Statistical Analysis Plan

Sponsor:	Actelion Pharmaceuticals US, Inc.
Protocol No:	AC-055-205
Version No./Date	3.0/10-Mar-2017
Title	A prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation
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1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Actelion Pharmaceuticals US, Inc. Protocol AC-055-205.

This SAP should be read in conjunction with the study protocol and case report forms (CRF). This version of the plan has been developed using the protocol version 3 dated 10MAR2017 and CRF version 11.0 dated 24OCT2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Once the SAP is finalized programming can begin. Changes following approval of SAP will be tracked in the SAP Change Log **(spreadsheet PRS 005 T 19)** and a SAP amendment.

1.1 Changes from Protocol

The protocol defines prior medications relative to the date of signing informed consent. However prior medications are defined in the analysis plan as any treatment for which the end date is prior to Study Day 1 (which is based on the first dose of study medication or randomization). In addition the protocol does not classify medications which are ongoing at the start of the study into either a prior or concomitant category. The analysis plan assigns these medications as both prior and concomitant to study treatment.

According to the protocol, the Screened Analysis Set (SAS) should be used for patient disposition. However it is the patient population table that will be presented for the SAS instead since information on completion of the study is not collected for screen failures.

2.0 Study Objectives

2.1 Primary objective

The primary objective is to evaluate the effect of macitentan 10 mg on pulmonary vascular resistance (PVR) as compared to placebo in patients with pulmonary hypertension (PH) after left ventricular assist device (LVAD) implantation.

2.2 Secondary objectives

The secondary objectives are:

- To evaluate the effect of macitentan 10 mg as compared to placebo on cardio-pulmonary hemodynamics and disease severity in patients with PH after LVAD implantation.
- To evaluate the safety and tolerability of macitentan 10 mg in patients with PH after LVAD implantation.

2.3 Exploratory objectives

- To explore the potential effect of macitentan 10 mg as compared to placebo on right ventricular function in patients with PH after LVAD implantation.
- To explore the potential effect of macitentan 10 mg as compared to placebo on selected clinical events in patients with PH after LVAD implantation.
- To explore the potential effect of macitentan 10 mg as compared to placebo on renal function as measured by the glomerular filtration rate (GFR) in patients with PH after LVAD implantation.

3.0 Study Design

This is a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 2 study. It is planned to randomize 78 patients into 2 groups (macitentan 10 mg or placebo) in a 1:1 ratio by an Interactive Web Randomization System (IXRS). Approximately 50 sites in the United States are planned. The study duration is planned to be approximately 36 months from first patient, first visit to last patient, last

visit. Patient participation in the study is up to 90 days from LVAD (screening period) + 12 weeks (double-blinded treatment period) + 30 days (safety follow-up period). The key inclusion criteria are:

- Surgical implantation of LVAD within 90 days prior to Randomization.
- Hemodynamic evidence of PH on Baseline right heart catheterization (RHC) by the thermodilution method. Baseline RHC is defined as the last hemodynamic measurements after LVAD implantation and prior to the first dose of study drug treatment. PH is defined as:
    - Mean pulmonary arterial pressure (mPAP) ≥ 25 mmillimeter of mercury (mmHg) and
    - Pulmonary artery wedge pressure (PAWP) ≤ 18 mmHg and
    - PVR > 3 WU (Wood units).
- Stabilization of the patient for 48 hours prior to the Baseline RHC, defined as:
    - No LVAD pump speed/flow rate changes and
    - Stable dose of oral diuretics and
    - No intravenous (i.v.) inotropes or vasopressors and
    - Patient able to ambulate.
- Patient must be randomized within 14 days of Baseline RHC.

The study consists of the following study periods:

Screening period: Commences immediately following LVAD implantation and ends with patient randomization (up to a maximum of 90 days after surgical implantation of LVAD). The Screening visit is the date at which signature on the Informed Consent Form (ICF) is obtained prior to initiation of any study-mandated procedures. Screening and Randomization visits may be conducted on the same day, provided that eligibility is confirmed and all study-mandated procedures are completed prior to Randomization.

Treatment period: Study treatment is defined as the dosing (intake) by the patient of double-blind study drug (macitentan or placebo). The treatment period starts immediately after Randomization with the first dose of study drug at the end of Visit 2 (Day 1 of study) and ends with end of treatment (EOT) on the day of the last dose of study drug (scheduled Day 84, Week 12), or earlier in case of premature discontinuation of study treatment.

Patients who prematurely discontinue study treatment must have an EOT visit within 7 days of study treatment discontinuation.

Post-treatment safety follow-up period: Patients who complete the study treatment as planned, i.e., a full 12-week study period, and those who prematurely discontinue study treatment will enter a 30-day safety follow-up period, which ends with the End-of-Study (EOS) visit at least 30 days after the permanent discontinuation of study treatment.

In addition, Unscheduled Visits may also take place during treatment and follow-up periods.

For an individual patient, the study ends once the EOT has been performed and the 30-day safety follow-up is complete (EOS).

The study is considered complete when all patients have ended as detailed above.

An Independent Statistical Center (managed by PRA and excluding Actelion) has access to the study data and patients' treatment assignment for review by the Independent Data Monitoring Committee (IDMC). The IDMC will be fully operational prior to enrollment of the first patient into the study. The composition and operation of the IDMC is described in the IDMC charter.

Hospital admissions for heart failure (HF), as an exploratory endpoint, will be adjudicated by the clinical events committee (CEC) for this study.

3.1 Sample Size Considerations

An integrated analysis of two bosentan studies, BENEFIT (AC-052-366) and EARLY (AC-052-364), the hemodynamic sub-study of SERAPHIN (AC-055-302), and the recently completed MERIT study (AC-055E201) of macitentan in patients with inoperable chronic thromboembolic pulmonary hypertension, suggest that the treatment group difference on PVR is expected to be around -0.28 on log scale (ranged from -0.45 to -0.17 with 95% confidence interval: −0.35, −0.21) and that the within group standard deviation is around 0.40 (90% confidence interval: 0.38, 0.42) on log scale.

Based on the following assumptions:

- Type I error of 2.5% (1-sided)
- 80% power
- Treatment assignment ratio 1:1 between placebo and macitentan 10 mg
- Treatment group difference on PVR ratio of Week 12 to Baseline −0.28 (a geometric mean ratio (GMR) of 0.76 macitentan/placebo)
- Within group SD of 0.41
- A normal distribution for the log-transformed percent of Baseline PVR

Seventy evaluable patients will be needed for 80% power (35 patients per group) to test the primary hypothesis of interest. Accounting for 10% non-evaluable patients, approximately 78 patients need to be randomized.

3.2 Randomization

Eligible patients will be randomized into two groups (macitentan 10 mg or placebo) in a 1:1 ratio by an IXRS, with no stratification. Block randomization is performed within each investigator site. The pre-defined block size is masked from the investigators and all study personnel except for the statistician who is preparing the randomization schedule at the IXRS vendor and the independent IDMC statistician. At Visit 1 (Screening), all screened patients will be assigned a study-specific patient number by the IXRS provider. At Visit 2 (Randomization), and after having confirmed the eligibility of the patient and prior to the start of study treatment, the investigator/delegate will contact the IXRS to randomize the patient. The IXRS will assign a randomization number to the patient, and will assign the treatment bottle number which matches the treatment arm assigned by the randomization list to the randomization number. The bottle with this unique number will be dispensed to the patient and the first dose is administered.

Assignment to the treatment arms is based on a computer-generated randomization schedule created before the start of the study. The randomization schedule has been prepared by a statistician not otherwise involved in the conduct of the study.

The randomization list is generated by another independent Contract Research Organization (CRO), Parexel, and kept strictly confidential.

3.3 Study Endpoints

3.3.1 Efficacy endpoints

3.3.1.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is PVR ratio of Week 12 to Baseline. PVR is obtained by the thermodilution method.

The primary efficacy endpoint PVR will be calculated as (mPAP − PAWP) / CO and will be presented in WU, where the thermodilution method has been used.

If the thermodilution method was not used for CO then PVR by thermodilution will not be calculated.

3.3.1.2 Secondary efficacy endpoints

- Change from Baseline to Week 12 in the following hemodynamic measurements all measured at rest:
    - mean right atrial pressure (mRAP)
    - mPAP
    - PAWP
    - cardiac index (CI), CI will be calculated as CO/body surface area (BSA); where CO is captured on CRF and BSA will be calculated as specified in section 5.6.1.
    - total pulmonary resistance (TPR), calculated as mPAP / CO and
    - mixed venous oxygen saturation (SvO2). (This is recorded on CRF as Pulmonary arterial oxygen saturation.
- Change from Baseline to Week 12 in N-terminal prohormone of brain natriuretic peptide (NT-proBNP).
- Change from Baseline to Week 12 in World Health Organization functional class (WHO FC).

3.3.1.3 Exploratory efficacy endpoints

- Change from Baseline to Week 12 in echocardiographic variables that include:
    - 2D global right ventricle (RV) longitudinal strain (global right ventricular longitudinal strain [RVLS])
    - RV sphericity index (RVSI)
    - RV end systolic area (RVSA)
    - RV end diastolic area (RVDA)
    - Tricuspid annular plane systolic excursion (TAPSE)
    - S', Tricuspid peak annular velocity s' (TPAVS)
    - RV fractional area change (RVFAC)
    - E', Tricuspid peak diastolic annular velocity (TPDAV)
    - A', Tricuspid Inflow Peak E-Velocity (TIFE)
- Time to first occurrence of clinical events, from enrollment (using the Study Day 1 definition in section 5.7.3) to Week 12. These clinical events include:
    - Hospital admission for HF
    - Re-initiation of i.v. diuretics ≥ 48 h duration
    - Re-initiation of i.v. inotropes ≥ 48 h duration
    - Initiation of phosphodiesterase type 5 inhibitors (PDE5I) inhibitors
    - Need for RVAD / total artificial heart (TAH)
    - Need for renal replacement therapy (RRT)
    - Death
- Days in the hospital after hospitalization for HF.
- Change in GFR from Baseline to Week 12

3.3.2 Safety endpoints

- Treatment-emergent adverse events (AEs) up to 30 days after study treatment discontinuation.
- AEs leading to premature discontinuation of study treatment.
- Death up to 30 days after study treatment discontinuation.
- Treatment-emergent serious AEs (SAEs) up to 30 days after study treatment discontinuation.
- Change from Baseline to EOT in vital signs.
- Occurrence of liver function test alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) abnormality [≥ 3 × upper limit of normal (ULN); ≥ 3 and < 5 × ULN; ≥ 5 and < 8 × ULN; ≥ 8 × ULN] up to EOT.
- Occurrence of ALT and/or AST abnormality ≥ 3 × ULN associated with bilirubin ≥ 2 × ULN up to EOT.
- Proportion of patients with treatment-emergent hemoglobin abnormality (< 10.0 g/dL, and < 8.0 g/dL) as compared to Baseline up to EOT.
- Treatment-emergent marked laboratory abnormalities up to EOT. Marked laboratory abnormalities are defined in Section 8.6.3.

3.3.3 Biomarker endpoints

Change in NT-proBNP will be assessed from Baseline to Week 12 (EOT) as part of the secondary efficacy endpoints analysis.

Additional circulating biomarkers may be analyzed in an exploratory format (post-hoc) based on available scientific evidence. No genetic testing will be performed.

- Interleukin-6 (IL-6)
- Tumor necrosis factor-α (TNF- α)
- High sensitivity C-reactive protein (hsCRP)
- ET-1
- Galectin-3
- Growth differentiation factor-15 (GDF-15)
- Interleukin 1 receptor ST2
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Copeptin
- High sensitivity cardiac troponin T (hs-cTnT)
- Cystatin-C
- Osteopontin

4.0 Predetermined Covariates and Prognostic Factors

In addition to treatment as a prognostic factor there are several predetermined covariates.

- Baseline log PVR is the predetermined covariate for the primary analysis of the log ratio of Week 12 to Baseline PVR. See Section 8.5.1 and 8.5.1.2.

- The secondary analysis of change from baseline to Week 12 (without log transformation) in pressure-volume variables (e.g., mRAP, mPAP, PAWP, CI, TPR) and SVO2 will be adjusted for Baseline log PVR which did not use planned treatment group median for imputation in Section 8.5.1.2, and the Baseline of the variable to be analyzed.
- Baseline log NT-proBNP is the predetermined covariate for the secondary analysis of NT-proBNP.
- Baseline WHO FC group (I/II *vs*. III/IV), is the predetermined covariate for the secondary analysis of WHO FC.
- For the exploratory analyses of echocardiographic variables, Baseline log PVR which did not use planned treatment group median for imputation in Section 8.5.1.2 and Baseline TAPSE, S', RVFAC, E', A', RVLS, RV area, and RVSI are predetermined covariates for the separate analyses of TAPSE, S', RVFAC, E', A', RVLS, RV area, and RVSI, respectively.
- Baseline GFR and Baseline log PVR which did not use planned treatment group median for imputation in Section 8.5.1.2 are the predetermined covariates for the exploratory analysis of GFR.

5.0 Definitions

In the following sections the item numbers on the blank CRF specification have been referred to.

5.1 Adverse Events

5.1.1 Treatment-emergent AEs and treatment-emergent laboratory values

Treatment-emergent AEs are those that occur on the date of or after the first dose of study medication and within 30 days of the date of last dose of study medication. There should be no missing or partial event dates. In the event that there is a missing date start date for the AE, the AE will be considered to be treatment emergent.

Treatment-emergent laboratory values are those that occur on a date after the first dose of study medication and within 37 days of the date of last dose of study medication. If a patient had abnormalities outside the limits defined in the laboratory table for liver function abnormalities at both Baseline and post-Baseline (or just during the post-Baseline period), the patient still qualifies as having treatment-emergent abnormalities.

5.1.2 Death / AEs leading to death

Even though deaths are being adjudicated, the number of deaths and time to death will be based on the CRF data, and not the adjudication database. AEs leading to death will only be based on the number of treatment-emergent AEs where at least one of the following is true:

- the outcome is equal to Fatal or
- the answer to the question "Did the adverse event result in death?" is Y or
- there is a non-missing date of death on the SAE CRF page.

5.2 Exposure and Compliance

5.2.1 Total number of tablets taken

The total number of tablets taken will be calculated as follows:

Total number of tablets taken = total number of tablets dispensed – total number of tablets returned

5.2.2 Compliance

Study treatment compliance is based on study treatment accountability on the Study Drug Dispensing and Accountability CRF page, as per formula below:

Compliance = [(total number of tablets dispensed – total number of tablets returned) / duration of therapy (days)] x 100

If the number of tablets returned and/or the number of tablets dispensed is missing the CRF question "number of doses missed" will be used in the calculation as follows:

Compliance = (duration of therapy in days – total number of doses missed)/duration of therapy x 100

5.2.3 Total exposure

Total exposure (mg) will be calculated by statistical programming as:

(total number of tablets dispensed across all visits – total number of tablets returned across all visits) x 10

If there is a missing number of dispensed and/or returned tablets then the total exposure will be calculated as:

(duration of therapy in days – total number of doses missed) x 10

5.2.4 Average daily dose (mg/day)

Average daily dose will be calculated by statistical programming as total exposure / duration of therapy (days).

5.2.5 Patient-year of exposure

Patient-year of exposure will be calculated as follows:

Patient-year of exposure = Number of patients x mean exposure (years)

5.2.6 Duration of therapy

Duration of therapy will be calculated by statistical programming using the date of first dose of study medication on the Study Drug Dispensing and Accountability CRF page and the date of last dose of study medication on the End of Treatment CRF page. The date of last treatment visit will not be used if the date of last dose of study medication is missing (i.e. the duration of therapy will be set to missing if the date of last dose of study medication is missing). It will be calculated as follows:

Date of last dose of study medication on the End of Treatment CRF page - date of first dose of study medication on the Study Drug Dispensing and Accountability CRF page + 1

For deliveries prior to database freeze (e.g. IDMC deliveries, three-monthly reports, Development Safety Update Reports but not the pre-freeze dry run, post-freeze dry run or the post-lock delivery) if the data of last dose of study medication on the end of treatment CRF page is missing it will be imputed with the data cut date.

5.3 Medications

5.3.1 Imputation of prior and concomitant medication dates

Partial dates can be entered into the CRF (missing date parts are presented as "UNK").

If the day of the start date is missing:

- If the month and the year is the same as the month and the year of Study Day 1 then the day of Study Day 1 will be imputed
- Otherwise the 1st of the month will be imputed.

If the month of the start date is missing:

- If the year is the same as the year of Study Day 1 then the month of Study Day 1 will be imputed

- Otherwise January will be imputed.

If the day of the end date is missing then the last day of the month will be imputed.

If the month of the end date is missing then December will be imputed.

If the complete date is missing then it will not be imputed.

The imputed dates will only be used for derivations. The raw (partial) dates will be presented in the listings.

5.3.2 Prior and study-treatment concomitant medications

Study-treatment concomitant medications are defined as medications that were recorded on the Prior and Concomitant Medications CRF page and taken from the day after the date of first dose of study drug but no later than the earliest of Week 12 (Day 84) or premature discontinuation of study treatment. This means the following medications are to be classified as study-treatment concomitant:

- Start date is before Study Day 1, and end date is on or after Study Day 1 or missing
- Start date is between Study Day 1 and the last dose day (inclusive), and end date is on or after Study Day 1 or missing
- Start date is missing, and end date ≥ Day1
- If both start and end date are missing

Prior (to study treatment) medications are defined as medications that were recorded on the Prior and Concomitant Medications CRF page and taken on the day of Study Day 1 or earlier. This means the medications are to be classified as prior if:

- Start date is before Study Day 1, and end date is any date or missing
- Start date is missing, and end date is before Study Day 1
- If both start and end date are missing, then “Ongoing at start of treatment” can be answered as No or Yes

It is possible for medications to be classified as both prior and concomitant, provided they meet the criteria of both concomitant and prior medication definitions.

The following table summarizes the above text and gives the corresponding assigned values for PREFL (prior flag Y/N/blank) and ONTRTFL (concomitant flag Y/N/blank).

Med Start Date	Med End Date	Prior/Concomitant	PREFL	ONTRTFL
< Day 1	< Day1	Prior	Y	N
< Day 1	≥ Day1 and ≤ Last Dose Day	Prior and Concomitant	Y	Y
< Day 1	> Last Dose	Prior and Concomitant	Y	Y
< Day 1	Missing	Prior and Concomitant	Y	Y
≥ Day1 and ≤ Last Dose Day	< Day1	not possible, query	<blank>	<blank>
≥ Day1 and ≤ Last Dose Day	≥ Day1 and ≤ Last Dose Day	Concomitant	N	Y
≥ Day1 and ≤ Last Dose Day	> Last Dose	Concomitant	N	Y
≥ Day1 and ≤ Last Dose Day	Missing	Concomitant	N	Y
> Last Dose	< Day1	not possible, query	<blank>	<blank>

Med Start Date	Med End Date	Prior/Concomitant	PREFL	ONTRTFL
> Last Dose	≥ Day1 and ≤ Last Dose Day	not possible, query	<blank>	<blank>
> Last Dose	> Last Dose	Neither (Post treatment)	N	N
> Last Dose	Missing	Neither (Post treatment)	N	N
Missing	< Day1	Prior	Y	N
Missing	≥ Day1 and ≤ Last Dose Day	query	Y	Y
Missing	> Last Dose	query	Y	Y
Missing	Missing	query	Y if "Ongoing at start of treatment" = No or Yes	Y

5.3.3 Study-concomitant medications

Study concomitant medication consist of medication recorded on the Prior and Concomitant Medications CRF page that is ongoing or initiated after signing of informed consent, or initiated up to 30 days after the study treatment discontinuation i.e. where the start date is up to and including 30 days after the date of last dose of study medication (Week 12/Day84 or premature discontinuation of study treatment). This means the medications with the following start and end dates are to be classified as study concomitant:

- Start date is before the informed consent date, and end date is on or after the informed consent date or missing
- Start date is between the informed consent date and the last dose day + 30 (inclusive), and end date is on or after the informed consent date or missing
- Start date is missing, and end date is between the informed consent date and last dose day + 30 (inclusive)
- If both start and end date are missing

The following table summarizes the above text and gives the corresponding assigned values for ONSTUDFL (on study Y/N/blank).

Med Start Date	Med End Date	Concomitant Study	ONSTUDFL
< IC date	< IC Date	No	N
< IC date	≥ IC and ≤ Last Dose Day + 30	Study Concomitant	Y
< IC date	> Last Dose + 30	Study Concomitant	Y
< IC date	Missing	Study Concomitant	Y
≥ IC and ≤ Last Dose Day + 30	< IC Date	not possible, query	<blank>
≥ IC and ≤ Last Dose Day + 30	≥ IC and ≤ Last Dose Day + 30	Study Concomitant	Y
≥ IC and ≤ Last Dose Day + 30	> Last Dose + 30	Study Concomitant	Y
≥ IC and ≤ Last Dose Day + 30	Missing	Study Concomitant	Y
> Last Dose + 30	< IC Date	not possible, query	<blank>
> Last Dose + 30	≥ IC and ≤ Last Dose Day + 30	not possible, query	<blank>
> Last Dose + 30	> Last Dose + 30	No	N
> Last Dose + 30	Missing	No	N
Missing	< IC Date	No	N
Missing	≥ IC and ≤ Last Dose Day + 30	Study Concomitant	Y
Missing	> Last Dose + 30	query	<blank>
Missing	Missing	query	Y

5.3.4 Prohibited Medications

Prohibited medications will fall in the general categories below: but not limited to the following:

- PAH-specific therapy (as defined in section 8.3.2)
- Inhaled nitric oxide
- Strong CYP3A4 inhibitors and inducers
- Inotropes
- Vasopressors
- Diuretics
- Any investigational drug

The specific prohibited medication list is a working list and will be updated by the sponsor as needed.

5.3.5 Pulmonary artery hypertension medications

Pulmonary artery hypertension medications will be identified by programming by name and route:

- Epoprostenol IV
- Treprostinil ORAL, RESPIR, IV, SC
- Iloprost RESPIR
- Bosentan
- Ambrisentan
- Sildenafil
- Tadalafil
- Riociguat
- Selexipag ORAL
- Avanafil
- Vardenafil
- Nitric Oxide RESPIR

This medication list is a living definition and will be updated when there are new medications added to the list.

5.4 Miscellaneous

5.4.1 Body mass index

Body mass index (BMI) is entered by the investigators directly on the CRF. However BMI will be calculated as follows by the statistical programmers using the height and weight:

Weight in [kilograms (kg)] /(Height at Baseline in m)^2

5.4.2 Hospital admission for HF

Data on hospital admission for HF and death is collected on the CRF and adjudicated by the CEC. The sites would be queried in cases of discordance between the CEC and the site. However, if agreement

cannot be reached, since the CEC is adjudicating HF admissions, their data will be used in the analysis of hospital admission for HF as explained below.

The number of patients admitted to hospital for HF will be equal to the number of patients who have "Y" answered at least once to the question:

- "Does the submitted case constitute a hospital admission for heart failure as the primary reason for admission?" for any adjudicated event according to the CEC/Adjudication Evaluation data

I.e. if no records have "Y" answered for the above question then the patient will be counted as having no hospital admission for HF. A missing answer to the CRF question will *not* be considered to be a "Yes". Other questions such as the answer to the CRF questions:

- "Was hospitalization for heart failure rehabilitation only?" on the AE CRF page and
- "Indication/Reason for prescribing" equal to "Hospital admission for HF" on the Prior and Concomitant CRF page

will *not* be taken into consideration in the definition of hospitalization for HF.

If the investigator updates the clinical database data used for adjudication and the adjudication committee re-reviews then an additional visit will be added to the adjudication data. The adjudication data will have multiple rows per SAE row number and the latest adjudication record based on the adjudication date for each SAE row number will be used in the analysis.

5.4.3 Need for RVAD/TAH

The number of patients needing RVAD will be defined as the number of patients who have at least one *treatment-emergent* AE (see section 5.1.1) where:

- "Yes" is answered on the AE CRF page to the question "Did the adverse event require Right Ventricular Assist Device implantation?"

The number of patients needing TAH will be defined as the number of patients who have at least one *treatment-emergent* AE where:

- "Yes" is answered on the AE CRF page to the question "Did the Adverse Event require a Total Artificial Heart?"

Having a medication on the Prior and Concomitant Medication CRF page where "Indication/Reason for prescribing" is equal to either "Needed for RVAD" and / or "Needed for TAH" will not qualify the patient as needing RVAD/TAH.

5.4.4 Need for RRT

The number of patients needing RRT will be defined as the number of patients who have at least one *treatment-emergent* AE where the question "Did the adverse event require Renal Replacement Therapy?" was answered "Yes".

5.4.5 eGFR-prog

Estimated Glomerular Filtration Rate(eGFR)) will be calculated as CKD-EPI Creatinine Equation (2009) by the statistical programmer (GFR-calc), unit as mL/min/1.73 m^2

$$eGFR\_prog = 141 \times \min\left(\frac{S_{Cr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{S_{Cr}}{\kappa}, 1\right)^{-1.209} \times 0.993^{Age} \times 1.018[if\ female] \times 1.159[if\ Black]$$

Where S_{Cr} = Standardized serum creatine, mg/dL in CRF

$\kappa = 0.7\ (female)\ or\ 0.9\ (male)$

$\alpha =$ -0.329 (female) or -0.411 (male)

min = minimum of $\frac{S_{Cr}}{\kappa}$ or 1

max = maximum of $\frac{S_{Cr}}{\kappa}$ or 1

Age = Age at visit, years

If the subject is a non-'black or African American' male:

141 × min(standardized serum creatinine/0.9, 1)$^{-0.411}$ ×

max(standardized serum creatinine/0.9, 1)$^{-1.209}$× 0.993^{Age}

If the subject is a black or African American male:

141 × min(standardized serum creatinine/0.9, 1)$^{-0.411}$ ×

max(standardized serum creatinine/0.9, 1) $^{-1.209}$ × 0.993^{Age} × 1.159

If the subject is a non-'black or African American' female:

141 × min(standardized serum creatinine/0.7, 1)$^{-0.329}$ ×

max(standardized serum creatinine/0.7, 1) $^{-1.209}$ × 0.993^{Age} × 1.018

If the subject is a black or African American female:

141 × min(standardized serum creatinine/0.7, 1)$^{-0.329}$ ×

max(standardized serum creatinine/0.7, 1) $^{-1.209}$× 0.993^{Age} × 1.018 × 1.159

The programmatically derived values will be used in efficacy analyses.

5.5 Populations

5.5.1 Patients randomized

The definition of patients randomized is patients who have a date of randomization on the Enrolled CRF page. This set of patients will define the Full Analysis Set (FAS).

5.5.2 Derivation of patients with at least one dose of study drug

Those patients who have the date of first dose of study medication on the Study Drug Dispensing and Accountability form and for whom the total number of tablets dispensed is greater than zero and the total number of tablets returned will be considered to have taken at least one dose of study drug. This set of patients will define the Safety Set (SS) and the modified FAS (MFAS).

5.6 Right Heart Catheterization Parameters (RHCA)

The following definitions only cover parameters that are programmed/derived outside of the CRF.

5.6.1 BSA-prog

Body surface area (BSA) will be derived as follows by statistical programming:

BSA-prog = 0.007184 × weight (kg)$^{0.425}$ × Baseline height ((centimeters (cm))$^{0.725}$

5.6.2 mPAP-prog

Although mean pulmonary artery pressure (mPAP) is calculated by the CRF, it is also derived by statistical programming as:

mPAP-prog = 0.61 x sPAP + 2

where sPAP = systolic pulmonary artery pressure entered in the CRF.

5.6.3 PVR-prog

$$\text{PVR\_prog} = \frac{\text{mPAP} - \text{PAWP}}{\text{Thermodilution CO}}$$

where the following CRF parameters are used: mPAP = Mean pulmonary artery pressure (mmHg) (end-expiratory mean line), PAWP = Pulmonary artery wedge pressure (mmHg) (end-expiratory mean line), and Thermodilution CO= Cardiac Output (L/min), thermodilution.

In addition, the thermodilution PVR-prog will be imputed to using the methods in section 8.5.1.2 (Handling of Missing Data for the Primary Analysis).

5.6.4 PVR ratio of Week 12 or EOT to Baseline

The PVR ratio of Week 12 or EOT to Baseline will be derived by statistical programming as follows:

$$\text{PVR ratio} = \frac{\text{Week 12 or EOT PVR\_prog}}{\text{Baseline PVR\_prog}}$$

Section 8.5.1.2 (Handling of Missing Data for the Primary Analysis) provides details about how to impute PVR ratio for primary analysis.

5.6.5 PVR ratio of Week 12 or EOT to Baseline, Investigator

PVR ratio_inv = Week 12 or EOT PVR-Inv / Baseline PVR using PVR-inv

where PVR-inv = thermodilution PVR entered in the CRF by the investigator

5.6.6 CI-prog

Although cardiac index (CI) is calculated in the CRF, it is also derived by statistical programming as:

CI-prog = CO / BSA-prog

where CO = Thermodilution Cardiac Output (L/min) from the CSR.

5.6.7 TPR-prog

Although Total Pulmonary Resistance (TPR) is calculated in the CRF, it is also derived by statistical programming as:

TPR-prog = mPAP / CO

where the following CRF parameters are used: mPAP = Mean pulmonary artery pressure (mmHg) (end-expiratory mean line), and CO = Thermodilution Cardiac Output (L/min).

5.6.8 TPG-prog

Although Transpulmonary gradient (TPG) is calculated in the CRF, it is also derived by statistical programming as:

TPG-prog = mPAP – PAWP

where the following CRF parameters are used: mPAP = Mean pulmonary artery pressure (mmHg) (end-expiratory mean line), and PAWP = Pulmonary artery wedge pressure (mmHg) (end-expiratory mean line).

5.6.9 DPG-prog

Although Diastolic pressure gradient (DPG) is calculated in the CRF, it is also derived by statistical programming as:

DPG-prog = dPAP - PAWP

where the following CRF parameters are used: dPAP = Diastolic pulmonary artery pressure (mmHg), and PAWP = Pulmonary artery wedge pressure (mmHg) (end-expiratory mean line).

5.6.10 PAPi-prog

Although Pulmonary Artery Pulsatility index (PAPi) is calculated in the CRF, it is also derived by statistical programming as:

$$\mathrm{PAPi-prog} = \frac{\mathrm{sPAP - dPAP}}{\mathrm{mRAP}}$$

where the following CRF parameters are used: sPAP = systolic pulmonary artery pressure dPAP = Diastolic pulmonary artery pressure (mmHg), and mRAP = mean right atrial pressure (mmHg) – mean of the a wave.

5.6.11 PAC-prog

Although Pulmonary arterial compliance (PAC) is calculated in the CRF, it is also derived by statistical programming as:

$$\mathrm{PAC\_prog} = \frac{\frac{\mathrm{CO}}{\mathrm{HR}} \times 1000}{\mathrm{sPAP - dPAP}}$$

where the following CRF parameters are used:

CO = Thermodilution Cardiac Output (L/min),

HR = Heart rate (HR) (bpm) (per ECG during PAP measurement)

sPAP= Systolic pulmonary artery pressure (sPAP) (mmHg),

dPAP = Diastolic pulmonary artery pressure (mmHg)

5.6.12 RVSWI-prog

Although Right ventricle stroke work index (RVSWI) is calculated in the CRF, it is also derived by statistical programming as:

$$\mathrm{RVSWI_{prog}} = (\mathrm{mPAP - mRAP}) \times \left(\frac{\mathrm{CI_{prog}}}{\mathrm{HR}} \times 1000\right) \times 0.0136$$

where CI-prog(5.6.5) and the following CRF parameters are used: mPAP = Mean pulmonary artery pressure (mmHg) (end-expiratory mean line), mRAP = mean right atrial pressure (mmHg) – mean of the a wave, and HR = hearth rate (bpm) (per ECG during PAP measurement).

5.6.13 Ea-prog

Although Effective arterial elastance (Ea) is calculated in the CRF, it is also derived by statistical programming as:

$$\mathrm{EA\_prog} = \frac{\mathrm{sPAP}}{\frac{\mathrm{CO}}{\mathrm{HR}} \times 1000}$$

where the following CRF parameters are used: sPAP = systolic pulmonary artery pressure. CO = Thermodilution Cardiac Output (L/min), and HR = hearth rate (bpm) (per ECG during PAP measurement).

5.6.14 VO2-prog

Resting oxygen consumption is recorded on CRF as Resting ***maximum*** consumption. Although Resting maximum oxygen consumption (VO2) is calculated in the CRF, it is also derived by statistical programming as:

VO2-prog = BSA-prog × 125

5.6.15 Indirect Fico CO-prog

$$\text{Indirect Fick CO\_prog} = \frac{\text{VO2\_prog}}{\text{Hgb} \times 13.6 \times (\text{SpO2} - \text{SvO2})} \times 100$$

where VO2-prog (5.6.14) and the following CRF parameters are used: Hgb= Hemoglobin (Hgb) (g/dL), SpO2= Pulse oximetry (SpO2) (%) (during PAP measurement) on: room air (RA) or O2 at (L/min), SvO2= Pulmonary arterial oxygen saturation (SvO2) (%)

5.6.16 Indirect Fick PVR-prog

$$\text{Indirect Fick PVR} = \frac{\text{mPAP} - \text{PAWP}}{\text{Indirect Fick CO\_prog}}$$

where Indirect Fick CO_prog (5.6.14) the following CRF parameters are used: mPAP = Mean pulmonary artery pressure (mmHg) (end-expiratory mean line), PAWP = Pulmonary artery wedge pressure (mmHg) (end-expiratory mean line)

5.6.17 Direct Fick PVR-prog

$$\text{Direct Fick PVR\_prog} = \frac{\text{mPAP} - \text{PAWP}}{\text{Direct Fick CO}}$$

Where the following CRF parameters are used: mPAP = Mean pulmonary artery pressure (mmHg) (end-expiratory mean line), PAWP = Pulmonary artery wedge pressure (mmHg) (end-expiratory mean line), Direct Fick CO= Cardiac Output (L/min) Direct Fico.

5.7 Study Times, Dates, Visits, and Windows

5.7.1 Baseline

Baseline is defined as the last non-missing measurement post LVAD implantation (on or after LVAD implantation) and before or *on* the date of the first dose of double-blind study drug (i.e. it is assumed that measurements taken on the date of the first dose occur before the first dose). It is thus possible for the Baseline date to differ between parameters. Baseline RHC is defined as the last RHC visit where the question 'Was a right heart catheterization performed?' was answered with 'Y'. Any pre-study RHC data is

collected on the Pulmonary Hypertension Relevant Disease History form and is thus automatically not considered as Baseline by programming.

5.7.2 Change from Baseline

Change from Baseline will be calculated by statistical programming as follows:

Post Baseline measurement – Baseline measurement

5.7.3 Study Day 1

Study Day 1 is the date of first study drug administration (Date of first dose of study medication on the Study Drug and Accountability page). For patients who are randomized but not dosed after the initial randomization, Study Day 1 is defined as the date of randomization.

5.7.4 Study day

A study day will be calculated by statistical programming as follows:

- Before date of Study Day 1:

  Study Day = (Date of the assessment – date of Study Day 1)

- On or after date of Study Day 1:

  Date of the assessment – date of Study Day 1 + 1

Adding 1 day enables randomization to be calculated as Day 1 and, Day 84 for example to be at 12 weeks.

This variable will be used in the windowing of laboratory variables and in the AE listings.

5.7.5 Laboratory visits and laboratory visit windowing

For laboratory variables, in order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT plus 37 days will be assigned to the most appropriate visit time point according to the most appropriate time-window for that assessment.

Lab Visit Window	**Value to be presented in the table per parameter**
Screening	Visit label is 'Visit 1 Screening' and no other windows apply
Day 1	Baseline as defined in section 5.7.1
Day 28	Non-missing post-Baseline value closest to Day 28 in the window of Day 1 – Day 42, on or before the last dose
Day 56	Non-missing post-Baseline value closest to Day 56 in the window of Day 43 – Day 70, on or before the last dose
Day 84	Non-missing post-Baseline value closest to Day 84 in the window of Day 71 – Day 98, on or before the last dose
End of Study	Visit label is 'Visit 6 End of Study' regardless of whether the date falls within any other window except Day 1.
Derived Record	
Last visit post-Baseline	Last non-missing value post-Baseline
Overall post-Baseline	Worst post baseline value. The highest value post baseline is selected for the serum chemistry and hepatic parameters. The lowest value post baseline is selected for hematology parameters.

For descriptive summaries (e.g. result and change from Baseline), if more than one actual visit (including the unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the first visit with non-missing data will be considered for analysis. If two non-missing laboratory assessments are on the same day, then the later of the two will be used for descriptive summaries.

For abnormality tables by timepoint or shift summaries by timepoint (e.g. of post-Baseline hemoglobin abnormalities by timepoint), the worst value within the window will be used. For the marked abnormality tables the worst of both directions will be presented. Thus a patient could be counted in both LLL and HH for a visit. However for the shift summary from low, normal to high laboratory values the worst value is defined as follows i.e. only one direction will be considered:

- For serum chemistry and hepatic parameters such as ALT and AST the highest value within the window will be the worst.
- For hematology parameters such as hemoglobin the lowest value within the window will be the worst.

The Baseline definition will be the same for all analyses as defined in section 5.7.1 i.e. there is not a separate definition to take the worst value within the window.

5.7.6 Last follow-up date

The last follow-up date is used in the censoring of the Kaplan-Meier analyses for events from Day 1 to Week 12. Thus the last follow-up will be defined as the last/latest of the following, provided the date is on or before Day 84:

- date of last dose of study medication on the EOT CRF page
- date of last treatment visit on the EOT CRF page

Otherwise, if the dates above occur *beyond* Day 84 then the last follow-up date will be set to the last date out of the following visits (scheduled and unscheduled):

- study drug dispensing and accountability visits up to Day 98
- last laboratory sample up to Day 98
- RHC up to Day 98
- echocardiogram up to Day 98.

Otherwise, if no last follow-up date has been assigned it will be set to the date of Day 98.

The statistical programmers will incorporate warnings into the derived data set program and inform the lead statistician if a patient has a missing last follow-up date.

5.7.7 Missing and partial dates

It is not expected that any dates apart from medications or medical history will be partially completed. No imputation of medical history dates will be performed. AE data is recorded with a complete date and time. The date is the only information used for determining treatment emergence. Imputations will be defined prior to final database lock.

5.7.8 Days in the hospital after hospitalization for heart failure

For hospital admission for HF adjudicated by the adjudication committee (see definition in section 5.4.2), the SAE number will be used to link SAE eCRF where information will be obtained to calculate the duration as follows:

Days in the hospital after hospitalization for heart failure will be calculated by statistical programming based on the "Hospitalization Admission Date" and "Hospitalization Discharge Date" on the SAE CRF page as follows:

Hospitalization Discharge Date – Hospitalization Admission Date + 1 - Duration of HF rehab (days).

The duration will be set to missing if a patient was hospitalized due to HF but has a missing or partial Hospitalization Discharge or Admission Date. Should a patient have more than one hospital admission for HF stay, the durations will be summed to a total within a patient for the analysis.

5.7.9 Date of heart transplant

It will be derived as the date of heart transplant as procedure.

5.7.10 Date last patient completed the study

The date the last patient completed the study will be defined as the last of the following dates across all patients:

- date of last treatment visit (on the EOT CRF page)
- date of last dose of study medication (on the EOT CRF page)
- date of contact (on the follow-up CRF page)

5.7.11 Time from Left Ventricular Assist Device (LVAD) implantation to treatment

Time from LVAD implantation to treatment will be calculated by statistical programming as follows:

Study Day 1 - Date of Left Ventricular Assist Device (LVAD) implantation.

5.7.12 Time to first occurrence of clinical events, from Day 1 to week 12

The earliest of the following dates on or after Study Day 1 but before study day 98 will be used to calculate the time to occurrence of the first clinical event. The dates will be obtained as follows:

- Hospital admission for HF

  The Hospitalization Admission Date on the SAE eCRF for the SAE where the question "Does the submitted case constitute a hospital admission for heart failure as the primary reason for admission?" has been answered as Y based on latest adjudication performed (see section 5.4.2).

- Re-initiation of i.v. diuretics ≥ 48 hours duration

  The number of patients needing re-initiation of i.v. diuretics ≥ 48 hours will be based on the number of patients for whom at least one of the answers to the question "Indication/Reason for prescribing" is "Re-initiation of i.v. diuretics >/=48 h duration" on the Prior and Concomitant Medication CRF page, provided the medication was classified as a study-treatment concomitant medication. The start date of the medication will be used as the event date in the calculation of time to event. The question "Did the adverse event require re-initiation of i.v. diuretics >/= 48 h duration?" on the AE CRF page will not be considered when defining re-initiation of i.v. diuretics ≥ 48 hours to allow for consistency between time to re-initiation calculations and the number of patients re-initiating.

- Re-initiation of i.v. inotropes ≥ 48 hours duration

  The number of patients needing re-initiation of i.v. inotropes ≥ 48 hours will be based on the number of patients for whom at least one of the answers to the question "Indication/Reason for prescribing" is "Re-initiation of i.v. inotropes >/=48 h duration" on the Prior and Concomitant Medication CRF page, provided the medication was classified as a study-treatment concomitant medication. The start date of the medication will be used as

the event date in the calculation of time to event. The question “Did the adverse event require re-initiation of i.v. inotropes >/= 48 h duration?” on the AE CRF page will not be considered when defining re-initiation of i.v. inotropes ≥ 48 hours.

- Initiation of PDE5 inhibitors, start date of PDE5 inhibitors from the concomitant medication CRF page will be used.
- Need for RVAD / total artificial heart (TAH), the Right Ventricular Assist Device implantation date/Total Artificial Heart Date from the AE CRF page will be used.
- Need for RRT, the “Renal Replacement Therapy Date” from the AE CRF page will be used as the event date.
- Death (all cause)

  Date of Death on the SAE CRF page for the treatment-emergent AE where death was indicated according to the definition in section 5.1.2**Error! Reference source not found.**. If the date of death is missing but the patient died according to this definition, then the date of last follow-up will be used as the event date in the calculation below instead.

Time to the event will be calculated as:

The earliest of the above dates – the date of Study Day 1 +1.

Patients who have none of the above clinical events will be censored at the last follow-up date and the time will be calculated by statistical programming as follows:

Last follow-up date – the date of Study Day 1 +1.

No patients should have a missing value for time to first clinical event or censoring.

A censoring variable will be derived as indicator for censoring at the end of the time interval (0 = if the subject had a clinical event, 1 = if the subject had a heart transplant, and 2 = otherwise) for the survival analyses. In the Kaplan-Meier analysis values of 1 and 2 will be considered censored.

6.0 Analysis Sets

6.1 Screened Analysis Set

This analysis set includes all patients who were screened and received a patient ID on the screening CRF page (i.e. all patients who signed the informed consent form). The usage of this analysis set is described in section 6.7.

6.2 Screen Failure Set

This analysis set includes all patients who were screened but for whom the question “Did the subject fail screening” was answered Y. No summaries will be generated based on this analysis set. Only a data listing of screen failure will be created.

6.3 Safety Set

The SS includes all patients who received at least one dose of study drug. Patients who receive the wrong treatment in error are analyzed as treated and not as randomized. If a patient has been randomized to placebo but receives active treatment at any time, they will be analyzed as an active patient. However if a patient who has been randomized to active treatment receives at least one dose of active treatment, they will be analyzed under the active treatment, even if they received placebo as well at any time.

I.e. a placebo-randomized patient will be counted in the macitentan arm if, at least at one visit, according to the bottle number on the drug accountability CRF page, the patient erroneously received a bottle/kit number that corresponds to macitentan treatment in the IXRS master kit data set. However if a patient who

has been randomized to macitentan receives a macitentan kit/bottle at least at one visit according to the bottle number on the drug accountability CRF page, she or he will still be analyzed under the macitentan arm, even if they erroneously received a bottle/kit corresponding to placebo at one of the other visits.

6.4 Full Analysis Set

The FAS includes all patients randomized. Patients who receive the wrong treatment in error are still analyzed as randomized and not as treated.

6.5 Modified Full Analysis Set

The modified FAS includes all patients in the FAS that have received at least one dose of study drug in the treatment period and have a Baseline, and at least one post-Baseline PVR measurement for the primary endpoint (after the imputations in section 8.5.1.2 have been performed). Patients who receive the wrong treatment in error are still analyzed as randomized and not as treated.

6.6 Per-Protocol Set

The Per-Protocol Set (PPS) comprises all patients included in the FAS without important protocol deviations that affect the main analysis of the primary efficacy variable. See section 8.2 for the explanation of how important protocol deviations are being defined on an ongoing basis. For the reasons for excluding patients from the PPS see section 8.2. A separate document file will be finalized to list reasons of exclusion from PP for each subject in FAS.

6.7 Evaluable Set

The Evaluable Set comprises all patients in the FAS that have received at least one dose of study drug in the treatment period and have baseline and at least one post-baseline thermodilution PVR after imputation, but no treatment group specific median was used for imputation in section 8.5.1.2.1 (PAWP imputation) or 8.5.1.2.3 (PVR ratio imputation). Patients who receive the wrong treatment in error are still analyzed as randomized and not as treated.

6.8 Usage of the Analysis Sets

The primary efficacy analyses will be performed on the FAS based on treatment as randomized. Secondary and exploratory efficacy analyses will be performed on the FAS. Sensitivity analyses of the ANCOVA for the primary efficacy variable will be performed as described in subsequent sections based on the PPS, Modified FAS, and Evaluable set.

Safety analyses related to the double blind treatment period will be performed on the SS based on treatment as received. Patient listings will be based on the SS, unless otherwise specified.

Patient populations will be described for the SAS and listed for the FAS. The Screen Failure Set will be used in the Screen Failure listing.

The FAS will be used in the randomization assignments listing, enrollment by center, disposition, prior and concomitant medication tables and in the listing of discontinued patients, and protocol deviations.

7.0 Data Review

The data provided to statistical programming for the pre-freeze deliverable will be a clean data snapshot.

7.1 Data Handling and Transfer

Please see the Data Management Plan.

7.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

Review of a pre-freeze TFL run on clean patients and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The pre-freeze TFLs will be run on clean patients (definition of clean will be outlined in Data Transfer Plan) and a post-freeze TFL will be run on the frozen database. The post-freeze TFL will be discussed with Actelion in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and Actelion must approve database lock.

8.0 Statistical Methods

All analyses will use SAS Version 9.4 or higher. Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place; except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. A row for missing values will only be presented if there are any missing values for the specific variable and the missing value observations will be included in the denominator used to calculate percentages. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, lower and upper quartiles (Q1, Q3), minimum and maximum. The median, Q1, Q3, minimum and maximum values will be displayed to the same level of precision as the raw data, the mean to a further decimal place and the SD to two additional decimal places. The overall type I error is $\alpha = 0.05$ (two-sided). The p-values presented for the ANCOVAs will be from two-sided tests unless otherwise specified. P-values presented for survival analyses and the logistic regression will be two-sided. There will be no adjustments for multiplicity. 95% confidence intervals will be displayed for summary statistics.

The only stratification in the analysis will be treatment group. All summary tables will be presented for Macitentan and Placebo only, i.e. no total column, with the exception of the IDMC tables, demographics, patient populations’ tables, and one time to first clinical event Kaplan-Meier analysis for clinical events (FAS) table, which will include a total column. No pooling of centers or other variables is planned, nor is a treatment-by-center interaction since center is not included in the models. No other interaction terms will be explored.

8.1 Patient Disposition

The number and percentage of patients in each analysis set will be presented. The number and percentage of patients who stopped study treatment prematurely according to the question “Did the patient complete all 12 weeks of study treatment?” on the EOT CRF page and a breakdown of the corresponding reasons for stopping study treatment will be presented in a separate table.

A tabulation of the number and percentage of patients randomized at each center will be presented. A separate table will present the following dates for the SAS:

- first patient screened
- first patient randomized
- last assessment date of primary endpoint
- last patient completed study

A listing of details of whether the patients completed or discontinued study treatment prematurely will be presented as will a listing of Patient Populations. The screen failure data will be listed for the Screen Failure Set. Details on informed consent will be listed for the FAS.

8.2 Protocol Deviations

Per PRA processes, protocol deviation data will be entered into our Clinical Trials Management System (CTMS). The study team and the sponsor would conduct on-going reviews of the protocol deviation data from CTMS and the resulting set of evaluable patients throughout the study, adjusting the protocol deviation criteria as seems appropriate. Important protocol deviations will exclude patients from the PPS. The set of evaluable patients must be finalized at the post-freeze data review meeting (or earlier), prior to database lock. No statistical programmatic checks of protocol deviations will be done in addition to edit check and monitoring. The important protocol deviations excluding patients from PPS will all have been confirmed prior to database lock and unblinding for final analysis by reviewing the listing of protocol deviations.

Please see the SOPRANO Protocol Deviation Guidelines for a list of criteria for protocol deviations.

Unimportant protocol deviations correspond to the protocol deviations listed in the protocol deviation plan as having N against the “Important protocol deviation (Y/N)” column. The number of patients who had at least one important protocol deviation, along with a break down as follows.

The protocol deviations will be sorted by important/unimportant classification and then according to the descending order of frequency of the following protocol deviation category order:

- Inclusion criteria
- Exclusion criteria
- Study drug
- Assessment - safety
- Efficacy Endpoints
- Visit window
- Informed consent
- Contraception
- Met Discontinuation Criteria
- Drug Not Interrupted
- ICH/GCP
- Other

A listing of protocol deviations will be presented based on the protocol deviation data entered into CTMS.

8.3 Treatments

8.3.1 Extent of Study Drug Exposure and Compliance

The duration of therapy, average dose per day and total dose will be presented using summary statistics along with the number and percentage of patients in each of the compliance categories (< 80%, ≥ 80% and ≤ 120%, and > 120%) for the SS. Information on study drug exposure, dispensing and accountability and compliance will be listed in separate listings for the SS.

8.3.2 Concomitant Medications

Anatomic Therapeutic Classification (ATC) coding will be performed for this study according to WHODRUG (version 01Mar2016 Drug Dictionary Enhanced (DDE) with yearly upgrades).

The number and percentage of patients using study-treatment concomitant medications will be displayed together with the number and percentage of patients using at least one medication within each second level ATC category (e.g., “A01”), and WHO preferred name (i.e., generic level, code ending in 01001). Records

are assigned as study-treatment concomitant based on the rules described in section 5.3.2. Study-concomitant medications will also be presented by second level ATC category and WHO preferred name.

Prior medications will also be displayed together with the number and percentage of patients using at least one medication within each second level ATC category (e.g., “A01”), and WHO preferred name (i.e., generic level, code ending in 01001) for the FAS.

A listing of prior and concomitant medications will be presented for the SS. The prohibited and PAH medications will be flagged in a listing. A second listing of the prior and concomitant medications will detail the medical history and AEs associated with the medications for the SS. A listing of medications that are started after 30 days of the last dose will be presented.

8.4 Demographic and Baseline Characteristics

Demographic characteristics will be presented for the FAS. The distribution of race, ethnicity, sex, age and sex distribution within each age group will be presented. Age groups will be categorized as < 65 years, ≥ 65 years – < 75 years, and ≥ 75 years. Baseline characteristics will be presented for the FAS. BMI, height, weight, Baseline functional class, time from LVAD implantation to treatment, and the following RHC parameters will be presented in a table:

- Heart rate
- Systemic blood pressure: mean (non-invasive or invasive)
- Systemic blood pressure: systolic (non-invasive or invasive)
- Systemic blood pressure: diastolic (non-invasive or invasive)
- Hemoglobin
- Peripheral arterial oxygen saturation (SpO_2) by pulse oximetry
- mRAP
- Kussmaul Sign
- Right atrial oxygen saturation
- Right ventricle systolic pressure (RVSP)
- Right ventricle end-diastolic pressure (RVEDP)
- sPAP
- Diastolic pulmonary artery pressure
- mPAP (end-expiratory mean line)
- SvO_2
- PAWP (mean of the wave)
- PAWP (end-expiratory mean line)
- LVEDP
- Pulmonary artery wedge oxygen saturation
- LVAD Speed
- LVAD flow rate
- LVAD power
- Thermodilution CO
- Direct Fick CO

- Thermodilution PVR-inv
- Thermodilution PVR-prog
- Direct Fick PVR - calculated
- Indirect Fick PVR - calculated
- Indirect Fick CO
- mPAP (calculated directly on the CRF as 0.61 x sPAP + 2)
- BSA
- CI
- TPR
- Transpulmonary gradient (TPG)
- Diastolic pressure gradient (DPG)
- Pulmonary Artery Pulsatility index (PAPi)
- Pulmonary arterial compliance (PAC)
- Right ventricle stroke work index (RVSWI)
- Effective arterial elastance (Ea)
- Resting maximum oxygen consumption (VO2).

No imputations using planned group median will be performed on PAWP and thus the results may be slightly inconsistent with the primary analysis.

Demographic and Baseline characteristics will be listed for the FAS.

Medical history and pulmonary hypertension relevant disease history will be listed in separate listings. Medical history will be coded using the MedDRA version 19.0 with yearly updates. The Baseline thermodilution PVR-inv presented in the demographics table will also be based on the following raw CRF variable (thermodilution method):

Pulmonary vascular resistance (PVR) [mPAP-PAWP]/CO (WU)

Baseline thermodilution PVR-prog will also be presented in the demographics table for the thermodilution method.

The demographics and Baseline characteristics table will present both thermodilution PRV-inv and the thermodilution PVR-prog.

8.5 Efficacy Analyses

Fixed effects will be used in all models. Hemodynamic measurements from RHC CRF page which are conducted post a heart transplant at any time during or prior to the study will be excluded from statistical analysis but included in the listings.

8.5.1 Primary Endpoint

The primary analysis will be performed on the FAS. Thermodilution PVR-prog will be summarized by time point and treatment group using descriptive statistics as well as geometric means and coefficients of variation (CVs). The ratio of Week 12 to Baseline thermodilution PVR-prog will be summarized similarly.

The ratio of Week 12 to Baseline thermodilution PVR-prog will be log-transformed (base e) and analyzed using an ANCOVA with a factor for treatment group (macitentan vs. placebo) and a covariate for Baseline

log thermodilution PVR-prog. The treatment group difference (on log scale) and its 95% CI will be estimated based on the model. The GMR (macitentan vs. placebo) and its 95% CI will be obtained by exponentiation.

The null hypothesis is that the mean PVR ratio is the same in the macitentan and placebo groups.

The alternative hypothesis is that the mean PVR ratio is lower in the macitentan group as compared to the placebo group.

The null hypothesis will be rejected if the entire 95% CI is below one.

The treatment effect will be expressed as (GMR−1) × 100%, where a negative value indicates a reduction of PVR in the macitentan group as compared to the placebo group.

The log transformation for PVR is justified by the fact that ratios versus Baseline follow a normal distribution more closely after a log transformation. In addition, mean absolute changes from Baseline on log scale can be translated into (geometric) mean ratios by exponentiation. Code similar to the below will be used:

```
proc mixed data=pvr;
      class trt;
      model logratio_Week_12_to_Baseline_PVR = baseline_log_PVR trt;

      /* active treatment / Placebo at 12 weeks */
      estimate 'Macitentan vs Placebo'       trt  1 -1 /cl;
      lsmeans trt / diff cl;
      ods output Estimates=Est LSMeans=lsmeans Diffs=Diffs;
run;
```

where logratio_Week_12_to_Baseline_PVR = is the variable for the logarithm of the ratio of Week 12 to Baseline.

The p-value obtained from the above code is two-sided, and if this p-value is less than 0.05 then the ratio will be considered to be statistically significant (provided that the estimated mean PVR ratio is less than one).

The derived thermodilution PVR-prog variable without imputation will be listed for the FAS. The PVR data measured post-heart transplant will be included in the listing of PVR, but will not be used in the primary and secondary efficacy analysis.

8.5.1.1 Assumption Checking

8.5.1.1.1 Homogeneity of Covariate Regression Coefficients

ANCOVA assumes homogeneity of covariate regression coefficients. This is ANCOVA's "equality of regressions" or "homogeneity of regressions" assumption. Because a single slope is used to adjust all observations in the experiment, the covariate coefficients (i.e. the slopes of the regression lines) must be the same for each level of the categorical variable being analyzed (i.e. all slopes must estimate the same common slope β). In other words, the adjustment of the Y values using a single β for all treatments is based on the assumption that there is a constant regression relationship among groups. The test for heterogeneity of slopes tests the validity of this assumption; that is, it tests whether or not the regression coefficients are constant over groups.

A regression relationship that differs among treatment groups reflects an interaction between the treatment groups and the independent variable or covariate. To test the assumption of homogeneity of slopes, this assumption will be checked using a scatter plot of the log of the ratio of Week 12 thermodilution PVR-prog (including imputed values) vs. Baseline logged thermodilution PVR-prog by treatment group for the FAS.

8.5.1.1.2 Normality of Residuals

To test for normality of residuals, the residuals from the ANCOVA model will be plotted. If the assumptions for the ratio are violated, non-parametric tests may be investigated in an exploratory analysis.

8.5.1.2 Handling of Missing Data for the Primary Analysis

The following imputation methods will be performed on the following primary endpoints.

- thermodilution PVR-prog = [mPAP-PAWP]/thermodilution CO (WU) (derived by programming) at baseline and the Day 84 or EOT visit
- PVR ratio = Week 12 PVR / Baseline PVR

8.5.1.2.1 PAWP imputation

When missing, PAWP (mmHg) (end-expiratory mean line) will be imputed as follows:

1.1 If PAWP is missing but the left ventricular end-diastolic pressure (LVEDP) from the RHCA CRF page is not-missing at the same visit, then PAWP will be imputed with LVEDP.

1.2 Else if PAWP and LVEDP are missing, then PAWP will be imputed with the closest non-missing PAWP value in days, choosing the later day if 2 visits are equally close.

1.3 Else if no other PAWP or LVEDP values are available for that subject, then PAWP will be imputed with the median imputed PAWP values over all other subjects in the Full Analysis Set from the same planned treatment group and same visit.

8.5.1.2.2 PVR-prog imputation

When missing, PVR-prog will be imputed as follows:

2.1 For the baseline visit, if mPAP and CO are not missing, then PVR-prog will be imputed using the imputed PAWP value at baseline.

For the Day 84 or EOT visit:

2.2.1 If mPAP, CO and an imputed PAWP are not missing, then PVR-prog will be imputed using the imputed PAWP value at Day 84 or EOT.

2.2.2 Else PVR-prog will be imputed using the last post-baseline unscheduled PVR-prog before Week 84 or EOT.

8.5.1.2.3 PVR ratio

When PVR is non-missing at Baseline, but still missing Day 84 or EOT after imputation at 8.5.1.2.2, then PVR ratio will be imputed with the median imputed PVR ratio values over all other subjects with non-missing PVR ratio in the Full Analysis Set from the same planned treatment group and same visit.

The above imputations will be performed on all PVR analyses, including the sensitivity analyses. Specifically, they will be applied in both the primary summary statistic table and the ANCOVA as well as the analysis of the primary variable in the FAS and modified FAS. The imputations for Baseline thermodilution PVR-prog will be used in both the calculation of the primary endpoint (ratio of Week 12 to Baseline of thermodilution PVR) and for the covariate adjustment of the primary endpoint (Baseline log thermodilution PVR-prog).

The imputation rules will not be applied to the results presenting change from Baseline in PVR.

Multiple imputation is not planned.

8.5.1.3 Sensitivity Analysis

8.5.1.3.1 Ratio of Week 12 to Baseline PVR for the Modified FAS

To investigate the robustness of the results, the same analysis and descriptive statistics of primary endpoint will be performed in the Modified FAS in section 6.5.

8.5.1.3.2 PVR based on investigator-reported/calculated results

The analysis of primary endpoint will be repeated for the FAS based on the thermodilution PVR-inv recorded on the eCRF.

8.5.1.3.3 Ratio of Week 12 to Baseline PVR based on the Evaluable Set

The analysis of primary endpoint will be repeated for the evaluable set in section 6.7, where no planned treatment group specific median used for imputation in section 8.5.1.2.1 (PAWP imputation) or 8.5.1.2.3 (PVR ratio imputation)

8.5.1.3.4 Ratio of Week 12 to Baseline PVR for the PPS

The analysis of primary endpoint will be repeated for the Per Protocol set in section 6.6.

8.5.2 Multiplicity

No adjustments for multiplicity will be made.

8.5.3 Pooling of Sites

Pooling of sites is not planned since site is not included in any of the models.

8.5.4 Secondary Endpoints

Secondary efficacy analyses will be performed on the FAS using 95% CIs. No correction for multiple testing will be applied for these analyses and no imputation of missing values will be performed, except for BSA. For BSA the last observed value, including baseline and screening values, will be carried forward. Secondary analyses will be conducted based on the FAS for selected secondary endpoints as described below.

Changes from Baseline to Week 12 in pressure-volume variables (i.e., mRAP, mPAP, PAWP, CI, TPR and SVO_2) will be analyzed, but without the log-transformation or imputation. The ANCOVAs for mRAP, mPAP (end-expiratory mean line), PAWP, CI, TPR and SVO_2 will be adjusted for Baseline log PVR and the Baseline of the variable to be analyzed as in section 4.0, e.g. for mRAP the ANCOVA will be adjusted for Baseline log thermodilution PVR which did not use planned treatment group median for imputation in section 8.5.1.2,) and Baseline mRAP. A summary table for change from Baseline will be presented for the following parameters on the RHCA CRF page:

- Heart rate
- Systemic blood pressure: mean (non-invasive or invasive)
- Systemic blood pressure: systolic (non-invasive or invasive)
- Systemic blood pressure: diastolic (non-invasive or invasive)
- Hemoglobin
- SpO2 by pulse oximetry
- mRAP
- Right atrial oxygen saturation
- RVSP

- RVEDP
- sPAP
- Diastolic pulmonary artery pressure
- mPAP (end-expiratory mean line)
- SvO2
- PAWP (mean of the wave)
- PAWP (end-expiratory mean line)
- LVEDP
- Pulmonary artery wedge oxygen saturation
- LVAD Speed
- LVAD flow rate
- LVAD power
- Thermodilution CO
- Direct Fick CO
- Thermodilution PVR-inv
- Thermodilution PVR-prog
- Direct Fick PVR - calculated
- Indirect Fick PVR - calculated
- Indirect Fick CO
- mPAP (calculated directly on the CRF as 0.61 x sPAP + 2)
- BSA
- CI
- TPR
- TPG
- DPG
- PAPi
- PAC
- RVSWI
- Ea
- VO2

The summary table will be repeated in the modified FAS for the calculated parameters (not those reported by the site). A table for Kussmaul Sign will be presented for the FAS and a separate table will also be presented in the modified FAS.

All data collected on the RHC CRF data will be listed (with the exception of the raw variables derived on the CRF for thermodilution PRV-prog and BSA since these will be derived by statistical programming). PVR-inv and thermodilution PRV-prog will be presented in a separate listing with CO.

For patients who receive a heart transplant at any time during or prior to the study, RHC conducted after heart transplant will be excluded from the above secondary efficacy analyses which are based on RHC variables. The PVR data for patients with post- heart transplant will be included only in the listing of right heart catherization parameters and will not be used for PVR calculation.

NT-proBNP will be summarized by time point and treatment group using descriptive statistics as well as geometric means and CVs. The ratio of Week 12 to Baseline NT-proBNP will be summarized similarly. The ratio versus Baseline in NT-proBNP will be log-transformed and analyzed using an ANCOVA with covariates for treatment group and Baseline log NT-proBNP. NT-proBNP and the ratio versus Baseline will be listed for the FAS. The summary table will be repeated in the modified FAS.

WHO FC will be summarized by time point and treatment group using frequency tables in the FAS and repeated in the modified FAS. A shift table will also be presented in the FAS.

Changes from Baseline in WHO FC will be categorized as worsening (change > 0 e.g. Class I at Baseline and class II to IV at the Week 12 / end of treatment visit) ; improvement (change < 0 : e.g. Class IV at Baseline and class I /II/III at the Week 12 / end of treatment visit); or no change (change =0 : remains in same class from baseline to Week 12/end of treatment visit) . The change of WHO FC will be compared using proportional odds model (ordered logistic regression, reference level= worsening) with covariates for treatment group and baseline WHO FC (I/II vs. III/IV) in the FAS. Improving will also be analyzed using the logistic regression model (reference level = no change or worsening) with covariates for treatment group and baseline WHO FC (I/II vs. III/IV) in the FAS.

Worsening will be analyzed using a logistic regression model (reference level =no change or improvement) with covariates for treatment group and Baseline WHO FC in the FAS. Baseline WHO FC will be entered in the model as a categorical covariate as (FC I/II vs. III/IV). The outcome to be modelled will be set to 1 if the patient has any worsening (i.e., change > 0) during the study (including any post-Baseline unscheduled visits) and 0 if the patient does not have any worsening (i.e., change <= 0) during the study. The treatment effect will be expressed in terms of an odds ratio. If a patient has no post-Baseline FC data they will be excluded from logistic regression. The dummy variable for treatment will be coded as macitentan=1 and placebo=0. WHO FC results will be listed for the FAS.

Analysis results for WHO FC will be reported if the models converge.

8.5.5 Exploratory Endpoints

Exploratory efficacy analyses will be performed on the FAS using 95% CIs.

Echocardiographic variables including TAPSE, S', RVFAC, E', A', RVLS, RV end systolic area, RV end diastolic area, and RVSI will be summarized by treatment and scheduled time point (Baseline, Week 12/EOT) using descriptive statistics (n, mean, SD, median, Q1, Q3, and range). Unscheduled visits will not be included in the table but will be listed in listings. Based on data availability, the change from Baseline to Week 12/EOT in these variables will be summarized similarly and analyzed using an ANCOVA with a factor for treatment and covariates including Baseline log PVR and Baseline TAPSE, S', RVFAC, E', A', RVLS, RV end systolic area, RV end diastolic area and RVSI, respectively. The adjusted treatment effect and its 95% CI will be presented. Echocardiography will be listed for the FAS. The assessment of clinically significance for echocardiography variables will also be listed for the FAS.

Time to first occurrence of clinical events, from enrollment to last follow-up date (section 5.7.6) will be summarized. These clinical events include:

- Hospital admission for HF
- Re-initiation of i.v. diuretics ≥ 48 hours duration
- Re-initiation of i.v. inotropes ≥ 48 hours duration
- Initiation of PDE5 inhibitors
- Need for RVAD / TAH

- Need for RRT
- Death

The number of patients with at least one post-Baseline clinical event and the number of patients with each type of clinical event will be presented in a summary table.

Survival analyses will also be performed on for the time to the first post-Baseline clinical event. The survival analysis will be presented overall for all the above clinical events, and not separately for each type of event.

Cox proportional hazards model will be used to estimate the hazard ratio for the time to the first clinical event and the 95% confidence interval of the hazard ratio. Treatment group will be the only covariate in the model.

A p-value will be calculated for the time-to-event treatment differences using the unstratified log-rank test and a Kaplan-Meier analysis will be performed to estimate the median, 25%, 75% time with 95% confidence intervals.

A summary table will present the number of patients by first clinical event. A separate table will present the cumulative number of patients with events, the number of patients at risk and the event-free survival estimate for the following time intervals:

- Day 0
- Day 7
- Day 14
- Day 28
- Day 56
- Day 84
- Day 98

A listing of first clinical event after Study Day 1 will be presented. If a patient has more than one type of event on the same day, the first alphabetically will be presented in the listing.

A Kaplan-Meier figure for the time to the first clinical event will be presented for this analysis in addition to the Cox proportional hazards model.

Duration of Hospitalization for HF will be summarized by treatment group. The descriptive summary statistics table will only be presented for patients who had hospitalization due to HF according to the adjudication committee. Hospitalization for HF will be listed for the FAS. The CEC data will also be listed for the FAS.

All AEs where an RVAD or a TAH was required will be listed for the FAS, including non-treatment emergent adverse events.

GFR derived from statistical programming in section 5.4.5 will be summarized by treatment and scheduled time point (Baseline, Week 12/EOT) using descriptive statistics (n, mean, SD, median, Q1, Q3, and range). Unscheduled visits will not be presented in the tables but will still be listed in the listing. The change from Baseline to Week 12/EOT in GFR will be summarized similarly. Change from Baseline in GFR will be analyzed using an ANCOVA with a factor for treatment and covariates Baseline log PVR and Baseline GFR as in section 4. The adjusted treatment effect and its 95% CI will be presented. GFR will be listed for the SS.

The additional “Systemic blood pressure: Mean, systolic and diastolic (mmHg) (Noninvasive or invasive)” variable will not be reported in any tables or listings or used in any derivations for the results created based on this SAP since the other systemic blood pressure variables are to be completed by the centers.

8.6 Safety Analyses

All safety data will be listed, with flags for quantitative abnormalities.

8.6.1 Adverse Events

A treatment-emergent AE is any AE temporally associated with the use of a study treatment and the full definition is provided in section 5.1.1. In practice all AEs which change in severity or relationship to study drug are assigned a new start date and captured as a new record. These events do not need combining since patients with AEs (rather than events) are the unit of analysis. A summary of treatment-emergent adverse events, including the number and percentage of patients reporting at least one adverse event, the number and percentage of patients discontinuing due to an adverse event, the number and percentage of patients with at least one SAE, severe AEs, related AEs, the number of patients with at least one AE of interest, the number of patients with any severe treatment-related AEs, the number of patients with any treatment-related serious AEs, the number of patients with any treatment-related AEs leading to treatment discontinuation and the number and percentage of deaths will be presented.

The number and percentage of patients experiencing treatment emergent AEs and SAEs at least once will be tabulated by treatment group and by:

- MedDRA System organ class (SOC) and individual preferred term within each SOC, in descending order of incidence for both the SOC and preferred term. Note that counting will be by patient not event and patients are only counted once within each SOC or preferred term. I.e. if a patient had Nausea and Vomiting, which are both coded under the SOC “Gastrointestinal disorders” this patient would be counted once under Nausea and again separately under the Vomiting preferred term, but only once under the SOC.
- Preferred term, in descending order of incidence.

Furthermore, treatment-emergent AEs will be tabulated as described above by maximum severity. Missing severities will be counted as severe in the table but listed as missing in the listings. A table of patients with related AEs by SOC and preferred term and a table of the number of patients with treatment-related AEs by preferred term will be presented for the SS. Missing relationship will be counted as related in the tables but listed as missing in the listings. For the related AE tables, patients with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that SOC or preferred term. For tables by severity, patients with multiple events within a particular SOC or preferred term will be counted under the category of their most severe event within that SOC or preferred term.

AEs leading to premature discontinuation of study treatment will also be summarized as described above. The table by SOC and preferred term will include both non-treatment-emergent and treatment-emergent AEs with an action taken of “Drug withdrawn”. The table by preferred term will only include treatment-emergent AEs with an action taken of “Drug withdrawn”.

Listings will be provided for all reported AEs, including AEs and SAEs. In addition, separate listings will be provided for AEs leading to premature discontinuation of study treatment. The discontinuation date will be the date of last dose of study medication on the End-of-Treatment CRF page. Two listings will present the results from the adjudication.

Version 19.0 of the MedDRA dictionary will be used and updated on a yearly basis.

Any heart transplant that is recorded on the AE or SAE page will be included in the AE outputs.

8.6.1.1 Events of Interest

An Event of Interest (EOI) is defined as a noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals (Council for International Organizations of Medical Sciences VI, 2005). The EOIs for this study will include:

- Anaemia
- Hypotension
- Oedema/fluid retention

AE preferred terms that are potentially representative of EOIs will be retrieved for review and analysis using the criteria in Appendix 6 Criteria for Adverse Events of Special Interest. The "narrow" or "wide" is irrelevant because (1) we work with preferred term lists, and because (2) we usually have Actelion Medical Queries (not SMQs) for which no scope is defined.

Patient incidence of treatment-emergent EOIs will be tabulated by treatment group, the type of event, and the maximum severity.

8.6.2 Deaths and Serious Adverse Events

Investigators complete the AE page (which is the input for the raw AE data set) and if the AE is serious a second page is opened (which is the input for the raw SAE data set). Thus there is information on SAEs in both the AE page and the SAE page. These two data sources can be linked through the investigator entering the SAE row number in the AE page should data recorded on the AE page about SAEs be required from the AE page.

The number and percentage of patients experiencing treatment-emergent SAEs at least once will be tabulated by treatment group and by:

- MedDRA SOC and individual preferred term within each SOC, in descending order of incidence. Note that counting will be by patient not event and patients are only counted once within each SOC or preferred term.
- Preferred term, in descending order of incidence.

AEs leading to death will also be summarized as described above. Please see section 5.1.2 for the definition of AE leading to death. In addition, separate listings will be provided for treatment emergent SAEs (SAE detail listing, the SAE relationship to study drug listing and the significant laboratory test results relevant to the SAE) and for AEs leading to death.

8.6.3 Laboratory Data

Descriptive summary statistics by visit and treatment group will be provided for observed values and absolute changes from Baseline, in both hematology and blood chemistry laboratory tests. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT plus 37 days will be assigned to the most appropriate visit time point according to the best fitting time window for that assessment. Once the windowing has been performed summary statistics for Baseline, Day 28, Day 56, Day 84, EOS will be presented in the table but any laboratory listings would still present all visits a patient attended.

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

A listing of marked laboratory parameters will be provided i.e. values of HHHH, HHH, HH, LL, LLL as per the table below.

Absolute values and changes from Baseline of laboratory values during the course of the study will be summarized using the usual location and scale summary statistics by treatment group.

The following laboratory variables will be presented in the units provided by the central laboratory:

- Hematology: hemoglobin, hematocrit, erythrocyte count, leukocyte count with differential counts, platelet count. For differentials only the K (1000 cells)/µL results will be presented in the table. Both percentage and K/µL results will be presented in the listings.
- Blood chemistry: AST, ALT, alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase (LDH), creatinine, blood urea nitrogen (BUN), uric acid (urate), glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, protein, albumin.

The number and percentage of patients with hemoglobin abnormalities will be tabulated by treatment group by presenting a shift table showing the number of patients whose hemoglobin was less than 8.0 g/dL at time points up to end of study (including overall post-Baseline), the number of patients whose hemoglobin was greater than or equal to 8.0 g/dL but less than 10.0 g/dL at time points up to end of study and for completeness the number of patients whose hemoglobin was ≥ 10 g/dL at the windowed time points up to the EOS and last visit post-Baseline. For this table, the lowest value within the visit window will be used in the table.

For the overall study period (Baseline to EOS), the following categories will be presented for hemoglobin abnormalities:

- Hemoglobin < 8.0 g/L
- Hemoglobin ≥ 8.0 and < 10.0 g/dL
- Hemoglobin decrease from Baseline ≥ 2.0 g/dL and < 5.0 g/dL
- Hemoglobin decrease from Baseline ≥ 5.0 g/dL
- Hemoglobin < 10.0 g/dL and concurrent (i.e., at the same time point) decrease from Baseline ≥ 2.0 g/dL

The lowest non-missing hemoglobin value at any post-Baseline time point of assessment up to the EOS will be considered in the evaluation of incidences. Thus a patient can only be counted once in either the "< 8.0 g/L" or "≥ 8.0 and < 10.0 g/dL" category, and once in the "decrease from Baseline ≥ 2.0 g/dL and < 5.0 g/dL" or "decrease from Baseline ≥ 5.0 g/dL" category.

The cumulative number and percentage of patients with liver function test abnormalities will be tabulated by treatment group. For the overall study period (Baseline to EOS), the proportion of patients falling in the following categories for liver test abnormalities will be presented:

- ALT and /or AST > 1 x ULN and < 3 x ULN
- ALT and /or AST ≥ 3 x ULN
- ALT and/or AST ≥ 5 x ULN
- ALT and /or AST ≥ 8 x ULN
- ALT and /or AST ≥ 3 x ULN and < 5 x ULN
- ALT and /or AST ≥ 5 x ULN and < 8 x ULN
- ALT or AST ≥ 3 x ULN and concurrent (i.e., at the same time point) total bilirubin ≥ 2 x ULN. The proportion of patients with ALT and/or AST abnormality ≥ 3 × ULN in combination with concurrent total bilirubin ≥ 2 × ULN from Baseline (exclusive) up to EOS will be presented i.e. treatment-emergent laboratory values are those that occur on a date after the first dose of study medication. The qualifying ALT or AST test result must be from the same blood sample as the total bilirubin result.

Patients will be counted once at the worst level within a category. Patients may be counted once in each of the ≥ 3 x ULN, ≥ 5 x ULN and ≥ 8 x ULN categories and a maximum of once in the worst of the remaining categories > 1 × ULN and < 3 × ULN, ≥ 3 × ULN and < 5 × ULN and ≥ 5 × ULN and < 8 × ULN.

The highest ALT or AST value at any post-Baseline time point of assessment up to the EOS is considered in the evaluation of incidences.

Separate listings of hematology, biochemistry, and l circulating biomarker results and their change from Baseline will be presented for the SS.

For both the tables and the listings there will be no exclusion of laboratory data, even if the reference range indicator is equal to E for exclusion and regardless of the data entered in the completion status variable.

Low, normal and high categories will be included in the table as per the central laboratory reference ranges. Thus a laboratory test abnormality is defined as any value outside the normal range as provided by the central laboratory. The direction of the abnormality (below or above the normal range) is indicated using 'H' and 'L'. A marked laboratory test abnormality is defined as any value up to EOS that fulfills the applicable condition for LL / HH. Marked abnormality variables of interest are defined in standard international units for the laboratory variables of interest and are listed in Table 1 below. The most severe marked abnormalities are indicated by LLL / HHH, where applicable.

Table 1 Laboratory Abnormalities

Parameter	LL marked	LLL marked	HH marked	HHH marked
Hemoglobin	< 10 g/dL	< 8 g/dL	[post-Baseline > (Baseline + 2 g/dL) *AND* (Baseline > ULN)] ***OR*** [post-Baseline > (ULN + 2 g/dL) *AND* Baseline ≤ ULN]	[post-Baseline > (Baseline + 4 g/dL) *AND* (Baseline > ULN)] ***OR*** [post-Baseline > (ULN + 4 g/dL) *AND* Baseline ≤ ULN]
Hematocrit	< 28 % for females < 32 % for males	< 20 %	> 55 % for females > 60 % for males	> 65 %
Platelets	< 75 × K/uL	< 50 × K/uL	> 600 × K/uL	> 999 × K/uL
Leukocytes (white blood cells)	< 3.0 × K/uL	< 2.0 × K/uL	> 20.0 × K/uL	> 100.0 × K/uL
Neutrophils	< 1.5 × K/uL	< 1.0 × K/uL	NA	NA
Eosinophils	NA	NA	> 5% ***OR*** > 5 × K/uL	NA
Lymphocytes	< 0.8 × K/uL	< 0.5 × K/uL	> 4.0 × K/uL K/uL	> 20 × K/uL

Parameter	LL marked	LLL marked	HH marked	HHH marked
ALT	NA	NA	> 3 × ULN	> 5 × ULN*
AST	NA	NA	> 3 × ULN	> 5 × ULN*
Alkaline phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Total Bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Direct Bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Creatinine	NA	NA	> 1.5 × Baseline ***OR*** > 1.5 × ULN	> 3 × Baseline ***OR*** > 3 × ULN
Glucose Random	< 54 mg/dL	< 40 mg/dL	> 160 mg/dL	> 250 mg/dL
Calcium	< 8.0 mg/dL	< 7.0 mg/dL	> 11.6 mg/dL	> 12.4 mg/dL
Sodium	NA	< 130 mmol/L	> 150 mmol/L	> 155 mmol/L
Potassium	< 3.2 mmol/L	< 3.0 mmol/L	> 5.5 mmol/L	> 6.0 mmol/L
Uric acid (Urate)	NA	NA	> 9.9 mg/dL	> 12.1 mg/dL
Albumin	< 3 g/dL	< 2 g/dL	NA	NA
Blood Urea Nitrogen	NA	NA	> 2.5 × ULN	> 5 × ULN

* Also HHHH as > 8 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable/available; ULN = upper limit of normal.

Treatment-emergent marked laboratory abnormalities are all marked laboratory abnormalities with onset after the study treatment start and before or on ET plus 37 days [see definitions in section 5.1.1], that were not present at Baseline. An additional “last visit post-Baseline” will also be presented. Shift tables will be included that summarize the number and percent of patients with LLL, LL, L, Normal, H, HH, HHH at each windowed visit and the last visit post-Baseline compared to the Baseline visit. L and H will be values outside the normal range but not reaching the marked abnormality criteria. If HH, HHH, LL or LLL is not defined for a variable, ‘NA’ will be displayed for LL, LLL, HH, and HHH categories. Percentages will be calculated based on the number of patients in the analysis set. Shift tables will be used to summarize the worst treatment-emergent laboratory abnormalities, based on the on the definition of the marked laboratory test abnormalities listed in Table 1, above. The worst category is taken for the analysis for each direction so a patient can be counted under LLL and HH within the same windowed timepoint. Note that worse categories in each direction can result from multiple records for a subject within a visit window, or one record satisfying 2 abnormalities in different directions.

8.6.4 Vital Signs

Blood pressure (i.e., diastolic blood pressure (DBP) and systolic blood pressure (SBP)), pulse rate, BMI as programmed by statistical programming and weight will be summarized at each scheduled study visit using the usual location and scale summary statistics by treatment group for both absolute values and changes from Baseline, i.e. no windowing will be necessary to include data from unscheduled visits; unscheduled visits would only be presented in any listings. Patients for whom no post-Baseline value is available are

excluded from the analysis of the changes from Baseline in the SS. Height, BMI calculated by the investigator, and mean blood pressure will not be included in the table.

Vital signs including the parameters listed above as well as height, BMI as programmed by statistical programming, BMI calculated by the investigator, and mean blood pressure will be listed.

8.6.5 Other Data

Pregnancy test results will be listed for the SS.

9.0 Validation

PRA Health Sciences' goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

10.0 References

National Research Council 2010. The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials http://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials

Little RJA, Rubin DB. Statistical Analysis with Missing Data. 2nd ed. New York: John Wiley, 2002

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
A'	Tricuspid Inflow Peak E-Velocity
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CCMP	Central clinical monitoring plan
CEC	Clinical Events Committee
CI	Confidence interval / Cardiac index
cm	Centimeters
CO	Cardiac output
CRF	Case Report Form
CRO	Clinical Research Organization
CTMS	Clinical Trials Management System
CV	Coefficient of variation
DBP	Diastolic blood pressure
DDE	Drug Dictionary Enhanced
DPG	Diastolic pressure gradient
E'	Tricuspid peak diastolic annular velocity
Ea	Effective arterial elastance
EOI	Event of interest
EOS	End of study
EOT	End of treatment
FAS	Full Analysis Set
GFR	Glomerular filtration rate
GLM	Generalized Linear Models
GMR	Geometrics Mean Ratio
h	Hours
HF	Heart failure

ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
inv	Investigator-reported
ISAC	Independent statistical analysis center
i.v.	Intravenous
IxRS	Interactive Web Response System
K/µL	Thousand cells per micro liter
kg	Kilograms
LDH	Lactate dehydrogenase
L/min/m^2	Liter/minute/meter squared
LVAD	Left ventricular assist device
LVEDP	Left ventricle/ventricular end-diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Milligrams of mercury
mPAP	Mean pulmonary artery pressure
mRAP	Mean right atrial pressure
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
ODS	Output Delivery System
PAC	Pulmonary arterial compliance
PAH	Pulmonary artery hypertension
PAPi	Pulmonary Artery Pulsatility index
PAWP	Pulmonary artery wedge pressure
PDE5I	Phosphodiesterase type 5 inhibitors
PH	Pulmonary hypertension
pmol/L	Pikomol per liter
PP	Per Protocol
PPS	Per Protocol Set
PRA	Pharmaceutical Research Associates
prog	As programmed by statistical programming
PVR	Pulmonary vascular resistance
Q1	Lower quartile
Q3	Upper quartile
RA	Room Air
RBC	Red Blood Cell

RHC	Right heart catheterization
RPM	Revolutions per minute
RRT	Renal replacement therapy
RV	Right ventricle
RVAD	Right ventricular assist device
RVEDP	Right ventricle end-diastolic pressure
RVFAC	Right ventricular fractional area change
RVLS	Global RV longitudinal strain
RVSI	Right ventricular sphericity index
RVSP	Right ventricle systolic pressure
RVSWI	Right ventricle stroke work index
S'	Tricuspid peak annular velocity S
SAP	Statistical Analysis Plan
SAS	Screened Analysis Set / Statistical Analysis System
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
Scr	Serum creatinine
SD	Standard deviation
SOC	System organ class
SOPRANO	Macitentan in pulmonary hypertenSiOn Post-left ventRiculAr assist device implantation
sPAP	Systolic pulmonary artery pressure
SpO_2	Peripheral arterial oxygen saturation
SS	Safety Set
SVO_2	Mixed venous oxygen saturation (Pulmonary arterial oxygen saturation)
TAH	Total artificial heart
TAPSE	Tricuspid annular plane systolic excursion
TFL	Tables, figures and listings
TPG	Transpulmonary Gradient
TPR	Total pulmonary resistance
ULN	Upper limit of normal
VO2	Resting maximum oxygen consumption Resting oxygen consumption
WBC	White Blood Cell
WHO FC	World Health Organization functional class
WU	Wood unit

Appendix 2 Tables, Figures, Listings, and Supportive SAS Output Appendices

See separate document containing tables, figures and listings specifications.

Appendix 3 List of Additional Protocol Violation/ Protocol Deviation Identification Listings

There are no additional listings defined but the following tables summarizes the post-text listings that will be looked at to identify protocol deviations/violations. A medical director at Actelion will look through the medications to determine any prohibited medications that may have been missed during the clinical research associates review.

List of Additional Protocol Violation/ Protocol Deviation Identification Listings:		
Output	Title 1	Title 2
Post-Text Listing 16.2.1.1.1	Inclusion and Exclusion Criteria (SAS)	
Post-Text Listing 16.2.2.1	Protocol Deviations (FAS)	
Post-Text Listing 16.2.3	Patient Populations (FAS)	
Post-Text Listing 16.2.4.4	Prior and Concomitant Medications (SS)	
Post-Text Listing 16.2.4.5.1	Prior and Concomitant Medications: Additional Information: Medical History and Adverse Events (SS)	
Post-Text Listing 16.2.5.1	Compliance (SS)	
Post-Text Listing 16.2.5.2	Study Drug Dispensing and Accountability (SS)	
Post-Text Listing 16.2.6.1	Right Heart Catheterization Parameters (FAS)	
Post-Text Listing 16.2.6.2.1	PVR (FAS)	

Appendix 4 Shells for In-Text Tables, Figures, and Listings

None are currently specified.

Appendix 5 Shells for Additional Protocol Violation/Deviation Identification Listings

No additional PDV listings are required to aid the identification of protocol deviations to ensure that the team has all the information required to identify the protocol violations/deviators, so no listing shells have been designed in the SAP.

Appendix 6 Criteria for Adverse Events of Special Interest

The MedDRA dictionary version is updated yearly. Actelion will provide any updates to the list of preferred terms to be included in the definition of the adverse events of special interest 90 days in advance of the delivery for which updates are needed.

Anaemia: The case will be included in this subgroup if it contains an event within the “Haematopoietic erythropenia” SMQ or the “Haematopoietic cytopenias affecting more than one type of blood cell” SMQ (with the exception of 2 unspecific PTs: “Blood disorder”, “Blood count abnormal”), or it contains an event with any MedDRA Preferred Term containing the text “anaemia”. This includes the following preferred terms in MedDRA:

Anaemia

Anaemia folate deficiency

Anaemia Heinz body

Anaemia macrocytic

Anaemia megaloblastic

Anaemia neonatal

Anaemia of chronic disease

Anaemia of malignant disease

Anaemia of pregnancy

Anaemia postoperative

Anaemia prophylaxis

Anaemia splenic

Anaemia vitamin B12 deficiency

Anaemia vitamin B6 deficiency

Aplasia pure red cell

Aplastic anaemia

Aspiration bone marrow abnormal

Autoimmune aplastic anaemia

Autoimmune haemolytic anaemia

Bicytopenia

Biopsy bone marrow abnormal

Blood incompatibility haemolytic anaemia of newborn

Blood loss anaemia neonatal

Bone marrow disorder

Bone marrow failure

Bone marrow infiltration

Bone marrow myelogram abnormal

Bone marrow necrosis

Bone marrow toxicity

Cardiac haemolytic anaemia

Cold type haemolytic anaemia

Congenital anaemia

Congenital aplastic anaemia

Coombs negative haemolytic anaemia

Coombs positive haemolytic anaemia

Cytopenia

Deficiency anaemia

Erythroblast count abnormal

Erythroblast count decreased

Erythroid maturation arrest

Erythropenia

Erythropoiesis abnormal

Febrile bone marrow aplasia

Foetal anaemia

Full blood count decreased

Haematocrit abnormal

Haematocrit decreased

Haematotoxicity

Haemoglobin abnormal

Haemoglobin decreased

Haemolytic anaemia

Haemolytic anaemia enzyme specific

Haemolytic icteroanaemia

Haemorrhagic anaemia

Hand and foot syndrome secondary to sickle cell anaemia

Hereditary haemolytic anaemia

Hereditary sideroblastic anaemia

Hexokinase deficiency anaemia

Hyperchromic anaemia

Hypochromic anaemia

Hypoplastic anaemia

Iron deficiency anaemia

Leukoerythroblastic anaemia

Melanaemia

Microangiopathic haemolytic anaemia

Microcytic anaemia

Myelodysplastic syndrome

Myelodysplastic syndrome transformation

Myelofibrosis

Myeloid metaplasia

Nephrogenic anaemia

Normochromic normocytic anaemia

Pancytopenia

Panmyelopathy

Pernicious anaemia

Plasmablast count decreased

Primary myelofibrosis

Proerythroblast count abnormal

Proerythroblast count decreased

Protein deficiency anaemia

Pyruvate kinase deficiency anaemia

Red blood cell count abnormal

Red blood cell count decreased

Refractory anaemia with an excess of blasts

Refractory anaemia with ringed sideroblasts

Reticulocyte count abnormal

Reticulocyte count decreased

Reticulocyte percentage decreased

Reticulocytopenia

Scan bone marrow abnormal

Sickle cell anaemia

Sickle cell anaemia with crisis

Sideroblastic anaemia

Spherocytic anaemia

Spur cell anaemia

Warm type haemolytic anaemia

Hypotension:

Blood pressure ambulatory decreased

Blood pressure decreased

Blood pressure diastolic decreased

Blood pressure orthostatic decreased

Blood pressure systolic decreased

Diastolic hypotension

Hypotension

Mean arterial pressure decreased

Orthostatic hypotension

Procedural hypotension

Oedema/fluid retention:

The case will be included in this subgroup if it contains an event with the MedDRA Preferred Term "Pulmonary congestion" or if within the SMQ "Haemodynamic oedema, effusions and fluid overload (SMQ)" with the exception of PTs containing "site". In addition to pulmonary congestion, this includes the following preferred terms in MedDRA:

Acute pulmonary oedema

Amyloid related imaging abnormalities

Ascites

Bone marrow oedema

Bone marrow oedema syndrome

Bone swelling

Brain oedema

Bronchial oedema

Capillary leak syndrome

Cerebral oedema management

Cervix oedema

Compression stockings application

Cytotoxic oedema

Effusion

Elephantiasis nostras verrucosa

Extensive swelling of vaccinated limb

Fluid overload

Fluid retention

Gallbladder oedema

Gastrointestinal oedema

Generalised oedema

Gestational oedema

Gravitational oedema

Heat oedema

Hydraemia

Hydrothorax

Hypervolaemia

Hypoosmolar state

Joint effusion

Joint swelling

Lipoedema

Local swelling

Localised oedema

Lymphoedema

Mouth swelling

Muscle oedema

Muscle swelling

Myocardial oedema

Non-cardiogenic pulmonary oedema

Oedema

Oedema due to cardiac disease

Oedema due to hepatic disease

Oedema due to renal disease

Oedema mucosal

Oedema neonatal

Oedema peripheral

Oedematous kidney

Oesophageal oedema

Pelvic fluid collection

Pericardial effusion

Perinephric effusion

Peripheral oedema neonatal

Peripheral swelling

Pleural effusion

Prevertebral soft tissue swelling of cervical space

Pulmonary congestion

Pulmonary oedema

Pulmonary oedema neonatal

Reexpansion pulmonary oedema

Retroperitoneal effusion

Retroperitoneal oedema

Scleroedema

Skin oedema

Skin swelling

Spinal cord oedema

Subdural effusion

Swelling

Testicular swelling

Vasogenic cerebral oedema

Visceral oedema

Appendix 7 Prohibited Medication List

The prohibited medication list is a living document and will be updated by the sponsor as needed. It includes PAH-specific therapy, inhaled nitric oxide, strong CYP3A4 inhibitors and inducers, inotropes, vasopressors, and diuretics.