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

Macitentan / ACT 064992

Macitentan in Fontan-palliated subjects

Protocol AC-055H302

RUBATO OL

Prospective, multi-center, single-arm, open-label long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects

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Macitentan / ACT-064992 **EudraCT 2018-002821-45**
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Treatment name / number

Macitentan / ACT 064992

Indication

Macitentan in Fontan-palliated subjects

Protocol number, study acronym, study title

AC-055H302, RUBATO OL, Prospective, multi-center, single-arm, open-label extension study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects.

I approve this protocol.

Title	Name	Date	Signature
Clinical Trial Physician	PPD		
Clinical Trial Scientist	PPD		
Clinical Trial Statistician	PPD		

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INVESTIGATOR SIGNATURE PAGE

Treatment name / number: Macitentan / ACT 064992

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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	Town	Date	Signature
Principal Investigator			_____	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3, Version 4	19 November 2020
Amendment 2, Version 3	16 July 2020
Amendment 1, Version 2	20 February 2019
Original Protocol, Version 1	16 July 2018

Amendment 3 (19 November 2020)

Overall Rationale for the Amendment: The purpose of this amendment is to align the study protocol with updates made for the AC-055H301 RUBATO study. Countries who did not enroll candidates for RUBATO OL during the RUBATO study were removed from the section on acceptable methods of contraception. Study treatment supply and storage information was simplified as part of the Actelion and Janssen integration.

The study duration is being adapted to help ensure treatment with macitentan is available after the expected treatment duration of 2 years per patient. Additionally, global safety updates were made to align the protocol with Janssen processes as part of the Actelion and Janssen integration. Furthermore, based on recent literature [Udholm 2018] on the potential prognostic value of cardiopulmonary exercise testing (CPET) in Fontan-palliated patients, the Sponsor added two new exploratory efficacy endpoint variables that have not been collected thus far but were already part of the CPET assessments evaluated by the central reading facility. One of these variables, oxygen update/consumption (VO_2) at ventilatory anaerobic threshold (VAT), has also been claimed [Goldberg 2019] to be of interest in a recently completed study with a phosphodiesterase 5 inhibitor (PDE5i). Finally, an appendix was added to facilitate evaluation of exclusion criterion 3.3.

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

Section number and Name	**Description of Change**	**Brief Rationale**
3.1.1 Study periods	Update of treatment period definition to state that 104 weeks of study treatment for each subject refers to after the last participant has completed the AC-055H301 treatment period The safety follow-up period definition was updated to state that subjects could enter a post-trial access program	Updated to clarify treatment period definition. Updated to clarity when subjects could enter the post-trial access program.

Section number and Name	Description of Change	Brief Rationale
	as soon as their eligibility had been confirmed. Statement added that no S-FU will be performed for subjects entering the post-trial access program.	Updated for clarity.
3.1.2 Study duration	Updated to state that the study will continue until the last subject has completed 104 weeks of treatment and their S-FU period.	Updated for clarity.
4.4 Exclusion criteria	Footnote 4 added.	Added for clarity.
4.5.2.1 Denmark, Germany, and UK	Removal of Germany from the subheading.	No longer applicable to this study
4.5.2.2 Czech Republic, and Poland	Removal of Ireland from the subheading.	No longer applicable to this study.
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.
5.1.6 Study treatment supply	Location of study drug manufacture sites removed.	Information removed to allow greater flexibility.
5.1.6.2.2 Study treatment storage	Specific temperature range for study drug storage removed. Highly detailed information regarding study drug storage temperature regulations and deviation reporting requirements removed.	Superfluous information removed for clarity.
5.1.10.1 Liver aminotransferase abnormalities; 7.2.4.1 Type of laboratory; 9.1 Definition of adverse events; 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.
6.1 Efficacy endpoints	Inclusion of change in VO_2 at VAT and change in oxygen update efficiency slope.	Added two exploratory efficacy endpoint variables as an alignment with the RUBATO study.
7.1.1 Enrollment	Information added regarding re-consenting of participants.	Added for clarity.

Section number and Name	**Description of Change**	**Brief Rationale**
7.1.2 Unscheduled visits	Table 2 updated to add visit 5 and add footnote 11. Additional text was added to footnotes 3 and 9 for clarity.	Table updated to state the changes in the study duration.
7.2.2.1 Cardiopulmonary exercise testing	Information about determination of VO2 at VAT and OUES is updated and corresponding reference is cited.	Updated as new efficacy endpoints were added during this amendment.
7.2.2.3 NT-proBNP measurement	Assessments at Visits 3 to 5 replaced with assessments at every 26 week visit.	Updated to reflect changes in study duration.
7.2.4 Laboratory assessments	Aminotransferase and hemoglobin tests at weeks 39, 65, and 91 replaced with assessments every 12 weeks.	Updated to reflect changes in study duration.
7.2.4.1 Type of laboratory	"Actelion Pregnancy Form" updated to Pregnancy Notification Form".	Updated to align with Janssen processes.
8.1 Study completion as per protocol	Included that study completion will occur after the last subject has had 2 years of treatment. Additional clarifications regarding the S-FU visit were added.	Updated to reflect changes in study duration.
8.2 Premature withdrawal from study	Inclusion of locator agencies.	Information added for clarity.
9 Safety definitions and reporting requirements	Introductory paragraph moved from section 9.5 to this location and modified to cover all AEs.	Updated for clarity and 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.
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	Text added defining sponsor responsibilities relating to AE and SUSAR reporting.	Included to align with Janssen processes.
9.3 Pregnancy	<u>9.3.1 Reporting of pregnancy</u> 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"	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

Section number and Name	**Description of Change**	**Brief Rationale**
	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 added.	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 moved from 9.5.2 to 9.7.	Updated to align with Janssen processes.
Synopsis; 10.2.1 Efficacy variables	VO_2 at VAT, OUES added.	Updated as these efficacy endpoints were added during this amendment
10.2.2 Safety variables; 10.2.2.1 Adverse events	Removal of respiratory tract infections from AEs of special interest.	Removed as not considered an AESI for macitentan.
10.3.2 Sub-group analyses	Subgroup analyses based on age (<18; ≥ 18 and < 65 and ≥ 65 years) and race (White, Asian, Other) & Ethnicity (Hispanic / Non-Hispanic) will not be conducted and hence deleted. Race (White, Asian, Other) & Ethnicity (Hispanic / Non-Hispanic).	Removed to align with RUBATO DB protocol.
13 References	References added.	Added to support reference included in the text.
Appendix 6 Comparison of RUBATO OL procedures versus standard of care: comparison of burden and risks	Frequency of liver function related common blood parameter assessments updated from every 3 months until Week 104 to every 12 weeks until EOT.	Updated to reflect changes in study duration.
Appendix 7 Child-Pugh Classification	Appendix Added.	Added as an aid to correctly evaluate exclusion criterion 3.3.

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

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AV	Atrioventricular
BP	Blood pressure
BR	Breathing reserve
CHD	Congenital heart disease
CPET	Cardiopulmonary exercise testing
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria For Adverse Events
CYP3A4	Cytochrome P450 3A4
DB	Double-blind
ECG	Electrocardiogram
ECHOC	Echocardiography
eCRF	electronic Case Report Form
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
ET	Endothelin
ET_A	Endothelin receptor A
ET_B	Endothelin receptor B
EU	European Union
FC	Functional class
FEV_1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GFR	Glomerular filtration rate

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
ISF	Investigator Site File
KM	Kaplan-Meier
LTMAS	Long-term Macitentan Analysis Set
MedDRA™	Medical Dictionary for Regulatory Activities
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)
OLES	Open-label Extension Set
OUES	Oxygen uptake efficiency slope
PA-Ac	Physical Activity measured by Accelerometer
PAH	Pulmonary arterial hypertension
PI	Principal Investigator
PLE	Protein-losing enteropathy
PORTICO	PORtopulmonary Hypertension Treatment wIth maCitentan – a randOmized Clinical Trial
PQC	Product quality complaint
QS	Quality System
RER	Respiratory exchange ratio

RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
S-FU	Safety follow-up
SIV	Site Initiation Visit
SpO_2	Peripheral oxygen saturation
SYE	Subject-years exposure
TMAS	Total Macitentan Analysis Set
ULN	Upper limit of normal
VAT	Ventilatory anaerobic threshold
VCO_2	Carbon dioxide production
VE	Minute ventilation
VO_2	Oxygen uptake/consumption ($\dot{V}O_2$ is a flow = a ratio of a volume by unit of time)

PROTOCOL SYNOPSIS AC-055H302 RUBATO OL

TITLE	Prospective, multi-center, single-arm, open-label, long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects
ACRONYM	RUBATO OL
OBJECTIVES	**Primary objective(s)** To assess the long-term safety and tolerability of macitentan in Fontan-palliated adult and adolescent subjects. **Secondary objectives** • To assess the effect of macitentan on exercise capacity (measured by peak oxygen uptake [VO_2]). • To assess the effect of macitentan on daily Physical Activity measured by Accelerometer (PA-Ac) **Other objectives** Other objectives are described in Section 2.3.
DESIGN	A prospective, multi-center, single-arm, open-label, long-term, Phase 3 study
PERIODS	**Enrollment period:** The enrollment period for a subject begins with the visit at Week 52 of the double-blind (DB) study, AC-055H301 RUBATO DB and signing of the informed consent form (ICF), and lasts until the administration of the first dose in the AC-055H302 RUBATO open-label (OL) study (Visit 1). **Treatment period:** The OL treatment period will start with the administration of the first dose of macitentan 10 mg and last until whichever of the following occurs first: • 104 weeks (2 years) of treatment for each subject after the last participant has completed the AC-055H301 RUBATO DB treatment period. • The subject or the investigator decides to discontinue the study drug. • The sponsor decides to stop this AC-055H302 RUBATO OL study.

	Safety follow-up (S-FU) period: For an individual subject, S-FU starts on the day after the last dose of OL study treatment and ends 30 to 35 days thereafter with the End-of-Study (EOS) Visit. **EOS:** For an individual subject, the study is completed with the EOS Visit. For all subjects, EOS corresponds to the last visit performed in this AC-055H302 RUBATO OL study.
PLANNED DURATION	Approximately 225 weeks from first subject, first visit, to last subject, last visit.
SITE(S) / COUNTRY(IES)	31 sites in 11 countries (planned).
SUBJECTS / GROUPS	Up to the maximum number of randomized subjects in the double-blind AC-055H301 RUBATO study, planned to be approximately 134 subjects* treated with macitentan 10 mg * Sample size of the DB part of the study may be increased to a maximum of 268 subjects, based on the interim analysis for sample size re-estimation during the double-blind AC-055H301 RUBATO DB study.
INCLUSION CRITERIA	1. Written informed consent/assent from the subject and/or a legal representative prior to initiation of any study-mandated procedures. 2. Subjects who have completed Week 52 of AC-055H301 RUBATO DB. 3. Women of childbearing potential must 3.1. Have a negative serum pregnancy test prior to first intake of OL study drug, and, 3.2. Agree to perform monthly pregnancy tests up to the end of the S-FU period, and, 3.3. Must use reliable methods of contraception from enrollment up to at least 30 days after study treatment discontinuation [see Section 4.5.2].
EXCLUSION CRITERIA	1. Clinical worsening leading to medical interventions including reoperation of Fontan circulation (Fontan take-down) during the enrollment period. 2. Systolic blood pressure (BP) < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height) at rest.

	3. Criteria related to macitentan use: 3.1. Hemoglobin < 75% of the lower limit of normal assessed by central laboratory at enrollment 3.2. Known or suspected pulmonary veno-occlusive disease 3.3. Known and documented severe hepatic impairment defined as Child Pugh Score C, [Appendix 7] 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 3.4. Serum aspartate and/or alanine aminotransferases > 3 × upper limit of normal range assessed by central laboratory at enrollment 3.5. Severe renal impairment (estimated creatinine clearance < 30 mL/min/1.73m^2) assessed by central laboratory at enrollment 3.6. Pregnancy, breastfeeding, or intention to become pregnant during the study, or women of childbearing potential not using a reliable method of contraception 3.7. Hypersensitivity to any active substance or excipient of any of the study drugs 3.8. 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 enrollment (Visit 1) 3.9. Treatment with a strong CYP3A4 inhibitor such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir, within 1 month prior to enrollment (Visit 1) 3.10. Criterion modified per Amendment 2 Treatment with a moderate dual CYP3A4/CYP2C9 inhibitor (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors within 1 month prior to enrollment (Visit 1) 4. General exclusion criteria: 4.1. Any factor or condition likely to affect protocol compliance of the subject, as judged by the investigator 4.2. Treatment with another investigational therapy during the OL study 4.3. Treatment with ERAs other than macitentan

	4.4. 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 4.5. Any planned surgical intervention (e.g., organ transplant) during the study period, except minor interventions (e.g., tooth extraction) 5. 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** Not applicable
ENDPOINTS	**Efficacy endpoints** • The change in peak VO_2, from baseline to each scheduled time point. • Change in ventilatory efficiency (assessed as minute ventilation [VE] / carbon dioxide production [VCO_2] slope), from baseline to each scheduled time point. • Change in VO_2 at ventilatory anaerobic threshold (VAT), from baseline to each scheduled time point. • Change in oxygen uptake efficiency slope (OUES), from baseline to each scheduled time point. • Change from baseline to each scheduled time point in mean count per minute of daily PA-Ac. • Change from baseline to each scheduled time point in daily mean time in minutes spent in sedentary, light, moderate, or vigorous PA-Ac. • Percent of baseline at each scheduled time point in N-terminal prohormone of brain natriuretic peptide (NT-proBNP). • Composite endpoint of event related to Fontan-palliated clinical worsening, time to first occurrence of clinical worsening up to EOS, defined as one or more of the following:

	○ Unscheduled hospitalization for Fontan-palliated morbidity event[1] ○ Signs and symptoms of heart failure[2], requiring change in diuretic therapy ○ Clinical worsening leading to interventions related to the Fontan-palliated condition ○ Worsening to New York Heart Association functional class (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 endothelin receptor antagonists), 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, atrioventricular valve repair/ replacement) – Worsening to NYHA FC IV, investigator assessed using the Specific Activity Scale [Appendix 4]. – Protein-losing enteropathy (PLE) – Plastic bronchitis/chyloptysis – Peritoneal, pleural, mediastinal, or pericardial effusions – Severe hepatic impairment (as described in exclusion criterion 3.3) – Severe renal impairment (as described in exclusion criterion 3.5) – Death related to Failing-Fontan

[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] 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.

	• Events related to Fontan palliated morbidity, time to first occurrence up to EOS of one or more of the following:
	  o Ventricular tachyarrhythmia or supraventricular tachyarrhythmia[3]
	  o Thrombotic or hemorrhagic complications (including thromboembolism and hemoptysis).
	• Time to death (all-cause mortality) up to EOS.
	Safety endpoints
	• Treatment-emergent adverse events (AEs) and serious AEs up to 30 days after study treatment discontinuation and AEs leading to death.
	• AEs leading to premature discontinuation of study treatment.
	• Change in vital signs (systolic and diastolic arterial BP and pulse rate), including peripheral oxygen saturation (SpO_2) and body weight over time.
	• Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation.
	• Change in laboratory parameters over time.
	Pharmacoeconomic endpoints related to hospitalization
	Pharmacoeconomic endpoints are described in Section 6.3

ASSESSMENTS	Refer to the schedule of assessments in Table 2.

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

STATISTICAL METHOD-OLOGY	**Analysis sets** There will be three main analysis sets: i. The Total Macitentan Analysis Set (TMAS) includes all subjects who received at least one dose of macitentan 10 mg either in the main study (AC-055H301 DB) or in the long-term study (AC-055H302 OL). ii. The Long-term Macitentan Analysis Set (LTMAS) includes all subjects randomized to macitentan 10 mg in the main study (AC-055H301 DB) regardless of subsequent enrollment into the AC-055H302 OL study. iii. The Open-label extension set (OLES) includes all subjects treated with macitentan 10 mg in AC-055H302 RUBATO OL. **Analyses** The long-term safety of macitentan will primarily be assessed on the TMAS. The long-term efficacy of macitentan will primarily be assessed on the LTMAS. Both efficacy and safety will also be assessed on the OLES. Variables are summarized using appropriate descriptive statistics: • For continuous variables (e.g. the change in peak VO_2 over time, the change in mean count per minute of daily PA-Ac, change in ventilatory efficiency, percent of baseline in NT-proBNP and absolute change from baseline in NT-proBNP, change in laboratory parameters): number of non-missing observations, mean, standard deviation, minimum, Q1, median, Q3 and maximum. • For dichotomous or categorical variables (e.g. treatment-emergent AEs, serious AEs (SAEs), AEs leading to premature discontinuation of study treatment, AEs leading to death, AE of special interest, vital signs abnormalities, treatment-emergent marked laboratory abnormalities: number of non-missing observations, and frequency with percentage per category. Denominators for percentages are the number of subjects in corresponding analysis data sets, unless otherwise specified. • For time-to-event variables (time to death, time to first occurrence of composite endpoint of events related to

	Fontan-palliated clinical worsening, time to first occurrence of events related to Fontan-palliated morbidity, number of events, number of subjects at risk, number of censored observations and Kaplan-Meier estimates with 2 sided 95% confidence intervals at relevant time points. To account for differences in the duration of treatment exposure among subjects, incidence rates of AEs, SAEs, AEs leading to discontinuation, AEs of special interest, and deaths will be presented as adjusted for subject-years exposure.
STUDY COMMITTEES	To ensure subjects' safety, an independent Data Monitoring Committee (IDMC) will review the data from the AC-055H302 RUBATO OL study on a regular basis until the end of the AC-055H301 RUBATO DB study (i.e., OL data will be reviewed only in combination with the data of the DB study). Once the AC-055H301 RUBATO DB study has concluded, the IDMC will no longer continue to monitor the AC-055H302 RUBATO OL study. After that, the sponsor will continue to review the data on an ongoing basis.

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 et al. 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 [Diller 2015].

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 on the efficacy and tolerability of endothelin (ET) receptor blockade in Fontan-palliated patients, after successful surgery [Derk 2015]. Among these studies, the placebo-controlled clinical study TEMPO [Hebert 2014] was conducted in Denmark and Sweden with bosentan in 75 Fontan-palliated patients. 69 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 (pulmonary vascular resistance [PVR] decrease) and functional improvement (NYHA) in adults and adolescents. This small prospective cohort study conducted without a control group by Agnoletti et al. [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 $*m^2$. 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 treated with 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 [Agnoletti 2017].

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

Detailed information on macitentan, is provided in 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 [Macitentan IB].

1.3 Purpose and rationale of the study

The purpose of the AC-055H302 RUBATO open-label (OL) study is to assess the long-term use of macitentan in Fontan-palliated adult and adolescent subjects beyond the 52 weeks of treatment in the AC-055H301 RUBATO double-blind (DB) study.

The primary objective of this study is to assess the long-term safety and tolerability of macitentan in this population.

The rationale of this study relies on the fact that the long-term safety of macitentan in this population is not known. The dynamic of the effect of macitentan over time is also unknown, e.g., whether the efficacy of macitentan (if any) is sustained beyond 52 weeks (end of the DB study).

In addition, the opportunity will be given to subjects who were on placebo in the AC-055H301 RUBATO DB study to receive macitentan 10 mg and potentially benefit from an active treatment.

1.4 Summary of known and potential risks and benefits

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

Effects on BP

Macitentan is a vasodilator. However, in the pivotal study in PAH [Pulido 2013], no difference in mean change from baseline in 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. In the pivotal placebo-controlled study in PAH (SERAPHIN [Pulido 2013] study) such events were reported with similar incidences for macitentan and placebo patients. 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, and 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 study 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 are provided in the IB [Macitentan IB].

Benefit

It is expected that macitentan treatment in Fontan-palliated patients 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 to stop subject's participation if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

2 STUDY OBJECTIVES

2.1 Primary objective

To assess the long-term safety and tolerability of macitentan in Fontan-palliated adult and adolescent subjects.

2.2 Secondary objectives

- To assess the effect of macitentan on exercise capacity (measured by peak VO_2).
- To assess the effect of macitentan on daily Physical Activity measured by Accelerometer (PA-Ac).

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 time to first occurrence of clinical worsening (or morbidity) events.
- To assess the effect of macitentan on pharmacoeconomic endpoints related to hospitalization.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, single-arm, open-label, long-term, Phase 3 study.

Up to the maximum number of randomized subjects in the double-blind AC-055H301 RUBATO study, planned to be approximately 134 subjects will be enrolled to macitentan 10 mg once daily (o.d.). Sample size may be increased to a maximum of 268 subjects depending on interim analysis for sample size re-estimation during the AC-055H301 RUBATO DB study. This study will be conducted in approximately 31 sites in 11 countries.

3.1.1 Study periods

The study comprises the following consecutive periods:

Enrollment period: The enrollment period for a subject begins with the visit at Week 52 in the DB study, AC-055H301 RUBATO DB and signing of the informed consent form (ICF), and lasts until the administration of the first dose in the AC-055H302 RUBATO OL study (Visit 1).

Treatment period: The OL treatment period will start with the administration of the first dose of macitentan 10 mg and last until whichever of the following occurs first:

- 104 weeks (2 years) of study treatment for each subject after the last participant has completed the AC-055H301 RUBATO DB treatment period.
- The subject or the investigator decides to discontinue the study drug.
- The sponsor decides to stop this AC-055H302 RUBATO OL study.

Safety follow-up (S-FU) period: For an individual subject, starts on the day after the last dose of OL study treatment and ends 30 to 35 days thereafter with the End-of-Study (EOS) Visit.

Subjects eligible to enter a post-trial access program 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 drug in a post-trial access program.

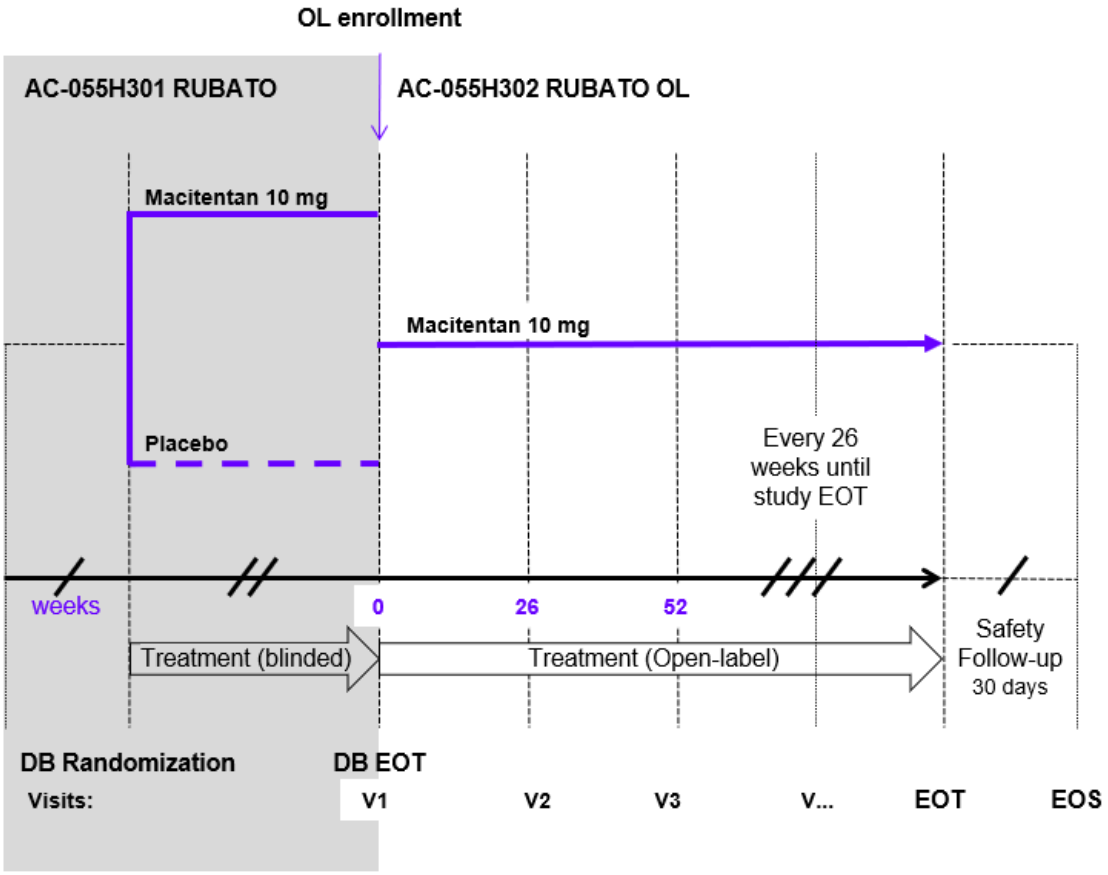
EOS: For an individual subject, the study is completed with the EOS Visit.

For all subjects, EOS corresponds to the last visit performed in this AC-055H302 RUBATO OL study.

The visit schedule and protocol-mandated procedures are performed according to the table of assessments [Table 2] and are described in Section 7.

The overall study design is depicted in Figure 1.

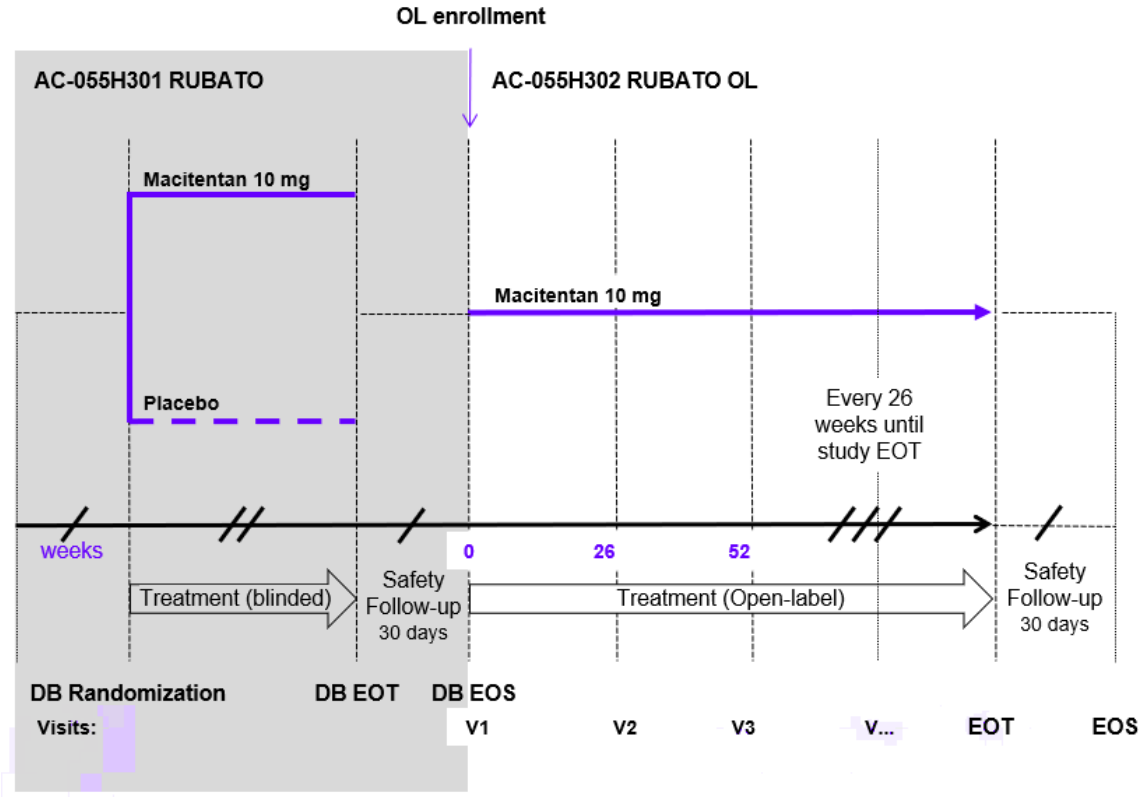
Figure 1 Study design



DB = Double-blind (study); EOS = End-of-Study; EOT = End-of-Treatment; OL = Open-label (extension); V = visit
☎= Telephone call (for visit).

In instances where administration of AC-055H302 RUBATO OL study drug does not immediately follow End-of-Treatment (EOT) in the AC-055H301 RUBATO DB study, the subject will enter the normal DB S-FU period until administration of the first dose of the OL study drug occurs [Figure 2].

Figure 2 Study design (with S-FU in the AC-055H301 RUBATO DB study)



DB = Double-blind (study); EOS = End-of-Study; EOT = End-of-Treatment; OL = Open-label (extension); S-FU = Safety Follow-up; V = visit; ☎= Telephone call (for visit).

No S-FU will be performed for subjects entering a post-trial access program at individual subject's EOT for the AC-055H302 RUBATO OL study.

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., first ICF signed) and ends with the last visit / telephone call of the last subject.

Study AC-055H302 RUBATO OL will continue at each site until the last subject has globally completed 104 weeks (2 years) of treatment and their S-FU period, or withdrawal from the study, or the sponsor decides to end the study.

3.2 Study design rationale

The AC-055H302 RUBATO OL study population consists of subjects who have completed Week 52 of AC-055H301 RUBATO DB. Subjects will be rolled over from the DB study to

this OL study without knowledge of their previous study treatment (macitentan 10 mg or placebo). The eligible subjects are those who fulfilled the inclusion and exclusion criteria prior administration of the first dose of macitentan in AC-055H302 RUBATO OL study.

The selection of subjects who complete the 52-week AC-55H301 RUBATO DB study period allows the inclusion only of those subjects who are sufficiently stable on study drug and/or on concomitant medications and hence can potentially benefit from further treatment. It should be noted that subjects who experience a disease progression during the DB study (see AC-055H301 RUBATO study protocol section 6.1.3) can be treated with the available standard of care. If they continue into the study up to the Week 52 Visit, they are allowed to enter this AC-055H302 OL extension, if they still fulfill the selection criteria.

3.3 Study committees

An Independent Data Monitoring Committee (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 operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter. This IDMC will monitor data from the AC-055H302 RUBATO OL study together with the data from the AC-055H301 RUBATO DB study. Once the AC-055H301 RUBATO DB study has concluded, the IDMC will no longer continue to monitor the AC-055H302 RUBATO OL study. After that, the sponsor will continue to review the data on an ongoing basis.

An ILSDRB (an external expert committee of hepatologists), has been appointed to provide ongoing assessment and advice regarding serious hepatic adverse events (AEs) of special interest that require further evaluation during the study as per the ILSDRB charter.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll adolescent (> 12 years) and adult male and female subjects who had previously participated in the AC-055H301 RUBATO DB study.

They must have completed Week 52 of AC-055H301 RUBATO DB.

Women of childbearing potential must not be pregnant, breastfeeding, or intend to become pregnant during the study, and must 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 (other than macitentan as study treatment) is not permitted during this study.

4.2 Rationale for the selection of the study population

The study population includes those subjects who have completed the AC-055H301 RUBATO DB study and have experienced good tolerability of study drug, with an absence of safety concerns that would have led to a premature EOT.

Therefore, it is ethically acceptable and possibly in their interest to continue on a potentially beneficial treatment.

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. Subjects who have completed Week 52 of AC-055H301 RUBATO DB.
3. Women of childbearing potential must:
   3.1. Have a negative serum pregnancy test prior to first intake of OL study drug, and,
   3.2. Agree to perform monthly pregnancy tests up to the end of the S-FU period, and,
   3.3. Must use reliable methods of contraception from enrollment up to at least 30 days after study treatment discontinuation [Section 4.5.2].

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. Clinical worsening leading to medical interventions including reoperation of Fontan circulation (Fontan take-down) during the enrollment period.
2. Systolic BP < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height) at rest.
3. Criteria related to macitentan use:
   3.1. Hemoglobin < 75% of the lower limit of normal assessed by central laboratory at enrollment
   3.2. Known or suspected pulmonary veno-occlusive disease

3.3. Known and documented severe hepatic impairment defined as Child Pugh Score C [Appendix 7][4], 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

3.4. Serum AST and/or ALT > 3 × upper limit of normal range assessed by central laboratory at enrollment

3.5. Severe renal impairment (estimated creatinine clearance < 30 mL/min/1.73m^2) assessed by central laboratory at enrollment

3.6. Pregnancy, breastfeeding, or intention to become pregnant during the study, or women of childbearing potential not using a reliable method of contraception

3.7. Hypersensitivity to any active substance or excipient of any of the study drugs

3.8. 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 enrollment (Visit 1)

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

3.10. Criterion modified per Amendment 2
Treatment with a moderate dual CYP3A4/CYP2C9 inhibitor (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors within 1 month prior to enrollment (Visit 1)

4. General exclusion criteria:

4.1. Any factor or condition likely to affect protocol compliance of the subject, as judged by the investigator

4.2. Treatment with another investigational therapy during the OL study

4.3. Treatment with ERAs other than macitentan

4.4. 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

4.5. Any planned surgical intervention (e.g., organ transplant) during the study period, except minor interventions (e.g., tooth extraction)

[4] The assessment for hepatic impairment must be fully documented in the medical notes for subjects that have clinical signs and evidence (from central or local labs) of hepatic impairment (Child Pugh Score as per Appendix 7). This means that for subjects who have no clinical signs of hepatic impairment, investigators must be requested to document in their medical notes that "based on clinical signs and evidence from local or central labs results the patient does not have severe hepatic impairment".

5. 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:

- Tubal sterilization (occlusion or ligation of tubes at least 6 weeks prior to screening),
- 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 during the enrollment period up to at least 30 days after study treatment discontinuation. Reliable contraception must be started at least 30 days prior to Visit 1.

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 Denmark and UK

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 the countries in reference, 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).

4.5.2.2 Czech Republic and Poland

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.

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.

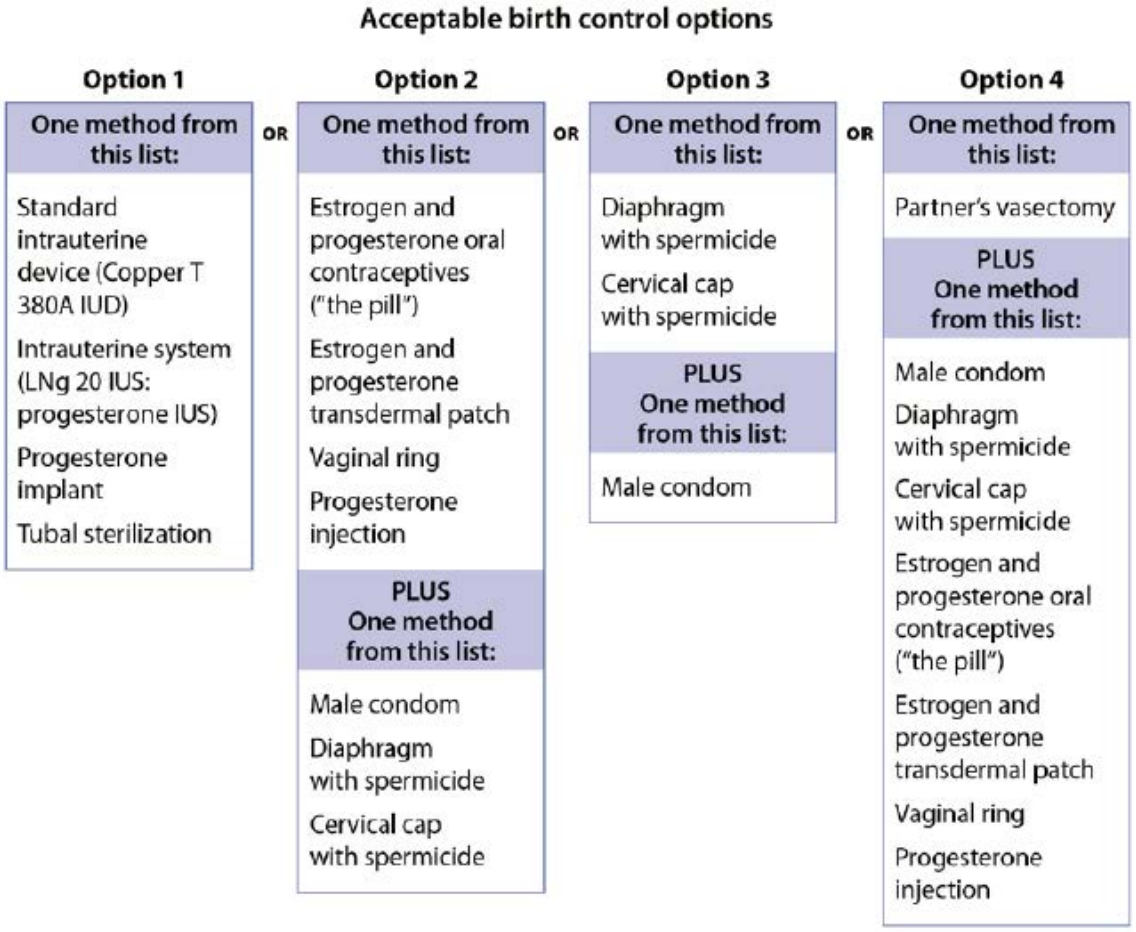
4.5.2.4 North America

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 3]. 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 3, 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 3 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 both sides, 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.

5.1.2 Comparator: Description and rationale

This is an open-label extension study of the AC-055H301 RUBATO DB study, and no comparator will be used.

Nevertheless, the Open Label Extension Set (OLES) will include information where subjects previously on placebo and those previously on macitentan in the AC-055H301 RUBATO DB study are described separately.

5.1.3 Study treatment administration

If the subject is eligible, the first intake of study treatment will take place at site, during the Enrollment visit (Visit 1), after successful completion of all eligibility 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
Treatment	Day 1 to EOT	Macitentan	10 mg o.d.
Follow-up	30 days after EOT	NA	NA

EOT = End-of-Treatment; NA = not applicable; o.d. = once daily.

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 1 to enroll the subject. The IRT will allocate medication bottles to the subject. All study drug bottle numbers must be assigned through the IRT.

5.1.5 Blinding

Blinding is not applicable as the AC-055H302 RUBATO OL study is conducted in an OL fashion, where all subjects receive active treatment of macitentan 10 mg o.d.

Subjects may receive information on the treatment they previously received in the AC055H301 DB study once database closure of that study has occurred.

5.1.6 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.

5.1.6.1 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.

5.1.6.2 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.

5.1.6.2.1 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.

5.1.6.2.2 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 drug handling and storage.

5.1.6.3 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 to / returned 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 5.1.6.2.2].

5.1.6.4 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.

5.1.7 Study treatment accountability and compliance with study treatment

5.1.7.1 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.

5.1.7.2 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 Investigation Medicinal Product (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.

The investigator must discuss the non-compliance with the subject to clarify the reasons and to take appropriate actions to avoid reoccurrence. This discussion and its outcome must be documented in the source documents.

5.1.8 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 5.1.10.

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.

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

5.1.9 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 (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 5.1.10.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until the follow-up period is complete, 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 for a safety follow-up visit 30-35 days after the last intake of study treatment.

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.

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

5.1.10.1 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.

5.1.10.2 Hemoglobin abnormalities

If there is a case of hemoglobin < 100 g/L accompanied by a change from baseline[5] of ≥ 50 g/L during the treatment period, 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:

- 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.

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

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.

5.1.10.3 Pregnancy

If a female subject becomes pregnant while on study treatment, study treatment must be interrupted immediately. For reporting of pregnancies, refer to Section 9.3.1.

5.1.10.4 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.

5.1.10.5 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.

5.1.10.6 Failing Fontan

Study treatment must be permanently discontinued if the subject in the AC-055H302 RUBATO OL study has one of the following Failing-Fontan circulation occurrences:

- Effective heart transplantation
- Fontan take down

- Severe hepatic impairment (as described in exclusion criterion 3.3)
- Severe renal impairment (as described in exclusion criterion 3.5)

5.2 Previous and concomitant medications

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 medications / auxiliary medicinal products / other therapies 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/pacemakers
- Beta blockers
- Pulmonary hypertension-specific drugs except ERAs

5.2.4 Forbidden concomitant therapy

Forbidden therapy includes agents interfering with CPET, or influencing drug exposure.

- 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].
- 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.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

The primary endpoint for this study is safety and tolerability. Efficacy endpoints are assessed only as exploratory secondary endpoints.

- The change in peak VO_2, from baseline to each scheduled time point.
- Change in ventilatory efficiency (assessed as minute ventilation [VE] / carbon dioxide production [VCO_2] slope), from baseline to each scheduled time point.
- Change in VO_2 at ventilatory anaerobic threshold (VAT), from baseline to each scheduled time point.
- Change in oxygen uptake efficiency slope (OUES), from baseline to each scheduled time point.
- Change from baseline to each scheduled time point in mean count per minute of daily PA-Ac.
- Change from baseline to each scheduled time point in daily mean time in minutes spent in sedentary, light, moderate, or vigorous PA-Ac.
- Percent of baseline at each scheduled time point in NT-proBNP.
- Composite endpoint of event related to Fontan-palliated clinical worsening time to first occurrence of clinical worsening up to EOS, defined as one or more of the following:

- Unscheduled hospitalization for Fontan-palliated morbidity event[6]
- Signs and symptoms of HF[7], 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, atrioventricular (AV) valve repair/replacement)
  - Worsening to NYHA FC IV, investigator assessed using the Specific Activity Scale [Appendix 4].
  - Protein-losing enteropathy (PLE)
  - Plastic bronchitis/chyloptysis
  - Peritoneal, pleural, mediastinal, or pericardial effusions
  - Severe hepatic impairment (as described in exclusion criterion 3.3)
  - Severe renal impairment (as described in exclusion criterion 3.5)
    - Death related to Failing-Fontan

- Events related to Fontan-palliated morbidity, time to first occurrence up to EOS of one or more of the following:
  - Ventricular tachyarrhythmia or supraventricular tachyarrhythmia[8]
  - Thrombotic or hemorrhagic complications (including thromboembolism and hemoptysis)
- Time to death (all-cause mortality) up to EOS.

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

[7] 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.

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

6.2 Safety endpoints

- Treatment-emergent AEs[9] and SAEs up to 30 days after study treatment discontinuation and AEs leading to death.
- AEs leading to premature discontinuation of study treatment.
- Change in vital signs (systolic and diastolic arterial BP and pulse rate), including peripheral oxygen saturation (SpO_2) and body weight over time.
- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation.
- Change in laboratory parameters over time.

6.3 Pharmacoeconomic endpoints related to hospitalization

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

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 General information

The study visits are listed in Table 2. 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. An S-FU visit 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 Enrollment

Enrollment starts with the signature of the informed consent. The date on which the first enrollment assessment is performed corresponds to the date of the Enrollment Visit.

The assessments are not to be repeated if they were done during the EOT Visit in the AC-055H301 RUBATO DB study, and if that visit was performed within 5 weeks of this

[9] 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.

visit. However, entry enrollment labs for AC-055H302 RUBATO OL study must be conducted if enrollment is later than 4 weeks after EOT of the AC-055H301 RUBATO DB study, or if those are not evaluable.

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 who agree to participate in the study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure.

It is permitted to re-screen subjects during the enrollment period [see Section 3.1.1], if the reason for non-eligibility was transient (e.g., abnormal laboratory test). 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 eligibility assessments that were out of the eligibility range 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	TREATMENT							FOLLOW-UP
VISITS[8]	Number	1	2	3	4	5…	EOT	U1, U2, …	FU
	Name	Enrollment[1]	Week 26	Week 52	Week 78	Week 104	End-of-Treatment	*Unscheduled visits*	End-of-Study[2] ☎
	Time	Day 1	Day 183 (± 7 days)	Day 365 (± 7 days)	Day 547 (± 7 days)	Every 26 weeks (± 7 days)	Once the last subject has completed Week 104	*Any day between Day 1 and end of EOS*	30 (+ 5) days after last dose
Informed consent		X							
Eligibility		X							
Previous/concomitant therapy		X	X	X	X	X	X	*X*	
Physical examination		(X)	X	X	X	X	X	*X*	
Vital signs (BP, HR, weight, height, SpO_2)		(X)	X	X	X	X	X	*X*	
NYHA FC (using Specific Activity Scale)		(X)	X	X	X	X	X	*X*	
Laboratory tests*[3]		(X)	X	X	X	X	X	*X*	X
NT-proBNP		(X)	X	X	X	X	X	*X*	
Pregnancy test. contraception & reassessment of childbearing potential[7]		X	Monthly (28 ± 7 days)					*X*	X
Echocardiography		(X)		X		X	X	*X*	
CPET (incl. ECG, spirometry)		(X)[10]		X		X[11]	X	*X*	
Physical Activity measured by Accelerometer (PA-Ac)[9]		X	X	X	X	X			
Worsening/morbidity event assessment		(X)	X	X	X	X	X	*X*	
Study treatment dispensing/return[4]		X	X	X	X	X	X	*X*	–
SAEs/AEs[5]		X	X	X	X	X	X	*X*	X

AE = adverse event; BP = blood pressure; CPET = cardiopulmonary exercise testing; ECG = electrocardiogram; EOS = End-of-Study; EOT = End-of-Treatment; FC = functional class; HR = heart rate; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; SAE = serious adverse event; SpO_2 = peripheral oxygen saturation; ☎= Telephone call (for visit).

*Transferred electronically by an external service provider

[1] The assessments denoted by '(X)' are not to be repeated if they were done during the EOT Visit in the AC-055H301 RUBATO DB study, and if that visit was performed within 5 weeks of this visit. Entry enrollment laboratory tests for AC-055H302 RUBATO OL study must be conducted if enrollment is later than 4 weeks after EOT of the AC-055H301 RUBATO DB study, or if those are not evaluable. Assessments denoted by 'X' must be performed regardless of whether the value was obtained in the EOT Visit in the AC-055H301 RUBATO DB study.

[2] Visit may be performed by telephone, as long as laboratory assessments are done with central lab kits.

[3] **Laboratory assessments are done for aminotransferases and hemoglobin monthly (28 ± 7 days) until Week 24. Subsequently, aminotransferases and hemoglobin are done at every 12 weeks and at EOT + 30 days. Additional liver tests may be performed as clinically indicated, and as recommended per local label.** Alpha-fetoprotein tests are only conducted every 52 weeks.

[4] Scheduled study medication dispensing/return procedures may be adapted according to the site practice.

[5] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported [see also Section 9].

[6] 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.

[7] Serum pregnancy test at enrollment 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 phone calls from the site.

[8] A visit may occur over more than one day.

[9] The device is given to the subject at Visit 1 (Enrollment), and data is collected for 9 consecutive daily daytime periods after Visit 1, Visit 2, Visit 3 (Week 52), Visit 4 (Week 78), and 9 days before Visit 5 (Week 104). No additional assessments are made in case treatment is prolonged for more than 104 weeks.

[10] The CPET assessment only needs to be completed during enrollment if no assessment is available from the AC-55H301 RUBATO DB study at Week 52.

[11] The CPET assessment will only occur every 52 weeks.

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 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. Study assessments performed during unscheduled visits will also be recorded in the eCRF. The following order of assessments is recommended:

1. Physical examination, vital signs and echocardiography
2. CPET (including electrocardiogram [ECG])
3. Blood sampling, 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 for the below-listed equipment used to perform study assessments must be available prior to the enrollment of the first subject. Calibration certificates of other equipment must be available as per local requirements.

- 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 Investigator Site File (ISF).

7.2.1 Demographics / baseline characteristics

For subjects enrolled in the AC-055H302 RUBATO OL study, the demographic and baseline characteristic data recorded in the database of the AC-055H301 RUBATO DB study will include: age, sex, race and ethnicity[10], body weight, height, NYHA FC, as well

[10] 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 CRF only where it is allowed.

as the reason why a woman is not considered to be of childbearing potential (if applicable). Body weight, height, NYHA FC, as well as the reason why a woman is not considered to be of childbearing potential (if applicable) may be re-evaluated at Week 52 of the AC-055H301 RUBATO DB study and may serve as baseline for the AC-055H302 RUBATO OL study.

For subjects who were not eligible to enter this AC-055H302 RUBATO OL study, the following data will be recorded in the eCRF if available:

- Reason for non-eligibility;
  - subject not eligible as per inclusion/exclusion criteria,
  - subject withdrew consent.

7.2.2 Efficacy assessments

7.2.2.1 Cardiopulmonary exercise testing

CPET will be conducted at study sites at visits listed in Table 2. Subjects entering the AC-055H302 RUBATO OL study after having prematurely discontinued treatment in the AC-055H301 RUBATO DB study, will need to perform a CPET at Visit 1 (Enrollment).

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 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 (FEV_1) × 40, as well as the peak VE using the following formula.

$BR\% = ([MVV - VE]/MVV) \times 100$

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.

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 device is given to the subject at Visit 1 (Enrollment), and data is collected for 9 consecutive daily daytime periods after Visit 1, Visit 2, Visit 3 (Week 52), Visit 4 (Week 78), and before Visit 5 (Week 104). The duration of physical activity data collection will allow including data during weekdays 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.

Should the AC-055H301 DB study analysis demonstrate no clear trend using PA-Ac, this assessment will be discontinued during the AC-055H302 OL study.

7.2.2.3 NT-proBNP measurement

NT-proBNP is measured at Visits 2 (Week 26), and at every 26 week visit, according to central laboratory working procedures. The baseline is the last assessment done prior to entering this AC-055H302 OL study, e.g. data for Visit 6 (Week 52) of the AC-055H301 DB study.

Should the AC-055H301 DB study analysis demonstrate no clear trend for NT-proBNP, this assessment will be discontinued during the AC-055H302 OL study.

7.2.2.4 Composite endpoint of time to clinical worsening

Occurrence of an event component of the 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 OL 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 OL treatment are derived from the reported AEs in the eCRF.

- Change in vital signs (systolic and diastolic BP and pulse rate), and body weight over time. 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 OL treatment discontinuation.
- Change in laboratory parameters over time. 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 enrollment (if necessary) includes the examination of the general appearance, 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 for 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 (except for abnormalities related to Fontan circulation), describing the signs related to the abnormality (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency). 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 safety follow-up.

Systolic and diastolic blood pressure 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), same arm (left/right) 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 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 enrollment (if necessary) and at Visits 3 and 5. 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).

If 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.

7.2.4 Laboratory assessments

Laboratory tests are conducted at every visit. Full hematology and clinical chemistry panels [see Section 7.2.4.2] are done at enrollment (if necessary) and every visit except for Alpha-fetoprotein which is only drawn every 52 weeks. Laboratory assessments are done for aminotransferases, hemoglobin, and pregnancy monthly (28 ± 7 days) until Week 24. Subsequently, aminotransferases and hemoglobin are done every 12 weeks and at EOT + 30 days. 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 (enrollment) and complemented with monthly 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. Any clinically relevant laboratory abnormalities (including ALT/AST abnormalities ≥ 3 × ULN) detected after administration of the first dose of study treatment 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 5.1.10.1]). 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

- 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 5.1.10.2.

Clinical chemistry

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

*only taken every 52 weeks

Rules for OL treatment interruption / permanent discontinuation and laboratory re-tests in case of ALT and/or AST elevation are provided in Section 5.1.10.1.

Creatinine clearance is estimated the Chronic Kidney Disease using Epidemiology Collaboration 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] × 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 INR

Pregnancy test

A serum pregnancy test for women of childbearing potential will be performed at enrollment, 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 Pharmacoeconomic assessments

Pharmacoeconomic parameters will be assessed as described in Section 6.3.

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

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

A subject who completed OL treatment until the last subject has had 2 years of treatment, Week 104 and had the S-FU, is considered to have completed the study as per protocol.
The overall study is considered completed when all subjects have completed their individual S-FU, and their status is known: alive or deceased, withdrawn consent or have been lost to follow-up.

Note that the S-FU visit may not be needed for subjects who continue macitentan treatment (e.g., special access program, clinical trial) at their individual EOT of AC-055H302; these subjects are still considered to have completed the study.

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, 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 the study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the Independent Ethics Committees (IECs) / Institutional Review Boards (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 the 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 the 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 as long as they are active for the AC-055H301 RUBATO DB study.

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.

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 OL treatment initiation until 30 days after OL treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed 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, which 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.

Ongoing AEs from AC-055H301 RUBATO DB will be reported on the ongoing AEs eCRF form for the AC-055H302 RUBATO OL, if an increase in intensity occurs for an ongoing AE, a new AE will be reported.

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 9.3.1]. 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.

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 must be recorded on specific AE pages of the 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 OL 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 for 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 hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

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 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. If the SAE is reported in AC-055H301 RUBATO DB, and occurs prior to the first dose of study medication in AC-055H302 RUBATO OL, it does

not need to be also reported in AC-055H302 RUBATO OL. However, complications that occur during OL treatment are AEs or SAEs (e.g., if a complication prolongs hospitalization) and must be reported in RUBATO OL.

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 Visit / 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

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 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 suspected unexpected serious adverse reaction (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.

9.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. 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

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 (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.

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 9.3.1.

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 SAE 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 Contract Research Organizations (CROs) supervised by Actelion.

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

10.1 Analysis sets

There are three main analysis sets [see also Section 10.3, Table 3].

10.1.1 Total Macitentan Analysis Set

The Total Macitentan Analysis Set (TMAS) includes all subjects who received at least one dose of macitentan 10 mg either in the main study (AC-055H301) or in the long-term study (AC-055H302).

10.1.2 Long-term Macitentan Analysis Set

The Long-term Macitentan Analysis Set (LTMAS) includes all subjects randomized to macitentan 10 mg in the main study (AC-055H301) regardless of subsequent enrollment into the AC-055H302 study.

10.1.3 Open-label extension Set (OLES)

The Open-label Extension Set (OLES) includes all subjects treated with macitentan 10 mg in AC-055H302 RUBATO OL.

10.1.4 Per-protocol Analysis Set

No Per-protocol Analysis Set is defined for AC-055H302 RUBATO OL. However, major protocol deviations that may have an impact on the safety or tolerability will be summarized by frequency tables.

10.2 Variables

All variables described hereafter are related to the endpoints defined in Section 6. As the primary objective of AC-055H302 RUBATO OL is long-term safety and tolerability, the primary endpoints are related to safety.

10.2.1 Efficacy variable(s)

- **Change in peak VO_2 to each scheduled time point**, i.e., per time point of assessment, the change is defined as a time assessment value minus baseline value.
- **Change in ventilatory efficiency from baseline to each scheduled time point** (VE/VCO_2 slope, VO_2 / heart rate, VO_2 at VAT, OUES and % predicted peak VO_2) will be also collected at all visits with CPET. Per variable of exercise capacity and per post baseline assessment, changes from baseline are defined as post baseline value minus baseline value.
- **Change from baseline to each scheduled time point in mean count per minute of daily PA-Ac**, i.e., per time point of assessment, the change is defined as a time assessment mean count per minute of daily PA-Ac minus the mean count per minute of baseline daily values.
- **Change from baseline to each scheduled time point in daily mean time in minutes spent in sedentary, light, moderate or vigorous PA-Ac**, similar definition to above.

The values used for variables above will be based on data evaluation by the central reading facility.

- **Percent of baseline at each scheduled time point in NT-proBNP**, i.e., per time point of assessment, the percent of baseline in NT-proBNP is defined as 100 times the point of assessment value divided by the baseline value. The percent change from baseline in NT-proBNP is defined as 100 times the absolute change from baseline divided by the baseline value. Also, the absolute change from baseline will be presented and it is defined as a post-baseline value minus baseline value.

The baseline values for above variables are defined as in Section 10.3 Description of statistical analyses.

- **Time to clinical events is defined as:**
  - Composite endpoint of event related to Fontan-palliated clinical worsening, time to first occurrence of clinical worsening up to EOS (where clinical worsening events are defined as in Section 6.1),
  - Events related to Fontan-palliated morbidity, time to first occurrence up to EOS where events are defined as in Section 6.1).

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

Subjects who did not experience an event will be censored at the date of last contact also reported in the eCRF.

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 first dose plus 1 divided by 7,
- for censored subjects: the EOS date minus date of first dose plus 1 divided by 7.

Time to death (all-cause mortality) up to EOS

Subjects who are known to be alive, lost to follow up or prematurely withdrawn from the study will be censored at the date of last contact (e.g., date of last 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.

10.2.2 Safety variables

The safety variables are the following:

- Treatment-emergent AEs and SAEs up to 30 days after OL treatment discontinuation
- AEs leading to premature discontinuation of study treatment
- AEs leading to death
- Change in vital signs (systolic and diastolic arterial BP and pulse rate) including peripheral oxygen saturation (SpO_2) and body weight up to all assessed time points during the study
- Treatment-emergent marked laboratory abnormalities at all assessed time points during the study
- Change in laboratory parameters from baseline to all assessed time points during the study
- AEs of special interest (anemia/hemoglobin decrease, hepatic adverse events of special interest, hypotension, edema/fluid retention).

10.2.2.1 Adverse events

An AE is defined as any event that is recorded on the AE CRF module regardless of the onset date. As all subjects have received study medication in the AC-055H301 RUBATO DB study, all AEs are treatment emergent up to 30 days after EOT. When using the OLE, treatment-emergent events are those with onset date/time ≥ start date/time of AC-055H302 RUBATO OL 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 at least ‘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.

AE of special interest (anemia/hemoglobin decrease, hepatic adverse events of special interest, hypotension, edema/fluid retention).

All AEs will be coded using the latest available version of MedDRA dictionary.

10.2.2.2 Laboratory data

Measured values and changes in laboratory data (as defined in the Section 7.2.4.2) from baseline are described by visit and treatment group by means of summary tables in SI units. In addition, treatment-emergent marked laboratory abnormalities will be summarized for each laboratory parameter by treatment group providing their incidence and frequency.

10.2.2.3 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.

10.2.2.4 Echocardiography

Single ventricle ejection fraction, Fontan circulation stenosis, and valvular defects (severe AV valve regurgitation, outflow obstruction) are measured at the enrolment and yearly visits and reported in the eCRF.

10.2.3 Other variables

10.2.3.1 Exposure to study drug

The duration of treatment exposure is defined as the time elapsing between study drug initiation and discontinuation, inclusive. Premature Discontinuation of treatment and study.

Number and percentage of subjects who prematurely discontinued treatment and study will be presented and adjustment for treatment exposure.

10.2.3.2 Pharmacoeconomic variables related to hospitalization

The number and percentage of subjects who are hospitalized per year and overall:

- All-cause hospitalizations

Fontan-related hospitalizations will be reported in the eCRF with an admission date.

10.3 Description of statistical analyses

Missing data for efficacy variables will be handled similarly to AC-055H301 RUBATO DB. Further details will be provided in the SAP.

The variables in Section 10.2 will be summarized as follows:

- The long-term safety of macitentan will be assessed on the TMAS. Results will be presented overall, and baseline for this will be the last non-missing assessment obtained prior to the start of macitentan.
- The long-term efficacy of macitentan will be assessed on the LTMAS. Results will be presented overall and over time until the end of AC-055H301 RUBATO DB or AC-055H302 RUBATO OL, whichever is the latest. Baseline for this will be the last non-missing assessment obtained prior to the start of macitentan in AC-055H301 RUBATO DB.
- Both efficacy and safety will also be assessed on the OLES. Results will be presented overall and by ex-placebo or ex-macitentan:
  - Ex-placebo subjects are defined as subjects who received placebo in AC-055H301 RUBATO DB and enrolled into AC-055H302 RUBATO OL, and
  - Ex-macitentan subjects are defined as subjects who received macitentan in AC-055H301 RUBATO DB and enrolled into AC-055H302 RUBATO OL.

  Baseline for this will be the last non-missing assessment obtained prior to the start of study drug intake in the AC-055H302 RUBATO OL extension.

Table 3 Usage of Analysis sets

LTMAS	OLES			TMAS
	Previously on DB macitentan	Previously on DB placebo	All subjects	All subjects
(N = 67)	(N = up to 67*)	(N = up to 67*)	(N = up to 134*)	N = up to 134*

DB = double-blind; LTMAS = Long-term Macitentan Analysis Set; OLES = Open-label extension Set; TMAS = Total Macitentan Analysis Set.
*See Section 10.5 Sample Size (Baseline is as defined in Section 10.1)

Variables are summarized using appropriate descriptive statistics:

- For continuous variables (e.g., the change in peak VO_2 over time, the change in mean count per minute of daily PA-Ac from baseline to post-baseline assessment, change in ventilatory efficiency from baseline to post-baseline assessment, percent of baseline in NT-proBNP and absolute change from baseline to post-baseline assessments in NT-proBNP, change in laboratory parameters from baseline to post-baseline assessment): number of non-missing observations, mean, standard deviation, minimum, Q1, median, Q3 and maximum.
- For dichotomous or categorical variables (e.g., treatment-emergent AEs, SAEs, AEs leading to premature discontinuation of study treatment, AEs leading to death, AE of special interest, change in vital signs, treatment-emergent marked laboratory abnormalities: number of non-missing observations, and frequency with percentage per category. Denominators for percentages are the number of subjects in corresponding analysis data sets, unless otherwise specified.

- For time-to-event variables (time to death, time to first occurrence of composite endpoint of event related to Fontan-palliated clinical worsening, time to first occurrence of events related to Fontan-palliated morbidity): number of events, number at risk, number of censored observations and KM estimates with 2 sided 95% confidence intervals at relevant time points.
- Rules for KM curves going upwards or downwards (curves will go upwards if there is a low number of events, i.e., the KM less than 50%) and the graphical presentation for KM follows the recommendations from Pocock [Pocock 2002].

Truncation of the x-axis when only 10% of the subjects are still in follow-up.

Graphical presentations for continuous variables, e.g., categorical and time-to-event variables will be included when appropriate. More details will be specified in the SAP:

Demographics, medical history, previous/current use of medications

Demographics and medical history, previous/current use of medications at baseline will be summarized for all analysis sets and per type of variables as explained above.

Exposure to study drug

The duration of treatment exposure, study drug interruption and duration of treatment duration of treatment exposure including interruption will be summarized as continuous variables for each analysis set.

Premature Discontinuation of treatment and study

Number and percentage of subjects who prematurely discontinued treatment and study will be summarized as a categorical variable for each analysis set.

AEs

The number and percentage of subjects with at least one treatment-emergent AE / with at least one SAE / with at least one AE leading to premature discontinuation of study treatment/ with at least on AE with fatal outcome will be tabulated for each analysis set and by:

- System Organ Class and Preferred Term within System Organ Class, in descending order of incidence.
- Preferred Term, in descending order of incidence

The same analysis will be performed considering the maximum intensity of reported AEs and relationship to study treatment.

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

Adjustment for treatment exposure

In order to account for differences in the duration of treatment exposure among subjects, incidence rates of AEs, SAEs, AEs leading to discontinuation, AEs of special interest, number of hospitalizations and deaths will be presented as adjusted for subject-years exposure (SYE).

Subject-time will be calculated as follows:

i) For subjects without events: by summing the days of treatment duration (study treatment end date – study treatment start date + 1);

ii) For subjects with an event: by summing the days of treatment duration up to the start date of first event (min [date of first event, study treatment end date] – study treatment start date + 1)

Subject-years exposure (SYE) will be calculated by dividing the total subject time by 365.25 days.

The incidence rate for an AE (or SAE) per 100 Subject-years will be calculated by dividing the number of subjects with AEs (or SAEs) by the SYE and multiplying by 100.

Adjusted Incidence Rate = 100 × (Number of subjects with at least one AE/SYE)

Laboratory variables

Using "evaluation of drug-induced serious hepatotoxicity" (eDISH) plots, graphical representations of total bilirubin versus ALT will be produced, to identify possible Hy's Law cases. Also, box plots over time will be produced to describe laboratory variables over time. This variable will be summarized for each analysis set.

Vital signs

Number and percentage of subjects with systolic BP drops to < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height) will be tabulated over time. In addition, absolute changes from baseline in vital sign parameters will be presented graphically via box plots for each analysis set.

Pharmacoeconomic variables related to hospitalization

The number and percentage of subjects who are hospitalized per year and overall will be summarized for each analysis set and adjusted by treatment exposure.

Efficacy variables

Analyses of efficacy variables will be descriptive and as specified under continuous/categorical variables above. Graphical presentation of variables over time will be shown. More details will be in the SAP.

10.3.1 Overall testing strategy

No formal hypothesis testing will be performed, as all efficacy analyses are considered exploratory. No inferential analysis is planned for the efficacy variables. Any p-values are presented for information only. No multiplicity adjustment will be made.

10.3.2 Sub-group analyses

Following sub-group analyses for AEs leading discontinuation, AE of special interest, and SAEs will be performed:

- Age (< 18, ≥ 18 years)
- Sex (Male, Female)
- Geographical region (America, Europe, Asia, Oceania),
- Region (US, non-US).
- Ventricular dominance (left ventricle, right ventricle/mixed).

Other subgroups will be defined in the CSR SAP.

10.4 Interim analyses

No interim analyses are planned for the OL study.

Periodic review of the efficacy data in parallel to the safety data will be performed, allowing an assessment of risk/benefit [see Section 3.3]. An independent statistical analysis center, involved in the main study but not otherwise involved in the design, conduct and analysis of the study, will prepare reports for review by the IDMC (for IDMC review meetings during the course of the trial) in accordance with the charter. There is no limit to the number of reviews meetings or reports, which have the aim of guaranteeing the safety of the subjects.

10.5 Sample size

This is an extension study of AC-055H301 RUBATO DB, hence the sample size will be up to the number of randomized subjects in AC-055H301 RUBATO DB study (planned to be approximately 134 subjects or may be increased to a maximum of 268 subjects based on the interim analysis for sample size re-estimation during the double blind AC-055H301 RUBATO DB study).

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 (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 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 enrollment.

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.

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

AEs are coded according to the latest Medical Dictionary for Regulatory Activities (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 Quality System documents. After database closure, the investigator will receive the case report forms 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 country in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator 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, 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.

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).

Assent must be obtained from study participants who are developmentally capable. The criteria for developmental capability to give assent follow 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.

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

Site personnel (according to local regulation) authorized 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. 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.

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.

For studies that offer reimbursement and/or compensation, use the following wording:

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, 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 and restricted access to study subjects only, to verify consistency between electronic source data and the CRF 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, 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 either with the subject's medical records or with the subject's CRF.

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 least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Actelion's instructions. If it were not possible for the CRA to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

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 CRFs 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 CRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data-collection times.

The PI must ensure that the CRF 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

The Sponsor's Global 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 [SOPs]) 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 publically 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 and the Steering Committee, 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 4 may be defined in the central laboratory manual.

Table 4 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
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	ND	< 130	> 150	> 155

Parameter (SI unit)	LL	LLL	HH	HHH
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 5.1.10]; 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.

---

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.

Borg-RPE-Scale®
© Gunnar Borg, 1970, 1985, 1998, 2015
English

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 OL procedures versus standard of care: comparison of burden and risks

SoC procedures	RUBATO OL procedures	Burden	Risk	Conclusion
Patients' status				
Anamnesis, clinical & physical examinations (yearly or bi-yearly)	3 Visits at a specialized cardiologist during a 12-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 and contributes to significant risk reduction (3 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)	With each CPET (once over 12 months).	Performed during the CPET: See CPET.	=	Same burden and same risk as SoC.
Worsening/morbidity event assessment (yearly or bi-yearly)	3 times (clinically) over 12 months. Monthly (clinically) for 12 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 (3 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.

SoC procedures	RUBATO OL procedures	Burden	Risk	Conclusion
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 OL procedures	Burden	Risk	Conclusion
Imaging				
Echocardiogram (yearly)	2 times over 12 months.	= Same monitoring in RUBATO OL.	=	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.
CPET (between twice a year to not necessarily every year)	1 times over 12 months.	= Same monitoring in RUBATO OL.	=	Same burden and same risk as SoC.

SoC procedures	RUBATO OL procedures	Burden	Risk	Conclusion
Blood tests				
Many blood parameters are surveyed (yearly or bi-yearly)	Comprehensive set of parameters are monitored in RUBATO. 3 times over 12 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.
Liver function related common blood parameters	Will be controlled monthly for the first 6 months and then every 12 weeks until EOT.	↗ 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)	1 times over 12 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 OL 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.
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.

SoC procedures	RUBATO OL procedures	Burden	Risk	Conclusion
Not part of SoC	Medications triggering a drug-drug-interaction with macitentan Not allowed in RUBATO OL.	= Exclusion at baseline or forbidden concomitant medications. Concomitant medications (with doses) are recorded at each visit.	↘ 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.
Non-medicinal treatment				
Pacemaker	Allowed in RUBATO OL.	**No burden**	**No risk**	
Implanted defibrillators	Allowed	**No burden**	**No risk**	

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.

AE = adverse event; CPET = cardiopulmonary exercise testing; DDI = drug-drug interaction; ERA = endothelin receptor antagonist; FC = functional class; OL = open-label; NYHA = New York Heart Association; PK = pharmacokinetic(s); SAE = serious adverse event; SoC = standard of care.

Appendix 7 Child-Pugh Score

The Child-Pugh classification will be used to assess the severity of the liver disease according to the following table.

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.

Appendix 8 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 amendment is provided below.

Amendment	Date	Main reason(s)
1	20 Feb 2019	Introducing the "flying nurse service" for laboratory collection; reducing mandatory safety monitoring after the first half year; clarifying contraception measures for new countries
2	16 Jul 2020	Updates to exclusion criteria, forbidden medication and concomitant therapy sections based on newly identified drug-drug interactions.
3	21 July 2020	To update the exclusion criteria, initiation of forbidden medication and concomitant therapy sections pertaining to newly identified drug-drug interactions (DDI) between macitentan and fluconazole (a dual moderate inhibitor of CYP3A4 & CYP2C9) from a pre-clinical study on implications of role of CYP2C9 in the metabolism of macitentan.

Actelion Pharmaceuticals Ltd
Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title
Prospective, multi-center, single-arm, open-label long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan palliated adult and adolescent subjects

RUBATO OL

Macitentan in Fontan-palliated subjects

Protocol AC-055H302; Phase 3

JNJ-67896062/ACT-064992 Macitentan

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

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-20.159

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 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 investigational 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 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 efficacy assessments**

  If subjects cannot conduct their cardiopulmonary exercise testing (CPET) assessments as expected, these should be done at the earliest possibility during a scheduled or unscheduled visit.

  For Week 104, the CPET assessment could be conducted up to 8 weeks later.

  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).

  The accelerometer will be assigned by sites and shipped to the subject 4 weeks prior to the expected visit. The subject will be instructed to wear it for 9 consecutive days **after (or for**

Week 104 before) the expected visit date, and subsequently ship the activity monitor back to the site at the end of the wear period.

Missed CPET or PA-Ac assessments will be identified as issues in the CTMS as "COVID-19-related issues" 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 measurements at the next planned IDMC meeting, as long as the AC-055H301 RUBATO study continues.

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): PPD

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.