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STATISTICAL ANALYSIS PLAN

FOR AC-055-303: SAP FOR CSR

SERAPHIN-OL: Study with an ERA in Pulmonary arterial Hypertension to Improve cliNical outcome (Open Label)

Long-term single-arm open-label extension study of the SERAPHIN study, to assess the safety and tolerability of macitentan/ACT-064992 in subjects with symptomatic pulmonary arterial hypertension

Purpose of Analysis	Clinical Study Report
Investigational Drug	JNJ-67896062/ACT-064992/Macitentan
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CRF	Case report form
CL	Confidence limit(s)
CSR	Clinical study report
DB	Double Blind
DOD	Date of death
eCRF	Electronic case report form
EOS	End-of-study
EOT	End-of-treatment
Hgb	Hemoglobin
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
OL	Open label
PAH	Pulmonary arterial hypertension
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SOC	System organ class
STRT302	first dosing date in SERAPHIN DB
STRT303	first dosing date in SERAPHIN OL
TEAE	Treatment-emergent Adverse Event
ULN	Upper limit of the normal range
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) details the final analysis conducted for the purpose of the production of the clinical study report (CSR) for the open-label (OL), extension study AC-055-303 (SERAPHIN OL) to the double-blind study AC-055-302 (SERAPHIN DB). This SAP also provides a description of the general considerations and assumptions, as well as the proposed list of tables, figures and listings for the pooled data of AC-055-302 (SERAPHIN DB) and AC-055-303 (SERAPHIN OL).

The pooling of AC-055-302 (SERAPHIN DB) and AC-055-303 (SERAPHIN OL) means that the data from the same patients randomized in SERAPHIN DB will be concatenated with their data from the OL extension study (SERAPHIN OL). The concatenation of data from the same patients is referred to as 'pooling' in this document.

The pooling will be done only for the survival and safety data of patients initially randomized to the Macitentan 10 mg dose in the SERAPHIN DB, up to the end of the study (if they did not participate in the SERAPHIN OL study) or end of SERAPHIN OL.

This SAP (unless explicitly specified) follows the derivations and conventions defined in the SERAPHIN DB SAP (AC-055-302 Analysis Plan, appendix 16.1.9 to AC-055-302 [SERAPHIN DB] CSR [D-12.425]).

2 STUDY DESIGN AND FLOW

2.1 Study design

A short summary of study design and its graphical presentation for AC-055-302 (SERAPHIN DB) and AC-055-303 (SERAPHIN OL) study are presented below.

SERAPHIN DB was a multicenter, randomized, double-blind, placebo-controlled, parallel group, event-driven Phase III study that compared oral once daily treatment with 3 mg and 10 mg doses of Macitentan versus placebo in patients with symptomatic pulmonary arterial hypertension (PAH).

Patients aged 12 years or over were eligible to be enrolled if diagnosed with World Health Organization (WHO) FC II–IV idiopathic PAH, familial PAH, PAH associated with connective tissue disease, PAH associated with simple congenital systemic-to-pulmonary shunts at least 1-year post-surgical repair, HIV infection, or drugs and toxins.

A total of 742 patients were randomized in a 1:1:1 ratio to Macitentan 3 mg (n = 250), Macitentan 10 mg (n = 242), and placebo (n = 250) in SERAPHIN DB.

The study took place from 25 May 2008 (first subject/first visit) until 15 March 2012 (last subject/last visit).

The Macitentan 10 mg treatment effect (active *vs.* placebo) was highly statistically significant and clinically relevant, with a hazard ratio for the composite endpoint (Death; Atrial septostomy; Lung transplantation; Initiation of intravenous (i.v.) or subcutaneous prostanoids; Other worsening of PAH) of 0.547 (97.5% confidence limits [CLs] 0.392, 0.762, logrank $p < 0.0001$). More details are available in the Clinical Study Report (D-12.425). The Macitentan 10 mg daily dose was approved by European Medicines Agency, Food and Drug Administration, and most other regulatory authorities around the world.

Patients who prematurely discontinued study treatment (DB) due to clinical worsening of PAH and obtained written approval from Actelion, and patients who completed the study as scheduled, could enter SERAPHIN OL. For patients who had opted not to participate or who were not eligible to participate in SERAPHIN OL a 28-day safety follow-up after end of treatment (EOT) was performed.

SERAPHIN OL is an open-label, non-comparative, multicenter, extension study to assess long-term safety and tolerability of Macitentan in patients with symptomatic PAH, who either completed the DB treatment period of SERAPHIN or had clinical worsening of PAH in SERAPHIN. The OL study enrolled 550 patients (first patient enrolled on 17 October 2008), all of whom received Macitentan 10 mg, irrespective of DB treatment allocation.

The study treatment period for each patient lasts from his/her enrollment date until the end of the trial defined as the earliest of:

(i) approval of Macitentan in this indication is obtained in the patient's country,

(ii) the sponsor decides to stop study AC-055-303 (SERAPHIN OL),

(iii) the subject's, investigator's, or sponsor's decision to discontinue study drug.

Figure 1 AC-055-302 (SERAPHIN DB) and AC-055-303 (SERAPHIN OL) study design

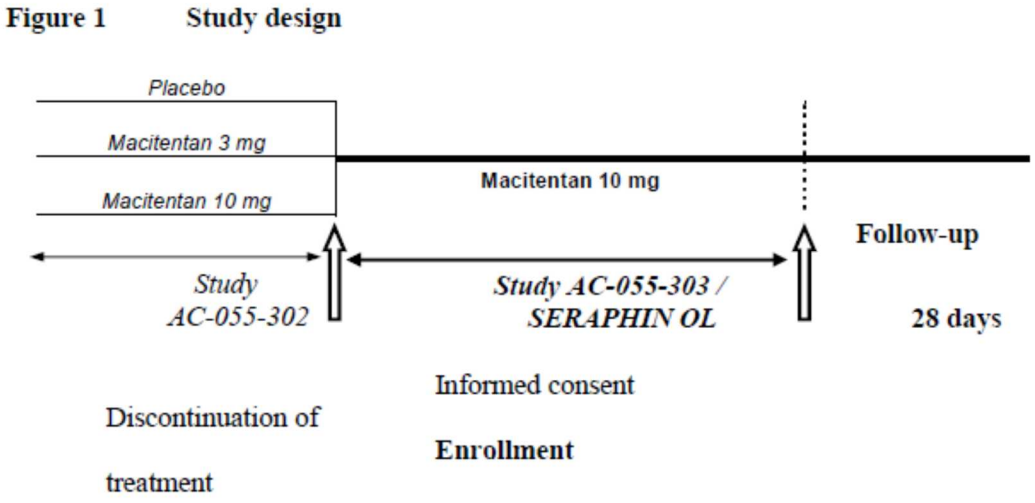

Table 1 All patients treated in SERAPHIN DB (AC-055-302) and/or SERAPHIN OL (AC-055-303)

Study number (Acronym)	Number of patients randomized to Macitentan 3 mg in AC-055-302 (SERAPHIN DB) N = 250		Number of patients randomized to Macitentan 10 mg in AC-055-302 (SERAPHIN DB) N = 242		Number of patients randomized to placebo in in AC-055-302 (SERAPHIN DB) N = 250	Number of patients in AC-055-303 (SERAPHIN OL) N= 550		
AC-055-302 (SERAPHIN DB) treatment / AC-055-303 (SERAPHIN OL) treatment	3 mg / none: N = 65	3 mg / 10 mg: N = 185	10 mg / none: N = 60	10 mg / 10 mg: N = 182	Placebo / 10 mg: N = 183	Placebo / 10 mg: N = 183	3 mg / 10 mg: N = 185	10 mg / 10 mg: N = 182

DB = double-blind, OL = open-label.
Patients who did not enter the open-label study are shown in the columns '3 mg / none' and '10 mg / none'. Those who received Macitentan in both the double-blind and open-label periods are shown in the '3 mg / 10 mg' and '10 mg / 10 mg' columns. Finally, those who received placebo in the double-blind study and entered the extension study are shown in the 'Placebo / 10 mg' column.

Analyses will be provided for the following cohorts (see below and Table 2):

- **Macitentan 10 mg OL** (550 patients): This cohort comprises all patients enrolled into SERAPHIN OL who took at least one dose of Macitentan 10 mg as an OL treatment (regardless of randomized treatment in SERAPHIN DB). As this group is heterogenous (initially the patients were randomized to different treatment regimens) it will be further analyzed by randomization groups.
    - Placebo DB/Macitentan 10 mg OL (183 patients)
    - Macitentan 3 mg DB/Macitentan 10 mg OL (185 patients)
    - Macitentan 10 mg DB/Macitentan 10 mg OL (182 patients)

- **Macitentan 10 mg DB/OL** (242 patients)**:** This cohort comprises all patients randomized to Macitentan 10 mg in SERAPHIN DB. For this group of patients, data from SERAPHIN DB and SERAPHIN OL will be pooled within patient.

Table 2 Template for summary tables

	Macitentan 10 mg (OL)			
Macitentan 10 mg (DB/OL) (N=242)	Placebo / 10 mg: (N = 183)	3 mg / 10 mg: (N = 185)	10 mg / 10 mg: (N = 182)	Total (N=550)

2.2 Study Visit and Assessment Schedule

Table 3 Visit and Assessment Schedule for Seraphin DB

Table 1 Visit and assessment schedule

PERIODS	SCREENING	TREATMENT PERIOD							FOLLOW-UP PERIOD	
VISITS	1 Screening	2 Randomization	3	4	5	6, 7 etc.	EVENT	End-of-Treatment (EOT)	End-of-Study[9] (EOS)	Follow-up
TIME POINTS / ASSESSMENTS	Day -28 to -1	Day 1	Month 3 ± 2 weeks	Month 6 ± 2 weeks	Month 12 ± 2 weeks	Every 6 months ± 2 weeks		Study drug discontinuation	Target number of events achieved	28 days after study drug discontinuation
Informed consent	X									
Medical history	X									
Concomitant medications	X	X	X	X	X	X	X	X		
Vital Signs, body weight	X	X	X	X	X	X	X	X		
12-lead ECG	X			X			X[8]	X		
Complete laboratory tests[1]	X		X	X	X	X	X[8]	X		
LFTs and PK sampling (serum)[10]			Monthly (+/- 1 week) monitoring up to at least 28 days after End-of-Treatment							
Pregnancy Test[2]	X	X[3]	Monthly (+/- 1 week) and up to at least 28 days after End-of-Treatment							
NT-pro-BNP		X		X						
Right heart catheterization		X[4]		X[5]						
Modified WHO class	X	X	X	X	X	X	X	X		
6MWT	X	X	X	X	X	X	X	X		
Borg dyspnea index	X	X	X	X	X	X	X	X		
PK sampling (plasma)				X[5]			X[8]	X		
QoL questionnaire (SF 36)		X		X	X		X[8]	X		
Study drug dispensing		X		X	X	X				
Adverse events[6]		X	X	X	X	X	X	X		X
Serious adverse events[6]	X[7]	X	X	X	X	X	X	X		X
Vital status									X	

[1] Includes hematology and chemistry; [2] Women of childbearing potential only; [3] Urine-dipstick pregnancy test if last negative serum pregnancy test older than 2 weeks; [4] Only to be performed if not done within 12 months (3 months for patients participating in the PK/PD sub study) prior to randomization; [5] In centers participating in the PK/PD sub-study; [6] AE and SAE reporting and follow-up: all AEs/SAEs from study drug initiation up to 28 days after study drug discontinuation, follow-up of ongoing AEs/SAEs only thereafter; [7] SAE reporting: during screening period, SAEs related to study-mandated procedures only; [8] Only if event leads to study drug discontinuation; [9] EOS Visit will coincide with EOT Visit if patient completes the study as scheduled; [10] PK in serum is only to be analyzed at EOS if liver aminotransferases is above 3 times ULN.

Table 4 Visit and Assessment Schedule for Seraphin OL

PERIODS	TREATMENT PERIOD			FOLLOW-UP PERIOD
VISITS	Enrolmnent (Visit 1)	Visit 2,3, etc.	End-of-Treatment (EOT)	End-of-Study (EOS)
TIMEPOINTS ASSESSMENTS	Day 1[1]	Month 6, and every 6 months thereafter ± 2 weeks		Up to 28 days after study drug discontinuation
Informed Consent	X			
Concomitant medication	X	X	X	X
Vital signs, Body weight **Physical examination**	Performed at each visit; Data will only be kept in patient's file			
Complete Laboratory Tests	X	X	X	
LFTs	X	Recommended monthly (+/−1 week) up to at least 28 days after End-of-Treatment		
Serum Pregnancy Test[2] (if applicable)	X	X	X	
Urine Pregnancy Test[2, 5] (if applicable)		Required monthly (+/−1 week) up to at least 28 days after End-of-Treatment		
Phone call for pregnancy test reminder and contraception counseling[2]		Required monthly (+/−1 week) up to at least 28 days after End-of-Treatment		
Study Drug Dispensing[4]	X	X		
Adverse Events[3]	X	X	X	X
Serious Adverse Events	X	X	X	X

[1]The tests are not to be repeated if measured during the End-of-Treatment visit of study AC-055-302/SERAPHIN that has been performed within 4 weeks of this visit. [2]Women of childbearing potential only; [3]AE reporting and follow-up: all AEs up to 28 days after study drug discontinuation. [4]Study drug may be dispensed on a monthly basis at each LFT visit. [5]Urine pregnancy test is required if no serum pregnancy test is performed.
AE = adverse event; LFT = liver function test.

3 STUDY OBJECTIVES

3.1 Objectives for SERAPHIN DB

Primary objective

The primary objective of this study was to demonstrate that either dose (3 mg or 10 mg) of Macitentan reduces the risk of morbidity and mortality in patients with symptomatic PAH.

Secondary objectives

- To demonstrate that either dose (3 mg or 10 mg) of Macitentan improves exercise capacity, WHO FC, and reduces the risk of death due to PAH or hospitalization for PAH up to end-of-treatment (EOT) in patients with symptomatic PAH.
- To demonstrate that either dose (3 mg or 10 mg) of Macitentan reduces the risk of death of all causes up to EOT and up to end-of-study (EOS).
- To evaluate the safety and tolerability of Macitentan in patients with symptomatic PAH

3.2 Objectives for SERAPHIN OL

To assess long-term safety and tolerability of Macitentan 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

This SAP was prepared based on the Protocol AC-055-303 OL version 7 (17 July 2020).

For the two cohorts described in section 2.1, the Safety Set is defined as:

Macitentan 10 mg DB/OL - all patients who received at least one 10 mg dose of Macitentan in DB/OL and with at least one post-baseline assessment.

Macitentan 10 mg OL (550) - all patients who were enrolled and received Macitentan in SERAPHIN OL study.

For details for safety set see Section 7.1.1.

Laboratory data will not be normalized but presented as collected.

Mean daily dose is not analyzed as most patients treated with Macitentan received 10 mg (610 / 675 = 90% patients, where 675 is number of patients who received Macitentan either in DB or OL period).

In the protocol no primary efficacy endpoint was defined for this OL extension study. However, long-term survival can be evaluated for those patients that entered the study, as well as for the pooled DB/OL cohort as defined above.

4.2 Changes in the conduct of the study / data collection

4.3 Clarifications concerning endpoint definitions and related variables or statistical methods

For the Macitentan 10 mg DB/OL cohort, time to death will be calculated using start of the Macitentan 10 mg treatment at the beginning of dosing in DB period. Full details for time to event analysis are given in section 5.5.1.

In this SAP the per-protocol dataset is not defined. Protocol deviations will be reported as per section 6.

Adverse events of special interest were not pre-specified in the protocol. They are defined in section 5.6.5.

Table 2 defines the cohorts to be presented for the summaries.

5 DEFINITIONS OF VARIABLES

The following dates will be used to define the treatment durations, survival, censoring and safety reporting periods: For imputation of partial/ missing date, refer to section 11.

- **Start date of Macitentan in SERAPHIN DB (STRT302)**: date of first administration of Macitentan in patients randomized to Macitentan 10 mg in SERAPHIN DB collected in the study drug log.
- **Enrollment date into SERAPHIN OL (STRT303)**: date of enrollment into SERAPHIN OL as reported in the Interactive Voice Response System (IVRS) system.
- **Date of death (DOD)**: actual date of death of a patient as reported in the SERAPHIN DB or SERAPHIN OL Case Report Forms (CRFs) prior to the SERAPHIN OL study closure.
- **CENS**: Censoring flag. Categorical: 0 (not censored) or 1 (censored).

- **SERAPHIN DB End Of Study (EOS302)**: This is the end of study (EOS) visit date of a patient from the SERAPHIN DB study.

Note that for all patients who did not withdraw prematurely from SERAPHIN DB, the **EOS302** occurred shortly after the administrative end of SERAPHIN DB announced by Actelion on 30 January 2012.

- **SERAPHIN OL EOS (EOS303)**: study completion date.

  Note that the end of the study in SERAPHIN OL is on a patient-by-patient basis, until the earliest between:

  - Death
  - The latest date between: Date of visit/ Contact or Date of discontinuation/ Last contact on the EOS/Permanent Discontinuation CRF page.

The EOS occurs when the approval of Macitentan is obtained in the patient's country or when the patient, investigator, or sponsor decides to discontinue study drug.

EOS302 and EOS303 (individual patient's end of study) will be referred in this SAP as end of study (EOS). The overall end of study up to the database lock will be referred as study closure.

- **End of Treatment in SERAPHIN DB (EOT302):** end of double-blind treatment in SERAPHIN DB, i.e., the last treatment date reported in the SERAPHIN DB study drug log.
- **End of Treatment in SERAPHIN OL (EOT303):** EOT in SERAPHIN OL, i.e., the last treatment end date reported in the study drug log.
- **SERAPHIN OL last contact date (LAST303)** No ongoing patients are expected anymore, therefore LAST303=EOS303
- **SERAPHIN DB last contact date (LAST302)** No ongoing patients are expected anymore, therefore LAST302=EOS302
- **Last contact date (LCTC) for SERAPHIN OL and DB:** This is the latest date between LAST303 and EOS302. For patients who did not enter SERAPHIN OL, the date will be EOS302.
- **EOT in SERAPHIN OL and DB:**
  - **For patients in the OL cohort** this is EOT303.
  - **For patients in the DB/OL cohort:**
    - If the patient entered SERAPHIN OL then this is EOT303.

- If the patient did not enter SERAPHIN OL then this is EOT302.

- **Time to death (TTD)** is estimated by the Kaplan-Meier (KM) product limit method and summarized for each cohort, except Macitentan total (SAP for sNDA Section 6.1).

For example, for cohort Macitentan 10 mg DB/OL, time to death was defined as the time of start of Macitentan 10 mg treatment in SERAPHIN DB up to the date of death (any cause) in either the DB or OL period. Patients who did not die prior to the study closure were censored at their last date of contact.

For patients in the Macitentan 10 mg DB/OL cohort **who died prior to study closure**, time to death is derived:
TTD=DOD - STRT302 and CENS=0 and,

For patients in the Macitentan 10 mg DB/OL cohort **who did not die prior study closure and therefore censored**:
TTD=LCTC - STRT302 and CENS=1
Where LCTC=max(EOS302, EOS303).

Imputation rules for missing or incomplete dates are listed in section 11.

5.1 Screening failures

Not Applicable for this SAP.

5.2 Patients characteristics

Baseline information for the patients in the Macitentan 10 mg OL cohort is defined as the latest available information prior to the first dosing date in the OL study.

Baseline information for patients in the Macitentan 10 mg DB/OL cohort is defined as the latest available information prior to the first dosing date in SERAPHIN DB (STRT302).

For patients in the Macitentan 10 mg DB/OL cohort, completion/discontinuation of study drug and the associated reasons will be counted either in SERAPHIN DB if the patients did not enter SERAPHIN OL (10 mg / none), or in SERAPHIN OL if the patients entered SERAPHIN OL (10 mg / 10 mg).

For patients in Macitentan 10 mg OL cohort, completion/discontinuation of study drug and associated reasons will be counted in SERAPHIN OL.

The study drug discontinuation rate will be adjusted on person-year of study duration for each cohort and each drug dose sequence.

5.2.1 Demographics

Demographics will include: age (years), age subgroups (Adolescents [< 18 years], from 18 to 64 years, from 65 to 84 years, and over 84 years), gender (Male, Female), race (White [including Hispanic], Asian, Other), height (cm), weight (kg) and body mass index (BMI; kg/m^2), geographical location (North America including Canada; Western Europe including South Africa and Israel; Eastern Europe including Turkey; Asia including Australia; Latin America).

Age (years) = (STRT303 - birth date + 1)/365.25 will be reported as number of completed years.

For the Macitentan 10 mg DB/OL, age is the age at the first dose in DB.

For the Macitentan 10 mg OL, age is the age at entry into OL.

For imputation of partial birth date, refer to section 11.

5.2.2 Baseline disease characteristics

Baseline disease characteristics will include PAH etiology at baseline (idiopathic, familial, associated with HIV infection, associated with drug use or toxin exposure, associated with collagen vascular disease, associated with repaired congenital shunts) and WHO FC at baseline.

5.2.3 Other baseline characteristics

Other baseline characteristics will include categorized Estimated Creatinine Clearance:

- no renal impairment (creatinine clearance ≥ 90 mL/min),
- mild renal impairment (creatinine clearance ≥ 60 and < 90 mL/min)
- moderate-severe renal impairment (creatinine clearance < 60 mL/min).

5.2.4 Medical history

Medical History is not summarized for this analysis as it was previously reported for the CSR of AC-055-302 (SERAPHIN DB).

5.2.5 Previous and concomitant medications

Previous and concomitant medications for SERAPHIN DB and SERAPHIN OL are coded using WHO Drug Dictionary version March 2019.

In SERAPHIN OL, collection in the CRF of previous and concomitant medications was introduced with Global Protocol Amendment 4 (27 August 2013). Medications taken prior to implementation of this protocol amendment were then collected retrospectively. Medications which were ‘ongoing at EOT’ in the SERAPHIN DB are reconciled with medications ‘ongoing at the start of AC-055-303’ (SERAPHIN OL). Since the SERAPHIN DB was closed prior to the retrospective data collection, any discrepancies identified in

this database cannot be corrected. These discrepancies are reported in a Data Management tracker by the Global Data Manager, and will be reported in a separate listing.

Patients who took the same medication more than once (as qualified by the same preferred term (PT) will be counted only once. In case the reported medication was assigned to several PTs, patients are counted for each individual PT.

5.2.5.1 Previous medications

A previous medication is any treatment for which the end date of treatment is prior to the start of the AC-055-303 (SERAPHIN OL) study (i.e., prior to signing the informed consent form). These are not included in the analysis as these are part of the AC-055-302 (SERAPHIN DB) CSR; these data were reported as previous or concomitant therapies.

5.2.5.2 Concomitant medications

Concomitant medications are all treatments that are ongoing or initiated after start of study (i.e., from the time of the patient signing the informed consent form) or initiated up to 28 days after the end of study treatment.

Concomitant medication at baseline is defined as any medication that is taken at the start of study drug (STRT303 for Macitentan 10 mg OL, STRT302 for Macitentan 10 mg DB/OL). This includes any medication with the tick box "ongoing at Baseline" checked, or with a start date before or on the day of study drug start (STRT303 for Macitentan 10 mg OL, STRT302 for Macitentan 10 mg DB/OL) and the end date not before study drug start (STRT303 for Macitentan 10 mg OL, STRT302 for Macitentan 10 mg DB/OL). Start and end dates that are incomplete will be handled according to the rules for partial and missing concomitant medication dates in section 11 **Appendix A**.

Note: the concomitant medications at baseline for patients in the Macitentan 10 mg DB/OL cohort will be derived using only the AC-055-302 (SERAPHIN DB) database. For patients in the Macitentan 10 mg OL cohort, both AC-055-302 (SERAPHIN DB) and AC-055-303 (SERAPHIN OL) databases will be used for the derivation of concomitant medications at baseline.

PAH therapies

PAH therapy includes phosphodiesterase-type 5 (PDE-5) inhibitors, prostanoids, and soluble guanylate cyclase stimulators, and comprises the following PT:

- PDE-5 inhibitors, including:
  - Sildenafil
  - Tadalafil
  - Vardenafil
- Drugs acting via prostacyclin pathway / prostanoids, including
  - Iloprost
  - Beraprost

  - Treprostinil
  - Epoprostenol
  - Selexipag
- Soluable guanylate cyclase stimulators, including:
  - Riociguat

In the medication selection for PAH therapy, any medication coded PT that contains one of the PT included in the definition above is used (e.g. "sildenafil citrate" is a PAH specific medication that belongs to the PDE-5 inhibitor category.)

Concomitant medications during the study include all concomitant medications at baseline plus the medication reported as 'ongoing at end of treatment/study' or with the start date on or after the start date of study drug treatment:

- STRT302 for Macitentan 10 mg [DB/OL],
- STRT303 for Macitentan 10 mg [OL]

and on or before the EOT+28 days.

The following summaries will be presented for each cohort:

- A summary of concomitant PAH therapy at baseline (for baseline DB and separately baseline OL) including the number and percentages of patients taking at least one PAH therapy (i.e., at least one PDE-5 inhibitor, at least one prostanoid).

Note: patients may receive more than one treatment and may be included in more than one treatment class.

- A summary of concomitant medication use at baseline for all medications taken by at least 5.0% patients in any cohort, by PT
- A summary of concomitant medication use during the study for all medications taken by at least 5.0% in any cohort, by PT.

A listing of concomitant medications will be provided.

5.3 Study treatment exposure and compliance

5.3.1 Exposure

The duration of treatment (exposure) is defined as the time from start of dosing of Macitentan 10 mg (for the Macitentan 10 mg DB/OL mg cohort it is from STRT302, for the Macitentan 10 mg OL cohort it is from STRT303) until EOT inclusive, regardless of treatment interruptions.

Duration of treatment exposure will be calculated by cohort as follows:

Duration (days) = EOT303 - STRT303 +1, for patients in the Macitentan 10 mg OL,

or

Duration (days) = max(EOT302, EOT303) - STRT302 +1, for patients in the Macitentan 10 mg DB/OL.

Duration (months) = Duration (days)/ 30.4375

5.3.2 Compliance with study treatment

Not Applicable

5.3.3 Study treatment discontinuation

Study treatment discontinuations include all patients, i.e., those who prematurely discontinued and those who completed treatment as per protocol, from eCRF study Drug log.

Reasons for study treatment discontinuation are retrieved from the study drug log CRF pages in SERAPHIN DB or OL as appropriate and are coded using Actelion Study Drug Log dictionary.

5.4 Study discontinuation

Study completion/discontinuation is collected in the eCRF study completion page.

5.5 Efficacy variables

5.5.1 Long term survival

Time to death (TTD; in months) in the two cohorts is defined as follows:

For the Macitentan 10 mg OL cohort:

TTD (in days) and censoring flag (CENS) will be derived using the dates defined as:

- **TTD = DOD - STRT303 and CENS = 0** for patients who died,
- **TTD = LCTC - STRT303 and CENS = 1** for patients who did not die.

For the Macitentan 10 mg DB/OL cohort:

- **TTD = DOD - STRT302** and **CENS = 0** for patients who died,
- **TTD = LCTC - STRT302** and **CENS = 1** for patients who did not die.

For both cohorts

TTD (in months) = TTD (in days) / 30.4375.

Patients censored will be those who did not die prior to study closure.

5.6 Safety variables

AEs are coded using MedDRA v.21.0. For imputation of AE onset/resolution date, refer to Section 11.

5.6.1 Adverse events

5.6.1.1 Treatment-emergent adverse events

Treatment-emergent adverse events (TEAEs) are defined as AEs occurring during Macitentan OL treatment period (defined in section 10) for the Macitentan 10 mg OL cohort and during the Macitentan DB/OL treatment period (defined in section 10) for the Macitentan 10 mg DB/OL cohort (see section 10), with onset date ≥ start date (STRT302 for Macitentan 10 mg [DB/OL], STRT303 for Macitentan 10 mg [OL]), and up to 28 days (inclusive) after EOT. Note: if AEs are recorded before STRT303, these AEs will not be included for Macitentan 10 mg (OL) cohort.

5.6.1.2 Frequency of treatment-emergent adverse events

Treatment-emergent AEs reported more than once by a patients will be counted only once in the frequency tables.

In the event that the reported TEAE is assigned to several PT, patients will be counted for each individual PT.

5.6.1.3 Intensity of treatment-emergent adverse events

The categories of intensity are defined as follows:

- Mild
- Moderate
- Severe

For TEAEs reported more than once for a patient within a specified analysis time period but with different intensities, the worst intensity is considered (i.e. severe). If intensity is missing, the event will be considered to be severe.

5.6.1.4 Relationship of treatment-emergent adverse events

Relationship to study treatment is defined as ‘related’ or ‘not related’ in the opinion of the investigator. For TEAEs reported more than once for a patients within the same time period, the worst relationship will be used (i.e. 'related'). Adverse events with missing relationships will be considered in any analysis to be ‘related’.

5.6.2 Deaths

Cause of death is derived as collected on the disposition CRF page. There can be more causes of death recorded per patient. All reported causes of death will be used.

5.6.3 Serious adverse events

SAEs refer to AEs qualified as “serious” by the investigator on the CRF AE page(s). If seriousness information is missing, then AEs will be summarized as ‘Serious AEs’ (the worst-case scenario).

5.6.4 Adverse events leading to discontinuation of study treatment

Adverse events leading to discontinuation of study treatment are those with an action taken with study drug of "permanently discontinued" recorded on the CRF AE page.

5.6.5 Other significant adverse events

AEs of special interest are defined using selection of PTs (Actelion Internal MedDRA Query). The selection is defined from medical review of terms in the MedDRA v. 21.0 dictionary and where applicable, Standardized MedDRA Queries (SMQs) were used (see SMQ Introductory Guide Version 19.1: September 2016 – MMSO-DI-6226-19.1.0). The full definition is included in Appendix C.

The following groups of AEs of special interest will be summarized:

- liver abnormalities,
- edema,
- anemia/ hemoglobin decrease,
- hypotension.

5.6.6 Vital signs and body weight

Not Applicable

5.6.7 Electrocardiogram

Not Applicable

5.6.8 Laboratory

All available laboratory data collected at local and central laboratory will be used for deriving laboratory abnormalities.

Baseline laboratory values are defined as the latest values recorded before or on the date of first dose of Macitentan for DB/OL and for OL before or on the date of first dose of Macitentan in OL. Treatment-emergent values are defined as post-baseline values occurring within EOT+28 days and will be considered in the tables.

5.6.8.1 Hematology and blood chemistry

Hematology and blood chemistry tests include hemoglobin, hematocrit, platelet, leukocyte, and erythrocyte counts, liver aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, creatinine, urea, glucose, sodium, potassium and albumin.

Marked laboratory abnormalities are defined according to Actelion internal guidelines for individual parameters (see Table).

Table 5 Laboratory Abnormalities

Parameter	***LL marked***	***LLL marked***	***HH marked***	***HHH marked***
Hemoglobin	< 100 g/L	< 80 g/L	post-baseline > (baseline + 20 g/L)	post-baseline > (baseline + 40 g/L)
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
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
Total Bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Creatinine	NA	NA	> 1.5 × ULN	> 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
Albumin	< 30 g/L	< 20 g/L	NA	NA

* Also HHHH as > 8 × ULN

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

5.6.8.2 Abnormal liver tests (including unscheduled visits)

Hepatic abnormality criteria are specified below:

- (ALT ≥ 3 × upper limit of normal [ULN]) **OR** (AST ≥ 3 × ULN)
- (ALT ≥ 5 × ULN) **OR** (AST ≥ 5 × ULN)
- (ALT ≥ 8 × ULN) **OR** (AST ≥ 8 × ULN)
- Total Bilirubin ≥ 2 × ULN
- {(ALT ≥ 3 × ULN) **OR** (AST ≥ 3 × ULN)} **AND** (Total Bilirubin ≥ 2 × ULN at any time)

For each patient, the worst treatment-emergent abnormal value (i.e., the highest ALT, AST or Total Bilirubin values) will be considered and assigned to the appropriate category (may be more than one category per patient).

5.6.8.3 Incidence of abnormal hemoglobin values

Hemoglobin (Hgb) abnormalities are specified as:

- Hgb ≤ 80 g/L
- Hgb ≤ 100 g/L
- Hgb decrease from baseline ≥ 20 g/L
- Hgb decrease from baseline ≥ 50 g/L

For each patient, the worst treatment-emergent abnormal value (i.e., the lowest Hgb value) will be considered and assigned to the appropriate category (may be more than one category per patient).

Hgb abnormalities for increase from baseline are specified as:

- Post-baseline Hgb > (baseline + 20 g/L)
- Post-baseline Hgb > (baseline + 40 g/L)

For each patient, the worst treatment-emergent abnormal value (i.e., the highest Hgb value) will be considered and assigned to the appropriate category (may be more than one category per patient).

6 DEFINITION OF PROTOCOL DEVIATIONS IN AC-055-303

Protocol deviations will be reported as per Appendix E for the Macitentan 10 mg OL cohort.

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 Safety analysis set

The safety analysis set (SAF) will include all patients who received at least one dose of Macitentan 10 mg. All summaries described in this SAP will be presented on the SAF. Safety population will consist of the 2 cohorts described below.

7.1.1.1 Macitentan 10 mg OL cohort

This cohort includes 550 patients enrolled to the AC -055-303/SERAPHIN OL (regardless of the randomized treatment in SERAPHIN DB). As this group is heterogenous (initially the patients were randomized to different treatment regimens), so in addition to Overall, it will be further analyzed by randomization groups:

- Placebo DB/Macitentan 10 mg OL (183 patients)
- Macitentan 3 mg DB/Macitentan 10 mg OL (185 patients)
- Macitentan 10 mg DB/Macitentan 10 mg OL (182 patients)

7.1.1.2 Macitentan 10 mg DB/OL cohort

This cohort includes 242 patients initially randomized to Macitentan 10 mg SERAPHIN DB. For this group of patients, information collected during SERAPHIN DB and SERAPHIN OL will be pooled within patient, meaning that the data from the same patients randomized in SERAPHIN DB will be concatenated with their data from the OL extension study (SERAPHIN OL).

7.2 Usage of the analysis set

Table 6 Summaries by Analyses Cohorts.

Summaries and analyses	Macitentan 10 mg DB/OL (N = 242)	Macitentan 10 mg OL			
		Placebo DB/ Macitentan 10 mg OL (N = 183)	Macitentan 3 mg DB/ Macitentan 10 mg OL (N =185)	Macitentan 10 mg DB/ Macitentan 10 mg OL (N = 182)	Macitentan 10 mg OL Total (N = 550)
Disposition of patients	Yes	Yes	Yes	Yes	Yes
Demographics and patient characteristics	Yes	Yes	Yes	Yes	Yes
Medical history of patients	No	No	No	No	No

Summaries and analyses	Macitentan 10 mg DB/OL (N = 242)	Macitentan 10 mg OL			
		Placebo DB/ Macitentan 10 mg OL (N = 183)	Macitentan 3 mg DB/ Macitentan 10 mg OL (N =185)	Macitentan 10 mg DB/ Macitentan 10 mg OL (N = 182)	Macitentan 10 mg OL Total (N = 550)
Concomitant Medication	Yes	Yes	Yes	Yes	Yes
Duration of Treatment exposure	Yes	Yes	Yes	Yes	Yes
Adverse events (AEs)	Yes	Yes	Yes	Yes	Yes
Serious Adverse Events (SAEs)	Yes	Yes	Yes	Yes	Yes
AEs of special interest* (as per Actelion Internal MedDRA Queries [AIMQ])	Yes	Yes	Yes	Yes	Yes
Deaths	Yes	Yes	Yes	Yes	Yes
AEs leading to permanent discontinuation of study treatment	Yes	Yes	Yes	Yes	Yes
Incidence of AEs over time	Yes	Yes	Yes	Yes	Yes
Incidence of abnormal liver test	Yes	Yes	Yes	Yes	Yes
Incidence of abnormal hemoglobin test	Yes	Yes	Yes	Yes	Yes
Time to Death (Survival Analysis using KM approach)	Yes	Yes	Yes	Yes	Yes

AE = adverse event, AIMQ = Actelion Internal MedDRA Query, DB = double-blind, KM = Kaplan-Meier approach, OL = open-label, SAE = serious adverse event, SMQ = standardized MedDRA query.
*AEs of special interest includes: liver abnormalities, anemia/ hemoglobin decrease, edema, hypotension.

8 DEFINITION OF SUBGROUPS

Not Applicable

9 GENERAL STATISTICAL METHODOLOGY

9.1 Overall testing strategy

Not Applicable

9.2 General rules for data presentations

Data will be listed by country, site and DB treatment group and OL overall. Data will be summarized by appropriate descriptive statistics:

- Number of non-missing observations, mean, standard deviation, minimum, median and maximum for continuous variables.
- Number of events, number of censored observations and Kaplan-Meier estimates of the survival function for time-to-event variables.
- Number of non-missing observations, number of missing observations and frequency with percentage per category for categorical variables.
- Absolute changes from baseline are defined as: post-baseline value minus baseline value, i.e., a positive sign indicates an increase as compared to baseline.
- A percentage (relative) change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100.

Data will be presented for cohorts defined in section 2.1 (Table 2).

9.3 Display of patients disposition, protocol deviations and analysis set

9.3.1 Subject disposition

The number of patients included in each cohort will be summarized by treatment received in DB/OL.

The number and percentage of patients in analysis populations will be reported per cohort: Macitentan 10 mg (DB/OL) cohort broken down by treatment received in OL (10 mg/None, 10 mg/10 mg) and overall, and Macitentan 10 mg (OL) broken down by DB randomization groups (Placebo/ 10 mg, 3 mg / 10 mg, 10 mg / 10 mg) and overall.

Patients who completed study treatment as per protocol, who prematurely discontinued study drug as well as the reason for study drug discontinuation, will be reported the same way.

The coded reasons (Actelion Study Drug Log dictionary) are displayed in the summary.

Additionally, study drug discontinuation rates adjusted on person-year of study duration will be summarized with associated 95% CL as detailed in section 10.4.

9.3.2 Protocol deviations

Protocol deviations will be reported as per Appendix E for the Macitentan 10 mg OL cohort.

PDs classified as "Important PD" will be summarized with a frequency table for SERAPHIN OL, the table should have columns corresponding to DB treatment group and total.

A listing of all protocol deviations in OL will be provided with a flag indicating whether the deviation is "Important PD".

A separate listing of all protocol deviations related to Covid-19 will be provided.

9.4 Analyses of patient characteristics

9.4.1 Demographics

For each cohort, demographics will be summarized descriptively. Macitentan 10 mg OL will be summarized Overall and per initial randomized treatment group.

9.4.2 Baseline disease characteristics

For each cohort baseline disease characteristics will be summarized descriptively. Macitentan 10 mg OL will be summarized overall and by initial randomized treatment arm.

9.4.3 Other baseline characteristics

For each cohort other baseline characteristics will be summarized descriptively. Macitentan 10 mg OL will be summarized overall and per initial randomized treatment group.

9.4.4 Medical history

Medical history will not be summarized for this CSR.

9.4.5 Previous and concomitant medications

For study reporting purposes, all therapies collected in the AC-055-303 (SERAPHIN OL) CRF page 105 will be reported in the patient listings with the appropriate flags for previous/concomitant status, started before/after EOT.

Study-treatment concomitant therapies will be summarized by therapeutic organ class and PT.

A summary of concomitant PAH therapy at baseline (for baseline DB and separately baseline OL) will be summarizing the number and percentages of patients taking at least one PAH therapy, i.e. at least one PDE-5 inhibitor, at least one prostanoids and will be also summarized for each PT in these classifications as per section 5.2.5.2.

Concomitant medications will be summarized by each cohort, presenting the numbers of patients and associated percentages having any concomitant medication, by PT presented

by descending frequency of the total macitentan OL cohort PT incidence. Multiple medications (PT) taken by a single patient will only be counted once.

The following summaries will be presented for each cohort:

- A summary of concomitant PAH therapy at baseline (for baseline DB and separately baseline OL) including the number and percentages of patients taking
    - at least one PAH therapy, i.e., at least one PDE-5 inhibitor, at least one prostanoid. Note: patients may receive more than one treatment and may be included in more than one treatment class.
- A summary of concomitant medication use at baseline of all medications taken by at least 5.0% patients in any cohort, by PT
- A summary of concomitant medication use during the study (at least 5.0% in any cohort), by PT.

A listing of concomitant medications will be provided.

9.5 Analysis of study treatment exposure and compliance

9.5.1 Exposure

Duration of treatment exposure for both cohorts, expressed in months, will be summarized descriptively. The distribution of exposure time by class intervals (in 6-month increments e.g., < 6 months, 6 – < 12 months, 84 – < 90 months, until the end of study) will be also tabulated to show the number and percentage of patients in each class interval. In addition, patient year exposure is displayed and is derived as the duration of exposure each patient received treatment in days, as defined above, divided by 365.25.

A listing of duration of Macitentan exposure and reasons for study drug discontinuation will be provided for the Macitentan 10 mg OL cohort (overall and by initial randomization).

9.5.2 Compliance with study treatment

Not applicable

9.6 Analysis of the exploratory efficacy variable(s)

9.6.1 Hypothesis and statistical model

Not applicable - the study is descriptive.

9.7 Analysis of safety variables

All safety analyses will be presented for Macitentan 10 mg OL overall and by randomization group, as well as for the Macitentan 10 mg DB/OL cohort.

All safety data will be included in listings, with flags for treatment-emergent and quantitative abnormalities, where appropriate (separately for initial randomization in DB groups).

9.7.1 Adverse events

For all dosed patients all AEs captured from signature of informed will be reported in the patient listings.

A table presenting an overall summary of the proportion of patients with at least one treatment-emergent adverse event, one treatment-emergent AE of special interest, one treatment-emergent AE leading to treatment discontinuation, one treatment-emergent SAE, one treatment-emergent SAE with fatal outcome and the proportion of deaths will be provided.

Treatment-emergent AEs will be summarized by presenting the number and percentage of patients having any AE, having an AE in each primary system organ class (SOC), and having each individual AE (by PT) by descending PT frequency and separately by descending SOC/PT.

Exposure adjusted incidence rates will be also tabulated with two-sided 95% CLs (using method 1 and separately method 2).

Treatment-emergent AEs related to study drug will be summarized by presenting the number and percentage of patients having any AE, having an AE in each primary SOC, and having each individual AE (by PT) by descending PT frequency and separately by descending SOC/PT.

Treatment-emergent AEs will be also summarized by worst intensity by presenting the number and percentage of patients having any AE, having an AE in each primary SOC, and having each individual AE (by PT) by descending PT frequency and separately by descending SOC/PT.

9.7.2 Deaths, other serious adverse events

9.7.2.1 Death

Data for deaths will be summarized for both cohorts as below.

The number and percentage of treatment-emergent deaths will be presented from study start up to EOT+28 days. The number of deaths after EOT+28 days will be presented separately. In addition a summary of all deaths up to the study closure will be summarized.

Cause of death will be tabulated by SOC (with patients counted once within each SOC), and separately by PT (with patients counted once for each PT). SOC and PT will be presented by descending frequency in the OL cohort.

Exposure adjusted incidence rates will be also tabulated with two-sided 95% CLs.

A listing of all deaths (i.e., treatment-emergent and non-treatment-emergent events) is provided. Treatment-emergent deaths are flagged.

9.7.2.2 Time to death

An analysis for survival up to study closure will be done, with end of study defined on a study basis (i.e. the data cut corresponding to data base lock).

For both cohorts, the proportion of patients surviving will be estimated by the Kaplan-Meier (KM) product-limit method and summarized for each group at pre-specified time-points (i.e., Day 0/Baseline, Month 6, Month 12, etc.), presenting number of patients at risk, number of patients with event (%), number of patients censored (%), KM estimates, and two-sided 95% CLs for the KM estimates. The standard error of the KM estimate will be calculated using Greenwood's formula [Collett 1994].

KM plot for time to death will be provided and will be truncated at the time when less than 10% of the patients within the treatment group are still at risk [Pocock 2002] or up to 108 months timepoint, whichever comes later.

The median time to death will be estimated from the KM curves, with corresponding 25% and 75% percentiles and associated 95% confidence intervals using the method of Brookmeyer [Brookmeyer 1982].

The corresponding listing of time to death will be provided.

Summary of study follow-up time will be summarized.

Details regarding how time to death is calculated are given in Section 5. SAS code examples are given in Appendix F.

9.7.2.3 Serious adverse events

The number and percentage of patients experiencing at least one serious TEAE will be presented by descending within each SOC /PT and separately descending PT frequency. Exposure adjusted incidence rates will be tabulated with two-sided 95% CLs.

The number and percentage of patients experiencing at least one SAE after study drug termination will be summarized separately.

A listing of all SAEs (i.e., treatment-emergent and non-treatment-emergent events) will be provided for each analysis set. Serious TEAEs are flagged.

9.7.2.4 Adverse events leading to study treatment discontinuations

Adverse events leading to study treatment discontinuation will be described similarly as the SAEs

9.7.2.5 Other significant adverse events

The number and percentage of patients experiencing at least one TEAE of special interest will be presented by descending PT frequency for each AE of special interest.

The summaries include the exposure-adjusted incidence rates with associated 95% CLs.

Patient listing of AEs of special interest will be provided.

9.7.3 Laboratory tests

Absolute values and change from baseline values of all laboratory parameters described in section 5.6.8.1 will be summarized by visit. Time windows of +/- 15 days will be used as per Table 7.

Table 7 Time windows for all assessments up to EOT+28 days

Mapping of visits LFTs:	Study day (nominal value)	Lower Limit study day	Upper Limit study day
Month 1	30	2	45
Month 2	60	46	75
Month 3	90	76	105
Month 4	120	106	135
Month 5	150	136	165
Month 6	180	166	195
Month 7	210	196	225
Month 8	240	226	255
Month 9	270	256	285
Month 10	300	286	315
Month 11	330	316	345
Month 12	360	346	375
Month 13	390	376	405
Month 14	420	406	435
Month 15	450	436	465
Month 16	480	466	495
Month 17	510	496	525
Month 18	540	526	555

Mapping of visits LFTs:	Study day (nominal value)	Lower Limit study day	Upper Limit study day
Month 19	570	556	585
Month 20	600	586	615
Month 21	630	616	645
Month 22	660	646	675
Month 23	690	676	705
Month 24	720	706	735
Month 25	750	736	765
Month 26	780	766	795
Month 27	810	796	825
Month 28	840	826	855
Month 29	870	856	885
Month 30	900	886	915
Month 31	930	916	945
Month 32	960	946	975
Month 33	990	976	1005
Month 34	1020	1006	1035
Month 35	1050	1036	1065
Month 36	1080	1066	1095
Month 37	1110	1096	1125
Month 38	1140	1126	1155
Month 39	1170	1156	1185
Month 40	1200	1186	1215
Month 41	1230	1216	1245
…			
Month X	X*30	X*30 - 14	X*30 +15
…			
Month 126	3780	3766	3795

Summary statistics of worst abnormalities post baseline will be provided for each parameter as described in Table 5 for Low abnormalities and high abnormalities separately.

A supportive listing of all laboratory data is provided with a flag for abnormal values.

9.7.4 Incidence of abnormal liver tests (including unscheduled visits)

Liver tests for ALT, AST, and total bilirubin will be presented using incidence (n [%]) with the two-sided 95% CLs based on Wald approximation, and tabulated for patients with abnormalities. Exposure adjusted incidence rates will be tabulated with two-sided 95% CLs.

A supportive listing will be provided for with all liver tests laboratory data collected. Treatment-emergent results will be flagged.

Using "evaluation of drug-induced serious hepatotoxicity" (eDISH) plots, graphical representations of total bilirubin versus ALT will be produced for each initial randomized treatment group and for Overall Macitentan 10 mg OL cohort to identify possible Hy's Law cases. The graph presents, for each patient, the peak total bilirubin × ULN against the peak ALT × ULN in the same reporting period, on a log10 scale. Two reference lines will be plotted identifying the 2 × ULN for total bilirubin and 3 × ULN for ALT. The peak is the maximum value from treatment start to last available assessment within the treatment period and up to EOT plus 28 days.

A supportive listing presents all liver test data over time for all patients in Hy's Law quadrant.

9.7.5 Incidence of abnormal hemoglobin values

Patient counts and percent (with corresponding two-sided 95% CLs based on the Wald method and using Poisson model with time as an offset variable) for the categories of Hgb abnormality occurring at any time post-baseline up to EOT + 28 days will be presented.

Exposure adjusted incidence will be tabulated with two-sided 95% CLs.

A supportive listing provides presents all hemoglobin values collected. Treatment-emergent results will be flagged.

9.7.6 Other laboratory parameters

All other laboratory parameters collected are listed.

10 GENERAL DEFINITIONS AND DERIVATIONS

10.1 Dates of interest

The dates of interest were defined in section "Definition of Variables".

10.2 Macitentan DB/OL treatment emergent period (for safety variables reporting)

The Macitentan DB/OL treatment-emergent period is defined as the period from the first intake of Macitentan to the Macitentan EOT date (max[EOT302, EOT303]) + 28 days.

For laboratory analyses, the Macitentan DB/OL treatment-emergent period defined above starts from the first administration of Macitentan.

10.3 Macitentan OL treatment emergent period (for safety variables reporting)

The Macitentan OL treatment-emergent period is defined as the period from **STRT303** up to the EOT303 + 28 days.

For laboratory analyses, the Macitentan OL treatment-emergent period defined above starts from Macitentan start date in OL.

10.4 Adjusted incidence rates

In order to account for differences in the duration of exposure of study treatment among the patient cohorts, incidence rates of AEs, SAEs, AEs leading to discontinuation, AESI, and deaths will be presented as adjusted for patient-years exposure (PYE).

There will be two slightly different methods:

Method 1: The same approach as in the original NDA submission in 2012 will be applied [D-12.548], where total treatment exposure for each patient is included in the calculation. This will be applied in order to make comparison versus the original submission.

Person-time will be calculated by summing the days of treatment duration (" EOT- STRT302 +1 OR EOT- STRT303 +1 as per section 5.3) for each patient.

PYE will be calculated by dividing the total patient time by 365.25 days.

The incidence rate for an AE per 100 person-years will be calculated by dividing the number of patients with AEs by the PYE and multiplying by 100.

Adjusted Incidence Rate = 100 x (Number of patients with at least one AE/PYE)

Method 2:

A similar approach as in the original NDA submission in 2012 but the treatment exposure will be calculated up to the first event for patients with events [Siddiqui 2009].The same as in the Method 1 except:

Person-time will be calculated:

i) by summing the days of treatment duration (EOT- STRT303 +1 as per section 5.3.1) for patients without events,

ii) by summing the days of treatment duration up to the start date of first event (min[date of first event, EOT] - STRT303] + 1) for patients with event,

iii) all other calculations for adjusted incidence rate follow the Method-1.

The adjusted incidence rate will be interpreted as the number of events occurring in 100-patient years. It is based on the assumption that the occurrences of a specific event are following an independent Poisson process, so the events occur with a constant rate over time. Hence, for each treatment group, the 95% Confidence Limit (CL) of the adjusted incidence rate will be computed using a Poisson regression model with log of time at risk as an offset (SAS PROC GENMOD, see Appendix B for code example).

Note for programming: For AEs, SAEs, AEs leading to discontinuation, AESI group level, and deaths, the overall adjusted event rates will be presented using method 1 (i.e. adjusted rate will not be presented for each PT, except for AEs, where will be presented overall and by SOC). Method 2 will be applied only for AEs and AESI group level.

11 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

The missing or incomplete dates for the variables defined below will be derived as follows:

1. Dates will be 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 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.
2. If a part expected to contain a number is not numeric, i.e., contains values such as for example ND, NA, --, ??, 2?, it is considered as missing.
3. If a part is missing, all other parts of a lower level are considered to be missing. This means that a ddmmyy date '21ND99' is considered as '----99'.
4. Missing parts are changed into acceptable non-missing values in a way depending on the type of date to be replaced.

'lower limit' and 'upper limit' refer to the minimum or maximum, respectively, of a possible date. For example, if 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 of different dates refer to the first or last date, respectively, when ordered in sequence. All other missing or incomplete data not mentioned below are treated as missing.

Type of date/time	Date/time is incomplete	Date/time is missing
Date of birth	Day missing: 15th of the month Day and month missing: 30th of June	No replacement

Type of date/time	Date/time is incomplete	Date/time is missing
EOT302	Use the earliest date between the: • upper limit • last contact date (LCTC) • date of death (if applicable) • treatment start date of 303-1	Use the earliest date between the: • 6 months after last available dispensing visit date, i.e., 180 days + randomization or Month 6 or Month 12 or Month 18, ... visit date • last contact date (LCTC) • date of death (if applicable) • Start treatment date of 303-1
EOT303	Use the earliest date between the: • upper limit • last contact date (LCTC) • date of death (if applicable)	Use the earliest date between the: • last contact date (LCTC) • date of death (if applicable)
DOD - Date of death	Use the lower limit if day is missing	
EOS303	Use the earliest date between the: • upper limit • date of death (if applicable)	
AE resolution date	The upper limit	No approximation, the AE is considered as ongoing.

Type of date/time	Date/time is incomplete	Date/time is missing
AE onset date	If the end date of the AE is not before the start of study treatment, and if the study treatment start falls in the range of possible dates, it is the study treatment start date. In all other cases, it is the lower limit. Of note, treatment start date is STRT302 for Macitentan 3 mg or 10 mg (DB/OL) and STRT303 for Macitentan 10 mg (OL).	The earlier of the end date of the AE and the start of study treatment (STRT302 for Macitentan 3 mg or 10 mg [DB/OL] and STRT303 for macitentan 10 mg [OL]).
Previous/ concomitant medication start date	Lower limit except when: Not tagged as ongoing at baseline AND Medication stop date not collected or with the upper limit after study drug start AND The treatment start day falls in the range of possible dates. In which case it is the study drug start day	No replacement, the medication is considered to have started before the study
Previous/ concomitant medication end date	Note that Medication stop date will not be imputed; however the upper limit may be used in determining the medication start date derivation.	No replacement

Type of date/time	Date/time is incomplete	Date/time is missing
AE resolution time	Time partially entered not allowed (considered as missing)	Taken as "23:59" if the corresponding AE resolution date is not missing, otherwise no replacement

Notes:

- Patient PPD in Macitentan 10 mg (DB/OL) group was considered as having no PAH therapy at baseline in analysis of DB data in 2012, based on a rule that if the end date was partial and upper limit of that end date was after the study drug start date and the tick box ongoing at baseline was not ticked the medication was ended before the study start date. This patient has a record of Sildenafil with a start date of PPD ' and end date of PPD ' and a study drug start date of 'PPD '. "ongoing at baseline" is not ticked however Month of start date is after the study drug start date. This medication is considered as ongoing at baseline.

- Patient PPD in Macitentan 3 mg (DB/OL) group (Macitentan start date PPD) was considered as having no PAH therapy at baseline in analysis of DB data in 2012 (SILDENAFIL/ Start date=PPD '/ End Date=PPD '). This patient has a conflicting record of SILDENAFIL collected during the OL phase (SILDENAFIL/ Start date='PPD '/ End Date='PPD). The patient is considered as having no PAH therapy at baseline for DB.

12 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

12.1 Patients disposition

Output name	Display	Title (Description)	Analysis set(s)
Table 1	T	Number of Patients in the different patient cohorts	SAF
Table 2	T	Number of Patients in the different patient cohorts and Reasons for Study Drug Discontinuation	SAF

T=Summary table, L= Listing, F=Figure

12.2 Protocol deviations

Output name	Display	Title (Description)	Analysis set(s)
Table 3	T	Summary of Important protocol deviations.	Macitentan 10 mg OL
Listing 1	L	All protocol deviations	Macitentan 10 mg OL
Listing 1.1	L	Protocol deviations related to Covid-19	Macitentan 10 mg OL

12.3 Patients characteristics

12.3.1 Demographics and Patient Characteristics

Output name	Display	Title (Description)	Analysis set(s)
Table 4	T	Summary of Demographic and Patient Characteristics	SAF

12.3.2 Previous and concomitant therapies

Output name	Display	Title (Description)	Analysis set(s)
Table 5	T	Summary of concomitant PAH therapy (for baseline DB and separately baseline OL)	SAF
Table 6	T	Summary of concomitant medication use at baseline (at least 5% in any cohort), by preferred term	SAF
Table 7	T	Summary of concomitant medication use during the study (at least 5% in any cohort), by preferred term	SAF
Listing 2	L	Patient listing of concomitant medications	SAF
Listing 3	L	Discrepancies in previous and concomitant medications	SAF

12.4 Study treatment exposure and compliance

12.4.1 Exposure

Output name	Display	Title (Description)	Analysis set(s)
Table 8	T	Summary of duration of Exposure to Study Drug	SAF
Listing 4	L	Patient listing of exposure and reasons for study drug discontinuation	SAF

12.5 Safety analyses

12.5.1 Adverse events

Output name	Display	Title (Description)	Analysis set(s)
Table 9	T	Proportion of patients with AEs, AEs of special interest, SAEs, SAEs with fatal outcome, AEs leading to permanent study drug discontinuation and number of patients who died from treatment start up to EOT+28 days	SAF
Table 10	T	Proportion of patients with AEs occurring from treatment start up to EOT+28 days by PT	SAF
Table 11	T	Proportion of patients with AEs occurring from treatment start up to EOT+28 days by SOC and by PT	SAF
Table 12	T	Proportion of patients with AEs related to study drug occurring from treatment start up to EOT+28 days by PT	SAF
Table 13	T	Proportion of patients with AEs related to study drug occurring from treatment start up to EOT+28 days by SOC and by PT	SAF
Table 14	T	Proportion of patients with AEs by severity occurring from treatment start up to EOT+28 days by PT	SAF
Table 15	T	Proportion of patients with AEs by severity occurring from treatment start up to EOT+28 days by SOC and by PT	SAF
Listing 5	L	Patient listing of all adverse events	SAF

12.5.2 Deaths

Output name	Display	Title (Description)	Analysis set(s)
Table 16	T	Deaths occurring from treatment start up to EOT+28 days by cause (by SOC and by PT)	SAF
Table 17	T	Deaths occurring from treatment start up to EOT+28 days by cause (by PT)	SAF
Table 18	T	Deaths occurring after EOT+28 days (by PT)	SAF
Table 19	T	Deaths occurring after EOT+28 days (by SOC and by PT)	SAF
Table 20	T	Deaths occurring from treatment start up to the study closure by cause (by PT)	SAF
Table 21	T	Deaths occurring from treatment start up to the study closure by cause (by SOC and by PT)	SAF
Listing 6	L	All deaths	SAF

12.5.3 Time to death

Output name	Display	Title (Description)	Analysis set(s)
Table 22	T	Summary of Time to Death up to the study closure	SAF
Listing 7	L	Patient listing of time to deaths up to study closure	SAF
Table 23	T	Summary of study follow up time - reverse Kaplan Meier method	SAF
Figure 1.1	F	Kaplan Meier curve of Time to Death up to the study closure	Macitentan 10 mg (DB/OL)
Figure 1.2	F	Kaplan Meier curve of Time to Death up to the study closure	Macitentan 10 mg (OL)

Output name	Display	Title (Description)	Analysis set(s)
Figure 1.3	F	Kaplan Meier curve of Time to Death up to the study closure by randomization group.	Macitentan 10 mg (OL)

12.5.4 Serious adverse events

Output name	Display	Title (Description)	Analysis set(s)
Table 24	T	Proportion of patients with SAEs occurring from treatment start up to EOT+28 days by PT	SAF
Table 25	T	Proportion of patients with SAEs occurring from treatment start up to EOT+28 days by SOC and by PT	SAF
Table 26	T	Proportion of patients with SAEs occurring after study drug termination by PT	SAF
Table 27	T	Proportion of patients with SAEs occurring after study drug termination by SOC and by PT	SAF
Listing 8	L	Patient listing of all SAEs	SAF

12.5.5 Adverse events leading to treatment discontinuation

Output name	Display	Title (Description)	Analysis set(s)
Table 28	T	Proportion of patients with treatment-emergent adverse events leading to permanent study drug discontinuation by PT	SAF
Table 29	T	Proportion of patients with treatment-emergent adverse events leading to permanent study drug discontinuation by SOC and by PT	SAF

Output name	Display	Title (Description)	Analysis set(s)
Listing 9	L	Treatment-emergent adverse events leading to permanent study drug discontinuation	SAF

12.5.6 Other significant adverse events

Output name	Display	Title (Description)	Analysis set(s)
Table 30	T	Proportion of Patients with AEs of special interest occurring from treatment start up to EOT+28 days by PT: <SMQ X>	SAF
Listing 10	L	Averse events of special interest <SMQ X>	SAF

12.6 Laboratory tests

Output name	Display	Title (Description)	Analysis set(s)
Table 31	T	Summary of absolute and absolute change for laboratory parameters from Macitentan 10 mg DB baseline, by analysis visit - Macitentan 10 mg (DB/OL)	SAF
Table 32	T	Summary of absolute and absolute change for laboratory parameters from Macitentan 10 mg OL baseline, by analysis visit - Macitentan 10 mg (OL)	SAF
Table 33	T	Proportion of patients with incidence of all laboratory abnormalities occurring from treatment start up to EOT+28 days	SAF
Table 34	T	Proportion of patients with Liver tests Abnormalities occurring from treatment start up to EOT+28 days	SAF
Listing 11	L	Abnormal Liver tests (ALT or AST > 3 x ULN) or total bilirubin > 2 x ULN	SAF

Figure 2	F	Peak Total Bilirubin vs. peak ALT (eDish plot) (one per cohort)	SAF
Listing 12	L	Patient listing of liver test data for all patients in Hy's Law quadrant over time.	SAF
Table 35	T	Proportion of patients with incidence of hemoglobin abnormalities occurring from treatment start up to EOT+28 days	SAF
Listing 13	L	Hemoglobin abnormalities (Hgb ≤ 100 g/L)	SAF
Listing 14	L	Patient listing of all other abnormalities	SAF
Listing 15	L	Patient listing of all laboratory data	SAF

13 REFERENCES

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14 APPENDICES

Appendix A Protocol Synopsis AC-055-303 (SERAPHIN OL)

TITLE	Long-term single-arm open-label extension study of the SERAPHIN study, to assess the safety and tolerability of macitentan/ACT-064992 in patients with symptomatic pulmonary arterial hypertension.					
ACRONYM	SERAPHIN OL: **S**tudy with an **ERA** in **P**ulmonary arterial **H**ypertension to **I**mprove cli**N**ical outcome (Open Label).					
OBJECTIVES	To assess the long-term safety and tolerability of ACT-064992 in patients with symptomatic pulmonary arterial hypertension (PAH).					
DESIGN / PHASE	Multicenter, open-label (OL) extension, single-arm, Phase III study					
STUDY PLANNED DURATION	**First patient First visit**	Q4/07	**Last patient First visit**	Q1/12	**Last patient Last visit**	Open
CENTERS / COUNTRIES	Approximately 180 centers in about 40 countries.					
PATIENTS / GROUPS	Up to 699 patients in one group.					
INCLUSION CRITERIA	• Signed informed consent prior to initiation of any study-mandated procedure. • Patients with pulmonary arterial hypertension and having completed the event-driven study, AC-055-302/SERAPHIN, or Patients who have experienced a clinical worsening of PAH in AC-055-302/SERAPHIN and for whom a written approval to roll over into this study has been obtained from the Sponsor. • Women of childbearing potential must have a negative pre-treatment serum pregnancy test and must use a reliable method of contraception during study treatment and for at least 28 days after study treatment termination.					

EXCLUSION CRITERIA	• Any major violation of protocol AC-055-302/SERAPHIN. • Pregnancy or breast-feeding. • AST and/or ALT > 3 times the upper limit of the normal range. • Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence or psychiatric disease. • Known hypersensitivity to ACT-064992 or any of the excipients.

Appendix B Example SAS code for incidence rates and 95% CL

Note: time should be in years for GENMOD

```
** example code to show derivation of rate and CI based on dummy data ** ;
** Create dummy data **;
 data aA;
  tot_eve=0;
  tot_time=0;
  do pn=1 to 110;
    time=ranuni(546546)*1000; ** time to event**;
    eve=(ranuni(5454)<.10);   ** event or censor **;
    tot_eve+eve;
    tot_time+time;
    l_time=log(time/365.25);
    if pn=110 then do;
      incidence=100*tot_eve/(tot_time/365.25); **incidence rate **;
    end;
    output;
  end;
run;

proc genmod data=aa;
  model eve= / dist=poisson link=log offset=l_time; /*** here is the exposure time in offset***/
  output out=out p=pcount xbeta=xb stdxbeta=std;
  ods output ParameterEstimates=param;
run;

data predrates;
  set out;
  obsrate=eve/time;        /* observed rate */
  lograte=xb-l_time;
  prate=100*exp(lograte);   /* predicted rate */
  lcl=100*exp(lograte-probit(.975)*std); ** Lower Limit **;
  ucl=100*exp(lograte+probit(.975)*std); ** upper Limit **;
run;

** derivation also available in PARAM**;
data param2;
  set param(WHERE=(parameter=("Intercept")));
  prate=100*exp(estimate);
  lcl=100*exp(LowerWaldCL);
  ucl=100*exp(UpperWaldCL);
run;
```

Appendix C Definition of AEs of special interest

1 LIVER ABNORMALITIES

AEs are included in this grouping if they contain an event PT within the 'Hepatic disorders' SMQ, including all of its sub-SMQs, with the exception of the 'Liver-related coagulation and bleeding disturbances' sub-SMQ and the PTs 'Ascites', 'Bacterascites', 'Biliary ascites', and 'Haemorrhagic ascites'[1], i.e., any of the following MedDRA PTs:

5'nucleotidase increased
Accessory liver lobe
Acquired hepatocerebral degeneration
Acute fatty liver of pregnancy
Acute graft versus host disease in liver
Acute hepatic failure
Acute hepatitis B
Acute hepatitis C
Acute on chronic liver failure
Acute yellow liver atrophy
Adenoviral hepatitis
Alagille syndrome
Alanine aminotransferase abnormal
Alanine aminotransferase increased
Alcoholic liver disease
Allergic hepatitis
Alloimmune hepatitis
Ammonia abnormal
Ammonia increased
Anorectal varices
Anorectal varices haemorrhage
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
AST/ALT ratio abnormal
Asterixis

[1] Excluded PTs: Ascites, Bacterascites, Biliary ascites, Haemorrhagic ascites, Acquired factor IX deficiency, Acquired factor VIII deficiency, Acquired factor XI deficiency, Acquired antithrombin III deficiency, Acquired protein S deficiency, Anti factor X activity abnormal, Anti factor X activity decreased, Anti factor X activity increased, Antithrombin III decreased, Blood fibrinogen abnormal, Blood fibrinogen decreased, Blood thrombin abnormal, Blood thrombin decreased, Blood thromboplastin abnormal, Blood thromboplastin decreased, Coagulation factor decreased, Coagulation factor IX level abnormal, Coagulation factor IX level decreased, Coagulation factor V level abnormal, Coagulation factor V level decreased, Coagulation factor VII level abnormal, Coagulation factor VII level decreased, Coagulation factor X level abnormal, Coagulation factor X level decreased, Hyperfibrinolysis, Hypocoagulable state, Hypofibrinogenaemia, Hypoprothrombinaemia, Hypothrombinaemia, Hypothromboplastinaemia, International normalised ratio abnormal, International normalised ratio increased, Protein C decreased, Protein S abnormal, Protein S decreased, Prothrombin level abnormal, Prothrombin level decreased, Prothrombin time abnormal, Prothrombin time prolonged, Prothrombin time ratio abnormal, Prothrombin time ratio increased, Thrombin time abnormal, Thrombin time prolonged.

Asymptomatic viral hepatitis
Autoimmune hepatitis
Benign hepatic neoplasm
Benign hepatobiliary neoplasm
Bile output abnormal
Bile output decreased
Biliary cirrhosis
Biliary fibrosis
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Bilirubin excretion disorder
Bilirubin urine present
Biopsy liver abnormal
Blood alkaline phosphatase abnormal
Blood alkaline phosphatase increased
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Blood cholinesterase abnormal
Blood cholinesterase decreased
Bromosulphthalein test abnormal
Cardiohepatic syndrome
Cerebrohepatorenal syndrome
Child-Pugh-Turcotte score abnormal
Child-Pugh-Turcotte score increased
Cholaemia
Cholangiosarcoma
Cholestasis
Cholestasis of pregnancy
Cholestatic liver injury
Cholestatic pruritus
Chronic graft versus host disease in liver
Chronic hepatic failure
Chronic hepatitis
Chronic hepatitis B
Chronic hepatitis C
Cirrhosis alcoholic
Coma hepatic
Complications of transplanted liver
Computerised tomogram liver abnormal
Congenital absence of bile ducts
Congenital cystic disease of liver
Congenital hepatic fibrosis
Congenital hepatitis B infection
Congenital hepatobiliary anomaly

Congenital hepatomegaly
Cryptogenic cirrhosis
Cystic fibrosis hepatic disease
Cytomegalovirus hepatitis
Deficiency of bile secretion
Diabetic hepatopathy
Dilatation intrahepatic duct congenital
Drug-induced liver injury
Duodenal varices
Fatty liver alcoholic
Focal nodular hyperplasia
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gallbladder varices
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased
Gastric variceal injection
Gastric variceal ligation
Gastric varices
Gastric varices haemorrhage
Gastrooesophageal variceal haemorrhage prophylaxis
Gianotti-Crosti syndrome
Glutamate dehydrogenase increased
Glycocholic acid increased
Glycogen storage disease type I
Glycogen storage disease type III
Glycogen storage disease type IV
Glycogen storage disease type VI
Graft versus host disease in liver
Granulomatous liver disease
Guanase increased
Haemangioma of liver
Haemorrhagic hepatic cyst
HBV-DNA polymerase increased
Hepaplastin abnormal
Hepaplastin decreased
Hepatectomy
Hepatic adenoma
Hepatic amoebiasis
Hepatic angiosarcoma
Hepatic artery flow decreased
Hepatic atrophy
Hepatic calcification
Hepatic cancer

Hepatic cancer metastatic
Hepatic cancer recurrent
Hepatic cancer stage I
Hepatic cancer stage II
Hepatic cancer stage III
Hepatic cancer stage IV
Hepatic candidiasis
Hepatic cirrhosis
Hepatic congestion
Hepatic cyst
Hepatic cyst infection
Hepatic cyst ruptured
Hepatic echinococciasis
Hepatic encephalopathy
Hepatic encephalopathy prophylaxis
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic failure
Hepatic fibrosis
Hepatic fibrosis marker abnormal
Hepatic fibrosis marker increased
Hepatic function abnormal
Hepatic gas gangrene
Hepatic haemangioma rupture
Hepatic hamartoma
Hepatic hydrothorax
Hepatic hypertrophy
Hepatic infection
Hepatic infection bacterial
Hepatic infection fungal
Hepatic infection helminthic
Hepatic infiltration eosinophilic
Hepatic lesion
Hepatic lymphocytic infiltration
Hepatic mass
Hepatic necrosis
Hepatic neoplasm
Hepatic pain
Hepatic sequestration
Hepatic steato-fibrosis
Hepatic steatosis
Hepatic vascular resistance increased
Hepatic venous pressure gradient abnormal
Hepatic venous pressure gradient increased

Hepatitis
Hepatitis A
Hepatitis A antibody abnormal
Hepatitis A antibody positive
Hepatitis A antigen positive
Hepatitis A virus test positive
Hepatitis acute
Hepatitis alcoholic
Hepatitis B
Hepatitis B antibody abnormal
Hepatitis B antibody positive
Hepatitis B core antibody positive
Hepatitis B core antigen positive
Hepatitis B DNA assay positive
Hepatitis B DNA increased
Hepatitis B e antibody positive
Hepatitis B e antigen positive
Hepatitis B reactivation
Hepatitis B surface antibody positive
Hepatitis B surface antigen positive
Hepatitis B virus test positive
Hepatitis C
Hepatitis C antibody positive
Hepatitis C core antibody positive
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C virus test positive
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis D
Hepatitis D antibody positive
Hepatitis D antigen positive
Hepatitis D RNA positive
Hepatitis D virus test positive
Hepatitis E
Hepatitis E antibody abnormal
Hepatitis E antibody positive
Hepatitis E antigen positive
Hepatitis E virus test positive
Hepatitis F
Hepatitis fulminant
Hepatitis G
Hepatitis H
Hepatitis infectious mononucleosis

Hepatitis mumps
Hepatitis neonatal
Hepatitis non-A non-B
Hepatitis non-A non-B non-C
Hepatitis post transfusion
Hepatitis syphilitic
Hepatitis toxic
Hepatitis toxoplasmal
Hepatitis viral
Hepatitis viral test positive
Hepatobiliary cancer
Hepatobiliary cancer in situ
Hepatobiliary cyst
Hepatobiliary disease
Hepatobiliary infection
Hepatobiliary neoplasm
Hepatobiliary scan abnormal
Hepatoblastoma
Hepatoblastoma recurrent
Hepatocellular carcinoma
Hepatocellular damage neonatal
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepato-lenticular degeneration
Hepatomegaly
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatosplenic abscess
Hepatosplenic candidiasis
Hepatosplenomegaly
Hepatosplenomegaly neonatal
Hepatotoxicity
Hereditary haemochromatosis
Herpes simplex hepatitis
Hyperammonaemia
Hyperbilirubinaemia
Hyperbilirubinaemia neonatal
Hypercholia
Hypertransaminasaemia
Hypoalbuminaemia
Icterus index increased
Immune-mediated hepatitis
Increased liver stiffness
Intestinal varices

Intestinal varices haemorrhage
Intrahepatic portal hepatic venous fistula
Ischaemic hepatitis
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Jaundice neonatal
Kayser-Fleischer ring
Kernicterus
Leucine aminopeptidase increased
Liver ablation
Liver abscess
Liver and pancreas transplant rejection
Liver carcinoma ruptured
Liver dialysis
Liver disorder
Liver function test abnormal
Liver function test decreased
Liver function test increased
Liver induration
Liver injury
Liver iron concentration abnormal
Liver iron concentration increased
Liver operation
Liver palpable
Liver sarcoidosis
Liver scan abnormal
Liver tenderness
Liver transplant
Liver transplant failure
Liver transplant rejection
Lupoid hepatic cirrhosis
Lupus hepatitis
Magnetic resonance imaging liver abnormal
Magnetic resonance proton density fat fraction measurement
Minimal hepatic encephalopathy
Mitochondrial aspartate aminotransferase increased
Mixed hepatocellular cholangiocarcinoma
Mixed liver injury
Model for end stage liver disease score abnormal
Model for end stage liver disease score increased
Molar ratio of total branched-chain amino acid to tyrosine
Multivisceral transplantation
Neonatal cholestasis

Neonatal hepatomegaly
Nodular regenerative hyperplasia
Nonalcoholic fatty liver disease
Non-alcoholic steatohepatitis
Non-cirrhotic portal hypertension
Ocular icterus
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Parenteral nutrition associated liver disease
Partial splenic embolisation
Perihepatic discomfort
Perinatal HBV infection
Peripancreatic varices
Periportal oedema
Peritoneal fluid protein abnormal
Peritoneal fluid protein decreased
Peritoneal fluid protein increased
Peritoneovenous shunt
Pneumobilia
Polycystic liver disease
Porphyria acute
Porphyria non-acute
Portal fibrosis
Portal hypertension
Portal hypertensive colopathy
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal pyaemia
Portal shunt
Portal shunt procedure
Portal tract inflammation
Portal vein cavernous transformation
Portal vein dilatation
Portal vein flow decreased
Portal vein pressure increased
Portal venous system anomaly
Portopulmonary hypertension
Primary biliary cholangitis
Progressive familial intrahepatic cholestasis
Radiation hepatitis
Regenerative siderotic hepatic nodule
Renal and liver transplant
Retinol binding protein decreased
Retrograde portal vein flow
Reye's syndrome

Reynold's syndrome
Schistosomiasis liver
Small-for-size liver syndrome
Spider naevus
Splenic varices
Splenic varices haemorrhage
Splenorenal shunt
Splenorenal shunt procedure
Spontaneous intrahepatic portosystemic venous shunt
Steatohepatitis
Stomal varices
Subacute hepatic failure
Sugiura procedure
Sustained viral response
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
Urobilinogen urine decreased
Urobilinogen urine increased
Varices oesophageal
Varicose veins of abdominal wall
Viral hepatitis carrier
Weil's disease
White nipple sign
Withdrawal hepatitis
X-ray hepatobiliary abnormal
Yellow skin
Zieve syndrome

2 EDEMA

AEs are included in this grouping if they contain an event with the MedDRA Preferred Term "Pulmonary congestion" or if within the SMQ "Haemodynamic oedema, effusions and fluid overload (SMQ)" with the exception of PTs containing "site", ie the case will be included if it contains an event with any of the following MedDRA PTs:

Acute pulmonary oedema
Amyloid related imaging abnormalities
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
Amyloid related imaging abnormality-oedema/effusion
Ascites
Bone marrow oedema

Bone marrow oedema syndrome
Bone swelling
Brain oedema
Bronchial oedema
Capillary leak syndrome
Cerebral oedema management
Cervix oedema
Circumoral swelling
Compression garment application
Cytotoxic oedema
Durotomy procedure
Effusion
Elephantiasis nostras verrucosa
Extensive swelling of vaccinated limb
Fluid overload
Fluid retention
Gallbladder oedema
Gastrointestinal oedema
Generalised oedema
Gestational oedema
Gravitational oedema
Heat oedema
Hydraemia
Hydrothorax
Hydrovarium
Hypervolaemia
Hypoosmolar state
Joint effusion
Joint swelling
Lipoedema
Localised oedema
Lymphoedema
Modified Rodnan skin score abnormal
Mouth swelling
Muscle oedema
Muscle swelling
Myocardial oedema
Negative pressure pulmonary oedema
Non-cardiogenic pulmonary oedema
Oedema
Oedema blister
Oedema due to cardiac disease
Oedema due to hepatic disease
Oedema due to renal disease
Oedema mucosal

Oedema neonatal
Oedema peripheral
Oedematous kidney
Oesophageal oedema
Oropharyngeal oedema
Pelvic fluid collection
Pericardial effusion
Perinephric collection
Perinephric oedema
Peripheral oedema neonatal
Peripheral swelling
Pleural effusion
Prevertebral soft tissue swelling of cervical space
Pulmonary congestion
Pulmonary oedema
Pulmonary oedema neonatal
Reexpansion pulmonary oedema
Retroperitoneal effusion
Retroperitoneal oedema
Scleroedema
Skin oedema
Skin swelling
Spinal cord oedema
Subdural effusion
Swelling
Testicular swelling
Vasogenic cerebral oedema
Visceral oedema

Excluded PTs
Administration site joint effusion
Administration site oedema
Administration site swelling
Application site joint effusion
Application site joint swelling
Application site oedema
Application site swelling
Catheter site oedema
Implant site oedema
Implant site swelling
Incision site oedema
Incision site swelling
Infusion site joint effusion
Infusion site joint swelling
Infusion site oedema
Infusion site swelling

Injection site joint swelling
Injection site oedema
Injection site swelling
Instillation site oedema
Medical device site joint effusion
Medical device site joint swelling
Puncture site oedema
Vaccination site joint effusion
Vaccination site joint swelling

3 ANEMIA/HEMOGLOBIN DECREASE

AEs are included in this grouping if they contain an event Preferred Term (PT) within either of the following Standardised MedDRA Queries (SMQs): 'Haematopoietic erythropenia', or 'Haematopoietic cytopenias affecting more than one type of blood cell' (with the exception of 2 unspecific PTs: 'Blood disorder', 'Blood count abnormal'), or if they contain an event with any MedDRA PT containing the text 'anaemia', i.e., any of the following MedDRA PTs:

Anaemia
Anaemia folate deficiency
Anaemia Heinz body
Anaemia macrocytic
Anaemia megaloblastic
Anaemia neonatal
Anaemia of chronic disease
Anaemia of malignant disease
Anaemia of pregnancy
Anaemia postoperative
Anaemia prophylaxis
Anaemia splenic
Anaemia vitamin B12 deficiency
Anaemia vitamin B6 deficiency
Aplasia pure red cell
Aplastic anaemia
Aspiration bone marrow abnormal
Autoimmune anaemia
Autoimmune aplastic anaemia
Autoimmune haemolytic anaemia
Autosomal recessive megaloblastic anaemia

Bicytopenia
Biopsy bone marrow abnormal
Blood incompatibility haemolytic anaemia of newborn
Blood loss anaemia
Blood loss anaemia neonatal
Bone marrow disorder
Bone marrow failure
Bone marrow infiltration
Bone marrow myelogram abnormal
Bone marrow necrosis
Bone marrow toxicity
Cardiac haemolytic anaemia
Cold type haemolytic anaemia
Congenital anaemia
Congenital aplastic anaemia
Congenital dyserythropoietic anaemia
Coombs negative haemolytic anaemia
Coombs positive haemolytic anaemia
Cytopenia
Deficiency anaemia
Erythroblast count abnormal
Erythroblast count decreased
Erythroid maturation arrest
Erythropenia
Erythropoiesis abnormal
Febrile bone marrow aplasia
Foetal anaemia
Full blood count decreased
Gelatinous transformation of the bone marrow
Haematocrit abnormal
Haematocrit decreased
Haematotoxicity
Haemoglobin abnormal
Haemoglobin decreased
Haemolytic anaemia
Haemolytic anaemia enzyme specific
Haemolytic icteroanaemia
Hand and foot syndrome secondary to sickle cell anaemia

Hereditary haemolytic anaemia
Hereditary sideroblastic anaemia
Hexokinase deficiency anaemia
Hyperchromic anaemia
Hypochromic anaemia
Hypoplastic anaemia
Immune-mediated pancytopenia
Iron deficiency anaemia
Leukoerythroblastic anaemia
Melanaemia
Microangiopathic haemolytic anaemia
Microcytic anaemia
Myelodysplastic syndrome
Myelodysplastic syndrome transformation
Myelofibrosis
Myeloid metaplasia
Nephrogenic anaemia
Normochromic anaemia
Normochromic normocytic anaemia
Normocytic anaemia
Pancytopenia
Panmyelopathy
Pernicious anaemia
Plasmablast count decreased
Primary myelofibrosis
Proerythroblast count abnormal
Proerythroblast count decreased
Protein deficiency anaemia
Pyruvate kinase deficiency anaemia
Red blood cell count abnormal
Red blood cell count decreased
Refractory anaemia with an excess of blasts
Refractory anaemia with ringed sideroblasts
Reticulocyte count abnormal
Reticulocyte count decreased
Reticulocyte percentage decreased
Reticulocytopenia
Scan bone marrow abnormal

Sickle cell anaemia
Sickle cell anaemia with crisis
Sideroblastic anaemia
Spherocytic anaemia
Spur cell anaemia
Warm type haemolytic anaemia

4 HYPOTENSION

AEs are included in this grouping if their coded PTs are included in the following list of PTs:

Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure orthostatic decreased, Blood pressure systolic decreased, Diastolic hypotension, Hypotension, Mean arterial pressure decreased, Orthostatic hypotension, Procedural hypotension.

Appendix D Discussion and further considerations of the applied statistical methods

NA

Appendix E Protocol deviation code list

Document Revision History:

TV-eFRM-10509_Protocol Violation Code

Appendix F. **Outputs and SAS code for KM estimates**

The LIFETEST SAS procedure in t-t2dth_sas.txt is used for the computation of the estimates. A selection of the relevant part of code to generate the results for the cohort Macitentan 10mg (DB/OL) is shown below for illustrative purposes with further elucidation for clarity:

```
data d1;
  set adam.addeath;
  where (saf1fl='Y' or saf2fl='Y');

proc sort data=d1 nodupkey;
  by usubjid cestdt;
run;

proc lifetest data=d1
    method=KM
    alphaqt=0.05
    CONFTYPE=loglog
    plots=survival(atrisk=0 to 126 by 6)
    outsurv=sci_1(rename=(_censor_=censor))
    timelist=0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120 126;
    time ttd1*cnsr(1) ;
    by pool1fl;
    where pool1fl='Y' and saf1fl='Y';
 run;
```

The key elements for the analysis are:
i) Dataset ADDEATH included in

ii) ADDEATH variables:
POOL1FL, SAF1FL for the selection of safety set in the cohort 10mg DB/OL data
POOL2FL, SAF2FL for the selection of safety set in the cohort 10mg OL data

TTD1 time to death in months for DB/OL cohort
TTD2 time to death in month for OL cohort
CNSR that is 0 for events and 1 for censoring

iii) Documentation: a full description of the datasets and variables including source and derivation is included in the define.xml and define.pdf

Document history

Version	Effective Date	Reason
Final 1.0	21-Dec-2020	