for peak VO_2 is calculated according to the Wasserman-Hansen equations [Wasserman 2005, Guazzi 2012], using age, height, and weight at the time of the test.

The respiratory exchange ratio (RER) defined as VCO_2/VO_2 is an indication of good exercise effort and achieving a value of 1.1 is expected for validating the primary endpoint and reaching exhaustion.

Ventilatory efficiency is defined as VE/VCO_2 slope (from the beginning of exercise to maximal effort), and oxygen pulse, a surrogate of stroke volume, as VO_2/HR.

VO_2 at VAT is determined using the modified V-slope method. The OUES is derived from the relationship between VO_2 and the log transformation of VE [Guazzi 2016a].

Validity of CPET will be confirmed by the site staff in the eCRF and the raw data will be made available to the central reading facility. Re-evaluation of the results based on raw data will be done in a blinded fashion. Data is then provided to Actelion.

Inclusion will be based on CPET data collected at Baseline and on interpretation of peak VO_2, RER and BR by the CPET site staff. These values will be captured in the eCRF. Furthermore, the baseline resting VO_2 will be captured in the eCRF.

Any incidental finding of an abnormality discovered by this external facility must be shared with the PI who is responsible for reporting the event (e.g., AE) in the eCRF as appropriate. Clinically relevant incidental findings will be followed up per local medical practice.

7.2.2.2 PA-Ac

The daily physical activity (counts/min) of the subject is assessed via accelerometer during daytime. The accelerometer is given to the subject at Visit 1 (Screening visit), and data is collected for 9 consecutive daily daytime periods after Visit 1, Visit 4 (Week 16), and before Visit 6 (Week 52). To establish a sufficient baseline, Visit 2 will have to occur ≥ 9 days after Visit 1. The duration of physical activity data collection will allow including data during week days and weekend days and will provide a reliable estimate of the usual physical activity of the subject. Only data collected during these 9-day periods will be used for the analysis of physical activity.

The investigator (or delegate) instructs subjects on how and when to wear the accelerometer (refer to the RUBATO Accelerometry Manual). The accelerometer is worn during waking hours of the subject and may be worn during activities when the device could get wet (except swimming). Subjects will receive a reminder from the site staff (e.g., telephone call, text message) to ensure that they are wearing the accelerometer during these periods. The accelerometers are pre-programmed to minimize patient handling and do not display the collected data. The subjects return the device to the study site and the investigator (or delegate) transfers the data to the accelerometry central reading facility as described in the RUBATO Accelerometry Manual.

The central reading facility will read daily counts/min and will analyze duration of daily activity and time (minutes) spent in sedentary, light, moderate, and vigorous physical activity based on the [Freedson 1998] and [Evenson 2008] cut-points for adults and adolescents, respectively. These data will be transferred to Actelion.

To be considered evaluable, physical activity should be measured for at least 4 complete daily daytime periods (out of 9 consecutive days) at a specific time point of assessment. A complete day is defined as a record of at least 7 hours of daily data (after excluding the periods when the device was apparently not worn [Troiano 2008]).

Accelerometer devices will be provided to the investigational site before the start of the study.

7.2.2.3 NT-proBNP measurement

NT-proBNP is measured at Visits 2 (Randomization), 4 (Week 16), and 6 (Week 52), according to central laboratory working procedures. The results will be disclosed after database lock and unblinding.

7.2.2.4 Composite endpoint of time to clinical worsening

Occurrence of a component of the time to clinical worsening endpoint is captured by the investigator via AE reporting, anamnesis (change in FC), appearance of laboratory abnormalities, assessment, or concomitant medication (initiation of new treatment).

These could occur at any time, although some parameters are only assessed at site visits [see Table 2].

7.2.3 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs and pregnancies are described in Section 9.

- Treatment-emergent AEs and SAEs up to 30 days after study treatment discontinuation are captured in the eCRF. Details include severity, causality with treatment, action taken with treatment, duration, outcome, need for hospitalization, relatedness of hospitalization due to Fontan-circulation problems, and duration of hospitalization.
- AEs leading to premature discontinuation of study treatment are derived from the reported AEs in the eCRF.
- Change in vital signs (systolic and diastolic BP and pulse rate), and body weight from Baseline (Visit 2) to all assessed time points during the study. Vital signs are assessed at each study visit and body weight is assessed during each CPET.
- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation.
- Change in laboratory parameters from Baseline (Visit 2) to all assessed time points during the study. Laboratory data will be provided via the central laboratory; the details on alert flags and normal ranges can be found in Appendix 1.

7.2.3.1 Physical examination

Physical examination at screening includes the examination of the general appearance, head, ears, eyes, nose, throat, neck, lymph nodes, extremities, neurological system, skin, musculoskeletal system, gastro-intestinal, heart and lungs. At subsequent visits, physical examination is tailored to organs that are prompted by *ad hoc* anamnesis or are needed to be assessed to detect morbidity events (e.g., edema).

Information from all physical examinations must be included in the source documentation at the study site. The observations should be reported according to body system in the eCRF as either normal or abnormal. If an abnormality is found it should be specified on the corresponding eCRF page, describing the signs related to the abnormality (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency). Clinically relevant findings (other than those related to Fontan circulation) that are present prior to signing of informed consent must be recorded on the Medical History eCRF page. Physical

examination findings made after signing of informed consent, which meet the definition of an AE [Section 9.1.1], must be recorded on the AE page of the eCRF.

7.2.3.2 Vital signs

Vital signs (BP, pulse rate) will be measured at all scheduled visits except S-FU.

Systolic and diastolic BP and radial pulse measurements will be measured in a supine or sitting position. It is recommended to allow the subject to rest for at least 5 minutes. The same position (supine or sitting) and same location (left/right arm) must be used throughout the study for an individual subject.

In addition, SpO_2 will be measured (by pulse oximeter) at all scheduled visits.

For each individual subject, the same device should be used throughout the study.

When applicable, vital signs are recommended to be measured before the CPET.

7.2.3.3 Weight and height

Height and body weight will be measured at all scheduled visits except S-FU. These are captured in the eCRF. Body weight will be measured in indoor clothing but without shoes. For each individual subject, the same device should be used throughout the study.

7.2.3.4 ECG assessment

ECG is assessed at Screening (Visit 1) and abnormalities (assessed by a cardiologist), if any, are reported as part of medical history in the eCRF.

Subsequently, ECG is assessed as part of CPET, and data are evaluated at site. ECG data will not be transmitted to the central reading facility apart from pre-exercise rhythm and HR for evaluation of CPET.

7.2.3.5 Echocardiography

Standard 2D/Doppler trans-thoracic echocardiography (ECHOC) is performed at Screening to determine the subject's eligibility and at EOT. The ECHOC will be read locally at the investigational site.

The measures/assessments evaluated by the ECHOC include, but are not limited to: single ventricle ejection fraction, Fontan circulation stenosis, and valvular defects (severe AV valve regurgitation, outflow obstruction).

The ejection fraction measured locally at Screening and at EOT will be recorded in the eCRF. If post-baseline ECHOC is performed according to medical practice or in case of deteriorating patient conditions, the results of the exams should be reported in the eCRF.

Detailed instructions on how to record ECHOC are provided in Appendix 2.

7.2.3.6 VSFU

A VSFU will be performed by the sponsor within 8 weeks after SCL announcement to determine each subject's vital status (alive, dead, or unknown) at this time:

This VSFU will be performed either:

- by the investigational site via a contact with the subject or parents/legal representatives/caregivers (phone call or any other means allowed per local regulations, e.g., access to public registries including the use of locator agencies) during the first 4 weeks following SCL announcement.

Or, if unsuccessful,

- by the investigational site assessing the vital status of the subject by any other means allowed per local regulations, e.g., access to medical registries, public, or governmental registries including the use of locator agencies during the following 4 weeks.

If the subject's individual EOS occurs within 4 weeks of the SCL announcement, VSFU does not need to be performed.

The outcome of the VSFU is reported in the eCRF.

7.2.4 Laboratory assessments

Laboratory tests are conducted at each visit. Full hematology and clinical chemistry panels [see Section 7.2.4.2] are done at Screening, Visits 2 (Randomization), 4 (Week 16), and 6 (Week 52). Laboratory assessments are done for aminotransferases, hemoglobin, and pregnancy monthly (28 ± 7 days) until Week 24. Subsequently, aminotransferases and hemoglobin are done at Week 32, Week 40, Week 52, and at S-FU. Additional liver tests may be performed as clinically indicated, and as recommended per local label. Pregnancy testing continues on a monthly basis.

7.2.4.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for the analysis of all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be automatically transferred from the central laboratory database to Actelion's clinical database.

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

If the results from the central laboratory are not available in time for randomization of the subject, an additional blood sample may be drawn to verify eligibility based on a local laboratory test. The local laboratory results (with the corresponding normal ranges) must be recorded in the eCRF.

A serum pregnancy test (for females of childbearing potential) will be analyzed at Visit 1 (Screening) and complemented with urine pregnancy tests up to 30 days after study drug discontinuation. Any positive urine pregnancy test must be followed up by a serum pregnancy test.

Other exceptional circumstances that will require recording of local laboratory results of the parameters described in Section 7.2.4.2 (with corresponding normal ranges) include hospitalization of the subject due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If two consecutive central laboratory samples are lost or cannot be analyzed for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time-window and these test results are available.

Under specific circumstances (e.g., if the subject lives far from the site and cannot return every month), laboratory samples may be collected at a laboratory close to where the subject lives (satellite laboratory for blood draw) and sent to the central laboratory for analysis. In such a case, the satellite laboratory must be provided with the central laboratory sampling kits. Shipment of the samples will be organized by the satellite laboratory. The supervision of the satellite laboratory remains the responsibility of the PI.

As an alternative option, the laboratory samples may be collected from subjects by a flying nurse service using central laboratory sampling kits.

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

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

- Any local laboratory result related to the diagnostic work-up (i.e., detection, confirmation and/or monitoring) of ALT and/or AST elevations of ≥ 3 × ULN. In such cases, the minimum data to be analyzed and entered in the eCRF are ALT, AST, AP, and total and direct bilirubin.

- Any local laboratory result related to the diagnostic work-up (i.e., detection, confirmation and/or monitoring) of hemoglobin decrease from baseline of ≥ 50 g/L, a value of hemoglobin < 100 g/L, or a hemoglobin decrease requiring transfusion.
- Any local laboratory test documenting the result of an assessment requested per protocol and for which no central laboratory result is available (e.g., in the case that no sample was sent to the central laboratory at a planned visit because the subject was hospitalized at another hospital, or in the case that the sample sent to the central laboratory is uninterpretable [e.g., hemolyzed]).
- Any local laboratory result related to the documentation or follow-up of an AE or an SAE, including clinically significant abnormal laboratory results and their follow-up.

In the event that several local laboratory samples have been collected on the same day, or if the sample was tested several times, the "worst" value (e.g., highest value for ALT/AST) should be reported in the eCRF (together with the local laboratory reference ranges). Central laboratory reports will be sent to the investigator. In case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion personnel and the concerned site personnel. Alert flags that will trigger such notifications are displayed in Appendix 1.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate within 5 working days of receipt and filed with the hospital chart. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of informed consent must be recorded on the Medical History page of the eCRF. Any clinically relevant laboratory abnormalities (including ALT/AST abnormalities ≥3 × ULN) detected after signing of informed consent must be reported as an AE or SAE as appropriate [see Section 9], and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant, except when otherwise specified (e.g., in the case of ALT/AST abnormalities [see Section 5.1.11.2]). Further laboratory analysis should be performed as indicated and according to the judgment of the investigator.

Any pregnancy occurring during the treatment period and up to 30 days after study drug discontinuation must be reported immediately to the sponsor using the Pregnancy Notification Form [see Section 9.3.1].Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.2.4.2 Laboratory tests

Hematology

Serum ferritin will be assessed at Visit 1 (Screening), the subsequent parameters for all regular visits.

- Hemoglobin
- Hematocrit
- Erythrocyte count (reticulocyte count)
- Leukocyte count with differential counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Platelet count

Rules for study treatment interruption in case of hemoglobin abnormalities including assessment of additional parameters are provided in Section 5.1.11.3.

Clinical chemistry

- ALT
- AST
- AP
- Total and direct bilirubin
- Gamma glutamyl transpeptidase
- Creatinine
- Blood urea nitrogen
- Uric acid
- Glucose
- Cholesterol
- Triglycerides
- Sodium, potassium, chloride, calcium
- Serum albumin
- Total protein
- Alpha-fetoprotein
- NT-proBNP*
- Cystatin-C

* Data of the samples from subjects will be provided after database closure.

Rules for study treatment interruption / permanent discontinuation and laboratory re-tests in case of ALT and/or AST elevation are provided in Section 5.1.11.2.

If creatinine clearance is estimated, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Levey 2009] will be used for adults and the Bedside Schwartz equation [Schwartz 2009] for adolescents, for determining glomerular filtration rate (GFR).

Adults:
$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

S_{cr}: serum creatinine in mg/dL
κ is 0.7 for females and 0.9 for males,
α is –0.329 for females and –0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

Adolescents:
GFR (mL/min/1.73m^2) = (0.41 × Height in cm) / Creatinine in mg/dL

Coagulation tests

- Prothrombin time and/or international normalized ratio

Pregnancy test

A serum pregnancy test for women of childbearing potential will be performed at screening, and subsequent monthly tests must be performed. These monthly tests can be done via urine dipstick. If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

During each visit at site, it must be verified whether the methods of contraception used previously are still valid, in accordance with the protocol, and correctly used by the subject. Reassessment of childbearing potential of female subjects is to be done at each study visit. Documentation that the discussion with the subject took place must be available in the subject's source documents.

7.2.5 Quality of life assessments

Quality of life parameters will be assessed for all subjects by 2 sets of QoL questionnaires including the EQ-5D-5L and the patient/clinician assessment of severity and assessment of change (PGA-S, PGI-C and CGI-S, CGI-C, respectively). These will be completed on paper, and site staff will enter the corresponding values in the eCRF.

The PGA-S and PGI-C are completed by subjects, while the CGI-S and CGI-C are completed by clinicians (a physician, either an investigator or sub-investigator). Completion should occur at the beginning of the visit [Appendix 7].

Disease Severity (PGA-S and CGI-S) is assessed at Randomization (Visit 2), Week 16 (Visit 4), and Week 52 (Visit 6), or EOT in case it occurs prior to Week 52.

Impression of Change (PGI-C and CGI-C) is assessed at Week 16 (Visit 4), and Week 52 (Visit 6), or EOT in case it occurs prior to Week 52.

The EQ-5D-5L questionnaires [Appendix 8] are completed by subjects at Randomization (Visit 2), Week 16 (Visit 4), Week 52 (Visit 6), or EOT in case it occurs prior to Week 52. If subjects enter the PTOP, the questionnaire will be also be completed using designated scripts.

Actelion has been granted license agreements for the use of the EQ-5D-5L questionnaires.

7.2.6 Pharmacoeconomic assessments

Pharmacoeconomic parameters will be assessed as described in Section 6.4.

Data elements to be collected on the eCRF include: Hospitalization admission date, discharge date, reason for admission.

7.2.7 Pharmacokinetic and pharmacodynamics assessments

7.2.7.1 Pharmacokinetic assessments

Trough (pre-dose) plasma concentrations of macitentan and its metabolite ACT-132577, are obtained via blood samples taken at Week 4 (during the regular corresponding monthly blood draw) and Week 16 (Visit 4), or at EOT in the case of premature study drug discontinuation prior to Week 16.

Importantly, blood samples must be drawn before the morning dose of study treatment and after BP measurement.

Approximately 2 mL of blood will be collected by direct venipuncture in an antecubital vein in the arm in Monovette tubes (or equivalent) containing K3-ethylenediaminetetraacetic acid. Immediately following collection of the required blood volume, the tubes will be slowly tilted backwards and forwards (no shaking) to bring the anti-coagulant into solution, and immediately cooled on ice. Within 30 minutes of collection, the tubes will be centrifuged at approximately 1500 G for 10 minutes at 2-8° C. When a centrifuge that can be cooled is not available, the blood samples and the bucket of the centrifuge must be cooled on ice prior to centrifugation. The plasma will be transferred into one labeled polypropylene tube avoiding carry-over of erythrocytes. All samples will be stored in an upright position at −20° C (± 4° C).

Note: a short duration of storage at temperatures below −20° C (± 4° C) is acceptable.

The date and the exact actual clock time of collection of the blood sample, time and date of last study treatment intake prior to PK sampling, as well as the time of intake of the next study treatment, will be entered in the eCRF.

Labeling and shipment

Details of the collection and regular shipment of the samples to the central laboratory can be found in the central laboratory manual. The tubes and labels for the samples will be provided to the site by the central laboratory. The labeling will comply with the applicable laws and regulations of the countries in which the study is conducted. The central laboratory will forward the samples to the bioanalytical laboratory or equivalent local option.

Bioanalysis

Data of the samples from subjects will be provided after database closure by the bioanalytical laboratory. No samples should be destroyed until the study report is signed off.

Macitentan and ACT-132577 plasma concentrations will be determined using a validated liquid chromatography coupled to mass spectrometry assay. The foreseen limit of quantitation is 1.00 ng/mL. Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analyzed throughout the study, their measured concentrations will be used to determine between-run and overall precision and accuracy of the analyses.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

A subject who completes the full 52 weeks and the S-FU period is considered to have completed the study as per protocol. This is true regardless of whether the 52 weeks were on treatment or not.

For an individual subject, the study is completed with the EOS, which corresponds to the S-FU visit performed 30–35 days after the EOT visit and the EOP (if applicable).

Note that the S-FU visit may not be needed for subjects who enter the AC-055H302 OL extension at EOT of AC-055H301; these subjects are still considered to have completed the study.

Study completion is reached once all subjects have completed the EOS and is communicated to the sites via the SCL announcement.

The VSFU will be collected in the eCRF and is performed after study completion.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes 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.

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual failed. 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, email 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, document all attempts, and enter the loss of follow-up information into the eCRF. 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. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home, use of locator agencies), 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.

If premature withdrawal occurs for any reason, the reason (if known) for premature withdrawal from the study, along with who made the decision (subject, investigator, or Actelion personnel) must be recorded in the eCRF, if known.

If for whatever reason (except death or loss-to-follow-up) a subject is withdrawn from the study, the investigator should make efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records, but it will not be collected in the eCRF. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

8.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If a study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the IECs/IRBs, 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, as described in Section 8.4. Actelion may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates a study without prior agreement from Actelion, the investigator must promptly inform Actelion personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

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

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

8.4 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations.

Contraceptive measures must continue up to at least 30 days after EOT.

Following completion of the AC-055H301 study, subjects are offered participation in the AC-055H302 OL extension study, if the study is approved at the respective investigational site.

Enrollment into the AC-055H302 OL extension study will depend on whether eligibility criteria for the AC-055H302 OL extension study are met, as well as the investigator's judgment about whether treatment with macitentan could be beneficial. The assessment of the benefit/risk will be performed at subject level, by the investigator.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQC, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The

sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

9.1 Adverse events

9.1.1 Definition of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Exacerbation of a pre-existing disease with the exception of efficacy endpoints and associated symptoms.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the signing of informed consent.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, that was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Hepatic AEs of special interest may be followed up using the hepatic event questionnaire distributed by the sponsor.

Overdose, misuse, abuse of the study treatment and study treatment errors will be reported as an AE [see Section 9.6].

9.1.2 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 pages of the eCRF.

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

For AEs ongoing at the start of study treatment, if the intensity worsens after the start of study treatment, the change in intensity and the date on which it occurred must be reported in the eCRF.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not usually influence daily activities, and normally 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 9.2.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

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

9.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment and reported as either related or not related. The determination of the likelihood that the study treatment caused the AE will be provided by the investigator who is a qualified physician.

9.1.4 Reporting of adverse events

All AEs with an onset date after signing of informed consent and up to 30 days after study treatment discontinuation or until initiation of study drug in the AC-055H302 OL extension

study, whichever occurs first, must be recorded on specific AE pages of the AC-055H301 eCRF.

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

9.1.5 Follow-up of adverse events

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 complaint (PQC) [see Section 9.5] as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant or until stabilization. The follow-up information obtained after the subject's EOS visit / telephone call will not be collected by Actelion, except in the case of serious adverse events [Section 9.2.4].

9.2 Serious adverse events

9.2.1 Definitions of serious adverse events

An SAE is defined by the 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 in-patient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- 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 not considered as SAEs:

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

- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or 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 such hospitalization are AEs or SAEs.

9.2.2 Reporting of serious adverse events

All SAEs, as well as PQCs, occurring after signing of informed consent up to 30 days after study treatment discontinuation or until initiation of study drug in the OL extension study, whichever occurs first, must be reported on AE pages in the eCRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

An SAE is defined as related to protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures (e.g., conduct of CPET).

9.2.3 Follow-up of serious adverse events

SAEs still ongoing more than 30 days after study treatment discontinuation must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the subject's EOS / telephone call must be reported to the sponsor, but it is not recorded in the eCRF.

9.2.4 After the 30-day follow-up period

For subjects in the PTOP, all SAEs until Week 52 have to be reported in the eCRF and to the sponsor within 24 hours of the investigator's knowledge of the event.

For subjects not participating in the PTOP, new SAEs occurring after the 30-day follow-up period must be reported to the sponsor within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.2.5 Reporting procedures

All SAEs must be reported by the investigator to the sponsor (or the CRO's drug safety department) within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be sent to the sponsor (contact details are provided on the SAE form). The investigator must complete the SAE form in English and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. Sponsor personnel may contact the investigator to obtain further information.

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.

The expectedness of an adverse reaction is determined by the sponsor in the reference safety information (RSI) section provided in the most recent version of the IB. Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

9.3 Pregnancy

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

9.3.1 Reporting of pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects occurring after study start (i.e., signing of informed consent) and with an estimated conception date up to 30 days following study treatment discontinuation must be reported to the sponsor by the study-site personnel within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Pregnancy Notification form, which is sent to the sponsor (or the CRO's drug safety department; see contact details provided on the Pregnancy form), and in the eCRF on an AE page.

9.3.2 Follow-up of pregnancy

Follow-up information regarding the outcome of the pregnancy in female subjects or partners of male subjects and any postnatal sequelae in the infant will be required and reported using the Product Exposure During Pregnancy Collection and End of Pregnancy Collection forms. Follow-up information exceeding the 30-day S-FU will only be entered in the Global Medical Safety database and will not affect SCL.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE pages in the eCRF. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs and must be reported on an SAE form as described in Section 9.2.5.

9.4 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific 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). In addition, an IDMC is monitoring safety data in an unblinded manner [see Section 3.3]. Actelion may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., medical imaging, local laboratory values) for the purpose of safety monitoring. Such additional data may be shared with external experts.

9.5 Product quality complaints

A product quality complaint (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. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability, monitoring, storage and distribution of the product.

9.5.1 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.

If the defect is combined with an SAE, the study site personnel must report the PQC to the sponsor according to the SAE reporting timelines [refer to Section 9.2.5].

9.6 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, e.g., 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 as an SAE on the AE page of the eCRF.

9.7 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 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated CROs supervised by Actelion, except for the IA, which will be conducted by the ISAC/SSG who will provide results to the IDMC.

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

The SAP will include the definition of protocol deviations leading to exclusion from analysis sets. The list of protocol deviations which might affect the evaluation of the effect of the study treatment on the primary efficacy endpoint is provided in Section 10.1.3 of this document. The protocol deviations will be identified by medically trained staff on an ongoing basis during study conduct before study database closure.

Individual subject listings will be provided for efficacy, quality of life, pharmacoeconomic, PK, 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 as appropriate.

Wherever possible, the data will be graphically presented, e.g., via box plots, scatter plots, KM curves, etc. The graphical presentation for KM follows the recommendations from Pocock on the following aspects [Pocock 2002]:

- Rules for KM curves going upwards or downwards (e.g., upwards if there is a low number of events)
- Termination of the vertical axis
- Truncation of the x-axis when only around 10–20% of the subjects are still in follow-up.

10.1 Analysis sets

10.1.1 Screened Analysis Set

The Screened Analysis Set (SCR) includes all subjects who are screened and have a subject identification number.

10.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible:

- Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received);
- All available data are included.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) comprises all subjects who received actual study treatment assigned by IVRS and who complied with the protocol sufficiently up to and including the Week 16 visit (Visit 4) to be likely to exhibit the treatment effects.

Criteria for sufficient compliance include:

- exposure to the study randomized treatment over 16 weeks, including the Week 16 window [Section 10.3.2.2], with a treatment compliance of at least 80% and no more than 120% and without study treatment interruptions of more than 4 consecutive weeks at any time prior to, and until the Week 16 visit (Visit 4),
- availability of peak VO_2 at Week 16 (Visit 4),
- absence of protocol deviations that have an impact on the treatment effect including, but not limited to:
  - Intake of forbidden concomitant therapy up to the Week 16 visit (Visit 4) as listed in Section 5.2.4,
  - Deviations from the selection criteria as listed in Sections 4.3 and 4.4 such that, in the opinion of the study team in blinded review, assessment of efficacy with respect to the primary endpoint is compromised, such as:

- Less than 12 years old at Screening,
- No LT- or EC-TCPC surgery,
- NYHA FC I or IV at Screening,
- Peak VO_2 < 15 mL/kg/min at Baseline.

The full list of criteria will be detailed in the SAP before making the full randomization information available.

10.1.4 Safety Set

The Safety Set (SS) includes all subjects who received at least one dose of study treatment.

10.1.5 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (PKS) includes all randomized and treated subjects, for whom a PK blood sample at trough has been collected and who do not deviate from the protocol in a way that might affect the evaluation of the trough concentrations.

10.1.6 Usage of the analysis sets

The FAS is used for the main and sensitivity analyses of the primary efficacy variable, for analyses of all secondary and other efficacy variables and for the description of the study population at baseline.

The PPS is used to perform sensitivity analyses on the primary and first secondary efficacy variables.

The SS is used for the analysis of the safety variables.

The PKS is used for analysis of the PK variables.

The SCR is used for the description of subject disposition.

Unless specified otherwise, individual subject data listings are prepared on the SCR, by randomized treatment group and for screening failures where appropriate.

10.2 Variables

All variables correspond to the respective study endpoints as described in Section 6.

10.2.1 Primary efficacy variable(s)

The primary efficacy variable is the change in peak VO_2 from Baseline to Week 16, defined as Week 16 value minus Baseline value. The values used for peak VO_2 at Baseline and Week 16 will be based on data evaluation by the central reading facility.

10.2.2 Secondary efficacy variables

10.2.2.1 Peak VO_2 over 52 weeks

This secondary efficacy variable is defined as the average change in peak VO_2 from baseline over time, i.e., averaged over the entire observation period with post-baseline assessments up to Week 52 (CPET is planned at Baseline and at Weeks 16 and 52; in addition, unscheduled CPET can occur). Per time point of assessment, the change is defined as post-baseline value minus baseline value. The overall average change over 52 weeks is the mean change thereof. The values used for peak VO_2 will be based on data evaluation by the central reading facility.

10.2.2.2 Change from Baseline to Week 16 in mean count per minute of daily PA-Ac

This secondary efficacy variable is defined as a Week 16 mean count per minute of daily PA-Ac minus the mean count per minute of baseline daily values. The values used for PA-Ac at Baseline and Week 16 will be based on data evaluation by the central reading facility.

10.2.3 Other efficacy variables

Variables related to exercise capacity:
Peak VO_2 at other visits than Week 16, VE/VCO_2 slope, VO_2/HR, % predicted peak VO_2, VO_2 at VAT, and OUES are collected at all visits with CPET. Details are given in Section 7.2.2.1. Per variable of exercise capacity and per post-baseline assessment, changes from baseline are defined as post-baseline value minus baseline value.

NT-proBNP:
Percent of baseline at Week 16 and percent of baseline in NT-proBNP over 52 weeks will be evaluated. The percent of baseline in NT-proBNP is defined as 100 times the post-baseline value divided by the baseline value.

Time to clinical events:
The individual components of the following two clinical events endpoints are defined in Section 6.1.3:

- Composite endpoint of events related to Fontan-palliated clinical worsening and,
- Composite endpoint of events related to Fontan-palliated morbidity.

The dates of occurrence of each component of the above two clinical event endpoints are reported in the eCRF.

For each composite endpoint, a subject is considered as having an event if the investigator reports the occurrence of any of the individual component in the eCRF.

Subjects who did not experience an event will be censored.

The times to clinical events are expressed in weeks and calculated as:

- for subjects with an event: the earliest date of occurrence of any of the individual components minus date of Randomization plus 1 divided by 7,
- for censored subjects: the EOS date minus date of Randomization plus 1 divided by 7.

Overall survival (OS):
The vital status (alive, dead, or unknown) will be reported in the eCRF [see Section 7.2.3.6].

Subjects who are known to be alive at the time of VSFU will be censored at the date of VSFU. Subjects with unknown vital status at VSFU will be censored at the time of the last contact (e.g., at the date of last study visit, last treatment day or EOS).

Time to death is expressed in weeks and calculated as the date of death minus date of Randomization plus 1, divided by 7 or, for censored subjects, as censoring date minus date of Randomization plus 1, divided by 7.

Physical activity:
Physical activity efficacy variables include:

- the change from Baseline to Week 52 in mean count per minute of daily activity and
- the change from Baseline to Weeks 16 and 52 in daily mean time in minutes spent in sedentary, light, moderate, or vigorous physical activity.

Changes from Baseline are defined as post-baseline value minus baseline value.

10.2.4 Safety variables

Adverse events:

An AE is defined as any event that is recorded on the AE eCRF module regardless of the onset date.

Treatment-emergent events are those with onset date/time ≥ start date/time of study treatment and ≤ 30 days after EOT.

Serious events are those with seriousness assessed as 'serious' by the investigator according to the definition in Section 9.2.1.

Related AEs are those with relationship to the use of study treatment judged as 'reasonably possible' by the investigator.

AEs leading to premature discontinuation of study treatment are those with action taken with study drug reported as 'permanently discontinued' by the investigator.

Laboratory data:

Laboratory analyses are based on data received from the central laboratory. All transferred central laboratory data are taken into account regardless of whether they correspond to scheduled or unscheduled assessments.

Baseline laboratory test refers to the latest laboratory test performed prior to the start of study treatment.

EOT laboratory test refers to the laboratory test performed at the EOT visit. If no laboratory data are available for the EOT visit, the results of the latest available post-baseline laboratory tests performed prior to EOT date/time are used for the analysis.

For a list of laboratory tests see Section 7.2.4.2. Per laboratory test and post-baseline assessment, changes from baseline are defined as post-baseline value minus baseline value. Marked laboratory abnormalities are those defined in Appendix 1. Treatment-emergent laboratory abnormalities are those with a sampling after the start of study treatment and ≤ 30 days after EOT.

Vital signs:

Systolic BP, diastolic BP, pulse rate, SpO_2, height and body weight are measured at all scheduled visits and reported in the eCRF. Per vital sign and post-baseline assessment, changes from baseline are defined as post-baseline value minus baseline value.

Baseline vital sign refers to the latest vital sign measurement performed prior to the start of study treatment.

Echocardiography:

Single ventricle ejection fraction, Fontan circulation stenosis, and valvular defects (severe AV valve regurgitation, outflow obstruction) are measured at the Screening and EOT visit and reported in the eCRF. Per ECHOC parameters and post-baseline assessment, changes from baseline are defined as post-baseline value minus baseline value.

10.2.5 Quality of life variables

Details will be included in the statistical analysis plan.

10.2.6 Pharmacoeconomic variables

The annualized rate of all-cause and Fontan-related hospitalizations will be calculated during the double-blind treatment period.

The all-cause hospitalizations are any hospitalization reported in the eCRF with an admission date during the treatment period.

Fontan-related hospitalizations are any hospitalization reported as part of a clinical worsening event in the eCRF.

10.2.7 Pharmacokinetic variables

To assess exposure to macitentan and its metabolite in this population, trough concentrations of macitentan and its metabolite ACT-132577 in plasma at Week 4 and Week 16, or at EOT in case of premature study drug discontinuation before Week 16, will be determined.

10.3 General Description of statistical analyses

Data are listed and summarized by appropriate descriptive statistics (tables or figures), including:

- Number of non-missing observations, mean, standard deviation (SD), minimum, Q1, median, Q3 and maximum for continuous variables,
- Number of events, number of censored observations, number of subjects at risk, and KM estimates of the survival function for time-to-event variables, hazard ratios and corresponding 95% confidence intervals,
- Number of non-missing observations, frequency with percentage per category (percentages based on the number of non-missing observations) for categorical safety variables,
- Number of missing observations and frequency with percentage per category (percentages based on the total number of observations) for categorical variables other than safety variables.

The number of missing values is displayed only if > 0. For continuous variables it is displayed after the number of non-missing observations, for categorical variables after the last category.

10.3.1 Overall testing strategy

The effect of macitentan 10 mg as compared to placebo will be statistically tested on the primary efficacy variable at an overall Type I error of 1% two-sided. The study would be 'conclusive' at the two-sided 1% level, it could also be declared 'positive' at a significance level of 5% on the primary efficacy variable.

This study implements one IA for unblinded sample size re-estimation which will be conducted approximately when the first 95 subjects (i.e., 70% of the pre-planned sample size) are randomized and have completed their Week 16 CPET assessment (i.e., Visit 4/Week 16), or withdrew from the study without a Week 16 CPET assessment. This sample size re-estimation allows the sample size to be potentially increased up to 268 subjects based on conditional power considerations for the primary efficacy endpoint [see Section 10.5.3]. This IA will be implemented through an IDMC. The SAP written by

Actelion will include the description of the statistical methods and analyses to be applied to the primary efficacy endpoint and the details on the statistical decision rules for the implementation of the IA, which may be used as guidance. The inverse normal combination method will be utilized to combine first-stage p-value (based on actual number of subjects available at the time of IA) and second-stage p-value (based on the remaining number of subjects required to reach the total sample size after IA results) for the control of the type-1 error rate [Lehmacher 1999]. The guideline for calculating the combination weights will be included in the SAP and will be based on the available individual information fractions at the time of the IA. Combination weights will not be adjusted based on the IA decision.

If the primary endpoint is statistically significant at a significance level $\alpha = 1\%$ two-sided at final analysis, the secondary efficacy endpoints will be analyzed at the same significance level as the primary efficacy endpoint (i.e., 1% two-sided) using a hierarchical testing procedure following the order of the endpoints as listed in Section 6.1.2.

Similar to the primary efficacy endpoint, the final analysis of the secondary efficacy endpoints will be conducted using the inverse normal combination method with pre-specified weights to combine first and second stage p-values.

Safety variables and other variables will not be formally statistically tested.

Guidelines for sample size re-estimation are defined in the SAP. Procedures to maintain data integrity in the presence of sample size adaptation are given in a separate document.

10.3.2 Analysis of the primary efficacy variable(s)

10.3.2.1 Hypotheses and statistical model

The statistical hypotheses for the primary endpoint are formulated in terms of the arithmetic means (M) of change in peak VO_2 in subjects treated with either placebo or macitentan 10 mg from Baseline (Visit 2) to Week 16 (Visit 4).

H_0: $M_{\text{macitentan 10 mg}} = M_{\text{placebo}}$ versus

H_A: $M_{\text{macitentan 10 mg}} \neq M_{\text{placebo}}$

The null hypothesis will be tested as per primary variable at a two-sided Type I error of 1% for conclusiveness.

Assuming the normal distribution of the primary variable, the null hypothesis will be tested by means of an analysis of covariance (ANCOVA) model on the change in peak VO_2 at Week 16. Model covariates will include randomized treatment, geographical region and peak VO_2 at Baseline (Visit 2).

For subject *k* in geographical region *j* under treatment *i*, the additive linear statistical model is

$$y_{ijk} = a + \beta_1 T_i + \beta_2 R_j + \beta_3 x_{ijk} + e_{ijk},$$

where,

- y_{ijk} denotes the change from baseline to Week 16 (Visit 4) in peak VO_2 for subject *k* in geographical region *j* under treatment *i*,
- a denotes the common intercept,
- T_i denotes the treatment group *i* with i=1 for macitentan 10 mg and i=0 for placebo,
- Rj denotes geographical region *j* with j=1 to the total number of regions (America, Europe, Asia, Oceania),
- x_{ijk} denotes the peak VO_2 value at Baseline (Visit 2) for subject *k* in geographical region *j* under treatment *i*,
- e_{ijk} denotes the random error term for subject *k* in geographical region *j* under treatment *i*, assumed to follow a normal distribution with mean 0 and SD σ, and
- β_1, β_2 and β_3 denote the model coefficients of the treatment, geographical region and baseline value effects, respectively.

The difference between treatments at Week 16 will be used to test the null hypothesis of equality of treatment effects. According to the model notation, null and alternative hypotheses above conform to H_0: $\beta_1 = 0$ versus H_1: $\beta_1 \neq 0$.

The primary estimand for the primary efficacy endpoint is defined as:

A. Population: All randomized Fontan-palliated adult and adolescent subjects defined through protocol inclusion/exclusion criteria (i.e., FAS).

B. Variable: peak VO_2 as change from baseline to Week 16.

C. Intercurrent events:

- Death occurring before W eek 16

  In case of death prior to Week 16, this will result in imputing the change from baseline to Week 16. A worst-case imputation will be applied as detailed in Section 10.3.2.2.

- Non-missing peak VO_2 value at Week 16 assessed as ‘invalid’ by the central reading facility

  In case an assessment at Week 16 has been evaluated as “invalid” by the independent central reading facility, it will not be included in the analysis and it will be handled as detailed in Section 10.3.2.2.

- Premature study treatment discontinuation before Week 16

  Premature study treatment discontinuation prior to Week 16 will be addressed by a "treatment-policy" estimand strategy by including any assessment in the Week 16 time window, irrespective of premature study treatment discontinuation, in the main analysis.

Population-level summary measure: difference in change in peak VO_2 from baseline to Week 16 between macitentan 10 mg and placebo, as estimated from the ANCOVA model including randomized treatment group, geographical region and baseline peak VO_2 as covariates in the model.

Based on the inverse normal combination of the stagewise test statistics to control for the adaptive design, the main estimator at final analysis will be the median unbiased estimator for the overall treatment effect and corresponding repeated confidence intervals (RCIs) based on the stage-wise ordering [see Section 10.3.2.3].

10.3.2.2 Handling of missing data

The primary variable is the change in peak VO_2 from Baseline (Visit 2) to Week 16 (Visit 4) and calculated as the Week 16 value minus baseline value in peak VO_2.

At baseline, no subject will have a missing value for peak VO_2 because the subject will not be able to be randomized via IRT in the event of missing peak VO_2. In case a subject has been randomized with a non-missing baseline value that has subsequently been evaluated as "invalid" by the independent central reading facility, it will be imputed with the median peak VO_2 value observed at baseline from the remaining subjects (across treatment groups).

During the conduct of the study, all efforts will be made to avoid missing values in peak VO_2 at Week 16. For Week 16, the time window interval is from study Day 99 (Week 14) to study Day 168 (Week 24).

Furthermore, if a subject discontinues treatment prematurely, a CPET will be conducted within 7 days of EOT. If treatment is discontinued prior to Week 16, and the subject enters the PTOP, it is requested that the subject return for a CPET assessment at Week 16 (in addition to the EOT assessment).

Any unscheduled visit will also be mapped to a time window.

Intercurrent events as defined in Section 10.3.2.1 will be handled as in table below as well as any other missing values which may occur in peak VO_2 at Week 16.

Reason	Strategy in handling the change from Baseline to Week 16
Death before Week 16	Imputed with the lowest observed change in peak VO_2 from Baseline to Week 16 (across both treatment groups) – Worst case.
Invalid peak VO_2 at Week 16/Other*	Imputed with the 25th percentile of the observed changes in peak VO_2 from baseline to Week 16 (across both treatment groups). If this leads to an improvement, a change of 0 (no change) will be imputed.

*Other could include: premature study treatment discontinuation because of an adverse event, lack of efficacy, or lost-to follow up.

After the imputation is applied, the ANCOVA model, as described in Section 10.3.2.1, will be used.

10.3.2.3 Main analysis

The primary statistical analysis will be performed on the FAS population using the model described in Section 10.3.2.1 for the 16-week change in peak VO_2 as a dependent variable. The ANCOVA model considers study treatment (macitentan 10 mg or placebo) and geographical region as fixed categorical factors and the baseline value of peak VO_2 as a fixed continuous covariate. Missing data will be imputed as described in Section 10.3.2.2 for the main analysis. Geographical regions are defined as Americas, Europe, Asia, Oceania.

Assumptions of normality and homogeneity of variance and assessing of ANCOVA model assumptions will be investigated and graphically presented when applicable (e.g., Q-Q and residual plots).

At final analysis, the primary efficacy endpoint will be tested by combining the p-values from the main ANCOVA analysis of first-stage (based on actual number of subjects available at the time of IA) and second-stage (based on the remaining number of subjects to reach the total sample size after IA results), using the weighted inverse-normal combination method [Lehmacher 1999] with fixed weights proportional to the information available at the time of the IA. The difference in the change in peak VO_2 from Baseline to Week 16 between macitentan 10 mg and placebo and corresponding p-value will be estimated at each stage separately (first-stage and second-stage) from the main ANCOVA model using a population-wise splitting of data approach. Final interpretation of the results will then be based on the final adjusted p-value, median unbiased estimator for the overall treatment effect and corresponding RCIs obtained by ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company).

Absolute values at Baseline and at Week 16 as well as absolute change in peak VO_2 from Baseline to Week 16 (for observed and imputed values) will also be summarized using descriptive statistics.

10.3.2.4 Supportive/sensitivity analyses

i) Sensitivity analyses for missing values at Baseline and Week 16 in peak VO_2

- The main ANCOVA model will be applied on the set of subjects with observed values only, i.e., without replacing missing values.
- The main ANCOVA model will be applied excluding subjects with invalid peak VO_2 at Baseline.

The resulting least square (LS) means and corresponding 95% and 99% CLs obtained in each treatment group, and the LS-means differences (95% and 99% CLs) for macitentan 10 mg vs placebo will be obtained from the ANCOVA model carried out on the total sample size (without the population wise splitting approach for the control of the adaptive design).

ii) Other sensitivity analyses

Other sensitivity analyses carried out on the total sample size, without the population-wise splitting approach for the control of the adaptive design, are:

- ANCOVA model applied for the PPS population
- ANCOVA model following while 'on-treatment' strategy. The assessments in the Week 16 time window will only be included in the analysis if assessed up to 7 days after last dose of study treatment.
- A first ANCOVA on ranks will be implemented to address possible deviations from the normality assumptions. It will be performed as follows:
  - imputation approach for Week 16 will be applied as per the primary endpoint analysis
  - ranking will be performed on the primary variable (changes in peak VO_2 from baseline to Week 16) and baseline peak VO_2
- A second ANCOVA on ranks will be implemented as a sensitivity to the primary imputation method. It will be performed as follows:
  - Each Week 16 value that is missing due to the patient's death prior to the Week 16 assessment receives a rank score corresponding to a value of the measurement that is worse than any actually observed
  - Each Week 16 value that is missing in patients not known to have died prior to the Week 16 assessment receives a rank score corresponding to a value of the

measurement that is worse than any actually observed but better than for any patient who died prior to Week 16

– The above imputation guarantees the following:

– rank (subjects who die) < rank (subjects with missing values) < rank (subjects without missing values)

- ANCOVA model with treatment-by-geographical region interaction effect added to the primary model proposed in Section 10.3.4.2,
- ANCOVA model with NYHA FC added to the primary model proposed in the Section 10.3.2.1.

Further details and potential further supportive analyses will be described in the SAP.

10.3.3 Analysis of secondary efficacy variables

10.3.3.1 Change from baseline over 52 weeks in peak VO_2

The change in peak VO_2 over 52 weeks is evaluated on the FAS population with the use of a mixed model repeated measures. The model will include randomized treatment group, time (via a categorical variable for visit), treatment-by-time interaction, baseline-by-time interaction and peak VO_2 at Baseline as fixed effects. An unstructured variance-covariance matrix will be specified.

Invalid peak VO_2 at Baseline will be handled similarly to the primary efficacy endpoint.

In case of missing values in peak VO_2 at Week 52 the following approach for imputation will be applied

- Death occurring before Week 52.

In case of death prior to Week 52, all scheduled assessments following the date of death will be imputed by a worst-case imputation (i.e., lowest observed change in peak VO_2 from Baseline value across both treatment groups and over all assessments).

- Peak VO_2 at Week 16 or Week 52 assessed as 'invalid' by the central reading facility.

In case an assessment at Week 52 has been evaluated as "invalid" by the independent central reading facility, it will be ignored. This will result in imputing the change from Baseline to Week 52 with the 25th percentile of the observed changes in peak VO_2 from Baseline value (across both treatment groups and over all assessments). If this leads to an improvement, a change of 0 (no change) will be imputed.

- Premature study treatment discontinuation before Week 52

If the premature study treatment discontinuation occurs prior to Week 16:

- if a valid assessment is available within the time window of Week 16, this will result in imputing only the change from Baseline to Week 52 with the 25th percentile of the observed changes in peak VO_2 from Baseline value (across both treatment groups and over all assessments). If this leads to an improvement, a change of 0 (no change) will be imputed.
- if no valid assessment is available within the time window of Week 16, all scheduled assessments following the date of event will be imputed by applying the 25th percentile of the observed changes in peak VO_2 from Baseline value (across both treatment groups and over all assessments). If this leads to an improvement, a change of 0 (no change) will be imputed.

If the premature study treatment discontinuation occurs after Week 16 and before Week 52 (and no valid assessment is available within the time window of Week 52), this will result in imputing the change from baseline to Week 52 with the 25th percentile of the observed changes in peak VO_2 from Baseline value (across both treatment groups and over all assessments). If this leads to an improvement, a change of 0 (no change) will be imputed.

Missing data arising from any other reason (e.g., administrative reason) are assumed to be missing at random, and as such, will require no further imputation, since the MMRM approach will implicitly impute these values.

Supportive/Sensitivity Analyses:

Additional sensitivity analyses will be similar to the primary endpoint (e.g., PPS, excluding subjects with invalid peak VO_2 at baseline and "while on treatment". For all sensitivity analyses, similar to the primary endpoint, the main MMRM model will be carried out on the total sample size (without the population wise splitting approach for the control of the adaptive design). At Week 52, the resulting LS means and corresponding 95% and 99% CLs obtained in each treatment group, and the LS-means differences (95% and 99% CLs) for macitentan 10 mg vs placebo will be provided.

10.3.3.2 Change from Baseline to Week 16 in mean count per minute of daily PA-Ac

The change from Baseline to Week 16 in mean count per minute of daily PA-Ac is evaluated on the FAS population by means of an ANCOVA including treatment group and baseline accelerometry value as covariates. Similar to the approach for the primary endpoint (main analyses) and based on the inverse normal combination of the stagewise test statistics to control for the adaptive design, the main estimator at final analysis will be the median unbiased estimator for the overall treatment effect and corresponding 99% confidence intervals based on the stage-wise ordering.

Only subjects with evaluable 9-day time period for the daily physical activity at Baseline will be included in the main analysis. In case of missing values in mean count per minute of daily PA-Ac at Week 16, the following approach for imputation will be applied:

Reason	Strategy in handling the missing change from Baseline to Week 16
Death before Week 16	Imputed with the lowest observed change in mean count per minute of daily PA-Ac from Baseline to Week 16 (across both treatment groups) – Worst case.
Other	A change of 0 (no change) will be imputed.

Supportive/Sensitivity analyses:

Additional sensitivity analyses will be on the PPS, based on observed cases.

The main model for all sensitivity analyses will be the same ANCOVA model as specified for the primary endpoint but carried out on the total sample size (without the population wise splitting approach for the control of the adaptive design).

10.3.3.3 Sub-group analyses

In order to assess the consistency of the treatment effect across different subject subgroups, analyses will be performed on the primary and secondary efficacy variables classifying subjects according to relevant demographic characteristics.

The subgroups to be considered are:

- Age group (adults of 18 years of age or more, adolescents of less than 18 years of age at Screening),
- Geographical region (America, Europe, Asia, Oceania),
- Region (US, non-US),
- Ventricular dominance: left ventricle (LV) versus right ventricle (RV) / mixed.

Analyses in subgroups on the FAS population are carried out the same way as on the entire population as described in Sections 10.3.2, 10.3.3.1, and 10.3.3.2 for primary and secondary efficacy variables, respectively. The treatment effect within subgroups will primarily be displayed with their corresponding 95% CLs and presented in a forest plot. An additional forest plot will be produced for the primary endpoint only, displaying 99% CLs instead of 95% CLs. Treatment-by-subgroup interaction is investigated by means of tests of heterogeneity.

Further details will be provided in the SAP.

10.3.4 Analysis of the safety variable(s)

The SS will be used to perform all safety analyses. Safety variables will be analyzed by actual treatment received.

10.3.4.1 Adverse events

AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA™) dictionary.

Listings will be provided for all reported AEs, including SAEs. Treatment-emergent AEs are flagged. In addition, separate listings will be provided for SAEs, for AEs leading to premature discontinuation of study treatment, and for AEs with fatal outcome.

The number and percentage of subjects experiencing treatment-emergent AEs, SAEs, related AEs, related SAEs, AEs with fatal outcome, and AEs leading to premature discontinuation of study treatment will be tabulated by treatment group, system organ class (SOC) and individual preferred term within each SOC, in descending order of incidence within the macitentan 10 mg treatment group. For SAEs, the number of such events is added to the table. In addition, tabulation will be by treatment group and individual preferred term, irrespective of SOC, in descending order of incidence within the macitentan 10 mg treatment group.

Furthermore, treatment-emergent AEs will be tabulated by treatment group, individual preferred term and maximum intensity.

The number and percentage of subjects experiencing treatment-emergent non-serious AEs, together with the number of such events, will be tabulated by treatment group, SOC and individual preferred term within each SOC, in descending order of incidence within the macitentan 10 mg treatment group, if the frequency of subjects exceeds 5% in any treatment group.

10.3.4.2 Laboratory data

All laboratory data, local and central, are listed in original, International System of Units (SI) and conventional units. Abnormal values and values representing treatment-emergent marked abnormalities are flagged. Measured values and changes in laboratory data from baseline are described by visit and treatment group by means of summary tables in SI units. All recorded assessments, including scheduled and unscheduled visits, will be assigned to the most appropriate visit time point according to the best-fitting time window for the assessment. In addition, worst low, worst high and last values post baseline will be described in the same way.

Treatment-emergent marked laboratory abnormalities will be summarized for each laboratory parameter by treatment group providing their incidence and frequency. In addition, shift tables of categories of marked laboratory abnormalities at baseline versus

post-baseline visits, worst low, worst high and last post-baseline will be displayed. Furthermore, frequency tables of liver, hemoglobin, estimated creatinine clearance, and albumin abnormalities will be presented:

- Proportion of patients with treatment-emergent ALT and/or AST abnormalities from baseline up to EOT defined as values:
  - ≥ 3 × ULN;
  - ≥ 3 × ULN and < 5 × ULN;
  - ≥ 5 × ULN and < 8 × ULN;
  - ≥ 8 × ULN.
- Proportion of patients with ALT and/or AST abnormality (≥ 3 × ULN) in combination with total bilirubin ≥ 2 × ULN from baseline up to EOT.
- Proportion of patients with treatment-emergent hemoglobin abnormalities up to EOT, classified as:
  - < 80 g/L
  - < 100 g/L
- Proportion of patients with treatment-emergent estimated creatinine clearance < 30 mL/min/1.73m^2.
- Proportion of patients with treatment-emergent albumin abnormalities < 30 g/L in combination with total protein < 50 g/L.

10.3.4.3 Vital signs

Listings will provide all data of vital signs, including SpO_2, height and body weight. Measured values and changes from baseline are described by visit and treatment group by means of summary tables.

Number of subjects with systolic BP drops to < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height) over 52 weeks will be tabulated and listed.

All recorded assessments, including scheduled and unscheduled visits, will be assigned to the most appropriate visit time point according to the best-fitting time window for the assessment.

10.3.4.4 Echocardiography

Listings will provide data of ECHOC parameters at Screening and EOT visits, together with the respective changes from baseline.

10.3.5 Analysis of other efficacy variables

Exploratory analysis of other efficacy variables will be conducted on the FAS. Missing values will not be imputed.

10.3.5.1 Peak VO_2 at other visits, VE/VCO_2 slope, VO_2/HR, VO_2 at VAT, OUES and % predicted peak VO_2

Other efficacy variables related to exercise capacity are summarized by treatment groups in tabular forms.

Changes from baseline in peak VO_2 at Week 52 will be analyzed by means of an ANCOVA including treatment group and baseline value as covariates.

Separate receiver operating characteristic curve analysis will be performed in order to identify the best cut-offs of VE/VCO_2 slope and peak VO_2 that discriminate patients with and without clinical events. In addition, the variables VE/VCO_2 slope and peak VO_2 will be categorized and the number and proportion of patients with clinical events will be presented overall and by treatment group for each category.

The % predicted peak VO_2 will be analyzed using a MMRM [Section 10.3.3.1] on the changes from Baseline over 52 weeks.

Changes from baseline to Week 16 in VO_2 at VAT and in OUES will be analyzed by means of an ANCOVA, including treatment group and baseline value as covariates.

In addition, the VO_2 at VAT and OUES will be analyzed using a MMRM [Section 10.3.3.1] on the changes from Baseline over 52 weeks.

If normal assumptions are not valid then ANCOVA on the transformed variable or ANCOVA on ranks will be applied.

10.3.5.2 NT-proBNP

The percent of baseline at Week 16 in NT-proBNP will be analyzed like the primary efficacy variable by means of an ANCOVA model as described in Section 10.3.2.1.

NT-proBNP is assumed to follow a log-normal distribution. Therefore, data is log transformed before analysis. Summary tables provide back transformed data by means of geometric means and 95% CL of NT-proBNP expressed as percent of baseline. Back-transformation is done by means of the exponential function of the least-squares mean of treatment difference and its corresponding CLs obtained on the log scale.

NT-proBNP at other visits than Week 16 will be summarized and presented graphically over time.

10.3.5.3 Mean time in minutes spent in different physical activities and mean count per minute of daily PA-Ac over time

The mean time in minutes spent in:

- sedentary physical activity,

- light physical activity,
- moderate physical activity and
- vigorous physical activity

will be described at each time point of assessment by calculating for each treatment group the average time spent in each category and will be displayed in both a graphical (bar plots) and a tabular form. The number of subjects who spent time in physical activity categories as defined above will be summarized in shift tables (categories at Baseline vs categories at post-baseline visits).

Repeated measure statistical methodology (a random coefficient regression model) that was proposed for the secondary endpoint [Section 10.3.3.1] will also be applied for change from Baseline (Visit 2) over 52 weeks in mean count per minute of daily PA-Ac.

In addition, the number of valid days of wearing the accelerometer at Baseline, Week 16, and Week 52, will also be summarized descriptively.

10.3.5.4 Clinical events

Time to clinical events will be analyzed using KM estimates along with 95% two-sided CLs at relevant time points for each treatment group in both graphical and tabular form. The estimated hazard ratio and corresponding 95% confidence interval will be obtained from a Cox regression model. In addition, the number of subjects with events, the number of subjects at risk, and the number of subjects censored will be computed at each time point for each group. Subjects without events will be right-censored at the last time known to be without the respective event.

10.3.6 Overall survival

Time to death up to SCL will be analyzed using the KM methodology as described in Sections 10.2.3 and 10.3.5.4 for the clinical events.

KM curves over time by treatment group will be graphically displayed. The number of subjects at risk, number of events (deaths), number of censored cases, KM estimate of the event-free rate at these time points, and corresponding confidence intervals for the estimated event-free rate at Weeks 16, and 52 will be presented. Additionally, a listing with all subjects and their vital status with corresponding date of death or censoring date will be provided.

10.3.7 Analysis of quality of life variables

The QoL endpoints will be analyzed descriptively on the FAS by randomized treatment group. Continuous scales (EQ-5D VAS) will be summarized as absolute and changes from baseline values at each time point. Categorical scales (PGA-S, CGI-S, PGI-C, CGI-C and EQ-5D-5L) will be summarized as the proportion of patients within each response category at each time point.

10.3.8 Analysis of pharmacoeconomic variables

Those endpoints will be summarized descriptively on the FAS by randomized treatment group.

10.3.9 Analysis of pharmacokinetic variables

Analysis of PK (i.e., trough concentration of macitentan and active metabolite) will be conducted on the PKS.

Individual subject listings of trough plasma concentrations will be provided.

Trough plasma concentrations of macitentan and its metabolite will be described by visit by means of summary tables. In addition, separate summary tables will be given by age group and by gender.

10.3.10 Exposure to and compliance with the study treatment

Exposure to study drug will be described in terms of duration and dose. The duration of study treatment is defined as the time in days elapsing between start and end of study treatment, inclusive. It includes potential periods of study treatment interruption. The end of study treatment is defined as the time of permanent discontinuation of study treatment. The duration of exposure in days is defined as the number of days with study treatment, excluding days without study treatment, i.e., excluding periods of study treatment interruption.

Compliance with study treatment, in percent, is defined as percent of doses taken divided by expected number of doses. The expected number of doses is derived from the planned duration of study treatment during the period of interest.

Analysis of study treatment exposure and compliance data is performed on the SS.

Individual subject listings of study treatment exposure and compliance data will be provided.

The duration of exposure, the duration of study treatment, and compliance will be described by treatment group by means of summary tables. It will be also summarized as a categorical variable: the cumulative distribution of exposure time by different class intervals (i.e., at least 4 weeks, at least 8 weeks, at least 16 weeks, and so on up to 52 weeks) will be tabulated to show counts and percentages of subjects in each class interval. The sum of duration of exposure across all subjects in years will be displayed as subject year exposure.

10.3.11 Demographic and baseline characteristics

Summaries for demographic and baseline characteristics will be performed on the FAS and displayed per treatment group and overall. In addition, demographic and baseline characteristics will be tabulated by geographical region, gender, and age group. Demographic variables include age (in years), age groups (adolescents, adults), gender,

body weight, height, BMI, race, ethnicity, country, and geographical region. Baseline characteristics include disease and other characteristics, medical history, previous and concomitant medications. Baseline disease variables include type of initial uni-ventricular heart, time since Fontan-palliation completion, type of TCPC, NYHA FC, peak VO_2 at baseline, NT-proBNP at baseline, and fenestration patency.

Previous and concomitant medications will be coded according to the WHO drug code and the Anatomical Therapeutic Chemical class code and summarized by tabulating the number and percentages of subjects having received each treatment.

Medical history will be coded using MedDRA™ and summarized in a similar manner to AEs.

10.3.12 Subject disposition

A study flowchart will show the disposition of study subjects throughout the progression of the study. It will display the numbers of subjects screened and undergoing randomization with the latter divided into the placebo and macitentan 10 mg treatment groups to which they were randomized. The number of subjects by treatment group continuing and discontinuing treatment and the study, along with reasons for discontinuations will be displayed. The final row of the flowchart will result in the number of subjects completing the study in each treatment group.

The items in the flowchart will be supported by tables and listings on the FAS related to each level and will be presented by randomized treatment group. In addition, it will be presented by geographical region, country and age group.

The number and percent of subjects included in and excluded from each analysis set, based on the set definitions in Section 10.1, will be summarized, supported by a summary table of protocol deviations leading to exclusion from FAS (i.e., used for derivation of PPS). Protocol deviations will be displayed by treatment, geographical region, country and site.

10.4 Interim analysis

One IA for unblinded sample size re-estimation will be implemented through an IDMC. Only the IDMC and the ISAC/SSG will be unblinded to the data.

The IA will be conducted by the ISAC/SSG on the primary efficacy endpoint to allow unblinded sample size re-estimation when approximately the first 95 subjects i.e., 70% of pre-planned sample size) are randomized and have completed their Week 16 CPET assessment (i.e., Visit 4/Week 16), or withdrew from the study without a Week 16 CPET assessment. The ISAC/SSG will make unblinded results available to the IDMC. The IDMC will review the interim results and make corresponding recommendation to the Sponsor Committee in line with the IDMC charter. The IDMC may recommend, based on the

unblinded interim data, that the sponsor continues the study as initially planned (i.e., a total of 134 subjects) or with reassessed sample size, to a total between $134 < N \leq 268$ subjects.

Under the IDMC recommendation of sample size adaptation, the sample size will be re-estimated at the IA based on treatment effect and variability for the primary efficacy endpoint (i.e., change from baseline to Week 16 in peak VO_2), following rules as described in the SAP. Only an upward adjustment of the initially planned sample size is allowed. An upper bound of the sample-size adjustment is considered up to a 100% increase of the initially planned sample size (i.e., total sample size of 268 subjects).

Detailed guidelines for interim decision-making are further described in the SAP written by Actelion for the ISAC/SSG [see Section 10.5.3, for preliminary details], outlining the statistical methods and analyses to be applied to the primary efficacy endpoint for the sample size re-estimation.

10.5 Sample size

The sample size is based on the primary efficacy endpoint, the 16-week change from baseline in peak VO_2. The study is powered for the treatment comparison on a FAS. The aim of the trial is to reject the statistical hypothesis of no treatment difference.

All calculations were performed using the East software version 6.3.

10.5.1 Sample size and justification

Assuming that the macitentan versus placebo difference is expected to be no worse than the bosentan versus placebo difference, a 2.4 mL/kg/min difference of macitentan to placebo on the change in peak VO_2 is hypothesized. The variation of macitentan is assumed to be greater than that observed in the TEMPO study of bosentan versus placebo in subjects with Fontan-palliated circulation [Hebert 2013, Hebert 2014], namely a standard deviation of 4.0 mL/kg/min yielding an effect size of 0.6.

It is further assumed that all randomized subjects are evaluable. The family-wise two-sided Type I error is set to 1% (i.e., the level of significance), and the minimum statistical power to achieve is set to 80% (i.e., Type II error β of 20%).

Under the assumption of normal distributions (based on a two-sample t-test with equal unknown variances), sample size is determined for different scenarios. Data will be analyzed by means of ANCOVA taking further explanatory potentially confounding factors into account, therefore adjusting for the estimated treatment difference and reducing variability in the data. If the assumptions are not met, it is only a slight acceptable loss in efficiency.

Based on the above assumptions and with a 1:1 randomization ratio, a total of 134 subjects, i.e., 67 per treatment group, are required to establish superiority of macitentan 10 mg over

placebo to correctly reject the null hypothesis, when it is false, in favor of the alternative hypothesis.

10.5.2 Sample size sensitivity

In a range of effect size from 0.4 to 0.8, here corresponding to a range of SD from 3.0 to 6.0 mL/kg/min for the primary efficacy endpoint, the 16-week change from baseline in peak VO_2, alternative sample size scenarios are given in Table 4.

Table 4 Sample size with treatment effect of 2.4 mL/kg/min and statistical power 1-β of 80% in a 1:1 randomization ratio by level of significance α and effect size (with selected sample size in bold face)

α	Effect size	SD	n per arm	Total N
1%	0.4	6.0	148	296
	0.5	4.8	96	192
	0.6*	**4.0**	**67**	**134**
	0.8	3.0	39	78
5%	0.4	6.0	100	200
	0.5	4.8	64	128
	0.6	4.0	45	90
	0.8	3.0	26	52

SD: standard deviation with a treatment difference of 2.4 mL/kg/min; n: sample size per arm (macitentan 10 mg or placebo) with a 1:1 ratio; N: total sample size required for randomization.
*selected

10.5.3 Unblinded sample size re-estimation

The sample size will be re-estimated at the IA [see Section 10.4] based on conditional power considerations under the observed unblinded treatment effect estimates. Sample size may be increased to a maximum of 268 subjects to target 80% conditional power. If the conditional power at the IA is below 5% or is above 80%, the sample size shall not be changed.

The detailed methodology for sample size re-estimation as well as the operating characteristics of the design under a range of effect sizes are described in the SAP.

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timelines 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.

eCRF data will be captured via electronic data capture (EDC; using the Rave system provided by Medidata Solutions, Inc, a web-based tool). The investigator and site personnel 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 US 21 CFR Part 11).

Subject screening and enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject enrolled, regardless of study treatment 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, the reason must be noted on the eCRF. Refer to Section 7.2.1 for the data to be collected in the eCRF for subjects who failed screening.

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to Actelion and any CROs, subjects must be identified only by number and never by their name or initials, hospital numbers, or any other identifier. The investigator/delegate must keep a subject identification code list at the site, showing the screening/randomization 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.

11.3 Database management and quality control

eCRFs will be used for all subjects. The investigators will have access to the site eCRF data until the database is closed. Thereafter, they will have read-only access. 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 instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable)

and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in 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.

This process will continue until database closure.

Laboratory samples will be processed through a central laboratory and the results will be electronically sent to Actelion. PK samples will be shipped at regular intervals and analyzed by the bioanalytical lab.

CPET and PA-Ac data are processed by a central reading facility and results will be sent to Actelion.

AEs are coded according to the latest MedDRA™ used by Actelion.

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 Actelion QS docs. After database closure, the investigator will receive the eCRFs of the subjects of his/her site (including all data changes made) on electronic media or as a paper copy.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

Actelion personnel 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 countries in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator or sponsor will submit this protocol and any related document(s) provided to the subject or parent(s)/ legally designated representative and the subject (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study and must be documented in a dated letter to the investigator, clearly identifying the study, investigator, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 12.6].

A list of members participating in the IEC/IRB meetings 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 member of the study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.3 Informed consent

Pediatric subjects are legally unable to provide informed consent. Therefore, full informed consent must be obtained from parent(s) or a legally designated representative.

Assent must be obtained from study participants who are developmentally capable. The criteria for developmental capability to give assent follows local requirements. Distinct assent forms are provided per age categories. Subjects who come of age during their study participation must be consented to continue their participation in the study. The age when subjects are considered capable to give informed consent must follow local regulations.

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study and/or legally designated representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject and/or legally designated representative to consider his or her decision to participate in the study and it shall be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

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

Site personnel authorized (according to local regulation) to participate in the consent process and/or to obtain consent from the subject and/or legally designated representative will be listed on the Delegation of Authority form supplied by Actelion. In European countries the informed consent must be obtained by a physician. A study physician must always be involved in the consent process.

The subject and/or legally designated representative and authorized site personnel listed on the Delegation of Authority form supplied by Actelion must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin.

A copy of the signed and dated ICF is given to the subject and/or legally designated representative; the original is filed in the site documentation. The informed consent process must be fully documented in the subject's medical records. This must include at a minimum the study reference, the subject number, the date and, if applicable, time when the subject was first introduced to the study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject, and any additional third party (e.g., legally designated representative, impartial witness) present during the consent process (relationship with the subject), and the information that a copy of the signed ICF was given to the subject / third party (e.g., legally designated representative, impartial witness).

If the site intends to recruit subjects who are considered as vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure subject's rights are respected and the consent obtained is legally valid. Actelion, the regulatory authorities (if applicable), and the IEC/IRB 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 IEC/IRB, according to procedures and before subjects are recruited.

12.4 Indemnification, compensation and refund of expenses 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 indemnification of the subject in the event of study-related injuries will comply with applicable regulations. Study subjects will be reimbursed for the study-related expenses (e.g., travel costs, meals, hotel) and may be offered financial compensation for their participation in the study only to the extent permitted by applicable local regulations.

12.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is 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 deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to Actelion or (overruling) local requirements.

All protocol deviations will be reported in the clinical study report (CSR). IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. An amended protocol must be submitted to the IEC/IRB and regulatory authorities, according to their requirements.

12.7 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, and for electronic source data also complete, consistent, enduring, and available when needed.

These records are to be classified into two different categories of documents: ISF and subjects' source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (i.e., 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 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.

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 CRA has been provided personal, read-only and restricted access to study subjects only, 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 it could not be confirmed that the system is validated or if the CRA could not be provided access to the system according to the requirements of Actelion QS documents, the site is requested to print the complete set of source data needed for verification by the CRA. 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 having the same

information as the original source data. The printouts will be considered as the official clinical study records and must be filed with the subject's medical records.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA 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 CRA does not need to verify this process for all data of all subjects but at random and for key data only (e.g., eligibility criteria, primary and key secondary endpoints) as per Actelion's instructions.

12.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the SIV.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, 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 guidelines. The frequency of the monitoring visits will be specified in the monitoring guidelines based on subject recruitment rate and critical data-collection times.

The PI must ensure that the eCRF is completed after a subject's visit (site visit or telephone call), and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(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, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active subjects and all follow-up issues have been resolved. In case a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of Actelion.

12.9 Investigator Site File

Each site will be provided with an ISF prior to the SIV. It will contain all the essential documents that are required to be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of content listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP, as well as instructions from Actelion. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the PI must immediately inform Actelion.

If the PI will change, or if the site will relocate, the CRA must be notified as soon as possible.

12.10 Audit

Sponsor's quality management representatives 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, and applicable regulations; adherence to Actelion's requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

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

12.11 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study (during the study or after its completion) at the site.

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform Actelion (usually via the CRA) that such a request has been made.

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

12.12 Reporting of study results and publication

Actelion will post the key elements of this protocol and the summary of results on Actelion's Clinical Trial Register and within the required timelines on publicly accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by Actelion representatives and the Coordinating Investigator (or PI for single-center studies).

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

The Coordinating Investigator, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion personnel prior to submission to a peer-reviewed journal or presentation at a congress.

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

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or 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; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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 at a congress. 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.

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14 APPENDICES

Appendix 1 Central laboratory abnormalities and alert flags

The adult 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.

Laboratory abnormalities

Laboratory values below or above the normal range will be graded at three levels (H, HH, HHH for values above normal range and L, LL, LLL for values below the normal range) where L stands for "low", H for "high".

The term "marked abnormality" describes laboratory values with grading of abnormalities at two levels: LL/HH and LLL/HHH. These thresholds have been defined by the sponsor in order to flag and/or communicate abnormal laboratory results from the central laboratory to the investigators, and for the purpose of standardized data analysis and reporting by the sponsor. The definitions of marked abnormal values are based mainly on the Common Terminology Criteria for Adverse Events (CTCAE) [CTCAE 2010] grading system and, in specific cases (e.g., lymphocyte levels), are adjusted based on the known pharmacodynamic effect of the study drugs (e.g., LLL threshold for lymphocytes).

The term ALERT here corresponds to a protocol-defined test result threshold requiring an action from the investigator as described in the protocol (e.g., repeat the test; interrupt or discontinue the study drug) and should not be confused with the term "call alert" used by the central laboratory for laboratory results, which will be communicated to the investigator. Not all ALERTS listed in this table will be "call alerts" from the central laboratory and vice versa.

PLEASE NOTE: Thresholds for abnormality of level L or H are not provided in this appendix but will be provided in the central laboratory manual. Parameters for which no threshold is defined in Table 5 may be defined in the central laboratory manual.

Table 5 Thresholds for marked laboratory abnormalities

Parameter (SI unit)	LL	LLL	HH	HHH
Hemoglobin (g/L)	< 100 **ALERT:** **< 100 (re-test)**	< 80 **ALERT:** **< 80 (re-test)**	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)
MCH (pg/Cell)	ND	ND	ND	ND
MCV (fL)	ND	ND	ND	ND
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) > 0.60 (male)	> 0.65
Platelet count (10^9 /L)	< 75	< 50	> 600	> 999
Eythrocyte count (10^{12} /L)	ND	ND	ND	ND
Leukocyte count (10^9 /L)	NA	< 1.9	> 20.0	> 100.0
Lymphocyte (10^9 /L)	ND	< 0.2	> 4.0	> 20
Neutrophils (10^9 /L)	< 1.5	< 1.0	ND	ND
Eosinophils (10^9 /L)	ND	ND	> 5.0	ND
Monocytes (10^9 /L)	ND	ND	ND	ND
Basophils (10^9 /L)	ND	ND	ND	ND
Polymorphonuclear leucocyte/Band cells (%)	ND	ND	> 90%	> 95%
AST (U/L)*	ND	ND	≥ 3 ULN **ALERT:** **≥ 3 ULN** (exclusion at baseline or re-test)	≥ 5 ULN **ALERT:** **≥ 5 ULN** (re-test) **≥ 8 ULN** (discontinuation)

Parameter (SI unit)	LL	LLL	HH	HHH
ALT (U/L)*	ND	ND	≥ 3 ULN **ALERT:** **≥ 3 ULN** (exclusion at baseline or re-test)	≥ 5 ULN **ALERT:** **≥ 5 ULN** (re-test) **≥ 8 ULN** (discontinuation)
Total bilirubin (umol/L)	ND	ND	≥ 2 ULN **ALERT:** **≥ 2 ULN combined with ALT or AST ≥ 3 ULN** (discontinuation)	≥ 5 ULN
Alkaline Phosphatase (U/L)	ND	ND	> 2.5 ULN	> 5 ULN
INR*	ND	ND	≥ 1.5 ULN or ≥ 1.5 × above baseline if on anticoagulation	≥ 2.5 ULN or ≥ 2.5 × above baseline if on anticoagulation
Lactate dehydrogenase	ND	ND	ND	ND
Creatinine (umol/L)*	ND	ND	>1.5 ULN or >1.5 baseline	> 3 ULN or >3 × baseline
eGFR (mL/min/1.73 m^2)	< 60	< 30 **ALERT: < 30** (exclusion at baseline)	ND	ND
Urea (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
Albumin (g/L)	< 30 **ALERT: < 30 combined with total protein < 50** (exclusion at baseline)	< 20	ND	ND
Protein total (g/L)	ND	ND	ND	ND
C-reactive protein (mg/L)	ND	ND	ND	ND
Glucose (mmol/L)	< 3.0	< 2.2	> 8.9	>13.9

Parameter (SI unit)	**LL**	**LLL**	**HH**	**HHH**
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	ND	< 130	> 150	> 155
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1
Chloride (mmol/L)	ND	ND	ND	ND
Triglyceride (mmol/L)	ND	ND	> 3.42	> 11.4
Cholesterol (mmol/L)	ND	ND	> 7.75	> 12.92
Serum pregnancy test	ND	ND	ND	Positive **ALERT:** **Positive**

* HH and HHH based on CTCAE 2010 v4.03 [CTCAE 2010]

ALERT = study-specific alerts that trigger specific actions by the investigator [see Section 5.1.11]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = International Normalized Ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; may be complemented by definitions provided by the central laboratory (see central laboratory manual); NA = not applicable; ND = not defined; SI = international system of units; ULN = upper limit of normal.

Appendix 2 Echocardiography

Image optimization

- Using maximal frequency to increase axial resolution
- Reducing sector width to area of interest in order to increase frame rate.
- Reducing depth to increase size of image on the screen.
- Bringing focus at point of interest to increase lateral resolution
- Adjusting time gain compensation in order to optimize the distribution of gain at different penetration depths
- Optimizing gain and resolution to identify endocardial borders and structures

2D Biplane Simpson method

The Simpson method assumes that the ventricle is cylindrical in shape, which may not apply to a univentricular heart. The Simpson method will split the trace of the ventricle into sections from the apex to the mitral valve. The volume of each section is calculated by multiplying the diameter and the thickness of the slice. The volume of each section is then summed to calculate the total left ventricle volume. It is more accurate to carry out a Simpson measurement in two planes (apical 4 chamber and apical 2 chamber). If done in a single plane it is assumed that the ventricle is circular at each level. By carrying out a Simpson measurement in both the apical 4 and 2 chamber views, the cross-sectional area of each section can be more accurately measured [Leeson 2012].

Apical 1 chamber view

The apical 1 chamber view is obtained by placing the probe at the apical window, which is usually located on the anterior axillary line in the fifth intercostal space. The image obtained should show the chambers at their maximum size and clear images of the infero-septal and antero-lateral walls with optimized views of the endocardial borders.

The ventricular diastolic volume is obtained using the Simpson method:

The end diastolic frame is selected using ECG identification of the R wave.

The endocardial border is then traced from where the basal systemic ventricle wall meets the systemic valve's annulus of the septal wall, to where the basal systemic ventricular wall meets the systemic valve's annulus of the antero-lateral wall.

The ventricular systolic volume is obtained using the Simpson method:

The end systolic frame is selected using ECG identification of the end of the T wave.

The endocardial border is then traced from where the basal systemic ventricular wall meets the systemic valve's annulus of the septal wall, to where the basal systemic ventricular wall meets the systemic valve's annulus of the antero-lateral wall.

The stroke volume is the volume of blood ejected from the heart at end-systole. It is calculated by:

- Systemic ventricle diastolic volume (mL) – systemic ventricle systolic volume (mL) = stroke volume(mL)

The ejection fraction is the percentage change in systemic ventricle volume divided by the initial volume [Otto 2002]. This is calculated by:

- (Systemic ventricle diastolic volume (mL) – systemic ventricle systolic volume (mL))/ systemic ventricle systolic volume × 100 = ejection fraction (%)

The first of the atrial volumes are also measured in this frame using the area length method. The border of the atrium is traced starting from the one side of the AV valve annulus, following the contour of the atrial wall, and finishing at the other side of the valve annulus.

Apical 2 chamber view

To obtain the apical 2 chamber view, begin with the apical 1 chamber image. The probe is then rotated to around 90 degrees in an anticlockwise direction, just before the left ventricular outflow tract is shown. The mitral valve should be kept in the same place and the image shouldn't be foreshortened. The image should then be optimized so clear endocardial borders can be seen.

The ventricular diastolic volume is obtained using the Simpson method:

The end diastolic frame is selected using ECG identification of the R wave.

The endocardial border is then traced from where the basal systemic ventricular wall meets the systemic valve's annulus of the inferior wall, to where the basal systemic ventricular wall meets the systemic valve's annulus of the anterior wall.

The ventricular systolic volume is obtained using the Simpson method:

The end systolic frame is selected using ECG identification of the end of the T wave.

The endocardial border is then traced from where the basal systemic ventricular wall meets the systemic valve's annulus of the inferior wall, to where the basal systemic ventricular wall meets the systemic valve's annulus of the anterior wall.

The following data will be obtained from this method:

- Systemic ventricle diastolic volume (SVDV)
- Systemic ventricle systolic volume (SVSV)
- Stroke volume (mL)
- Ejection fraction.

Those measurements will then form the biplane SVDV, SVSV, stroke volume and ejection fraction results.

The second of the atrial volumes are also measured in this frame, again using the area length method. The border of the atrium is traced starting from the one side of the AV valve annulus, following the contour of the atrial wall, and finishing at the other side of the valve annulus.

Three Chamber apical view

The probe is rotated a further 30 degrees anticlockwise beyond the apical 2 chamber view to bring the left ventricular outflow tract into view and to display the anterolateral and anterior walls of the ventricle.

Cut-off values for valvular defects

Severe AV valve regurgitation is present where the vena contracta is ≥ 7 mm and/or the effective regurgitant orifice is ≥ 0.4 cm^2.

Presence of left ventricular outflow obstruction is confirmed by a pulsed-wave Doppler velocity > 2.5 m/s.

Sources: [AHA/ACC Guideline 2014], [Silversides 2010], [ESC Guidelines 2014].

Appendix 3 Cardiopulmonary exercise testing

Important instructions:
These instructions must be followed for the conduct of the study and supersede any local guidelines for conducting cardiopulmonary exercise testing (CPET). Any deviation from the guideline for the conduct of CPET must be reported to Actelion.
Conditions should be in line with the protocol. Baseline conditions (e.g., same device, about the same time of the day, etc.) for a patient should apply for subsequent tests as much as possible to minimize variability.

General instructions:
CPET is to be carried out within the Cardiology Departments or a dedicated research lab of the hospital/clinic.

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1. Prior to the test, eligibility of the patient for CPET needs to be confirmed (including confirmation of adherence to local safety regulations).

2. Staffing
A minimum of two members of staff are needed for a technician-led CPET, consisting of either:
- Two qualified cardiac physiologists/physiotherapists (or local equivalent).
- A qualified cardiac physiologist/physiotherapist (or local equivalent) and a student who has been signed off on exercise testing.
- A qualified cardiac physiotherapist (or local equivalent)/supervising cardiologist.

CPET led by a cardiologist may be performed without additional personnel.

At least one member of staff must have been on a CPET course or have on the job training (leading the conduct of 25 or more CPET assessments). The leading member of staff should be at least intermediate life support trained and the assisting member of staff should be at least be basic life support certified.

3. Equipment
The following equipment is needed during CPET:
- Bicycle ergometer
- Control unit to control the ergometer
- Electrocardiogram (ECG) recording equipment with printer
- Blood pressure measuring unit and/or manual sphygmomanometer with appropriate cuff sizes
- Chair
- Couch/exam table
- Resuscitation equipment
- Height measure and scales
- Calibration gas
- Masks/mouth pieces and flow meters with associated fittings of various sizes
- Gas and flow analysis equipment
- Pulse-oximetry monitor

All equipment should be appropriately checked before a test is started; the resuscitation equipment should be checked once daily.

4. Before a test is started
The following tasks will need to be completed before a test is started:
- The gas analysis unit should be allowed a minimum of 30 minutes warm-up time.
- The temperature, barometric pressure and humidity should be calibrated against the monitor mounted on the control unit.

5. Before the test
   - The gas analysers and flow meter used for this patient should be calibrated before start (best practice is that this occur within 10 minutes of the start of data collection). Calibration reports should be printed and kept in the site file.
   - The patient's data should be entered into the control unit.
   - The patient's identity should be confirmed.
   - The patient's height and weight should be measured.
   - The patient should be encouraged to ask any questions(s) he might have about the test, which need to be answered as accurately as possible.
   - Explain the rating of the perceived exertion using the Borg scale to the patient.
   - A non-verbal sign for stopping the test should be agreed upon with the patient.
   - Ensure that the patient wears suitable/non-restrictive clothing for the test (e.g., no jeans, no sandals, not multiple layers of clothing)
   - ECG leads should be attached:

     Prepare the skin: shave if necessary, remove skin oils with a cleansing solution followed by light abrasion. If possible, check that the electrode impedance is as low as possible.

     Do not use baby wipes if the patient has eczema or dry skin as this might damage the skin further and is unlikely to decrease the skin-to-electrode impedance in these patients.

     Attach ECG electrodes to the patient's skin using the modified Mason-Likar positions. (The electrodes normally placed on the extremities should be placed on the torso instead.)

     Female patients should be encouraged to wear a brassiere during exercise even if this has been removed to aid electrode positioning.

   - A blood pressure cuff should be place on the patient's arm making sure that the diaphragm is positioned directly over the brachial artery.
   - A mask should be fitted to the patient's face, making sure there are no leaks between the patient's skin and the mask. The calibrated flow meter and the sampling line should be attached to the mask. Alternatively, a mouthpiece can be used.
   - A protocol should be chosen based on the patient's ability to exercise.

6. Data storage (full disclosure); keep original test measurements for transfer to central reading facility.

Patient dialogue

Patient Consent

Ensure written patient consent has been obtained before testing.
The reason for the CPET should be clearly explained, including the risks and benefits of the test.
The patient should be told that they are required to give "maximal effort".
They should be warned that they may feel discomfort, particularly close to maximal exertion.
It should be explained that the test can be stopped at any time if the patient feels "extreme breathlessness, chest pain, light-headed, or nauseated".

The testing protocol should be briefly outlined to the patient:

"This is an exercise test that requires maximal effort. The more effort you put in, the more information we will obtain. The test will begin with a collection of resting measurements, including a breathing test with no pedaling. You will then go into the exercise task and be asked to pedal at approximately 55–65 rpm. After a 3-minute warm up, every minute the workload (resistance) will increase with pedaling becoming more difficult until you won't be able to continue."

Patient information:

"We expect that the test will take 6–12 minutes. It is usually only hard during the last few minutes when we collect the most important data. Throughout the test we want you to pedal between 55–65 rpm. During the test we will be taking your blood pressure and monitoring your heart rhythm to make sure it is safe to keep exercising. When the test has finished we want you to ride for another 5 minutes at a very low workload to help your body recover from the exercise. In the 5 minutes of recovery we will take the mask/mouthpiece off after 30 seconds but keep on the electrodes to measure heart beat and ECG reactions."

"If at any stage you feel any major discomfort such as strong chest pain, severe leg pain or nausea, let us know (we will keep checking with you) and we will stop the test. Otherwise, carry on pedaling until your legs or breathing prevents you from continuing. We will be asking you to indicate on a scale how short of breath you are and how tired your legs are."

Standard operating procedure for a CPET assessment with a bicycle

1. Physical measurements
    - Height (measure without shoes)
    - Weight (measure without shoes and with light clothing)
2. CPET on bicycle with ergometry, ECG registration and blood pressure measurement.
    - Connect gas analyser and perform local calibration protocol before every CPET
    - Make sure patient cannot see the amount of Watt during cycling. Rotation per minute (rpm) should be visible.
3. Test protocol for peak oxygen uptake (VO_2):
    - Basic spirometry should be performed to measure the Forced Expired Volume over 1 second (FEV1), which will then be used to calculate breathing reserve.
    - Allow patient to acclimatize for 3 minutes
    - During this time, collect gas exchange data to ensure the patient shows physiologic response.
    - Measure baseline blood pressure and heart rate (HR) while sitting on the bicycle
    - Cycle for 3 minutes at 10 Watt with an rpm between 55–65
    - Optimal test duration 6–12 minutes
        - Choose individualized continuous RAMP protocol
          RAMP 60 (every minute 6 watt is added)
        - RAMP 90 (every minute 9 watt is added)
        - RAMP 120 (every minute 12 watt is added)
        - Etc.
    - Use the **same** protocol at every test
    - Start RAMP and let patient cycle between 55–65 rpm

   Terminate the test when exhausted:
    - Aim to surpass the anaerobic threshold (ventilatory threshold 2/respiratory compensation point = rise of VE/VCO_2)
    - Aim at RER > 1.1
    - Aim at Borg scale (6–20) > 17
4. After termination of the test, let the patient cycle for 5 minutes at 10 Watt
    - Register reason for test termination and Borg score
    - Register HR after 1 minute (HR recovery)
5. Keep original test measurements for transfer to core center.
    - Complete the CPET worksheet, and if needed the tabular data report for the core center.
    - Complete the source document for investigational sites with appropriate parameters, including resting VO_2, peak VO_2, RER at max, and breathing reserve.
    - Peak VO_2 = mean of highest 30-sec measurement.

Borg-RPE-Scale® Perceived exertion

We want you to rate your perception of exertion, i.e., how heavy and strenuous the exercise feels to you. This is mainly felt as strain and fatigue in your muscles and as breathlessness or possible aches. Try to be as honest as you can. Don't think about the actual physical load. It is your own feeling of effort and exertion that is important. Don't underestimate it, but don't overestimate it either. Look at the scale and the expressions and then give a number. Use whatever numbers you want, also numbers between the expressions.

6	**No exertion at all**	No physical load.
7	**Extremely light**	Very, very light.
8		
9	**Very light**	Such as walking slowly a short while.
10		
11	**Light**	Such as a light exercise at your own pace.
12		
13	**Somewhat hard**	Fairly heavy. Somewhat breathless.
14		
15	**Hard**	Heavy and strenuous. An upper limit for daily exercise.
16		
17	**Very hard**	Very strenuous. You are very tired and breathless.
18		
19	**Extremely hard**	The most strenuous work you have ever experienced.
20	**Maximal exertion**	Maximum effort.

Appendix 4 Specific Activity Scale

Directions:

This scale will help you learn how much exercise and activity your patient is capable of. Ask questions based on your patients' activity in the last 30 days.

Start with # 1 and then follow the messages under the YES or NO to move through this scale. When your message is "Stop", that means you are finished and do not need to read any further. Place an "x" in the box next to the word "Stop". You are finished.

1. Can you walk down a flight of steps without stopping?

YES

2. Can you do any of the following?

a. Carry anything up a flight of 8 steps without stopping

b. Have sexual intercourse without stopping
c. Garden, rake, or weed
d. Roller skate or dance foxtrot
e. Walk at a 4 miles (6.5 kilometers)-per-hour rate on level ground?

Any YES

NO STOP ☐

Class III

3. Can you do any of the following?

a. Carry at least 24 pounds (11 kilograms) up 8 steps
b. Carry objects that are at least 80 pounds (36 kilograms)
c. Do outdoor work- shovel snow, spade soil
d. Do recreational activities such as skiing, basketball, touch football, squash, handball

e. Jog or walk 5 miles (8 kilometers) -per-hour?

Any YES STOP ☐

NO STOP ☐

Class I

Class II

NO

4. Can you do any of the following?

a. Shower without stopping

b. Strip and make a bed
c. Mop floors
d. Hang washed clothes

e. Clean windows

f. Walk 2.5 miles (4 kilometers)-per-hour
g. Bowl
h. Play golf (walk and carry clubs)
i. Push power lawn mower?

Any YES STOP ☐

Class III

5.a. Are you unable to dress without stopping because of symptoms?

Or

5.b. Do you have symptoms when eating or when standing, sitting, or lying relaxed?

NO STOP ☐

YES STOP ☐

Class III

Class IV

Modified from [Goldman 1981].

Appendix 5 Tanner stages (self-assessment)

This assessment is only needed for girls who have not had their menarche.

Instructions for the patient

"*Look at the pictures and read the descriptions in the images below. Think about which stage fits best with your own body and tick the box next to that stage.*"

	Breast	Pubic Hair
☐ **Stage 1**	Small nipples. No breast. 	No pubic hair. 
☐ **Stage 2**	Breast and nipples have just started to grow. The areola has become larger. Breast tissue bud feels firm behind the nipple. 	Initial growth of long pubic hairs. These are straight, without curls, and of light color. 
☐ **Stage 3**	Breast and nipples have grown additionally. The areola has become darker. The breast tissue bud is larger. 	The pubic hair is more widespread. The hair is darker, and curls may have appeared. 
☐ **Stage 4**	Nipples and areolas are elevated and form an edge towards the breast. The breast has also grown a little larger. 	More dense hair growth with curls and dark hair. Still not entirely as an adult woman. 
☐ **Stage 5**	Fully developed breast. Nipples are protruding, and the edge between areola and breast has disappeared. 	Adult hair growth. Dense, curly hair extending towards the inner thighs. 

Modified from [Rasmussen 2015]

Appendix 6 Comparison of RUBATO procedures versus standard of care: comparison of burden and risks

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Patients' status				
Anamnesis, clinical & physical examinations (yearly or bi-yearly)	4 site visits at a specialized cardiologist during a 14 month period.	↗ More frequent monitoring. Content of anamnesis and physical examination not more bothersome. No invasive procedures.	↘ Reduced risk, as more frequent visits could detect earlier signs of deterioration.	Burden is reduced to a minimum and contributes to significant risk reduction (4 site visits over 12 months in RUBATO, versus 1 or 2 for SoC). The significantly reduced natural disease evolution risks outweigh the inconvenience of more frequent visits.
Electrocardiogram (yearly or bi-yearly)	Once at the beginning of the study (and 3 times, i.e., with each CPET) over 14 months.	Performed outside of the CPET assessment. = Performed during the CPET: See CPET.	=	Same burden and same risk as SoC.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Worsening/morbidity event assessment (yearly or bi-yearly)	6 times (clinically) over 14 months. Monthly (clinically) for 10 months, for liver enzymes and hemoglobin.	↗ More frequent monitoring visits. Content of physical examinations and anamnesis not more bothersome. No invasive procedures.	↘ Reduced risk: more frequent visits could detect earlier signs of deterioration. More frequent visits could detect adverse signs of tolerability or safety.	Burden is reduced to a minimum and contributes to significant risk reduction (5 visits over 12 months in RUBATO, versus 1 or 2 for SoC). The reduced study and natural disease evolution risks outweigh the inconvenience of more frequent visits.
Adverse Events & Serious Adverse Events reporting	Mandatory AE and SAE reporting likely more systematic during RUBATO.	= Reporting of AEs or SAEs does not affect the patient	↘ Indirect risk reduction for each patient, as s/he could benefit from the experience provided by other patients in the study.	No burden for the patients, but reduced risks.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Imaging				
Echocardiogram (yearly)	2 times over 14 months.	= Same monitoring in RUBATO.	=	Same burden and same risk as SoC.
Exercise capacity				
NYHA Functional class (yearly)	At each visit The Specific Activity Scale is used as an additional guideline.	= The Specific Activity Scale questionnaire does not take much more time than asking for the NYHA Functional Class.	↘ The Specific Activity Questionnaire is a more systematic (and more objective) evaluation. It should reflect the investigator's opinion, and therefore should avoid bias by patients who tend to underestimate their FC.	Burden is reduced to a minimum and the test is more objective.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
CPET (between twice a year to not necessarily every year)	4 times over 14 months.	↗ It is necessary to document the primary efficacy variable.	↘ Regular performance of CPET provides a detailed evaluation (including ECGs) of patient's improvement or deterioration.	Extra burden contributes to significant risk reduction by having a more frequent and thorough assessment of the patients' exercise capacity.
QoL questionnaires				
Patient interview (at regular visits)	up to 4 times 2–5 questions over 14 months.	= Regular discourse on how the condition affects every day life is part of the interview, and although frequency is higher, the number of replies is minimal.	↘ Using a tool to consistently capture QoL at more frequent intervals provides a granular evaluation of patient's improvement or deterioration.	Using a tool to consistently capture QoL across sites and over time will help establish a baseline for the Fontan population in general.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Blood tests				
Many blood parameters are surveyed (yearly or bi-yearly)	Comprehensive set of parameters are monitored in RUBATO. 4 times over 14 months	↗ More frequent monitoring blood tests = Content of blood tests not more bothersome	↘ Reduced risk, as more frequent, more systematic blood tests could detect earlier signs of deterioration	Burden is reduced to a minimum and contributes to significant risk reduction by providing more frequent results on disease progression. The reduced study and natural disease evolution risks outweigh the inconvenience of more frequent visits.
Is not universally (but increasingly) used as SoC	NT-ProBNP 4 times over 14 months	= Blood collected for NT-ProBNP does not add burden, as it does not entail more frequent collection, nor more blood collected at each blood draw.	↘ Reduced risk, as it may help assess early progression / improvement of heart failure	No extra burden for the patients, but reduced risks.
SoC procedures	**RUBATO procedures**	**Burden**	**Risk**	**Conclusion**

Is not (yet) SoC	Cystatin-C 4 times over 14 months	= Blood collected for Cystatin-C does not add burden, as it does not entail more frequent collection, nor more blood collected at each blood draw.	↘ Reduced risk, as it may help avoid a biased assessment (due to a likely decreased muscular mass of the patients) of the Glomerular Renal Function.	No extra burden for the patients, but reduced risks.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Blood tests				
Liver function related common blood parameters	Will be controlled monthly for the first 6 months and then every 3 months until Week 52,	↗ More frequent, systematic monitoring.	↘ Reduced risk, as it may help detect early progression or liver fibrosis and or cirrhosis.	Burden is reduced to a minimum (local blood draw allowed) and contributes to significant risk reduction by providing more frequent results on disease progression. The reduced study and natural disease evolution risks outweigh the inconvenience of more frequent visits.
Alpha fetoprotein (may not be performed systematically enough)	4 times over 14 months. No invasive procedures.	↗ More frequent, systematic monitoring.	↘ Reduced risk, as it may give early information about liver carcinoma.	Burden is reduced to a minimum and contributes to significant risk reduction by providing more frequent results on disease progression. The reduced study and natural disease evolution risks outweigh the inconvenience of more frequent visits.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Macitentan and metabolite	Pharmacokinetics (PK) of macitentan and metabolites.	↗ These are not routine blood monitoring tests. The only burden involved are 2 extra venipunctures.	↘ Reduced risk, as it provides information that is yet unknown in patients with Fontan-palliation. No macitentan PK data are currently known from adolescents.	Some extra burden justified by the necessity to collect specific PK data in adolescents and adults being administered macitentan in Fontan-palliated patients. No PK data in in Fontan patients exist, so far.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Medicinal treatment				
There are no approved specific drug treatments available for the Fontan-palliated condition. Many medications, although neither approved for this condition nor confirmed for their benefit / risk, are commonly chronically administered to Fontan-palliated patients	Same as for SoC + study drug Only the medications listed in forbidden medications are excluded.	=	=	Same burden and same risk as SoC.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
	Study treatment interruption is allowed for a length of up to 4 weeks	=	=	Same burden and same risk as SoC. The extension of the allowed interruption from 2 to 4 weeks provides more opportunity for subjects (who had a study treatment interruption) to resume study medication and continue to potentially benefit from it. Increased potential overall benefit with no expected negative impact on compliance (neither for adults nor adolescents).

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Examples of these medications:				
Anti-aggregates or anticoagulants	Allowed in RUBATO. Concomitant medications (with doses) are recorded at each visit.	=	=	Same burden and same risk as SoC.
Antiarrhythmics	Allowed in RUBATO. Concomitant medications (with doses) are recorded at each visit.	=	=	Same burden and same risk as SoC.
Medical heart failure therapy, etc.	Allowed in RUBATO. Concomitant medications (with doses) are recorded at each visit.	=	=	Same burden and same risk as SoC.
Not part of SoC	Medications triggering a drug-drug-interaction with macitentan Not allowed in RUBATO.	= Exclusion at baseline or forbidden concomitant medications. Concomitant medications (with	↘ This is to reduce the risk of DDI. If patients have potential drug interactions then they are excluded from the study.	No extra burden for the patients, but reduced risks. These patients are not included in the study.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
		doses) are recorded at each visit.		

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Non-medicinal treatment				
Pacemaker	Not allowed Patients with pacemakers are excluded from RUBATO, because it may interfere with the interpretation of the primary efficacy endpoint.	**No burden**	**No risk** Patients with pacemakers are excluded from study.	These patients are not included in the study.
Implanted defibrillators	Allowed	**No burden**	**No risk**	

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Life-Style recommendations				
Contraception (pregnancies advised only in rare cases)	Initial blood pregnancy tests. Monthly urine tests. These tests are needed because macitentan, like all ERAs, is teratogenic (teratogenicity is a class effect of ERAs). Blood and urine pregnancy tests are needed to ascertain the compliance with the contra-indication.	↗ One initial blood test. Content of blood test not more bothersome. ↗ Monthly urine tests constraining.	↘ This is to reduce the risk of an undesired pregnancy, which in addition to mitigating the inherently increased risks due to a pregnancy in Fontan-palliated patients, helps reduce the risk of a child's congenital defects.	Burden is reduced to a minimum and contributes to significant risk reduction by providing frequent confirmation of non-pregnancy.
Childbearing potential	Self-assessment of puberty by Tanner stage (only for female pre-pubescent subjects)	= Regular evaluation at site visits is not more constraining than answering a few questions.	↘ This is to reduce the risk of an undesired pregnancy, while ensuring contraceptive measures are only imposed on those who need them.	Burden is small as it is a self-assessment ensuring the subject's privacy, while ensuring that appropriate contraceptive measures are initiated when necessary.

SoC procedures	RUBATO procedures	Burden	Risk	Conclusion
Participate in regular exercise	Formal training program excluded. There are no recommendations for performance of physical exercise. This is entirely at the discretion of the patients. Daily physical activities recorded by accelerometer.	= Needed to evaluate the secondary efficacy endpoint. This is a passive (non-invasive) assessment performed for 4 visits, with 9-day sampling periods. This shall not be more constraining than wearing a "fitbit" type of activity device that are very commonly used by many people.	↘ Shall provide patients (once study is finished) with objective information on their lifestyle that could help implement corrective measures (if insufficient physical exercise is detected) or reinforce and encourage further activity (in case of adequate exercise regimen).	Very limited extra burden justified by the necessity to collect daily spontaneous physical activity. Results may contribute to motivate individual patients to exercise more. Collectively these results may document recommendations for physical activity in Fontan-palliated patients.

AE = adverse event; CPET = cardiopulmonary exercise testing; DDI = drug-drug interaction; ERAs = endothelin receptor antagonists; FC = functional class; NT-ProBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; PK = pharmacokinetic(s); SAE = serious adverse event; SoC = standard of care;

Appendix 7 Disease Severity and Impression of Change questionnaires

General Instructions

Questionnaires are completed at the beginning of visits by patients (PGA-S and PGI-C) and clinicians (CGI-S and CGI-C) prior to any study assessment. Clinicians rely on patient interviews rather than assessments performed during past visits to complete the CGI-S and CGI-C.

- Disease severity questionnaires (PGA-S and CGI-S) are completed **at the beginning of each visit** from Randomization (Visit 2) to Week 52 (Visit 6), or EOT in case it occurs prior to Week 52.
- Impression of change questionnaires (PGI-C and CGI-C) are completed **at the beginning of each** visit from Week 16 (Visit 4) to Week 52 (Visit 6), or EOT in case it occurs prior to Week 52.

7.1 Questionnaires to be answered by the subject

The following questions refer to symptoms (e.g. shortness of breath) and impact (e.g. effort to perform daily activities) you may experience due to your heart condition.

Patient Global Assessment of Disease Severity (PGA-S)

Please choose the response that best describes the overall severity of your symptoms and impact you may have experienced due to your heart condition over the past 7 days (week). (Check one response)

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

Patient Global Impression of Change (PGI-C)

Please think about the symptoms and impacts you may have experienced due to your heart condition over the past 7 days (week). Choose the response that best describes the change in overall severity of your symptoms and impact compared to the week before you started treatment.
(Check one response)

- ☐ Very Much Better
- ☐ Moderately Better
- ☐ A Little Better
- ☐ No Change
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very Much Worse

7.2 Questionnaires to be answered by the investigator

The following questions refer to symptoms (e.g. shortness of breath) and impact (e.g. effort to perform daily activities) that the patient may have experienced due to their Fontan-palliated condition.

Clinician Global Impression of Severity (CGI-S)

Please choose the response that best describes the overall severity of the patient's symptoms and impact due to their Fontan-palliated condition over the past 7 days (week). (Check one response)

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Clinician Global Impression of Change (CGI-C)

Please think about the symptoms and impact the patient may have experienced due to their Fontan-palliated condition over the past 7 days (week). Choose the response that best describes the change in overall severity of the patients' symptoms and impact compared to the week before the patient started treatment. (Check one response)

- ☐ Very Much Better
- ☐ Moderately Better
- ☐ A Little Better
- ☐ No Change
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very Much Worse

Appendix 8 EQ-5D-5L questionnaire

General Instructions

Questionnaires are completed at the beginning of visits by subjects.

- The EQ-5D-5L questionnaires are completed at Randomization (Visit 2), Week 16 (Visit 4) and Week 52 (Visit 6), or EOT in case it occurs prior to Week 52.
- If subjects enter the PTOP, the questionnaire will be also be completed over the phone using designated scripts.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

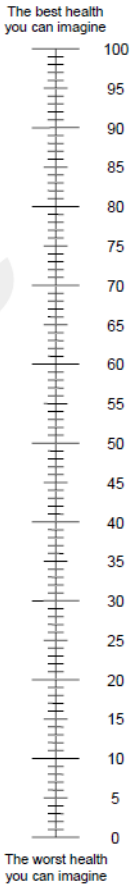
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 9 Protocol Amendment History

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

Amendment	Date	Main reason(s)
1	1 Feb 2017	FDA requests in the context of a special protocol assessment: relegating NT-proBNP to other endpoints and adding accelerometry as secondary endpoint, changing the imputation rule for the primary endpoint and extending the time window for collection of data, including adjustment for missing data in the sample size re-estimation, adding safety measures with regard to hypotension
2	26 Apr 2017	FDA request for vital status at study closure and reporting by ventricular dominance; Voluntary Harmonization Procedure (VHP) request for highly effective contraceptive measures for Europe and comparison of study assessments to standard of care
3	27 Jun 2017	Address restrictions for contraceptive use for European countries (France) not participating in the VHP
4	20 Feb 2018	Introduction of an open-label extension for subjects completing the double-blind study; change of Tanner stage to self-assessment; increase in allowed time for treatment interruption; addition of quality of life and pharmacoeconomic variables
5	27 Aug 2018	Address concerns from BfArM, regarding the new protocol template by reverting to initial safety monitoring modalities. Clarification of subjects' medical care after study completion by confirming that the proposed open-label extension will be accessible to all subjects who complete the study, including those who were in the post-treatment observation period (PTOP).

6	19 Nov 2018	Implementation of Advisory Board recommendations to make the protocol more patient-centric by converting two site visits to phone calls; reducing the number of monthly safety labs; introducing a flying nurse service to reduce the time commitment for the study; updating contraception requirements for new countries.
7	18 Dec 2019	Replacing the blinded SSRE with an IA/unblinded SSRE; formal testing of secondary endpoints; introducing additional exploratory CPET endpoints; adding clarifications for contraceptive use and study completion; introducing use of estimands for the primary endpoint analyses.
8	15 Jul 2020	Updates to forbidden medication and concomitant therapy sections based on newly identified drug-drug interactions.

Appendix 10 Child-Pugh Score

Clinical and Lab Criteria	**Points**		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time Seconds prolonged International normalized ratio	 <4 <1.7	 4-6 1.7-2.3	 >6 >2.3
Child-Pugh class obtained by adding score for each parameter (total points): Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease Class C = 10 to 15 points (most severe liver disease)			

Adapted from Child-Pugh (2012), FDA 2003

Hepatic encephalopathy scoring will be based on the following criteria:

- Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram.
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves.
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cycles per second delta activity.

Actelion Pharmaceuticals Ltd
Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title
Prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group study assessing the efficacy and safety of macitentan in Fontan-palliated adult and adolescent subjects

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RUBATO

Macitentan in Fontan-palliated subjects

Protocol AC-055H301; Phase 3

JNJ-67896062/ACT-064992 Macitentan

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

Status: Approved
Date: 17 June 2020
Prepared by: Actelion Pharmaceuticals Ltd
Document number: D-20.158

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

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 study participants/subjects 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 subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in-person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects 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 subjects on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the subject, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the electronic case report form (eCRF).

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 subject 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

Subject Visits and Assessments

If the regular site visit schedule cannot be maintained due to COVID-19-related restrictions, the site staff must discuss available options with the subject (eg, discontinuation of treatment vs performing visits by telephone) and document the decision in the subject's chart. If the decision is made to remain in the study, the guidance below is to be followed:

- **General handling of surrogacy for on-site assessments performed remotely:**

  If a visit is conducted remotely, information on any adverse event, serious adverse event, clinical worsening/morbidity event, NYHA functional class, and concomitant medication, as well as the EQ-5D-5L questionnaire, should be collected, and data recorded in the eCRF with the actual date of the telephone call documented. Information on physical examinations and vital signs may also be reported, if these have been conducted locally. These will be captured in the source notes and any relevant abnormalities reported as adverse events.

- **Handling of safety monitoring**

  If medical oversight of safety assessments (including but not limited to laboratory values) cannot be performed and reviewed by the investigator, the investigator may decide to interrupt or discontinue study intervention if it is in the best interest of the subject.

  Options for conduct of safety laboratory assessments are described in protocol section 7.2.4.1 and include laboratory samples taken at study site, at a satellite laboratory, collected via home healthcare (HHC) visits service (also known as "flying nurse service)", or taken and analyzed locally.

  If in-(subject) person collection of safety assessments at the investigational study site is not possible, these alternative options continue to be valid.

  For women of childbearing potential, monthly pregnancy tests are required. If a subject cannot come to the site, the urine pregnancy tests provided to the site for on-site visits may be shipped (if allowed per local regulation) to the subject for use at home under guidance from the site.

  Laboratory samples that are missed or delayed due to the COVID-19 pandemic will be identified as issues in the clinical trial management system (CTMS) as "COVID-19-related issue" and/or as protocol deviations in the Medidata RAVE system (eCRF) as "COVID-19-related protocol deviation".

- **Handling of pharmacokinetic (PK) assessments**

  Pharmacokinetic (PK) samples that cannot be collected at study site may either be collected at a local laboratory or via HHC. If samples are collected by HHC, a central laboratory kit will be used. Missed PK samples may be collected at another study site visit, provided that the subject is still under study treatment.

- **Handling of efficacy assessments**

  If subjects cannot have their cardiopulmonary exercise testing (CPET) assessments conducted at the study site as expected, these CPET should be done at the earliest possibility during a scheduled or unscheduled visit.

  For Week 52, the CPET assessment could be conducted up to 8 weeks later and as long as subjects have not started open-label treatment.

  If a site visit cannot be conducted, devices for data collection of Physical Activity measured by Accelerometer (PA-Ac) may be shipped to study subjects (and returned to site by them) as already described for certain visits in the RUBATO Accelerometry Manual (as applicable to protocol V 7 and V 8).

  CPET or PA-Ac assessments that were missed specifically due to COVID-19 will be identified in the CTMS as "COVID-19-related issue" and/or as protocol deviations in the Medidata RAVE system (eCRF) as "COVID-19-related protocol deviation".

- **Handling of safety and efficacy data integrity**

  The study Independent Data Monitoring Committee (IDMC) will be provided with listings of COVID-19-related protocol deviations and will be asked to evaluate their impact on study safety and efficacy outcomes at the next IDMC meeting.

  In parallel, the sponsor will continue to monitor the COVID-19 related protocol deviations and evaluate their impact on study safety and efficacy outcomes.

Study treatment supply

- Every effort should be made to keep study subjects on treatment as deemed clinically appropriate. If a subject cannot come to the site to receive study treatment, the study treatment may be provided via a direct-to-patient shipment to the subject's home or distributed to a subject's relative/caregiver in accordance with local regulations.

  The subject will be asked to return empty study medications bottles / unused tablets at their next site visit. Treatment compliance will meanwhile be assessed via monthly phone calls.

  This distribution and shipment of study treatment will be done if the treating physician can ensure that they maintain subject safety oversight (based on clinical evaluation, results of laboratory tests and pregnancy test [if applicable] as described in the section above "Handling of safety monitoring").

Premature discontinuations from study treatment or from the study due to the COVID-19 pandemic will be documented in the Medidata RAVE system (eCRF) with the reason "COVID-19-related".

Source Data Verification/Monitoring

- 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.

COVID-19 Illness in Subjects

- The investigator should consider the risk/benefit of continuing study treatment based on the nature and status of the subject's underlying condition and the potential risks associated with COVID-19.

- Positive test results for COVID-19 as well as any associated symptoms should be recorded as adverse events, and if the subject is hospitalized in relation to COVID-19, the event should be captured as a serious adverse event.

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.

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): Thierry Francis Briand

Institution: Actelion Pharmaceuticals Ltd

Signature: PPD Date: PPD
(Day Month Year)

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