STATISTICAL ANALYSIS PLAN

FOR CSR (AMENDMENT 1)

A prospective, multicenter, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on Right vEntricular remodeling in Pulmonary ArterIal hypeRtension assessed by cardiac magnetic resonance imaging

The REPAIR study

Purpose of Analysis	Clinical Study Report
Investigational Drug	Macitentan / ACT-064992
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TABLE OF CONTENTS

NCT02310672

NCT02310672

LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	Six-minute walk-distance
AE	Adverse event
BP	Blood pressure
bpm	Beats per minute
CFR	(US) Code of Federal Regulations
CRF	Case report form
CI	Confidence interval
CRO	Contract research organization
CL	Confidence limit(s)
CSR	Clinical study report
ECG	Electrocardiograph
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End-of-study
EOT	End-of-treatment
FAS	Full analysis set
FC	(WHO) Functional Class
FDA	(US) Food and Drug Administration
FSFV	First subject first visit
GCP	Good Clinical Practice
GDF	Growth Differentiation Factor
IAC	Imaging Acquisition Center
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IVRS	Interactive voice recognition system
IWRS	Interactive web recognition system
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
LDH	Lactate dehydrogenase

NCT02310672

LSLV	Last subject last visit
LV	Left Ventricle
LVEDP	Left ventricular end diastolic pressure
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LVSV	Left Ventricular Stroke Volume
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
NCI	(US) National Cancer Institute
NT-proBNP	N-terminal pro-brain natriuretic peptide
OLE	Open Label Extension
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-protocol analysis set
PVR	Pulmonary Vascular Resistance
QT_CF	QT interval corrected for heart rate using Fridericia's formula
RHC	Right heart catheterization
RV	Right Ventricle
RVEDV	Right Ventricular End Diastolic Volume
RVEF	Right Ventricular Ejection Fraction
RVESV	Right Ventricular End Systolic Volume
RVSV	Right Ventricular Stroke Volume
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SOC	System organ class
SOP	Standard operating procedure
SDTM	Study Data Tabulation Model
SI	Standard International
TNF	Tumor Necrosis Factor

NCT02310672

ULN	Upper limit of the normal range
WHO	World Health Organization
WHO FC	WHO Functional Class
WHODRUG	WHO drug dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical data analyses conducted for the purpose of the CSR of the study AC-055-403 (REPAIR).

The CSR analyses will be performed on the locked database following completion of study core phase only (approximately 52 weeks). Data from the Open Label extension (OLE, France) will be presented at time of core phase completion in listings and included in some additional tables.

An interim analysis will be performed when 42 patients have available data for both primary endpoints. The study is single-arm, open-label with data available on ongoing basis, therefore all analyses (interim and final) will be performed without any restriction to data access or separated team.

1.1 Study documents

The following study documents are used for the preparation of the SAP:

- Protocol AC-055-403, version 06, dated 08 Nov. 2016,
- Case Report Form (CRF): version 08, dated 05 Dec 2016,
- PD Code list, version 4, dated 10 Jun. 2016.

Any change to any of those documents affecting the biostatistics deliverables will require this SAP and related documents to be updated accordingly.

2 STUDY DESIGN AND FLOW

The section below describes the protocol key features only, for additional details please refer to the protocol.

2.1 Study design

The study is a prospective, multicenter, single-arm, open-label, Phase 4 study. It is planned to be conducted in 100 adult patients with idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, PAH associated with connective tissue diseases or PAH associated with congenital heart diseases under certain conditions as defined in the protocol. An interim analysis will be performed when 42 patients have available data for both primary endpoints.

The study planned to include three sub-studies that are conducted in selected centers, where eligible patients for the main study are offered to participate in the sub-study(ies).

- Metabolism sub-study (selected US sites only).
- Biopsy sub-study (cancelled on 18-Aug-2017).
- Echo sub-study.

2.2 Study visit and assessment schedule

The study includes 3 main periods:

1. Screening period: from the date of informed consent signature to initiation of study treatment (excluded), may last up to 28 days.

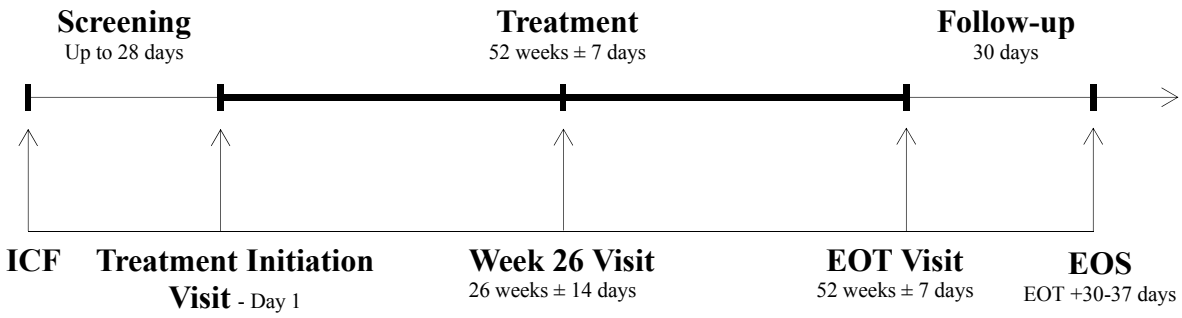
2. Treatment period: from the first dose intake (Day 1) to the date of End of Treatment (EOT) which may occur as per protocol at Week 52 ± 7 days, or earlier in case of premature discontinuation of study treatment. For patients in France entering the OLE, EOT is the last date of treatment in the core phase of the study.
3. Safety follow-up period: from the date of EOT (excluded) until the date of the End of Study (EOS) visit, and lasts at least 30 days. Patients that enter the OLE are not included in this safety follow-up period, as they continue to take study treatment.

EOTOLE is the date of the last study treatment in the open label extension.

When this SAP refers to EOT or EOS, unless otherwise indicated, this means EOT and EOS relating to the core part of the study (excluding the open label extension).

The overall study design is depicted in Figure 1.

Figure 1 Study design (without extension)



3 OBJECTIVES

3.1 Primary objectives

- To evaluate the effect of macitentan on *right ventricular* and on *hemodynamic properties* in patients with symptomatic PAH.

3.2 Secondary objectives

- To evaluate the safety and tolerability of macitentan in patients with symptomatic PAH.

3.3 Exploratory objectives

- To investigate the effect of macitentan on disease-related circulating biomarkers in patients with symptomatic PAH.
- To explore a potential association between change in right ventricular properties and clinical outcome in patients with symptomatic PAH.
- To investigate the effect of macitentan on ventriculo-arterial coupling in patients with symptomatic PAH.

- To evaluate the effect of macitentan on left ventricular properties in patients with symptomatic PAH.

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes to the analyses planned in the study protocol

Following changes are considered in SAP:

- The RVSV primary variable will be "Change from baseline to Week 26 in Right Ventricular (RV) Stroke Volume (RVSV) assessed by cardiac MRI from pulmonary artery flow" as stated in protocol section 6.1.1, but without the adjustment specified in protocol section 11.3.2.2. That is, the primary variable will always be RVSV from pulmonary artery flow, and not RVSV determined by RV volumes.
    - Note that the adjustment only comes into effect when LVSV determined from aortic flow" differs from "RVSV from pulmonary artery flow" by more than 20% (in either direction).
    - The RVSV including the adjustment specified in protocol section 11.3.2.2 will be an exploratory analysis, with the analysis of RVSV by volumes and LVSV.
      Reason: The adjustment (implicitly) assumes that when "LVSV determined from aortic flow" differs from "RVSV from pulmonary artery flow", that "RVSV determined by RV volumes" would be close to "LVSV determined from aortic flow". Early data (from the first 12 subjects) shows that this is not necessarily the case. Therefore, "RVSV from pulmonary artery flow" is used as a simpler and more precise primary variable.
- It is clarified in this SAP that all analyses for secondary/exploratory endpoints are performed on mFAS and SS. Similarly, analyses for the sub-studies will use all patients from the SS that are in the sub-study, and repeated for sub-study patients in the mFAS. The main reporting will use the SS, results for the mFAS for secondary / exploratory / sub-study endpoints are for reference,
  Reason: to use all available data for the (secondary/exploratory) endpoints; subjects who do not have data for both primary endpoints are excluded from the FAS and mFAS, but may have data on secondary endpoints.
- Subgroup analyses have been added (see Section 8 for the definition of subgroups).
  Reason: to further investigate the data.
- Safety analysis: specific areas of clinical interest for macitentan have been defined (see Section 5.6.5) to further characterize AEs. Therefore, the unplanned safety analysis on *"Treatment-emergent AEs of special interest"* has been added.
  Reason: to further characterize AEs.
- For PCWP/LVEDP imputations mentioned in Section 10.7.2, the largest analysis set (SS) is used instead of mFAS.
  Reason: To include all data for these endpoints.

- Borg Dyspnea Index is not listed as efficacy endpoint in protocol. However this parameter is recorded in the CRF and will be summarized descriptively and listed. Reason: for complete reporting of the study.
- The following data will be listed only: Arterial elastance (mmHg/mL); RV end-systolic elastance (mmHg/mL) and RV maximum isovolumic pressure (mmHg). These were listed as exploratory endpoints in the protocol, with an associated exploratory objective.
  Reason: The analysis of right ventricular pressure-volume loops requires both cardiac MRI and RHC in suitable digital data. There were difficulties in obtaining suitable RHC files from the sites. Consequently very little data was available.
- Ventriculo-arterial coupling will be listed
- Data for the metabolism sub-study will be listed only, due to the lack of patients.

4.2 Changes in the conduct of the study / data collection

The biopsy sub-study was cancelled on 18-Aug-2017 (without any patient having an ICF date in the CRF for the biopsy sub-study) and therefore no data will be reported. Reason: futility due to no recruitment.

4.3 Clarifications concerning endpoint definitions and related variables or statistical methods

Following clarifications are considered in SAP:

- For PPS, the analysis will be restricted to patients who had a post-baseline measurement taken between 22 weeks and 30 weeks of treatment for both primary endpoints (as mentioned in protocol Section 11.3.2.4).
  Reason: The PPS is used for reporting of the primary endpoints at Week 26.
- P-values boundaries have been also specified in case of a 2-sided test (Section 10.11).
- The required monthly laboratory liver and hemoglobin tests will be summarized.

5 DEFINITIONS OF VARIABLES

Note that applies to all variables: for patients entering OLE, EOT will consider last dose in core phase. All data with start date during the OLE will be reported in listings, and included in certain additional tables. Unless otherwise specified, variables and tables will only include data up to EOT or EOS in the core phase. Exposure data, AE data, liver and hemoglobin laboratory abnormalities for the OLE will be included in additional tables.

5.1 Screening failures

A patient who did not have a Day 1 visit (*i.e.* no data in CRF available at Day 1 visit), is considered a screening failure.

If a subject is screened twice, only the data assessed during the second screening attempt if before the study treatment initiation are displayed and included in any analysis. The data coming from the first screening are included in the corresponding analysis if not available at re-screening or they are assessed after or on treatment initiation.

5.2 Subject characteristics

5.2.1 Demographics

The following baseline variables were collected in the CRF during the screening period for all screened patients:

- Age, sex, height, weight,
- Country
- Race as allowed by local regulations, ethnicity
- Childbearing potential.

Demographics include the BMI (kg/m^2) calculated as:

$$BMI = \frac{Body\ weight}{Height^2}$$

5.2.2 Baseline disease characteristics

Baseline disease characteristics include:

- PAH etiology,
- Age at PAH diagnosis (years)
- 6-minute walk-distance (6MWD, meter),
- Borg dyspnea index (rated dyspnea on scale from 0 to 10),
- WHO Functional Class (severity score based on symptoms: I, II, III and IV),
- Heart Rate (HR, bpm) assessed by RHC,
- Calculated Pulmonary Vascular Resistance (PVR, $dyn.sec.cm^{-5}$) assessed by RHC,
- Mean Pulmonary Arterial Pressure (mPAP, mmHg) assessed by RHC,
- Systolic Pulmonary Arterial Pressure (sPAP, mmHg) assessed by RHC,
- Diastolic Pulmonary Arterial Pressure (dPAP, mmHg) assessed by RHC,
- Pulmonary Capillary Wedge Pressure (PCWP, mmHg) assessed by RHC,
- Left Ventricular End Diastolic Pressure (LVEDP, mmHg) assessed by RHC,
- Mean Right Atrial Pressure (mRAP, mmHg) assessed by RHC,
- Cardiac Output (CO, L/min) assessed by RHC.

PVR ($dyn.sec.cm^{-5}$) as calculated by the investigator and recorded in eCRF will be listed only. All PVR analyses will be based on calculated PVR (see formula in Section 5.5.1).

5.2.3 Other baseline characteristics

Other baseline characteristics include:

- Treatment strategy (Patient previously treated with a PDE-5 inhibitor, PAH-specific treatment-naive patient with intention to start study drug only, PAH-specific treatment-naive patient with intention to start upfront PDE-5 inhibitor and study drug combination therapy), as ticked on CRF.

5.2.4 Medical history

Collected information on medical history includes:

- Clinically significant past or concomitant disease or diagnosis (yes/no)
- Main Disease or Diagnosis (prior and/or ongoing)

Any disease or diagnosis is defined as concomitant if 'Ongoing at Screening' is answered with 'Yes'; all other diseases/diagnoses are considered as previous.

5.2.5 Previous and concomitant therapies

5.2.5.1 Previous therapies

A previous therapy is any treatment for which the end date of treatment is prior to the start of study treatment.

If the end date is missing and the start date is prior to the date of study treatment start, then the therapy is considered as previous if "Ongoing at start of treatment?" is not ticked with "Yes".

5.2.5.2 Study-concomitant therapies

Study-concomitant therapies are all treatments that are ongoing or initiated after start of study (i.e., signed informed consent), or initiated up to EOS. Study-concomitant therapies at Baseline are treatments taken on the day of first dose (see Section 11.3). All data with start date in the OLE will be reported in listing only.

5.2.5.3 Study-treatment concomitant therapies

Study-treatment concomitant therapies are any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period. All data with start date in the OLE will be reported in listing only.

Previous, study-concomitant therapies (including therapies concomitant at baseline) and study treatment concomitant therapies are retrieved from the Concomitant Medication and Contraceptive Methods forms of the eCRF.

Concomitant medications and contraceptive methods collected on the eCRF forms Concomitant Medication - Open Label Extension and Contraceptive Methods - Open Label Extension respectively will be only listed.

5.2.5.4 PAH-specific and PAH-related therapies

PAH-specific therapies are any of the following medications:

Table 1 - PAH-specific treatment

Class	Active compound
Oral PDE5i	sildenafil
	tadalafil
	vardenafil
Prostanoid	beraprost
	treprostinil
	iloprost
	epoprostenol
	selexipag
ERA	bosentan
	ambrisentan
	Macitentan
sGC stimulator	riociguat

Note: selection of terms should be done by searching terms provided in active compound only in the preferred term. For example any occurrence of "sildenafil citrate" will be reported under 'Oral PDE5i'.

5.2.6 Other subject characteristics

The following historical pulmonary function tests (Pulmonary Function Test form) are reported at Screening only:

- FEV_1/FVC [%] irrespective of bronchodilator administration,
- FEV_1 as a percent of predicted value irrespective of bronchodilator administration [%],
- Total Lung Capacity (TLC) as a percent of predicted value [%],
- DLco (Diffusing capacity of the lung for carbon monoxide) as a percent of predicted value [%],
- FVC as a percent of predicted value [%],

Under protocol version 3, the pulmonary function test was to be done after administration of a bronchodilator. This was not required in subsequent versions of the protocol.

- FEV_1 and TLC are collected in the eCRF from protocol version 3 onwards.
- DLco and FVC are collected in the eCRF with protocol versions 5 and 6.
- FEV_1/FVC is collected in the eCRF with protocol versions 3 and 4, but not collected with protocol versions 5 and 6.

Data will be summarized as collected in the eCRF; data will not be derived.

5.3 Study treatment exposure and compliance

5.3.1 Exposure

Study treatment exposure is recorded via the study drug log in the eCRF ('Study Drug Log' and 'Study Drug Log - OLE' forms) and retrieved from the SDTM EX domain. The number

of subjects exposed will be displayed per 4-week interval over time. Exposure to study drug will be described in terms of duration in weeks.

The study treatment duration for the core phase is defined as the number of weeks elapsing between study drug initiation and discontinuation, inclusive, regardless of treatment interruptions, calculated as:

$$\frac{treatment\ end\ date\ (EOT) - treatment\ start\ date + 1}{7}$$

Study treatment exposure including the OLE will be summarized separately, from the treatment start date to the last dose in the OLE (EOTOLE):

$$\frac{treatment\ end\ date\ (max(EOT, EOTOLE)) - treatment\ start\ date + 1}{7}$$

5.3.2 Compliance with study treatment

Compliance (in %) with study treatment is calculated based on recorded drug accountability data retrieved from the eCRF forms: 'Study Drug Dispensing & Accountability' and 'Study Drug Dispensing & Accountability OLE'. Dispensing and returns for the OLE will be listed only and will not be included in the calculation of study drug compliance [for the core phase].

Compliance with study treatment is assessed through drug accountability. Compliance, in percent, is calculated as:

$$100 \times \frac{(number\ of\ tablets\ provided\ to\ subject\ -\ number\ of\ tablets\ returned)}{Expected\ number\ of\ tablets\ taken\ during\ the\ treatment\ period}$$

Where the number of tablets provided and number of tablets returned relates to study treatment for the core phase only, and the expected number of tablets taken during the core treatment period is defined as:

$$(treatment\ end\ date\ (EOT) -\ treatment\ start\ date + 1)$$

as macitentan 10 mg is taken once daily. If the no bottles are returned, (no returns at any timepoint), then compliance is also missing. If there are some returns, the compliance will be calculated using the all dispensing and available returns data (assume zero if the bottle is not returned).

Compliance will not be calculated for the OLE. Dispensing and returns for the OLE will be listed only.

5.3.3 Study treatment interruptions

Study treatment interruptions are recorded in the Study drug Log. A subject is considered to have had a study treatment interruption if the reason for treatment end is either 'Temporarily interrupted due to an AE' or 'Temporarily interrupted not due to an AE'.

For each period of temporary interruption, the duration of study treatment interruption is determined as

$$Treatment\ restart\ date - treatment\ end\ date - 1$$

and summed up per subject.

Treatment exposure in days is determined as the study treatment duration subtracted by the sum of days of treatment interruption.

5.3.4 Premature discontinuation of study treatment

A subject is considered to have prematurely discontinued study treatment if the "reason for treatment end" in the Study Drug Log eCRF is 'Premature Discontinuation'. The reason for premature discontinuation will be taken from the Premature Discontinuation of Study Treatment form of the eCRF.

5.4 Study discontinuation

Subjects who completed the study as per protocol are those with the question "Did the subject complete the Follow up?" answered "Yes" in the End of Follow Up form of the eCRF.

On the other hand, a subject is considered to have prematurely discontinued the study if the answer to the question 'Did the subject complete the Follow up?' in the End of Follow Up eCRF form is 'No'.

The date and the reason for end of study are collected in the same form.

The date of withdrawal of consent from sub-study is collected in the Withdrawal of Consent from Sub-study form.

5.5 Efficacy variables

5.5.1 Primary efficacy variable(s)

The study has two primary efficacy endpoints:

- Change from Baseline at Week 26 in RVSV assessed by cardiac MRI from pulmonary artery flow.
- Ratio of Week 26 to Baseline PVR (assessed by RHC).

While PVR value was computed by the investigators and entered into the CRF, the PVR value used for the statistical analyses will be re-computed in the analysis datasets using PCWP (or LVEDP if missing PCWP) according to the formula:

$$PVR = 80 * \frac{mPAP - (PCWP\ or\ LVEDP\ if\ PCWP\ not\ available)}{CO}$$

The PVR computed by the investigators (and entered into the CRF) will be listed only.

Programming note: RVSV in the SDTM morphology data (SDTM.MO) has 2 subcategories (variable MOSCAT, which is in capitals): "Determined from pulmonary artery flow" and "Determined from RV volumes". These sub-categories also apply to RVEF, LVSV and LVEF. There are also 2 sub-categories (variable MOSCAT) for HR by Cardiac MRI: "During cine imaging" or "During flow imaging"

5.5.2 Secondary efficacy variables

As for the primary endpoints, secondary endpoints consist of *change from Baseline at Week 26* of the following right ventricular and functional characteristics:

- RVEDV (mL) assessed by cardiac MRI
- RVESV (mL) assessed by cardiac MRI
- RVEF (%) based on pulmonary artery flow assessed by cardiac MRI
- RV mass (g) assessed by cardiac MRI
- 6MWD (m)
- WHO FC

5.5.3 Other efficacy variables

Other efficacy variables are used to assess the effect of macitentan on different aspects of the disease.

5.5.3.1 Hemodynamic variables and pressure-volume variables

First set of variables include endpoints that are usual tools to monitor disease progression, and are expressed as change from Baseline at Week 26 of:

- mPAP (mmHg) assessed by RHC,
- mRAP (mmHg) assessed by RHC,
- Cardiac index (L/min/m^2) calculated according to the formula:
  - $CI = \frac{CO}{BSA}$, where BSA is body surface area (m^2) where
    CO = Cardiac Output assessed by RHC
    BSA [m^2]= 0.007184 × weight$^{0.425}$ [kg] × height$^{0.725}$ [cm].

For the calculation of CI, considering that multiple weight measures are recorded during the study, all the weight assessments will be first re-assigned to the most appropriate visit according to the time windows described in Section 11.9 and then used for deriving the parameter. Height at Baseline is used for the calculation of CI.

Pressure-volume variables (assessed by combining cardiac MRI and RHC):

- Arterial elastance (mmHg/mL),
- RV end-systolic elastance (mmHg/mL),
- RV maximum isovolumic pressure (mmHg)
- Ventriculo-arterial coupling.

5.5.3.2 Variables related to maintenance of treatment effect

The additional variables include endpoints aiming at assessing maintenance of treatment effect by change from Baseline at Week 52 of:

- RVSV (mL) by pulmonary artery flow or by RV volumes as described in Section 5.5.1 assessed by MRI,
- RVEDV (mL) assessed by MRI,
- RVESV (mL) assessed by MRI,
- RVEF (%) by RV volumes assessed by MRI,
- RV mass (g) assessed by MRI,
- 6MWD (m),
- WHO FC.

RVSV and RVEF by RV volumes are included as these are traditional ways of measuring. Where corresponding endpoints to Week 26 are not primary or secondary, the endpoints to Week 26 are included as exploratory.

5.5.3.3 RVSV with imputation from RV volumes

RVSV assessed by cardiac MRI including imputation according to the formula in the protocol: RVSV will be based on pulmonary artery flow. If, however, RVSV determined from pulmonary artery flow differs from volume determined from aortic flow (which refers to the variable "LVSV determined from aortic flow") by more than 20% (in either direction), then RVSV determined by RV volumes is used (equal to RVEDV minus RVESV). This will be calculated for weeks 26 and 52.

The following calculation will be used (all these assessments are by Cardiac MRI):

1. Percentage difference = 100 * abs(RVSVp - LVSVa) / min(RVSVp,LVSVa)
2. If this percentage <= 20%, then use RVSVp
3. If this percentage > 20%, then use RVSVv = RVEDV - RVESV

Where:

RVSVp = RVSV based on pulmonary artery flow
LVSVa = LVSV determined from aortic flow
RVSVv = RVSV determined by RV volumes (equal to RVEDV minus RVESV);

Programming note: The percentage difference (1) will need to be calculated and RVSV derived from RVSVp and RVSVv according to the above rules.

5.5.3.4 Variables related to the left ventricle

The following variables aim at analyzing change from Baseline at Week 26 and at Week 52 of left ventricle characteristics:

- LVSV (mL) determined from aortic flow as assessed by MRI,
- LVSV (mL) determined from LV volumes
- LVEDV (mL) assessed by MRI,
- LVESV (mL) assessed by MRI,
- LVEF (%) determined from aortic flow as assessed by MRI,
- LVEF (%) determined from LV volumes

- LV mass (g) assessed by MRI,
- RVEDV/LVEDV ratio assessed by MRI,
- RVESV/LVESV ratio assessed by MRI.

LVSV and LVEF by LV volumes are included as these are traditional ways of measuring.

5.5.3.5 Potential variables for disease monitoring

The following exploratory endpoints aim to investigate potential simple laboratory methods for disease monitoring, as opposed to RHC, MRI or echocardiography:

Change from Baseline at Week 26 and at Week 52 of:

- N-terminal pro-brain natriuretic peptide NT-proBNP (ng/L)
- Uric acid (umol/L)
- Red cell distribution width (%)
- Activin A (ng/L)
- Cystatin C (mg/L)
- Follistatin (ng/L)
- Galectin-3 (ug/L)
- GDF-15 (ng/L)
- Cardiac troponin T (ng/L)
- LDH (IU/L)
- Osteoprotegerin (pmol/L)
- TNF alpha (ng/L).

5.5.3.6 Clinical endpoint

The time to first clinical worsening event is used to investigate patient outcome, and is defined as the time from start of study treatment to first occurrence of any of the following:

- More than 15% decrease from Baseline of 6MWD associated with worsening in WHO FC, if either 6MWD or WHO FC are missing, then clinical worsening will (only) be identified by initiation of sc/iv prostanoid therapy, hospitalization for PAH or death,
- Initiation of s.c. or i.v. prostanoid therapy,
- Hospitalization for PAH (investigator's assessment),
- Death.

The date of the clinical worsening event 'Decrease from Baseline of 6MWD > 15% associated with worsening in WHO FC' is the first between the dates of the 6MWD and WHO FC assessment falling in the same time window, according to Table 5 of Section 11.9.

The date of initiation of s.c. or i.v. prostanoid therapy is the first date after the study treatment start date (see definition in Section 11.3) corresponding to treatment with s.c. or i.v. treprostinil or iloprost or epoprostenol (see Section 5.2.5.4).

The tick boxes "Did the Adverse Event require subject hospitalization?" and " If yes, due to PAH?" in the Adverse Event form of the CRF are used for the definition of the hospitalizations due to PAH; the date of admission is used in the time to event derivation of PAH worsening.

For time of event endpoint, patients without a PAH-worsening event are right censored at the End of Study (EOS) date (see Section 11.7 for definition), or the date of the first dose from the OLE, whichever is earlier. Data from the OLE are not included as neither 6MWD nor WHO FC are recorded in the OLE.

5.6 Safety variables

The following safety variables are considered for the core phase:

- Treatment-emergent AEs and SAEs up to 30 days after study drug discontinuation in the core phase (EOT+30), except patients in the OLE who will be evaluated up to EOT.
- AEs leading to premature discontinuation of study treatment.
- Treatment-emergent AEs of special interest up to 30 days after study drug discontinuation in the Core phase (EOT+30), except patients in France entering open label extension who will be evaluated up to EOT.
- Treatment-emergent marked laboratory abnormalities up to 30 days after study drug discontinuation (EOT+30), except patients in France entering open label extension who will be evaluated up to EOT. .
- Changes in vital signs body weight, and BMI from baseline to all assessed time points during the study up to EOT,
- Changes in laboratory variables from baseline to all assessed time points during the study up to EOT.

For tables including the core phase and the OLE, the following safety variables are considered:

- Treatment-emergent AEs and SAEs up to 30 days after study drug discontinuation (EOT+30) or (EOTOLE+30), whichever is later.
- AEs leading to premature discontinuation of study treatment,
- Treatment-emergent AEs of special interest up to 30 days after study drug discontinuation (EOT+30) or (EOTOLE+30), whichever is later.
- Treatment-emergent liver and hemoglobin laboratory abnormalities up to 30 days after study drug discontinuation (EOT+30) or (EOTOLE+30), whichever is later.

5.6.1 Adverse events

All below statements also apply to all types of AEs. All adverse events with start date in OLE (patients in France) will only be included in the additional tables that specifically include the OLE, and will be reported in the listings with a specific flag.

5.6.1.1 Treatment-emergent adverse events

Treatment-emergent AEs are defined as those AEs occurring from treatment start up (included) to 30 days after end of study treatment (except patients in France entering open label extension who will be evaluated up to EOT).

Treatment-emergent AEs including OLE are defined up to 30 days after study drug discontinuation (EOT+30) or (EOTOLE+30), whichever is later.

5.6.1.2 Frequency of treatment-emergent adverse events

Treatment-emergent AEs reported more than once within a subject (as qualified by the same preferred term(s)) are counted once in the frequency table.
In the event that the reported AE is assigned to several preferred terms, subjects are counted for each individual preferred term.

5.6.1.3 Intensity of treatment-emergent adverse events

For treatment-emergent AEs reported more than once within a subject (as qualified by the same preferred term(s)) with different intensities, the worst intensity is considered. The categories of intensity are defined as follows:

- Mild
- Moderate
- Severe

If intensity is missing, the event is considered severe.

5.6.1.4 Relationship of treatment-emergent adverse events

Relationship to study treatment is defined as ‘related’ (yes) or ‘not related’ (no). For treatment-emergent AEs reported more than once within a subject (as qualified by the same preferred term(s)), the strongest relationship reported (i.e. 'related') is considered. Adverse events with missing relationship are considered in any analysis as related.

5.6.2 Deaths

Death is considered to have occurred if it is recorded in the eCRF death form.

The original terms used by the investigators to describe deaths (i.e., death cause) are assigned PTs for classification and tabulation using the latest implemented MedDRA version dictionary.

Treatment-emergent AEs with fatal outcome occurring from treatment start, up to 30 days after EOT will be summarised (except patients in France entering open label extension who will be evaluated up to EOT). Other deaths occurring outside this time frame, if reported, will be listed only.

5.6.3 Serious adverse events

A SAE is an AE for which the corresponding [Serious] field in the CRF AE form is ticked "Yes". Treatment-emergent SAEs occurring from treatment start, up to 30 days after EOT will be summarised, (except patients in France entering open label extension who will be evaluated up to EOT).

Treatment-emergent SAEs including OLE is defined up to 30 days after study drug discontinuation (EOT+30) or (EOTOLE+30), whichever is later.

5.6.4 Adverse events leading to discontinuation of study treatment

An AE is defined as leading to discontinuation of study treatment if the corresponding [Action taken with study treatment] field in the eCRF AE form is ticked "PERMANENTLY DISCONTINUED". Discontinuations on or after the date of first dose in the OLE will only be counted in the additional table including the OLE.

5.6.5 Other significant adverse events

The following treatment-emergent adverse events of special interest will be analyzed:

- *"Edema and fluid retention"*

Any treatment-emergent AE with PT listed in the Standardised MedDRA Query (SMQ) "Haemodynamic oedema, effusions and fluid overload (SMQ)" or with PT equal to "Pulmonary congestion" defined in the latest available MedDRA version with the exception of PTs containing "site".

- *"Anemia"*

Any treatment-emergent AE with a PT within the SMQs "Haematopoietic erythropenia" OR "Haematopoietic cytopenias affecting more than one type of blood cell (SMQ)" (with the exception of two unspecific PTs: "blood disorder", "blood count abnormal") OR an event with any MedDRA PT containing the text "anaemia".

5.6.6 Physical examinations, Vital signs and body weight

Vital signs data and physical examinations are collected at Screening, at treatment initiation (Day 1), prior to initiation of rescue therapy, at Week 26 and Week 52/EOT (unscheduled assessment could be performed if clinically indicated).

Vital sign data includes: weight, BMI, heart rate, systolic blood pressure and diastolic blood pressure. Note that heart rate is also collected as part of the RHC and will be listed.

5.6.7 Electrocardiogram

Not applicable.

5.6.8 Laboratory

Safety laboratory parameters include:

- Hematology: hemoglobin, hematocrit, erythrocyte count (reticulocyte count), leukocyte count with differential counts, platelet count.

- Blood chemistry: AST, ALT, alkaline phosphatase, total and direct bilirubin, LDH, creatinine, urea, blood urea nitrogen, uric acid, glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, protein, albumin.
- Coagulation tests: prothrombin time, INR, aPTT.
- Pregnancy test: serum and urine pregnancy tests for women of childbearing potential.

Laboratory tests will be summarized for baseline, Week 26 and Week 52, The required monthly liver and hemoglobin laboratory tests (hemoglobin, hematocrit, AST, ALT, alkaline phosphatase, total and direct bilirubin and LDH) will be summarized by month for the first 6 months, in addition to baseline and Week 52.

Treatment-emergent marked laboratory abnormalities are defined as those lab marked abnormalities occurring from treatment start up to 30 days after end of study treatment (except patients in France entering open label extension who will be evaluated up to EOT), that were not present at baseline (see section 11.1 for definition). If central and local laboratory results are available for the same day, the central results are to be used.

Liver and hemoglobin test abnormalities will also be evaluated for the entire study (including data for OLE).

For the occurrence of post-baseline liver test abnormalities the following events are considered:

- ALT and /or AST $\geq 3\times$ ULN,
- ALT and/or AST $\geq 5 \times$ ULN,
- ALT and /or AST $\geq 8 \times$ ULN,
- ALT and /or AST $\geq 3 \times$ ULN and $< 5 \times$ ULN,
- ALT and /or AST $\geq 5 \times$ ULN and $< 8 \times$ ULN,
- ALT and/or AST $\geq 3 \times$ ULN and at the same time total bilirubin $\geq 2 \times$ ULN.
- ALT and/or AST $\geq 3 \times$ ULN and at any time total bilirubin $\geq 2 \times$ ULN.

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

Treatment-emergent liver test abnormalities are those which were not present at baseline.

For the occurrence of post-baseline hemoglobin abnormalities the following events are considered in the evaluation of incidences:

- Hemoglobin ≤ 80 g/L,
- Hemoglobin > 80 and ≤ 100 g/L,
- Hemoglobin decrease from baseline ≥ 20 g/L and < 50 g/L,
- Hemoglobin decrease from baseline ≥ 50 g/L,
- Hemoglobin < 100 g/L and concurrent (i.e. at the same time) decrease from baseline $\geq$20 g/L.

The lowest hemoglobin value at any post-baseline time point of assessment is considered in the evaluation of incidences.

Treatment-emergent hemoglobin abnormalities are those that were not present at baseline.

Marked lab abnormalities are defined according to Actelion internal guidelines for individual parameters (see Table 2). When determining treatment-emergent marked laboratory abnormalities, all assessments (including the unscheduled ones) are considered.

For women of childbearing potential, urine as well as serum pregnancy tests are performed, but these results will not be summarized as part of the laboratory data. Positive pregnancy tests (if any) will be reported.

Data from the OLE will be listed.

Table 2 Laboratory Abnormalities

Parameter	LL marked	LLL marked	HH marked	HHH marked
Hemoglobin	< 100 g/L	< 80 g/L	[post-baseline > (baseline + 20 g/L) *AND* (baseline > ULN)] ***OR*** [post-baseline > (ULN + 20 g/L) *AND* baseline ≤ ULN]	[post-baseline > (baseline + 40 g/L) *AND* (baseline > ULN)] ***OR*** [post-baseline > (ULN + 40 g/L) *AND* baseline ≤ ULN]
Hematocrit	< 0.28 L/L for females < 0.32 L/L for males	< 0.20 L/L	> 0.55 L/L for females > 0.60 L/L for males	> 0.65 L/L
Platelets	< 75 × 10^9/L	< 50 × 10^9/L	> 600 × 10^9/L	> 999 × 10^9/L
Leukocytes	< 3.0 × 10^9/L	< 2.0 × 10^9/L	> 20.0 × 10^9/L	> 100.0 × 10^9/L
Neutrophils	< 1.5 × 10^9/L	< 1.0 × 10^9/L	NA	NA
Eosinophils	NA	NA	> 5% ***OR*** > 5 × 10^9/L	NA
Lymphocytes	< 0.8 × 10^9/L	< 0.5 × 10^9/L	> 4.0 × 10^9/L	> 20 × 10^9/L
ALT	NA	NA	> 3 × ULN	> 5 × ULN*
AST	NA	NA	> 3 × ULN	> 5 × ULN*
Alkaline phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Bilirubin	NA	NA	> 2 × ULN	> 5 × ULN

Parameter	LL marked	LLL marked	HH marked	HHH marked
INR	NA	NA	> 1.5 × ULN ***OR*** > 1.5 times above baseline	> 2.5 × ULN ***OR*** > 2.5 times above baseline
Creatinine	NA	NA	> 1.5 × baseline ***OR*** > 1.5 × ULN	> 3 × baseline ***OR*** > 3 × ULN
Glucose	< 3.0 mmol/L	< 2.2 mmol/L	> 8.9 mmol/L	> 13.9 mmol/L
Calcium	< 2.0 mmol/L	< 1.75 mmol/L	> 2.9 mmol/L	> 3.1 mmol/L
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
Magnesium	< 0.5 mmol/L	< 0.4 mmol/L	NA	> 1.23 mmol/L
Uric acid, Urate	NA	NA	> 590 umol/L	> 720 umol/L
Albumin	< 30 g/L	< 20 g/L	NA	NA
Blood Urea Nitrogen	NA	NA	> 2.5 × ULN	> 5 × ULN

* Also HHHH as > 8 × ULN

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

5.6.9 Other safety variables

No additional safety data will be summarized.

5.7 Pregnancy test

Contraceptive Methods (type, start/end date, etc...) for women of childbearing potential are collected in the Contraceptive Methods form of the CRF.

5.8 Quality of life variables

Not applicable.

5.9 Pharmacoeconomic variables

Not applicable.

5.10 Pharmacodynamic variables

Not applicable.

5.11 Pharmacokinetic variables

Not applicable.

5.12 Sub-studies

Biopsy sub-study was cancelled (without any patient) and therefore no data will be reported.

For metabolism sub-study, variables are changes from baseline to Week 26 and to Week 52 in:
- RV 18F-fluorodeoxyglucose (FDG) uptake
- Aortic 18F-FDG uptake
- Right common carotid 18F-FDG uptake
- Left common carotid 18F-FDG uptake.

For echo sub-study, variables are changes from baseline to Week 26 and to Week 52 in:
- Pericardial effusion size scored from 0 to 4

- 2D RV dimension (mm) end-diastole
- RV end diastolic area (cm^2)
- RV end systolic area (cm^2)
- RV fractional area change (%)
- Tricuspid annular plane systolic excursion (TAPSE, cm)
- Tricuspid peak annular velocity s' (cm/s)
- Tricuspid peak E-wave velocity (cm/s)
- Tricuspid peak A-wave velocity (cm/s)
- Tricuspid deceleration time (ms)
- Tricuspid peak early diastolic annular velocities (cm/s) e' and a'

- RV acceleration time (ms), by tissue Doppler and by pulsed wave Doppler
- RV ejection time (ms), by tissue Doppler and by pulsed wave Doppler
- RV Early diastolic velocity (m/s) of the jet of pulmonary valve regurgitation
- RV End-diastolic velocity (m/s) of the jet of pulmonary valve regurgitation
- RVSV (mL) determined by combining pulmonary valve Doppler and pulmonary annulus dimension

- Tricuspid regurgitation peak jet velocity (m/s)
- RV systolic pressure (estimated by tricuspid valve Doppler, mmHg)
- Total RV Systolic Time (duration of tricuspid insufficiency jet, ms) by tissue Doppler and by pulsed wave Doppler

- Doppler RV index (RV myocardial performance index) by tissue Doppler and by pulsed wave Doppler
- 2D Global Longitudinal RV strain (%)
- 2D circumferential RV strain (%)
- Time to peak RV strain (ms)

- Minimum diameter (cm) of the inferior vena cava (at inspiration)
- Maximum diameter (cm) of the inferior vena cava (at end-expiration)

- RVEDV (assessed in 3D, mL)
- RVESV (assessed in 3D, mL)
- RVSV (assessed in 3D, mL)
- RVEF (%)
- RV mass (g)

- LV eccentricity index at end-diastole
- LV eccentricity index at end-systole
- LVEDV determined from 2D measurements (assessed in BIPLANE MOD) (mL)
- LVESV determined from 2D measurements (assessed in BIPLANE MOD) (mL)
- Mitral peak E-wave velocity (cm/s)
- Mitral peak A-wave velocity (cm/s)
- Mitral E wave deceleration time (ms)
- Mitral annulus peak early diastolic velocity E' (cm/s)
- Mitral annulus peak late diastolic velocity a' (cm/s)
- Mitral E/A wave velocity ratio
- Mitral E/E' velocity ratio
- Left Ventricular Stroke Volume (LVSV, mL) by aortic flow (Doppler method)
- Cardiac output (mL/min) determined from LV outflow tract

- LVEDV assessed in 3D (mL)
- LVESV assessed in 3D (mL)
- Left Ventricular Stroke Volume (LVSV, mL) assessed in 3D
- LVEF (%)
- LV mass (g)

- RVEDV/LVEDV assessed in 3D
- RVESV/LVESV assessed in 3D

These variables will be listed only:
- Heart Rate (bpm)
- Pulmonary artery annulus dimension (mm)
- Pulmonic valve Doppler TVI (measured at annulus, cm)
- LV Short Axis (SAX) end diastole (parallel to septum and perpendicular to septum, cm)
- LV Short Axis (SAX) end-systole (parallel to septum and perpendicular to septum, cm)
- LV Outflow Tract dimension (mm)
- LV Outflow Tract pulsed wave Doppler TVI (cm)

Where the tests are done by "pulsed wave Doppler" and by "Tissue Doppler", these will be presented separately. The tests are distinguished in SDTM in the variable MOSCAT. There are also different sub-categories for:

- LVEDV (3D or biplane mod)
- LV SAX dimensions (parallel to septum or perpendicular to septum).

6 DEFINITION OF PROTOCOL DEVIATIONS

Protocol deviations include deviations from inclusion and/or exclusion criteria and deviations from the protocol during the conduct of the study. Moreover the PD will be classified, as per latest version of protocol deviation code list, as related to:

- Protocol Deviations at Screening or re-screening
- Protocol Deviations at study drug assignment in IVRS
- Protocol Deviations at Treatment initiation Visit and thereafter.

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 Screened Analysis Set

This analysis set (SCR) includes all patients who were screened and received a patient number.

7.1.2 Safety Set

The Safety Set (SS) includes all patients from the Screened Patients set who received at least one dose of study drug.

7.1.3 Full analysis Set

The Full Analysis Set (FAS) includes all patients from the SS who had a baseline as well as a post-baseline measurement for both primary endpoints (RVSV assessed by cardiac MRI from pulmonary artery flow and PVR by RHC).

7.1.4 Modified full analysis Set

The Modified FAS (mFAS) comprises all patients included in the FAS who had a post-baseline measurement *taken between 16 weeks and 30 weeks of treatment* for both primary endpoints.

Note: day window used to apply this definition will be [112; 210] with nominal value Day 182 (26 weeks), i.e. the planned time point.

7.1.5 Per-protocol analysis Set

The Per-protocol analysis Set (PPS) comprises all patients included in the mFAS without major protocol deviations that affect the main analysis of the primary efficacy variables.

The major protocol deviations leading to exclude the patients from the PPS are defined as: PD100, PD105, PD207, PD251, PD304. It also restrict to patients who had a post-baseline measurement *taken between 22 weeks and 30 weeks of treatment* for both primary endpoints.

The day window used to apply this definition will be [154; 210] with nominal value Day 182 (26 weeks).

7.1.6 Other analysis sets

The specific RVSV Modified FAS (RVSVmFAS) includes all patients from the SS who had a baseline as well as a post-baseline measurement *taken between 16 weeks and 30 weeks of treatment* for RVSV assessed by cardiac MRI from pulmonary artery flow.

The specific PVR Modified FAS (PVRmFAS) includes all patients from the SS who had a baseline as well as a post-baseline measurement *taken between 16 weeks and 30 weeks of treatment* for PVR.

The specific RVSV and PVR Modified FAS will only be used if the patients that are in both sets (i.e., the patients in the mFAS) corresponds to less than 70% of the patients that are in at least one of RVSVmFAS and PVRmFAS. These analysis sets will be created but will only be used if applicable (if criterion mentioned above is met).

7.2 Usage of the analysis sets

Primary efficacy analysis will be performed on the mFAS. Sensitivity analyses for primary endpoints will be performed on PPS, FAS, SS, RVSVmFAS and PVRmFAS (if condition from 7.16 is met).

Secondary and exploratory efficacy analyses will be performed on the mFAS and SS.

Safety analyses will be performed on the SS.

Patient disposition will be described for the SCR.

Patient listings will be based on the SCR.

Sub-studies analyses will be based on the mFAS and SS, restricted to subjects participating in each sub-study.

8 DEFINITION OF SUBGROUPS

The following subgroups will be considered as part of this analysis plan:

1. PAH background therapy (as ticked on CRF, variable 'Treatment Strategy' in the Treatment Strategy form):
   (1) "Patient previously treated with a PDE-5 inhibitor"
   (2) "Naïve patient with intention to start study drug only",
   (3) "Naïve patient with intention to start upfront PDE-5 inhibitor and study drug combination therapy",
   and pool of (1)+(2) – i.e. all patients that fall into either (1) or (2).
2. WHO FC groups at baseline: FC I-II, FC III-IV.
3. Sex: male, female.
4. Age at Screening: < 65, >= 65.

9 GENERAL STATISTICAL METHODOLOGY

SAS (Statistical Analysis System®) version 9.3 or higher will be used for all the statistical analysis.

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

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

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

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

10 STATISTICAL ANALYSES

10.1 Overall testing strategy

The overall type I error is $\alpha = 0.025$ (one-sided) and is split unequally between the two primary endpoints RVSV assessed by cardiac MRI from pulmonary artery flow ($\alpha = 0.02$) and PVR by RHC ($\alpha = 0.005$), which is equivalent to 2-sided overall type I error with $\alpha = 0.05$ (split into RVSV with $\alpha = 0.04$ and PVR with $\alpha = 0.01$). All analyses will be performed using 2-sided statistical tests. The justification for the unequal split is that PVR is a well-known endpoint (hence, the smaller part of the α), whereas RVSV is less well-known (hence, the larger part of the α).

If the analysis of at least one of those primary endpoints is statistically significant, i.e. p value below nominal alpha, the study is declared positive.

An interim analysis will be performed once 42 patients have available data for primary endpoint (see Section 10.11).

10.2 General rules for data presentations

General rules for data presentations as described here below are followed unless otherwise specified.

In general, data are listed and summarized by appropriate descriptive statistics (tables or figures) as described in Section 9.

Listings are grouped by country, site (if applicable, screen failures are listed last), subject number and assessment date as applicable.

Raw data listings if required are based on datasets as received. All data collected are displayed, including unscheduled visits (if any).

10.3 Display of subject disposition, protocol deviations and analysis sets

10.3.1 Subject disposition

The disposition of patients includes the following categories of patients:

- Screened patients,
- Treated patients,
- Patients who prematurely discontinued study treatment (core phase)
- Patients who completed study treatment (core phase)
- Patients who completed study (core phase)
- Patients who entered in the OLE

Number and percentage of patients within each category will be tabulated. Number and percentage of patients included in each sub-study will be summarized.

10.3.2 Protocol deviations

Number and percentage of patients within each protocol deviation (PD) category will be tabulated (important and all). Individual data listing will be provided for all screened patients.

10.3.3 Analysis sets

Number and percentage of patients within each analysis set will be tabulated. This table will consider all screened patients. All criteria/events which lead to exclusion of subjects from the analysis sets will be reported in a subject listing.

10.4 Analyses of subject characteristics

10.4.1 Disposition of patients

See Section10.3.1.

10.4.2 Demographics

The variables age, sex, race, ethnicity, height, country, as well as body weight, BMI, and childbearing potential status at baseline will be summarized using descriptive statistics for continuous and categorical data. Summaries are given for SS and mFAS.

10.4.3 Baseline disease characteristics

Baseline disease characteristics [as defined in Section 5.2.2] are summarized using descriptive statistics for continuous and categorical data. Summaries are given for SS and mFAS.

10.4.4 Other baseline characteristics

Treatment strategy will be summarized among baseline disease characteristics, by frequencies and proportions, on SS and mFAS.

10.4.5 Medical history

All previous and/or ongoing diseases/diagnoses are reported in a subject listing. Ongoing as well as previous diseases/diagnoses are flagged accordingly.

Previous and/or ongoing diseases/diagnoses including specific previous and/or concomitant diseases/diagnoses are summarized on SS, displaying counts and percentages of subjects having at least a disease/diagnosis. Counts and percentages of subjects having at least a disease/diagnosis are presented by system organ class (SOC) and individual PT within each SOC. The summary table is presented in descending order (e.g., SOC and individual PT within each SOC with the highest number of occurrences appears first). Equal frequency of different SOC/individual PTs is sorted in alphabetical order of the SOC/individual PT.

Subjects with two or more occurrences of the same disease (as qualified by the same PT[s]) are counted only once. In case the reported disease is assigned to several PTs, subjects are counted for each individual PT.

10.4.6 Previous and concomitant therapies

Previous and concomitant therapies are classified according to the Anatomic Therapeutic Chemical (ATC) class code and summarized by tabulating the number and percentages of subjects using the SS.

Study-treatment concomitant therapies are summarized by ATC class and PT.

For study reporting purposes, all previous and study-concomitant therapies are reported in the subject listings. It is indicated if the therapy is previous or concomitant.

Therapies present at baseline are those taken on the day of first dose.

Counts and percentages of subjects having taken at least a previous/concomitant therapy at baseline/concomitant medication are presented, separately, by ATC class and individual PT within each ATC class as well as by individual PT. The summary tables are presented in descending order (i.e., ATC and individual PT within each ATC with the highest number of occurrences appear first). Equal frequency of different ATC/individual PTs is sorted in alphabetical order of the ATC/individual PT. All percentages are based on the SS.

Subjects who took the same medication more than once (as qualified by the same PT(s)) are counted only once. In case the reported medication is assigned to several PTs, subjects are counted for each individual PT.

Separately, specific previous/concomitant therapy at baseline/concomitant medication are similarly presented with counts and percentages in summary tables.

10.4.7 Other subject characteristics

Historical pulmonary function test variables will be described using either descriptive statistics or frequencies and proportions as relevant.

10.5 Analysis of study treatment exposure and compliance

10.5.1 Exposure

Exposure to study drug will be described in terms of duration on SS.

The exposure time (weeks) will be summarized using descriptive statistics for continuous data. It will also be summarized as categorical variable: the cumulative distribution of exposure time by different class intervals (e.g., less than 12 weeks, at least 12 weeks, at least 24 weeks, and at every interval of 12 weeks thereafter) will be tabulated to show counts and percentages of patients in each class interval.

10.5.2 Compliance with study treatment

The study treatment compliance will be summarized on SS and tabulated by compliance category < 80%, 80 % - 120 % and >120%.

10.5.3 Study treatment interruptions

Study treatment interruptions defined in Section 5.3.3 are listed and summarized on SS using descriptive statistics for categorical data.

Frequency tables will be presented displaying the number of subjects with at least one interruption and the reasons from the study drug log CRF page “Temporarily interrupted due to an AE” and/or “Temporarily interrupted not due to an AE”. The numbers in the categories may sum to a number greater than the number of subjects with an interruption as a single subject could have multiple interruptions for multiple reasons.

Percentages of subjects with the sum of all interruptions of study drug intake of more than 7, 14, 21 and 28 days will be displayed. These counts will be “cumulative”, i.e., if a subject interrupts treatment for more than 21 days (but less than 28 days), they are counted in three categories: “more than 7 days”, “more than 14 days”, “more than 21 days”.

The total duration of study treatment interruptions will be summarized using descriptive statistics for continuous data.

10.5.4 Study treatment discontinuation

Proportion and number of patients having permanently discontinued study treatment will be provided on SS. The cause for permanent discontinuation will be tabulated as frequency and percentage.

10.6 Study discontinuation

Study discontinuation (see Section 5.4) reporting is conducted as part of subjects disposition described in section 10.3.1. Reasons for study discontinuation will be reported in a subject listing on SCR.

10.7 Analysis of the primary efficacy variable(s)

10.7.1 Hypothesis and statistical model

The null hypothesis is:

- The mean change from baseline to Week 26 in RVSV assessed by cardiac MRI from pulmonary artery flow is less than or equal to zero AND the geometric mean ratio of Week 26 to baseline PVR is greater than or equal to one.

The alternative hypothesis is:

- The mean change from baseline in RVSV is greater than zero OR the geometric mean ratio of Week 26 to baseline PVR is less than one.

10.7.2 Handling of missing data

RVSV assessed by cardiac MRI from pulmonary artery flow is taken from the raw data.

PVR is calculated as described in section 5.5.1. If PVR cannot be calculated due to missing PCWP and LVEDP but mPAP and CO are available for the same visit, one of the following methods is applied:

1. If PCWP and LVEDP are missing both at baseline and post-baseline, the study population median PCWP (baseline and post-baseline, respectively) is imputed (based on the SS).
2. If PCWP and LVEDP are missing either at baseline or post-baseline, the patient's available PCWP (or LVEDP if PCWP missing) is imputed.

This imputation is based on the clinical assumption that macitentan does not affect PCWP.

- Baseline: Patients with no RVSV assessed by cardiac MRI from pulmonary artery flow or PVR by RHC measurement at baseline will have missing values for the change and so are excluded from the analyses.
- Post-baseline: For patients with no RVSV assessed by cardiac MRI from pulmonary artery flow or PVR by RHC values at Week 26, the last post-baseline measurement (presumably taken at treatment discontinuation or initiation of rescue therapy) is carried forward, provided that this measurement was taken after at least 16 weeks of treatment. Week 26 measurements taken after 30 weeks of treatment are excluded from the analyses.

10.7.3 Main analysis

The primary analysis is performed on the mFAS.

RVSV assessed by cardiac MRI from pulmonary artery flow will be summarized by time point (baseline, Week 26) using descriptive statistics (n, mean, SD, median, Q1 and Q3). The change from baseline to Week 26 in RVSV will be summarized similarly.

Change from baseline in RVSV will be analyzed using an Analysis of Covariance (ANCOVA) with a factor for PAH background therapy as ticked on CRF and a covariate for

baseline RVSV. The mean change from baseline and its 96% confidence interval (CI) will be estimated based on the model and p-values will be interpreted based on boundaries set in Section 10.11.

PVR by RHC will be summarized by time point using descriptive statistics as well as geometric means and Coefficients of Variation (CVs). The Week 26 versus baseline ratio in PVR will be summarized similarly.

The ratio of Week 26 versus baseline PVR will be log-transformed (base e) and analyzed using an ANCOVA with a factor for PAH background therapy and a covariate for baseline log PVR. The mean change from baseline (on log scale) and its 99% CI will be estimated based on the model, and p-values will be interpreted based on boundaries set in Section 10.11. The geometric mean ratio (versus baseline) and its CI will be obtained by exponentiation.

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.

Listings of cardiac MRI variables and of Right Heart Catheterization (RHC) will be provided.

10.7.4 Supportive/sensitivity analyses

A sensitivity analysis will be performed on the FAS. Week 26 measurements performed after 30 weeks of treatment will be excluded from the Week 26 analysis.

Another sensitivity analysis will be performed on the PPS that will be restricted to completers, i.e., patients with RVSV assessed by cardiac MRI from pulmonary artery flow and PVR by RHC measurements at Week 26 taken between 22 and 30 weeks of treatment.

A sensitivity analysis will be performed on the SS for patients without post-baseline RVSV assessed by cardiac MRI from pulmonary artery flow or PVR by RHC. For those patients, the last available post-baseline measurement will be carried forward (see section 10.7.2 for details).

10.7.5 Subgroup analyses

The primary endpoints, i.e. RVSV assessed by cardiac MRI from pulmonary artery flow and PVR by RHC, will be analyzed on mFAS by status of PAH background therapy (as ticked on CRF) using the ANCOVA models as specified for the main analysis but excluding PAH background therapy factor from the model. In this analysis, 95% CIs will be used.
Similarly, those endpoints will be analyzed on mFAS by WHO FC category at baseline (FC I or II versus FC III or FC IV), sex (male versus female) and age group (< 65 versus >= 65). This will be done using same ANCOVA model as specified in section 10.7.3. In this analysis 95% CIs will be used.

10.7.6 Exploratory analyses of the primary endpoints

Exploratory analyses will be performed aimed at identifying prognostic factors for changes from baseline in RVSV assessed by cardiac MRI from pulmonary artery flow and change in log(PVR). This will be done on mFAS using ANCOVA analyses including all following candidate prognostic factors together in model:

- PAH etiology;
- Baseline 6MWD (m);
- Baseline WHO FC ("I-II", "III-IV");
- Sex (male, female);
- Age group (< 65, >= 65).

10.8 Analysis of the secondary efficacy variables

10.8.1 Hypothesis and statistical model

Secondary efficacy analyses will be performed on the mFAS and SS at $\alpha = 0.05$ (two-sided) using 95% CIs.

10.8.2 Handling of missing data

No specific imputation will be performed for secondary endpoints.

10.8.3 Statistical analysis

MRI-based secondary efficacy variables (changes from baseline to Week 26 in RVEDV, RVESV, RVEF by pulmonary artery flow and RV mass) will be summarized and analyzed as described for RVSV assessed by cardiac MRI from pulmonary artery flow in Section 10.7.3 (using 95% CI).

The 6MWD and the Borg dyspnea index will be summarized by time point using descriptive statistics. Change from baseline to Week 26 in 6MWD will be analyzed using an ANCOVA with a factor for PAH background therapy and a covariates for baseline 6MWD and WHO FC.

WHO FC will be summarized by time point using frequency tables. Changes from baseline to Week 26 in WHO FC will be dichotomized as worsening (i.e., change > 0) versus no change or improvement (i.e., change ≤ 0). Worsening at Week 26 will be analyzed using an exact logistic regression model with a factor for PAH background therapy as ticked on CRF.

NT-proBNP will be summarized by time point using descriptive statistics as well as geometric means and CVs. The Week 26 versus baseline ratio will be summarized similarly. The ratio versus baseline in NT-proBNP will be log-transformed and analyzed using an ANCOVA with a factor for PAH background therapy and a covariate for baseline log NT-proBNP.

10.8.4 Supportive/sensitivity analyses

Not applicable for secondary efficacy variables.

10.8.5 Subgroup analyses

Not applicable for secondary efficacy variables.

10.9 Analysis of other efficacy variables

Week 52 endpoints will be summarized and analyzed similarly to the Week 26 endpoints.

Hemodynamic variables will be summarized and analyzed by time point using descriptive statistics. Week 52 variables will be summarized and analyzed similarly to the corresponding Week 26 measurements.

Pressure-volume variables (arterial elastance, RV end-systolic elastance, RV maximum isovolumic pressure, ventriculo-arterial coupling) will be listed only.

Potential variables for disease monitoring, ratios RVEDV/LVEDV and RVESV/LVESV will be summarized and analyzed as PVR. The 95% CI and the associated p-value will be presented.

RVSV by RV volumes will be analyzed as an exploratory endpoint.

Variables related to the left ventricle will be summarized and analyzed similarly as the corresponding right ventricular variables.

An exploratory analysis will be performed using RVSV with imputation from RV volumes (see section 5.5.3.3), which are analyzed like the primary RVSV parameter (see section 10.7.3)5.5.3.3.

RVSV and RVEF by pulmonary artery flow and by RV volumes will be listed together with LVSV by aortic flow and LVSV by volumes. The percentage difference between RVSV from pulmonary artery flow and LVSV from aorta flow will be presented (see section 5.5.3.3). Differences of more than 20% will be flagged.

Potential laboratory variables for disease monitoring (see section 5.5.3.5 for definition) will be analyzed descriptively displaying observed values and absolute changes from baseline to Week 26 and Week 52. In this evaluation, only subjects who had both the assessments at baseline and the Week 26/Week 52 assessment (respectively) will be included.

In order to minimize missing data and to allow for unscheduled visits, all recorded assessments are assigned to the most appropriate visit time point according to the best fitting time window for the assessment. If laboratory test results are given by threshold values ('<x' or '>x'), the threshold values are considered for quantitative analysis.

Data will be presented in SI units. All the variables will also be displayed in a subject listing.

The clinical endpoint, time to first clinical worsening (as defined in section 5.5.3.6) will be summarized using a Kaplan-Meier (KM) plot. KM estimates and its associated 95% CI will also be provided. Association between (change from baseline to Week 26 in) cardiac MRI variables and time to first clinical worsening event will be explored using Cox models (analysis to be done only if at least 10% of patients have an event).

10.10 Analysis of safety variables

All safety analyses will be performed on the SS. All safety data will be listed. In the main summary tables, for patients entering the OLE, EOT will consider last dose in core phase. Where specified below, additional tables will be produced for all data in the study, including data for OLE.

10.10.1 Adverse events

All AEs captured from signature of informed consent up to EOS, including the open label extension, are reported in the subject listings.

The number and percentage of patients experiencing treatment-emergent AEs and SAEs at least once (see section 5.6.1.1 for definition) will be tabulated by:

- MedDRA system organ class (SOC) and individual preferred term (PT) within each SOC, in descending order of incidence.
- Frequency of patients with events coded with the same PT, in descending order of incidence.

The above tables will be repeated for all data including the OLE.

Furthermore, treatment-emergent AEs will be tabulated as described above by severity and relationship to study drug.

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

10.10.2 Deaths, other serious adverse events

10.10.2.1 Death

Treatment-emergent deaths will be tabulated (frequency and percentage), overall and by reason. Death along the causing reason will also be listed from screening to EOS, including the open label extension.

10.10.2.2 Serious adverse events

Treatment emergent SAEs will be tabulated as described in Section 10.10.1. Treatment emergent SAEs will also be tabulated by SOC and PT for all data including the OLE.

SAEs from screening to EOS will also be listed, including the open label extension.

10.10.2.3 Adverse events leading to study treatment discontinuations or death

AEs leading to premature discontinuation of study treatment will also be summarized as described above.

10.10.2.4 Other significant adverse events

For the disclosure of the results to EudraCT and ClinicalTrials.gov (and not for the purpose of the clinical study report), treatment-emergent non-serious AEs with frequencies ≥ 5% are summarized displaying counts and percentages of subjects with at least a treatment-emergent non-serious frequent AE plus the number of events (counted exactly the number of times they occurred also within a subject) by SOC and individual PT. The summary table is presented in descending order (i.e., SOC and individual PT within each SOC with the highest number of occurrences appears first). PTs that are reported at equal frequencies are sorted in alphabetical order.

For the disclosure of the results to EudraCT and ClinicalTrials.gov, a summary table with an overview of treatment-emergent AEs is provided displaying counts and percentages of subjects having experienced at least a treatment-emergent AE, a severe AE, a study-treatment

related AE, an AE leading to study treatment discontinuation, a non-serious frequent AE, a serious AE, a study-treatment related serious AE, a fatal SAE.

The above tables for disclosure will be repeated for all data including the OLE.

In addition, the adverse events of special interest (see Section 5.6.5 for definition) will be summarized on SS. For each area of clinical interest, treatment-emergent AEs of special interest will be summarized displaying counts and percentages of subjects having experienced at least a treatment-emergent AE of special interest. Counts and percentages of subjects having experienced at least a treatment-emergent AE will be presented by frequency of individual PT within each SOC.

10.10.3 Electrocardiography (ECG)

Not applicable.

10.10.4 Laboratory tests

All hematology and chemistry variables provided by the central and local laboratory are provided in a subject listing. Marked laboratory abnormalities are flagged accordingly. All laboratory data transferred are taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

If laboratory test results are given by threshold values ('<x' or '>x'), the threshold values are considered for quantitative analysis.

Laboratory data will be presented in SI units.

Laboratory tests will be summarized for baseline, Week 26 and Week 52, The required monthly liver and hemoglobin laboratory tests (hemoglobin, hematocrit, AST, ALT, alkaline phosphatase, total and direct bilirubin and LDH) will be summarized by month for the first 6 months, in addition to baseline and Week 52.

Descriptive summary statistics by visit are displayed for observed values and absolute changes from baseline. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOS are assigned to the most appropriate visit time point according to the best fitting time window for the assessment.

In each evaluation, only subjects are included who had both the assessments at baseline and the considered post-baseline assessment.

Treatment emergent marked laboratory abnormalities (i.e., fulfilling the applicable condition for LL / HH as listed in Table 2) are summarized for each laboratory parameter providing their incidence, frequency, and number of subjects with available assessments.

Percentages are calculated as number of subjects who had at least one occurrence of the abnormality, for the variable under consideration divided by the number of subjects with any post-baseline laboratory measurement.

Shift tables are used to summarize the worst treatment-emergent laboratory abnormalities, based on the definition of marked laboratory test abnormalities listed in Table 2. The worst category is taken for the analysis for each direction.

If HH, HHH, LL or LLL is not defined for a variable, "NA" will appear in the table for the corresponding variable. Percentages are calculated based on the number of subjects in the analysis set.

Separate tables with the incidence of liver test abnormalities and hemoglobin abnormalities are produced including summaries on criteria as defined in Section 5.6.8. An eDISH plot will also be produced for the core part of the study (excluding the OLE as liver values are not recorded in the eCRF for the OLE). For these plots the maximum post-baseline value of ALT / AST and total Bilirubin will be used, excluding samples taken after the start of the OLE.

The tables for liver and hemoglobin test abnormalities will be repeated for the entire study (including data for OLE).

10.10.5 Physical examinations, vital signs and body weight

Physical examinations data are listed only.

Vitals signs, body weight and BMI, including changes from baseline, are summarized over time for each parameter using descriptive statistics for continuous data.

In each evaluation, only subjects are included who had both the assessments at baseline and the considered post-baseline assessment.

All recorded assessments up to EOS are assigned to the most appropriate visit time point according to the best fitting time window for the assessment.

10.10.6 Other safety variables

Not applicable.

10.11 Interim analysis

An interim analysis will be conducted when the first 42 evaluable patients (i.e., included in the mFAS) are available for primary efficacy analysis.

The interim analysis will use a hierarchical testing approach to maintain the overall type I error. As a first step, change from baseline to Week 26 in RVSV assessed by cardiac MRI from pulmonary artery flow will be tested. If the test is negative, i.e., the pre-defined efficacy boundary (p-value) is not crossed, recruitment will continue until 100 patients are enrolled. If it is positive (pre-defined efficacy boundary crossed), then PVR (ratio of Week 26 to baseline) will be tested.

RVSV assessed by cardiac MRI from pulmonary artery flow is to be tested first, as the potential effects of PAH-specific therapy on this variable are not so well known. The effect of such therapies on PVR is better known with robust treatment effect estimates, i.e., there is less uncertainty on the treatment effect estimate.

If the test on PVR is also positive, then the study will be declared positive for its primary endpoint. If the test on PVR is negative, no conclusion can be made with regards to the primary endpoint, and patient accrual will continue until 100 patients are enrolled.

To declare the study positive at the interim analysis, both endpoints must be met. This contrasts with the final analysis, where it is sufficient to meet one endpoint. The reason for this choice is to mitigate the risk of closing the study too early to observe the full potential of macitentan.

The interim analysis will be performed on the mFAS. Efficacy boundaries are defined in Table 3 and Table 4, and are calculated with 90% power, 1-sided 0.02 alpha for RVSV test, 1-sided 0.005 alpha for PVR test and are based on assumptions described in protocol section 11.5 (sample size). To accommodate the need for the same number of patients included in the interim analysis of each primary endpoint, the selected information fraction (around 50%) is slightly different for RVSV and PVR.

The scenario retained to compute number of patients and p-value boundaries for interim/final analyses is based on conservative assumptions (lowest change and highest variability), and is described in Table 3 (RVSV) and Table 4 (PVR) below.

As stated in the protocol (section 11.3.2.3 final sentence) the primary analysis / hypothesis will only be tested at the final analysis (after study closure and database lock), if the interim analysis is not positive. If the interim analysis is positive, then analyses after final database closure are supportive, as the primary analysis is completed with the interim analysis.

Table 3 Efficacy boundaries for RVSV assessed by cardiac MRI from pulmonary artery flow at interim/final analyses

Change from baseline	SD	Information fraction for interim analysis	Number of patients needed at interim analysis	Number of patients needed at final analysis	Efficacy Boundary on p-value scale (Lan DeMets Pocock) – Interim analysis	Efficacy Boundary on p-value scale (Lan DeMets Pocock) – Final analysis
8	22	0.45	42	93	0.01149 (one-sided) or 0.02298 (two-sided)	0.01138 (one-sided) or 0.02276 (two-sided)

Table 4 Efficacy boundaries for PVR endpoint at interim/final analyses

Change from baseline on log scale	SD	Information fraction for interim analysis	Number of patients needed at interim analysis	Number of patients needed at final analysis	Efficacy Boundaries on p-value scale (LanDeMets Pocock) – Interim analysis*	Efficacy Boundaries on p-value scale (LanDeMets Pocock) – Final analysis
−0.19	0.43	0.5	42	84	0.0031 (one-sided) or 0.0062 (two-sided)	0.00247 (one-sided) or 0.00494 (two-sided)

* Test at interim only if RVSV crossed pre-defined efficacy boundary. The information fraction for PVR is higher than for RVSV to fit same number of patients at interim analysis for both endpoints.
** Boundary is 0.005 (one-sided) if not tested at interim

10.12 Analysis of pharmacoeconomic variables

Not applicable.

10.13 Analysis of epidemiological measures and risk-benefit evaluations

Not applicable.

10.14 Analysis of pharmacodynamic variables

Not applicable.

10.15 Analysis of pharmacokinetic variables

Not applicable.

10.16 Sub-studies analysis

Changes from baseline to Week 26 and Week 52 in echo variables (see Section 5.12) will be summarized using descriptive statistics on the FAS (restricted to subjects participating to each sub-study respectively). Echo variables will also be analyzed as for RVSV assessed by cardiac MRI from pulmonary artery flow.

Individual subject listings will be provided on the SCR (restricted to subjects participating to each sub-study respectively).

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Baseline

The baseline value is the value from the last non-missing assessment obtained prior to, i.e., before or on the day of the start of study drug.

11.2 Post-baseline assessment

Post-baseline assessment is any assessment performed after baseline and up to EOS.

11.3 Treatment period start date

It is the first day of intake of study treatment. It is derived from the first treatment start date (in chronological order) in the Study Drug Log CRF (retrieved from the STDM EX domain where EXCAT='STUDY DRUG').

11.4 Treatment period end date (EOT)

It is derived from the treatment end date, from the last interval in chronological order, recorded in the Study Drug Log CRF and the reason for treatment end is not " TEMPORARILY INTERRUPTED DUE TO AN AE" or "TEMPORARILY INTERRUPTED NOT DUE TO AN AE". If missing or incomplete, rules in Section 12 are followed according to Table 6

The treatment period is the period from the start up to the end of treatment (limits included).

11.5 Extension treatment period start date

It starts immediately after EOT for those subjects treated at French sites who completed the core phase of the study as scheduled and opt to continue receiving study treatment. It is derived from the first treatment start date (in chronological order) in the Study Drug Log eCRF where the 'Study Period' is 'OPEN LABEL EXTENSION STUDY DRUG'.

11.6 Extension period end date (EOTOLE)

This is the "Treatment end date" from the last interval, in chronological order, recorded in the study drug log eCRF where the 'Study Period' is 'OPEN LABEL EXTENSION STUDY DRUG'. If missing or incomplete, rules in Section 12**Error! Reference source not found.** are followed according to Table 6**Error! Reference source not found.**

The extension treatment period is the period from the start up to the end of extension treatment (limits included).

Note: for reporting purpose, in the exceptional situation that the end date of a period is equal to the start date of the next period (for example the end date of treatment period is equal to the start date of the extension treatment period), the 'event' is associated with the first of the two periods (in the example, it is associated with the treatment period).

11.7 End of Study (EOS) date

This is the date of the "End of Follow Up" form of the eCRF.

11.8 Study day

Is the number of days elapsed since the study treatment start date plus 1 (study treatment start date is considered Day 1). For dates prior to study treatment start date, study day is the negative number of days between the date under consideration and the study treatment initiation. Therefore, the study day is always different from 0.

11.9 Time windows

To allow analysis of data at the relevant planned (scheduled) visits, recorded assessments, including unscheduled ones, are re-assigned to the most appropriate visit according to the best fitting time-window for that visit (see Table 5). The visit windows are based on the number of days from study treatment start (study treatment days). The window for Week 26 is based on the protocol specification for the primary endpoint. The window for Week 52 is calculated similarly to Week 26 (resulting in a wider Week 52 window than the protocol window). As EOS is a telephone visit, EOS is not included in the list of visits, so summary statistics are not applicable for EOS.

Should more than one assessment fall within the same time window, then the closest value to the planned time point (nominal value) will be assigned for presentation in data summaries and analyses. In case of values that are equidistant to the planned time point, the later assessment will be considered for the analyses. If more than one value falls on the same time point then the one with the last sequential number in SDTM will be used. (For lab assessments, if more than one lab assessment falls on the same time point, the central assessment is to be used. If this is still more than one value, the last sequential number in SDTM will be used.)

Programming note: values that are not retained for presentation in summaries per visit should be kept in the datasets and used as appropriate when applying substitution rules for missing data.

Individual data listings consider all data by nominal visit identifier with data flagged if considered for time windows.

Table 5 - Visits time windows

Mapping of all visits to:	Study day (nominal value)	Lower limit study day	Upper limit study day
Baseline	1	No limit	1
Week 26 visit	182	112	210
Week 52 visit	364	294	434
For monthly lab tests (hemoglobin, hematocrit, AST, ALT, alkaline phosphatase, total and direct bilirubin and LDH):			
Baseline	1	No limit	1
Month 1	30	15	44
Month 2	60	45	74
Month 3	90	75	104
Month 4	120	105	134
Month 5	150	135	164
Month 6	180	165	210
Week 52 visit	364	294	434

Using an ITT approach, assessments are not required to be during treatment.

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

All dates and times used in the analyses are supposed to be complete, apart from the types included in the table below.

Missing or incomplete dates are handled as follows:

- Dates are split into 3 parts: year, month and day. Year is the top-level, month is medium level and day is low level. If a part that is expected to contain a number is numeric but the value is outside a valid range, the complete date is handled as missing. For example, if date = 44Nov2000 the whole date is considered to be missing.
- If a part that is expected to contain a number is not numeric, i.e., contains values like such as ND, NA, --, ??, 2?, it is considered to be missing.
- If a part is missing, all lower level parts are considered to be missing. This means that a ddmmyy date '21ND99' is considered as '----99'.

Missing parts for specific dates/times are changed into acceptable non-missing values depending on the type of date to be replaced.

In Table 6, 'lower limit' and 'upper limit' refer to the minimum or maximum of a possible date. As an example, if only the day is missing, the lowest limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last

day of the given year. The earliest and the latest dates refer to the first or last date, respectively, when ordered in sequence.

Table 6 Types of missing or incomplete date/time fields

Type of date/time	Date/time is incomplete	Date/time is missing
AE resolution date	The upper limit	No replacement, the AE is considered as ongoing in the analysis
AE onset date	If the end date of the AE is not before the study treatment start date, and if the study treatment start falls in the range of possible dates, the study treatment start date is used. In all the other cases, the lower limit is used.	The earlier of the date of resolution of the AE and the study treatment start date
Previous/ concomitant therapy start date	Lower limit except when: Not tagged as ongoing at start of treatment AND Therapy end date not collected or with the upper limit after the study treatment start date AND the study treatment start day falls in the range of possible dates. In which case it is the study treatment start day	No replacement, the therapy is considered to have started before the study
Previous/ concomitant therapy end date	Upper limit except when: Therapy start is before study treatment start or missing AND Upper limit is after the study treatment start AND Not tagged as ongoing at start of treatment. In which case it is 1 day before study treatment start	No replacement (considered ongoing)

Type of date/time	Date/time is incomplete	Date/time is missing
Hospitalization admission date	If the onset date of the AE leading to hospitalization falls in the range of possible dates, it is the onset date of the AE. In all the other cases, it is the lower limit.	The onset date of the AE leading to hospitalization
EOS	Upper limit	Core phase database lock date
EOT	Use the earliest date between the: upper limit EOS date of death	Use the earliest date between the: EOS date of death
EOTOLE	Use the earliest date between the: upper limit EOS date of death	Use the earliest date between the: EOS date of death
Death date	Use the lower limit	No replacement

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

This section lists all outputs (i.e., listings, tables and figures) produced to display the results of the analyses defined in the sections above. In addition, original SAS output will be provided in CSR section 16.1.9.

The table, listing and figures naming conventions have three components: ***Type*** (T, L, F), ***Name*** (free text, not longer than ten characters), ***Suffix*** (for example, for analysis sets, or subgroups, not longer than four characters). Multiple suffixes can be added; components/suffixes are separated by '_'.

Key deliverables are marked as being of priority.

All outputs flagged as key table will be produced at interim analysis.

13.1 Subject disposition

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
DISP	T	Disposition of subjects	SCR	✓	T1
ANSETOV	T	Overview of analysis sets	SCR	✓	T2

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
ANSETEXR	T	Reasons for exclusion from analysis sets	SS		T2a
ANSET	L	Listing of subject participation in the different analysis sets	SCR	✓	L35
ANSETEXR	L	Listing of reasons for exclusion from analysis sets	SCR	✓	L1
SUBST	T	Overview of each sub-study	SS		T6

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.2 Protocol deviations

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PRDEVI	T	Important protocol deviations	SS	✓	T8
PRDEVA	T	All protocol deviations	SS		T8
PRDEV	L	Listing of protocol deviations	SCR	✓	L4

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.3 Subject characteristics

13.3.1 Demographics

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
DEMOG	T	Demographic characteristics	SS, mFAS	✓	T10
DEMOG	L	Listing of demographic characteristics	SCR	✓	L5
AGECATEU	T	EudraCT age categories	SS		T10a

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.3.2 Baseline disease characteristics

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
BASDC	T	Baseline disease characteristics	SS, mFAS	✓	T11
BASDC	L	Listing of baseline disease characteristics	SCR	✓	L6

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.3.3 Medical history

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
MHSCPR	T	Medical history by primary system organ class (SOC) and preferred term	SS	✓	T12
CDSCPR	T	Concomitant diseases by primary system organ class (SOC) and preferred term	SS	✓	T12

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PCMHIST	L	Listing of subjects with previous and concomitant medical history	SCR	✓	L7

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.3.4 Previous and concomitant therapies

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
CTTATCPR	T	Study-treatment concomitant therapies by anatomic therapeutic chemical class (ATC) and preferred term	SS	✓	T14
CTSATCPR	T	Study concomitant therapies by anatomic therapeutic chemical class (ATC) and preferred term	SS		T14
CTSBLATCPR	T	Study concomitant therapies at baseline by anatomic therapeutic chemical class (ATC) and preferred term	SS		T14
PTATCPR	T	Previous therapies by anatomic therapeutic chemical class (ATC) and preferred term	SS		T14
CTTSP	T	Study treatment concomitant PAH specific therapies by preferred term	SS	✓	T15
CTSSP	T	Study concomitant PAH specific therapies by preferred term	SS		T15
CTSBLSP	T	Study concomitant PAH specific therapies at baseline by preferred term	SS		T15
PTSP	T	Previous PAH specific previous therapies by preferred term	SS		T15
PCTHER	L	Listing of subjects with previous and concomitant therapies	SCR	✓	L9

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, | PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.3.5 Other subject characteristics

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
HPFT	T	Historical Pulmonary function tests	SS, mFAS		T16
HPFT	L	Listing of historical Pulmonary function tests	SCR		L6a

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.4 Study treatment exposure and compliance

13.4.1 Exposure

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
TREXP	T	Study treatment exposure	SS	✓	T17

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
TREXP_OLE	T	Study treatment exposure including the Open Label Extension (OLE)	SS		T17
TREXP	L	Listing of exposure	SCR	✓	L16

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set; OLE=Open Label Extension

13.4.2 Compliance with study treatment

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
COMPA	T	Compliance (based on drug accountability)	SS		T18
COMPA	L	Listing of compliance (based on drug accountability)	SCR		L17

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.4.3 Study treatment interruption

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
TREINT	T	Reasons for study treatment interruptions	SS	✓	T19
TREINT	L	Listing of study treatment interruptions	SCR		L18

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.4.4 Study treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PDISCTR	T	Reasons for premature discontinuation of study treatment	SS	✓	T4

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.5 Study discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PDISCST	T	Reasons for premature study discontinuation	SS	✓	T5
PDISC	L	Listing of discontinued subjects	SCR	✓	L3

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.6 Primary efficacy analyses

13.6.1 Main analysis

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PVR	T	Change from baseline to Week 26 in PVR	mFAS, PVRmFAS (if applicable)	✓	T20
PVRSP	F	Scatterplot of PVR at Week 26 versus baseline	mFAS	✓	F2
PVRCI	F	Confidence interval of PVR at Week 26 expressed as percent of PVR at baseline	mFAS		F4
RVSV	T	Change from baseline to Week 26/52 in RVSV assessed by cardiac MRI from pulmonary artery flow	mFAS, RVSVmFAS (if applicable)	✓	T21
RVSVSP	F	Scatterplot of RVSV assessed by cardiac MRI from pulmonary artery flow at Week 26/52 versus baseline	mFAS	✓	F2
RVSVCI	F	Confidence interval of RVSV assessed by cardiac MRI from pulmonary artery flow at Week 26/ 52	mFAS		F4
MRI	L	Listing of cardiac MRI variables values	SCR	✓	L10
MRIC	L	Listing of cardiac MRI ventricular volumes, comparing RVSV and LVSV	SCR	✓	L12
RHC	L	Listing of Right Heart Catheterization (RHC) variables values	SCR	✓	L10

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis et, SS=Safety analysis set, mFAS: Modified full analysis set; PVRmFAS: PVR Modified full analysis set; RVSVmFAS: RVSV Modified full analysis set

The primary analysis is to Week 26 for mFAS. Analyses with PVRmFAS and RVSVmFAS are sensitivity analyses. Analyses to Week 52 are exploratory. A footnote will be added for the Week 52 analyses.

13.6.2 Supportive/sensitivity analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PVRO	T	Change from baseline to Week 26 in PVR by RHC (Observed data)	PPS		T20
RVSVO	T	Change from baseline to Week 26 and Week 52 in RVSV assessed by cardiac MRI from pulmonary artery flow (Observed data)	PPS		T21
PVR	T	Change from baseline to Week 26 in PVR by RHC (with LOCF imputation) *Programming note: please show the bracket (with LOCF imputation) only for SS*	FAS, SS		T20
RVSV	T	Change from baseline to Week 26 and Week 52 in RVSV assessed by cardiac MRI from pulmonary artery flow (with LOCF imputation) *Programming note: please show the bracket (with LOCF imputation) only for SS*	FAS, SS		T21

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PRIM1	F	Scatterplot of PVR absolute change from baseline to Week 26 versus RVSV assessed by Cardiac MRI from pulmonary artery flow absolute change from baseline to Week 26 *Note to programmer: figure is based on observed data*	mFAS		F3
PRIM2	F	Scatterplot of PVR Ratio of Week 26 to baseline versus RVSV assessed by Cardiac MRI from pulmonary artery flow Ratio of Week 26 to baseline *Note to programmer: figure is based on observed data*	mFAS		F3
PRIM3	F	Scatterplot of PVR absolute change from baseline to Week 26 versus six-minute walk-distance (6MWD) absolute change from baseline to Week 26 *Note to programmer: figure is based on observed data*	mFAS		F3
PRIM4	F	Scatterplot of RVSV assessed by Cardiac MRI from pulmonary artery flow absolute change from baseline to Week 26 versus six-minute walk-distance (6MWD) absolute change from baseline to Week 26 *Note to programmer: figure is based on observed data*	mFAS		F3
EXPL1	T	Analysis of change from baseline to week 26 in RVSV assessed by cardiac MRI from pulmonary artery flow using PAH etiology, baseline 6MWD, baseline WHO FC, sex and age group (< 65, >= 65) as prognostic factors	mFAS	✓	T45
EXPL2	T	Analysis of change from baseline to week 26 in log(PVR) PAH etiology, baseline 6MWD, baseline WHO FC, sex and age group (< 65, >= 65) as prognostic factors	mFAS	✓	T45

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.6.3 Subgroup analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PVRS	T	Change from baseline to Week 26 in PVR by subgroup	mFAS	✓	T20b
PVRS	F	Forest plot of PVR Ratio of Week 26 versus baseline by subgroup and overall	mFAS		F6
RVSVS	T	Change from baseline to Week 26 and Week 52 in RVSV assessed by cardiac MRI from pulmonary artery flow by subgroup	mFAS	✓	T21b
RVSVS	F	Forest plot of change from baseline to Week 26 and Week 52 in RVSV assessed by cardiac MRI from pulmonary artery flow by subgroup and overall	mFAS		F6

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set; PVR=pulmonary vascular resistance; RVSV=right ventricular stroke volume

13.7 Secondary/exploratory efficacy analyses

13.7.1 Main analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
MRI1	T	Change from baseline to Week 26 and Week 52 in the Right Ventricle (RV) assessments by cardiac MRI	SS, mFAS		T21
6MWD	T	Change from baseline to Week 26 and Week 52 in six-minute walk-distance (6MWD)	SS, mFAS	✓ (only on SS)	T21
BORG	T	Change from baseline to Week 26 and Week 52 in Borg index	SS, mFAS		T21
WHO	T	Shift table of change in WHO functional class from baseline to Week 26 and 52	SS, mFAS	✓ (only on SS)	T27
WHOLR	T	WHO functional class: Number (%) of subjects who worsened at Week 26 and Week 52	SS, mFAS	✓ (only on SS)	T27b
BNP	T	Change from baseline to Week 26 and Week 52 in NT pro-BNP	SS, mFAS		T20d
EFF	L	Listing of six-minute walk-distance (6MWD), WHO functional class and Borg index	SCR	✓ (only on SS)	L10

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.8 Other efficacy analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
MRI2	T	Change from baseline to Week 26 and Week 52 in the Left Ventricle (LV) assessments by cardiac MRI	SS, mFAS		T21
MRI3	T	Change from baseline to Week 26 and Week 52 in ratio RVEDV/LVEDV and ratio RVESV/LVESV assessed by cardiac MRI	SS, mFAS		T20c
RHC	T	Change from baseline to Week 26 in mPAP, mRAP and Cardiac Index (CI) assessed by Right Heart Catheterization (RHC)	SS, mFAS		T21
DISMON	T	Change from baseline to Week 26 and Week 52 in potential variables for disease monitoring	SS, mFAS		T20c
CLINW	T	Time to first clinical worsening event	SS, mFAS		T28
CLINW	F	Kaplan-Meier plot of time to first clinical worsening event	SS, mFAS		F5
PRESS	L	Listing of pressure-volume variables: Arterial elastance, RV end-systolic elastance and RV maximum isovolumic pressure values assessed by Cardiac MRI combined with Right Heart Catheterization (RHC)	SCR		L10
DISMON	L	Listing of potential laboratory variables for disease monitoring values	SCR		L10
CLINW	L	Listing of clinical worsening events	SCR		L11

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.9 Sub-studies

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
ECHO	T	Change from baseline to Week 26 and Week 52 in echo variables	SS, mFAS (restricted to subjects participating in the echo sub-study)		T21
ECHO	L	Listing of echo variables values	SCR (restricted to subjects participating in the echo sub-study)		L10
MTB	L	Listing of metabolism variables values	SCR (restricted to subjects participating in the metabolism sub-study)		L10

13.10 Safety analyses

13.10.1 Adverse events

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEOV	T	Overview of treatment-emergent adverse events (AE)	SS	✓	T33
AEOV_OLE	T	Overview of treatment-emergent adverse events (AE), including the Open Label Extension (OLE)	SS		T33
AESCPR	T	Treatment-emergent adverse events (AE) by system organ class (SOC) and preferred term	SS		T34
AESCPR_OLE	T	Treatment-emergent adverse events (AE) by system organ class (SOC) and preferred term, including the Open Label Extension (OLE)	SS		T34
AEPR	T	Treatment-emergent adverse events (AE) by preferred term	SS		T35
AEPRIN	T	Treatment-emergent adverse events (AE) by maximum intensity and preferred term	SS		T36
AERESCPR	T	Treatment-emergent adverse events (AE) related to study treatment by system organ class (SOC) and preferred term	SS		T34
AE	L	Listing of adverse events (AE)	SCR	✓	L23

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set; OLE=Open Label Extension

13.10.2 Deaths

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEFASCPR	T	Treatment-emergent adverse events (AE) with fatal outcome by system organ class (SOC) and preferred term	SS	✓	T34
AEFAPR	T	Treatment-emergent adverse events (AE) with fatal outcome by preferred term	SS		T35
DEAPR	T	Cause of death	SS	✓	T37
DEATH	L	Listing of deaths	SCR	✓	L24

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.10.3 Serious adverse events

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
SAESCPR	T	Treatment-emergent serious adverse events (SAE) by system organ class (SOC) and preferred term	SS	✓	T34
SAESCPR_OLE	T	Treatment-emergent serious adverse events (SAE) by system organ class (SOC) and preferred term, including the Open Label Extension (OLE)	SS		T34
SAEPR	T	Treatment-emergent serious adverse events (SAE) by preferred term	SS		T35
SAERESCPR	T	Treatment-emergent serious adverse events (SAE) related to study treatment by system organ class (SOC) and preferred term	SS		T34
SAE	L	Listing of serious adverse events (SAE)	SCR	✓	L23

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set; OLE=Open Label Extension

13.10.4 Adverse events leading to study treatment discontinuation

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEPDSCPR	T	Adverse events (AE) leading to premature discontinuation of study treatment by system organ class (SOC) and preferred term	SS	✓	T34
AEPDSCPR_OLE	T	Adverse events (AE) leading to premature discontinuation of study treatment by system organ class (SOC) and preferred term, including the Open Label Extension (OLE)	SS	✓	T34
AEPDPR	T	Adverse events (AE) leading to premature discontinuation of study treatment by preferred term	SS		T35
AEPD	L	Listing of adverse events (AE) leading to premature discontinuation of study treatment	SCR	✓	L23

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set; OLE=Open Label Extension

13.10.5 Other significant adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
NSAEFSCPRE	T	Occurrence of non-serious frequent (>=5%) treatment-emergent adverse events (AE)	SS		T38
NSAEFSCPRE_OLE	T	Occurrence of non-serious frequent (>=5%) treatment-emergent adverse events (AE), including the Open Label Extension (OLE)	SS		T38

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AESISCPR	T	Treatment-emergent adverse events of special interest (AESI) by system organ class (SOC) and preferred term	SS		T34
AESISCPR_OLE	T	Treatment-emergent adverse events of special interest (AESI) by system organ class (SOC) and preferred term, including the Open Label Extension (OLE)	SS		T34

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set; OLE=Open Label Extension

13.11 Laboratory tests

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LABCGTPHEM	T	Hematology: Change in laboratory tests from baseline to each time point	SS		T40
LABCGTPBCH	T	Chemistry: Change in laboratory tests from baseline to each time point	SS		T40
LABMLAHEM	T	Hematology: Marked laboratory abnormalities	SS	✓	T41
LABMLAHEM_OLE	T	Hematology: Marked laboratory abnormalities including the Open Label Extension OLE)	SS	✓	T41
LABMLABCH	T	Chemistry: Marked laboratory abnormalities	SS	✓	T41
LABMLABCH_OLE	T	Chemistry: Marked laboratory abnormalities including the Open Label Extension OLE)	SS	✓	T41
LABMLA	L	Listing of definitions of marked laboratory abnormality	NA		L24a
LABLHLA	T	Liver and hemoglobin laboratory abnormalities	SS	✓	T42
LABLHLA_OLE	T	Liver and hemoglobin laboratory abnormalities, including the Open Label Extension (OLE)	SS		T42
LABEDISH	F	eDISH plot showing maximum post-baseline ALT/AST against bilirubin	SS		F7
LABEDISH_OLE	F	eDISH plot showing maximum post-baseline ALT/AST against bilirubin, including the Open Label Extension (OLE)n	SS		F7
LABSHHEMLOW	T	Hematology: Shift in laboratory tests from baseline to the worst low value	SS		T43
LABSHHEMHIGH	T	Hematology: Shift in laboratory tests from baseline to the worst high value	SS		T43
LABSHBCHLOW	T	Chemistry: Shift in laboratory tests from baseline to the worst low value	SS		T43
LABSHBCHHIGH	T	Chemistry: Shift in laboratory tests from baseline to the worst high value	SS		T43
LABSI	L	Listing of individual laboratory measurements (SI units)	SCR		L25
LABORIG	L	Listing of individual laboratory measurements (original units)	SCR		L25

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LABLMA	L	Listing of individual laboratory measurements (subjects with at least one marked abnormality)	SCR		L25

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set; OLE=Open Label Extension

13.12 Physical examination, vital signs and body weight

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
VS	T	Change from baseline to each post-baseline assessment in vital signs, body weight and BMI	SS		T44
VS	L	Listing of vital signs, body weight, BMI and height	SCR		L30
PHYSF	L	Listing of physical findings	SCR		L34

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.13 Pregnancy test

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
CHILD	L	Listing of childbearing potential and contraception	SCR		L33a
PREGN	L	Listing of pregnancy test data	SCR		L33b

* T=Summary table, L= Listing, F=Figure, **SCR=Screened analysis set, FAS=Full analysis set, PPS=Per-protocol analysis set, SS=Safety analysis set, mFAS: Modified full analysis set

13.14 Other evaluations

13.14.1 Quality of life analyses

Not applicable

13.14.2 Pharmacoeconomic analyses

Not applicable

13.14.3 Benefit-risk evaluations

Not applicable

13.14.4 Pharmacodynamic analyses

Not applicable

13.14.5 Pharmacokinetic analyses

Not applicable

NCT02310672

14 REFERENCES

[Not applicable]

15 APPENDICES

A. Document history

Summarize the main changes and rationale for changes from one approved version to the next.

Version	Effective Date	Reason
1.0	20.Oct.2015	New
1.1	28.Oct.2015	Update according to comments from Clinical Science
1.2	29.Feb.2016	Adding the Shell outputs
1.0	31.May.2016	Final Version
Amendment 1 version 1.0	20.March.2018	Major updates following protocol amendment and change in vendor for statistics/programming.

ELECTRONIC SIGNATURES

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