Actelion Pharmaceuticals Ltd

Statistical Analysis Plan - Part 1

A DUE Prospective, multi-center, double-blind, randomized, active-controlled, triple dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy

Protocol AC-077A301; Phase 3

ACT-064992D **(**Macitentan/Tadalafil**)**

Status:	Approved
Date:	26 March 2020
Prepared by:	Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutical NV
Document No.:	D-20.112

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

AMENDMENT HISTORY

Not applicable.

ABBREVIATIONS

6MWD	6-minute walk distance
6MWT	6-minute walk test
ADaM	Analysis Data Model
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomic and therapeutic Class
BMI	body mass index
CEC	Clinical Events Committee
CI	Cardiac index
CL	Confidence limit
CO	Cardiac output
CRF/eCRF	case report form/electronic case report form
CSR	Clinical Study Report
DB	Double-blind
DBL	Database lock
dPAP	Diastolic pulmonary artery pressure
d-SAP	Diastolic systemic artery pressure
DMC	Data Monitoring Committee
EDBT	End of Double-blind Treatment
e-DISH	Evaluation of Drug-Induced Serious Hepatotoxicity
EOLT	End of Open-Label Treatment
EOS	End of Study
EOT	End of Treatment
EOT-DB	End of treatment in double-blind treatment period
EOT-OL	End of treatment in open-label treatment period
EQ-5D-5L	Euro Quality of Life-5D-5L
EQ VAS	Euro Quality of Life Visual Analogue Scale
ER	Emergency room
ERA	Endothelin receptor antagonist
FAS	full analysis set
FDC	Fixed Dose Combination
GM	Geometric mean
GMR	Geometric mean ratio
HIV	Human immunodeficiency virus
IA	Interim Analysis
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
INC	inverse-normal combination
IRT	Interactive Response Technology
IXRS	Interactive voice/web response system
LC	Loose combination
LOQ	Limit of quantification
LS	Least Square
LVEDP	Left ventricular end diastolic pressure
M/M	Morbidity/Mortality
M/T	Macitentan/tadalafil
M49	Standard Country or Area Codes for Statistical Use
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary artery pressure
MPD	Major protocol deviation
mRAP	Mean right atrial pressure
NT-proBNP	N-terminal pro B-type natriuretic peptide
OL	Open-label

OLS	Open-label Set
OR	Odds ratio
PAH	Pulmonary arterial hypertension
PAH-SYMPACT™	Pulmonary Arterial Hypertension-Symptoms and Impact
PAPi	Pulmonary artery pulsatility index
PAWP	Pulmonary artery wedge pressure
PDE-5i	Phosphodiesterase type-5 inhibitor
PPS	per protocol set
PT	Preferred term
PVR	Pulmonary vascular resistance
QoL	Quality of Life
RCI	Repeated confidence interval
RHC	Right heart catheterization
RVSWI	Right ventricular stroke work index
S-FU	Safety follow-up
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	standard deviation
SDTM	Clinical Data Interchange Standards Consortium Study Data Tabulation
SI	International System
SOC	system organ class
sPAP	Systolic pulmonary artery pressure
SS	Safety Set
s-SAP	Systolic systemic artery pressure
SSG	statistical support group
TEAE	treatment-emergent adverse event
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WCC	World Care Clinical
WHO	World Health Organization
WHO FC	World Health Organization Functional Classification
WPAI©	Work Productivity and Activity Impairment©
WPAI©: GH	Work Productivity and Activity Impairment©: General Health

1. INTRODUCTION

This Statistical Analysis Plan (SAP) Part 1 describes the planned statistical data analyses for the Clinical Study Report (CSR) of the double-blind (DB) part of study AC-077A301. In addition, the plans for the interim analysis (IA) and for periodic safety reviews conducted by the Independent Data Monitoring Committee (IDMC) are described within this SAP. Both DB and open-label (OL) data will be reviewed by the IDMC.

Plans for the reporting of the combined DB and OL part will be described in a separate document, the SAP Part 2.

This SAP is based on the AC-077A301 protocol dated 12 August 2019 (D-19.237), case report form (CRF) Version 8.01 dated 5 December 2019, the Independent Review Charter Version 1.0 dated 19 July 2019 and Data Monitoring Committee (DMC) charter dated 1 July 2019.

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM). Source data are those provided by Actelion Clinical Development Data Management from Life Science Analytics Framework via a HERMES drop zone to STAR. All descriptive or formal statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise specified.

1.1. Trial Objectives

1.1.1. Primary objective(s)

This study has two co-primary objectives:

1. To evaluate the effect of the macitentan/tadalafil fixed dose combination (M/T FDC) vs macitentan 10 mg alone on pulmonary vascular resistance (PVR) at end of double-blind treatment (EDBT) in subjects with symptomatic World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) who are PAH-specific treatment-naïve or are currently being treated with an endothelin receptor antagonist (ERA) as monotherapy.
2. To evaluate the effect of the M/T FDC vs tadalafil 40 mg alone on PVR at EDBT in subjects with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or are currently being treated with a phosphodiesterase type-5 inhibitor (PDE-5i) as monotherapy.

1.1.2. Secondary objectives

The secondary objectives are:

- To evaluate the effect of the M/T FDC compared to the respective monotherapies on:
  - Exercise capacity.
  - WHO Functional Classification (WHO FC).
- To evaluate the safety and tolerability of the M/T FDC in the subject population.

1.1.3. Other objectives

Other objectives for the 16-week DB treatment period are:

- To evaluate the effect of the M/T FDC compared to the respective monotherapies on:
  - PAH symptoms and their impacts on subjects' lives.
  - Time to first morbidity/mortality (M/M) event.
  - Time to death due to PAH or PAH-related hospitalization.
  - Other hemodynamic measures.
  - Subject's quality of life (QoL).
  - Subject's work and productivity.
  - Pharmacoeconomic measures.

Other objectives for the 24-month OL treatment period are defined in the protocol. The analysis plan for these objectives will be described in the SAP Part 2 and are not covered in SAP Part 1.

1.2. Trial Design

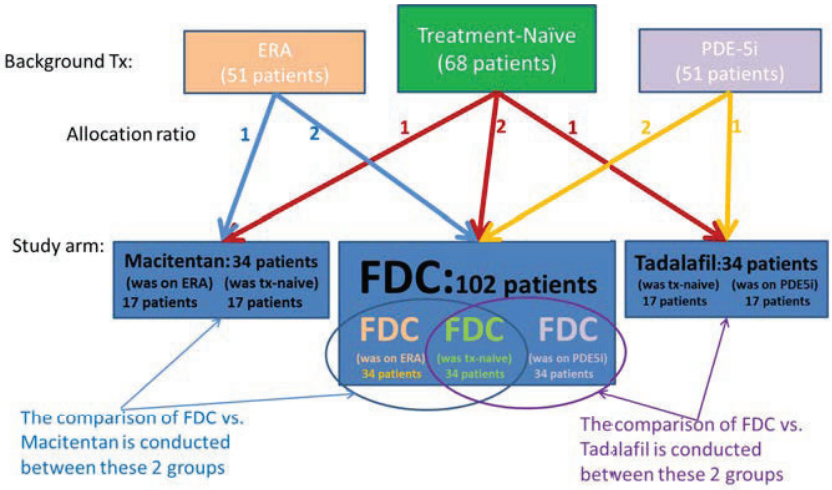
This is a prospective, multi-center, DB, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study with a treatment period duration of 16 weeks followed by a 24-month single-arm OL treatment period. In the DB treatment period, the FDC of macitentan 10 mg and tadalafil 40 mg (M/T FDC) is compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg given once daily.

For the analysis of the primary endpoint, PVR, results will be derived based on the values provided by the central reader (WorldCare Clinical [WCC]). WCC will evaluate the raw data from the right heart catheterization (RHC) in a blinded fashion and according to the independent review charter.

In total, 170 subjects are planned to be randomized into the study (range 120–250) to receive either M/T FDC, macitentan 10 mg, or tadalafil 40 mg given once daily. Subjects will also receive matching placebos for the two other study treatments to maintain the blind. As described in **Figure 1,** treatment allocation will be stratified by treatment status at baseline, ie, treatment-naïve or treated by an ERA or a PDE-5i as a monotherapy:

- 68 treatment-naïve subjects will be randomized in a 2:1:1 ratio to M/T FDC, macitentan, or tadalafil.
- 51 subjects on allowed ERA monotherapy will be randomized in a 2:1 ratio to M/T FDC or macitentan.
- 51 subjects on allowed PDE-5i monotherapy will be randomized in a 2:1 ratio to M/T FDC or tadalafil.

Figure 1 Schema of Study Treatment Groups Planned For Comparison



Tx = treatment.

After completion of the DB treatment period, subjects will continue the study in an OL treatment period for 24 months, during which all subjects will receive M/T FDC. All EDBT assessments must be completed before the subject enters the OL treatment period.

The study will be conducted in approximately 150 sites in approximately 25 countries.

An IA will be conducted when the information fraction (proportion of randomized subjects included in the IA divided by the total number of subjects required for each comparison) is at least 50% for each stratum. The recruitment rate within each stratum will be closely monitored in a blinded manner to ensure a proportional representation of the strata at the time of the IA.

This analysis can allow for early termination for efficacy or futility, or unblinded reassessment of sample size required for the primary endpoint. Following the IA, recruitment will be stopped if futility/superiority is demonstrated. Subjects already enrolled in the study will be allowed to continue through the end of the OL treatment period.

Full details about the timing of study analyses, unblinding considerations and the IA plans are presented in Section 3.

The study comprises the following consecutive periods as depicted in Figure 2:

Screening period: Lasts up to 30 days; starts with the signature of the Informed Consent Form (ICF; Visit 1) and ends the day prior to randomization (Visit 2).

Double-blind treatment period: Starts on the day of randomization (Visit 2) and ends on the day of the EDBT visit (Visit 8).

The DB treatment period consists of the titration phase (the first 2 weeks) and the maintenance phase (Week 3 through Week 16):

- **Titration phase:** Starts on the day of randomization (Visit 2, Day 1) and lasts 2 weeks, ending on Day 14 (end of Week 2).
  - Week 1: Loose combination (LC) 10/20: Subjects are treated with an LC of macitentan 10 mg and/or tadalafil 20 mg and relevant placebos, depending on treatment arm, for 7 days from randomization (Visit 2, Day 1) to the end of Week 1 (Day 7).
  - Week 2: LC 10/40 Up-titration: Subjects are treated with an LC of macitentan 10 mg and/or tadalafil 40 mg and relevant placebos depending on treatment arm from Day 8 to the end of Week 2 (Day 14).
  - Note: If a subject is already receiving a stable dose of PDE-5i within pre-specified dose ranges at baseline (ie, 40 mg tadalafil, 60–120 mg sildenafil, or 10 mg vardenafil daily), no up-titration is needed, and they will receive 40 mg tadalafil from Day 1.
- **Maintenance phase:** Subjects are treated with macitentan 10 mg, tadalafil 40 mg, M/T FDC, or their respective placebos, depending on treatment arm. The period starts on Day 15 and lasts until EDBT (Visit 8).
  - Note: If a subject cannot tolerate 40 mg tadalafil during the titration period, the subject will remain on 20 mg tadalafil. The subject is allowed to be up-titrated once again to 40 mg tadalafil during the first 2 weeks of the maintenance phase of the DB treatment period (ie, between Visits 4 and 5).
  - Note: if a subject prematurely discontinues DB study treatment, they will be asked to return for an EDBT visit (within ±2 days of the time of treatment discontinuation and before initiation of new PAH-specific therapy), a safety follow-up (S-FU) visit 30 days after last treatment administration, and all remaining visits up until the Week 120 visit (excluding Visits 9 and 10). If the subject did not withdraw consent for study participation and regular visits to the site are not possible, telephone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these telephone calls, M/M, adverse event (AE), and concomitant medication information will be collected

Open-label treatment period: For those subjects who complete 16 weeks of DB treatment, the OL treatment period starts with the first dose of the OL FDC study treatment. All subjects will have a titration phase of 2 weeks, during which the 2 drugs will be given as an LC. The OL treatment period ends 24 months later with the End-of-Open-Label-Treatment (EOLT) visit:

- **Titration phase[a]:** Starts on the first day of OL treatment and lasts for 2 weeks.
  - First week OL titration: Begins the first day of OL treatment and ends the seventh day of OL treatment. Subjects who received macitentan monotherapy, or could not tolerate 40 mg tadalafil, in the DB treatment period will receive an LC of macitentan 10 mg and tadalafil 20 mg. Subjects who had received the M/T FDC or tadalafil monotherapy treatment and could tolerate 40 mg tadalafil in the DB treatment period will receive an LC of macitentan 10 mg and tadalafil 40 mg during this week.
  - Second week OL titration: Begins the eighth day of OL treatment and ends on the 14th day of OL treatment. All subjects are treated with M/T FDC. Subjects who cannot tolerate

[a] The open-label titration phase treatment assignment will be done through Interactive Response Technology (IRT) to maintain blinding of the double-blind treatment period treatment.

40 mg tadalafil are not eligible to proceed to the OL treatment period maintenance phase and should complete an End of Study (EOS) visit.

- **Maintenance phase:** Begins the 15th day of OL treatment and ends with the EOLT. All subjects are treated with M/T FDC.
  - Note: if a subject prematurely discontinues study treatment, they will be asked to return for an EOLT visit within ±7 days of the time of treatment discontinuation and an S-FU visit 30 days after last treatment administration. If the subject did not withdraw consent for study participation, regular contacts will be conducted thereafter, at the scheduled visits until the Week 120 visit. If regular visits to the site are not possible, telephone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these telephone calls, M/M, AE, and concomitant medication information will be collected.

End-of-Treatment (EOT): For an individual subject is the end of all study treatment.

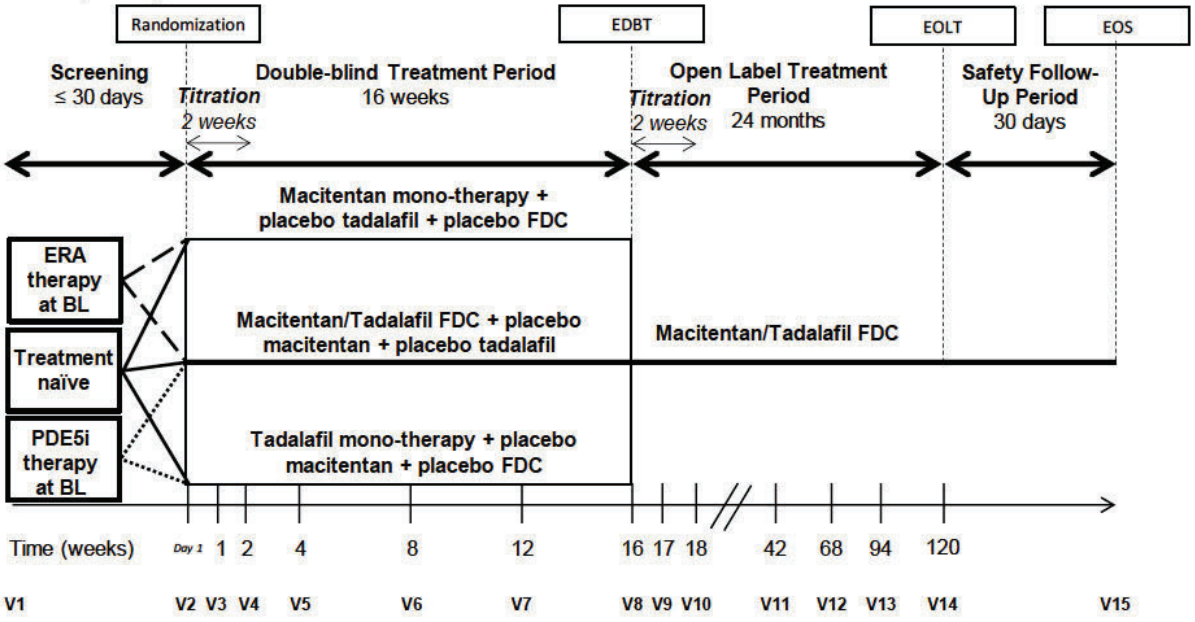
Safety follow-up (S-FU) period: Starts on the day after the last dose of study treatment and ends at the S-FU Visit 30-35 days thereafter.

End-of-Study (EOS): EOS is reached when all subjects have completed their EOS visit, died, or are lost to follow up.

For an individual subject, EOS visit is defined as follows:

- For subjects who complete treatment, EOS visit is defined as the S-FU visit 30-35 days after last study treatment intake.
- For subjects who prematurely discontinue study treatment, EOS visit is defined as either the S-FU visit 30-35 days after last study treatment intake or the Week 120 visit, whichever comes last.

Figure 2 **Study Design**



BL = baseline; EDBT = End of Double Blind Treatment; EOLT = End of Open Label Treatment; EOS = End of Study; ERA = endothelin receptor antagonist; FDC = fixed dose combination; PDE-5i = Phosphodiesterase type-5 inhibitor; V = visit.

The schedule of visits and assessments can be found in Table 4 and Table 5 of the protocol.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis is that the FDC of macitentan 10 mg and tadalafil 40 mg is superior to monotherapy macitentan 10 mg and tadalafil 40 mg, respectively, as assessed by the ratio of geometric means (GMR) of PVR from baseline to EDBT. More details about statistical hypotheses are described in Section 5.2.3.1.

1.4. Sample Size Justification

Sample size is calculated based on the statistical requirements to detect a clinically relevant difference between the FDC group and both monotherapy groups using a 2:1 randomization ratio for each pairwise comparison and taking into account an IA with unblinded sample size re-estimation. Each test comparing the FDC to a monotherapy arm has a two-sided Type I error of 5% and a Type II error of 12% (88% power).

The following assumptions are made:

- The effect of FDC is assumed to be of similar extent versus each monotherapy and consistent across the treatment-naïve, prior-ERA, and prior-PDE-5i strata, ie, a GMR of the EDBT / baseline PVR values equal to 0.75 for FDC versus the most efficient of the two monotherapies;
- A coefficient of variation of the ratio of 0.45;
- One IA is planned using an alpha spending function from the Hwang, Shih and DeCani class with (γ) = –2; and
- Normal distribution for the $\log_e$-transformed ratio of EDBT to baseline PVR values.

If the two comparisons between the FDC and each monotherapy were completely statistically independent, the overall power of the test for the global null hypothesis would be 77.4%. It is, however, expected that those two tests are not independent and therefore that the overall power will be in excess of 77.4% up to a maximum of 88%.

Under these assumptions, 68 FDC subjects and 34 monotherapy subjects are required for each pairwise comparison to establish superiority of FDC versus each monotherapy with between 77% and 88% power to correctly reject a false null hypothesis in favor of the alternative hypothesis.

This test is based on a two-sided ratio of means t-test for independent samples.

Given those requirements and to ensure a minimum of 50% treatment-naïve subjects in each pairwise comparison, the number of subjects will need to be fixed in each stratum as follows:

- 68 treatment-naïve (34 M/T FDC, 17 macitentan and 17 tadalafil).
- 51 prior-ERA (34 M/T FDC and 17 macitentan).
- 51 prior-PDE-5i (34 M/T FDC and 17 tadalafil).

Consequently, 170 subjects will be randomized overall into the trial (102 in the M/T FDC arm, 34 in the macitentan 10 mg arm, and 34 in the tadalafil 40 mg arm). Depending on the conditional power at the IA, the sample size can be re-calculated to between 120 and 250 subjects.

1.5. Randomization and Blinding

1.5.1. Randomization

At Screening, subjects will be assigned a study-specific subject number by the Interactive Response Technology (IRT) system. This number is kept throughout the study and is the main subject identifier. Note: in case of re-screening, a new subject number will be assigned.

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

The randomization list is generated by ALMAC Clinical Technologies.

Subjects will be stratified based on their prior PAH therapy: treatment-naïve, on ERA therapy, or on PDE-5i therapy.

The treatment-naïve subjects will be randomized in a 2:1:1 ratio into M/T FDC, macitentan 10 mg, or tadalafil 40 mg daily, respectively. Subjects on ERA therapy will be randomized in a 2:1 ratio to M/T FDC or macitentan 10 mg daily, respectively. Subjects on PDE-5i will be randomized in a 2:1 ratio to M/T FDC or tadalafil 40 mg daily, respectively.

Subjects will be assigned treatment for the OL treatment period titration phase by the IRT system in order to maintain the blind from the DB study period.

Further details are provided in the interactive voice/web response system (IXRS) Subject Management Requirements version 2.0 dated 13 June 2019 and IXRS3 System Reference Guide version 1 dated 18 June 2019 documents.

1.5.2. Blinding

The first 16 weeks of this study will be performed in a DB fashion. The investigator and study personnel, the subjects, the Clinical Research Associates, Actelion personnel, and Clinical Research Organization personnel involved in the conduct of the study will remain blinded to the study treatment until the final DB analysis, ie, until the last randomized subject has completed 16 weeks of DB treatment or prematurely discontinues from the study and the database is finalized, or until the study is stopped prematurely.

Treatment arm assignment in the DB treatment period will remain blinded when subjects enter the OL treatment period.

This is a triple-dummy study, subjects are randomized into the study to receive either M/T FDC, macitentan 10 mg, or tadalafil 40 mg. Subjects will also receive matching placebos for the 2 other study treatments to maintain the blind as described in protocol Section 3.1. Study treatments and their matching placebos are indistinguishable. All treatment kits will be packaged in the same way.

Actelion personnel responsible for clinical study supply distribution will need to be unblinded to ensure adequate supply of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file, and they will not take part in any Clinical Trial Team meetings after study set-up has been completed.

Until the time of sponsor unblinding, the randomization list is kept strictly confidential and accessible only to authorized persons who are not involved in the conduct of the study.

2. GENERAL ANALYSIS DEFINITIONS

General Definitions

End of treatment in the DB treatment period (EOT-DB) is defined as the last intake of study drug in the DB period.

"EDBT visit" is defined as the last visit in the DB treatment period; this is Visit 8 for subjects who complete the DB treatment period or the premature EDBT visit for subjects that prematurely discontinue study treatment during the DB treatment period.

End of treatment in the OL treatment period (EOT-OL) is defined as the last intake of study drug in the OL treatment period.

EOT is defined as the last study drug intake in the study, ie, max (EOT-DB and EOT-OL).

"EOLT visit" is defined as the last visit in the OL period; this is Visit 14 for subjects who complete the OL treatment period or the premature EOLT visit for subjects who discontinue study treatment prematurely in the OL treatment period.

2.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits for safety parameters. Table 1 lists the visit windows and the target days for each visit defined in the protocol. The reference day is Study Day 1 (see Section 2.5). If a subject has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses by visit but they can be used for determination of marked abnormalities. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

If more than one assessment falls on the same date, the worst assessment will be considered for categorical variables. For continuous variables the mean value of such assessments will be used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later visit window.

Table 1: Safety Visit Windows

Parameter	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Laboratory tests (central lab), vital signs	2	Baseline	<= 1	1
	5	Week 4	2 to 42	29
	6	Week 8	43 to 70	57
	7	Week 12	71 to 98	85
	8	Week 16	>= 99	113
Body weight, Body mass index (BMI)	2	Baseline	<= 1	1
	6	Week 8	2 to 84	57
	8	Week 16	>= 85	113

*Relative to Study Day 1. Assessments for treatment visits will be assigned to the visit windows only up to min(EOT-DB+30 days, start date of OL treatment).

2.2. Pooling Algorithm for Analysis Centers

Not applicable

2.3. Analysis Sets

The following analysis sets were introduced in protocol Section 10.1.

2.3.1. Screened Analysis Set

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

2.3.2. All Randomized Analysis Set

The All Randomized Analysis Set includes all subjects who were randomized in the study.

2.3.3. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of at least one study treatment.

Subjects are evaluated according to the study treatment they have been assigned to, which may be different from the study treatment they have received.

2.3.4. Safety Set

The Safety Set (SS) includes all subjects who received at least one dose of study treatment in the DB treatment period. Subjects are evaluated according to the study treatment received. The treatment received will be different from the treatment assigned at randomization (randomized treatment) only in the case of a dispensing error sustained throughout the entire DB study period. Short-term dispensing errors will not qualify for a change from the randomized treatment group.

2.3.5. QoL analysis sets

The Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™) Analysis Set includes all literate subjects included in the FAS for whom a suitable translation of the PAH-SYMPACT™ questionnaire exists and at least one baseline value is provided.

The Euro Quality of Life-5D-5L (EQ-5D-5L) Analysis Set includes all literate subjects included in the FAS for whom a suitable translation of the EQ-5D-5L questionnaire exists and at least one baseline value is provided.

The Work Productivity and Activity Impairment (WPAI©) Analysis set includes all literate subjects included in the FAS for whom a suitable translation of the Work Productivity and Activity Impairment: General Health (WPAI©: GH) questionnaire exists and at least one baseline value is provided.

2.3.6. Usage of the analysis sets

The main analyses of the primary, secondary, and other efficacy variables in the DB period will be performed on the FAS based on the treatment as randomized.

The QoL variables will be analyzed based on PAH-SYMPACT™, EQ-5D-5L, and WPAI© analysis sets, as applicable.

The analyses of safety variables will be performed on the SS for the DB treatment period based on study treatment received.

Listings will be prepared on the FAS, unless otherwise specified. Subject disposition will be summarized for the All Randomized Analysis Set and the FAS.

2.3.7. Presentation based on strata

For the comparison between M/T FDC and macitentan 10 mg, only subjects randomized to M/T FDC or macitentan 10 mg in the treatment-naïve or prior-ERA strata will be included.

For the comparison between M/T FDC and tadalafil 40 mg, only subjects randomized to M/T FDC or tadalafil 40 mg in the treatment-naïve or prior-PDE-5i strata will be included.

Data collected on subjects who did not tolerate up-titration to tadalafil 40 mg and remained on tadalafil 20 mg or tadalafil 20 mg + macitentan 10 mg as separate tablets will be kept in the statistical analysis under the tadalafil 40 mg and M/T FDC arms, respectively.

Treatment groups for each section will be presented based on strata in the following way:

Efficacy

Outputs will show 4 columns to present comparison between M/T FDC and macitentan 10 mg groups and between M/T FDC and tadalafil 40 mg groups separately. An example of treatment header for such a display is as follows:

Treatment-naïve and prior-ERA strata		Treatment-naïve and prior-PDE-5i strata	
Macitentan 10 mg	M/T FDC	Tadalafil 40 mg	M/T FDC

Safety

In addition to treatment groups specified for the efficacy section, a pooled M/T FDC group will be presented as well. An example of treatment header for such a display is as follows:

Treatment-naïve and prior-ERA strata		Treatment-naïve and prior-PDE-5i strata		All strata
Macitentan 10 mg	M/T FDC	Tadalafil 40 mg	M/T FDC	M/T FDC

This display will be used for safety, treatment exposure and compliance, and prior and concomitant medications outputs.

Disposition and Demographics

Treatment groups for the disposition and demographics section will be presented based on the strata for both comparisons together with the Total column within the strata and pooled M/T FDC.

Treatment-naïve and prior-ERA strata			Treatment-naïve and prior-PDE-5i strata			All strata
Macitentan 10 mg	M/T FDC	Total	Tadalafil 40 mg	M/T FDC	Total	M/T FDC

2.4. Definition of Subgroups

Subgroup	***Definition***
Geographical region	North America, Latin America, Asia, Eastern Europe, South and Western Europe, Oceania
Region	United States (US), non US
WHO FC	II, III

Countries will be assigned to geographical region based on the Standard Country or Area Codes for Statistical Use (M49) standard (unstats.un.org).

In order to assess the consistency of the treatment effect across different subject subgroups, analyses will be performed on the primary endpoint and the secondary endpoints (6-minute walk distance [6MWD] and WHO FC) for the subgroups described in the above table.

Analyses in subgroups on the FAS population are carried out in the same way as on the entire population, as described in Sections 5.2 and 5.3 for the primary and secondary endpoints, respectively. The analyses will be performed using the same models as for the entire population but separately in each subgroup in order to estimate the treatment effects within subgroups. These

will be primarily displayed with their corresponding 95% confidence limits (CLs) and presented in a forest plot. Treatment-by-subgroup interaction will be investigated by means of tests of heterogeneity. The interactions will be estimated from analyses performed on the entire population but with extra variables for the subgroup and the subgroup*treatment interaction added to the models.

In addition, the treatment effects of:

- M/T FDC vs each monotherapy arm will be assessed in the treatment-naïve stratum only;
- M/T FDC vs tadalafil 40 mg will be assessed in the prior-PDE-5i stratum only; and
- M/T FDC vs macitentan 10 mg will be assessed in the prior-ERA stratum only.

2.5. Study Day

Study Day 1 or Day 1 refers to the start of the first study treatment administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Day 1
- Visit date - Date of Day 1, if visit date < date of Day 1

There is no 'Day 0'.

2.6. Baseline

Baseline is defined as the last observation prior to the first study treatment administration. If the assessment is collected on the same day as the first study treatment administration, such assessment will be considered pre-dose and will be used for derivation of the baseline. The exceptions are AEs, prior and concomitant medications and hospitalizations. If such events start on Day 1 they will be considered treatment-emergent/concomitant.

If more than one assessment falls on the same date, the worse assessment will be considered as baseline for categorical variables. For continuous variables the mean value of such assessments will be chosen as a baseline.

2.7. Imputation Rules for Missing and Partial Dates

Missing and partial dates for AEs, prior and concomitant medications, hospitalizations, death date and date of diagnosis will be imputed based on the rules specified in this section. Partial and missing dates of other assessments will not be imputed and will be used as collected.

2.7.1. Adverse Events

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE is missing the day only, it will be set to:

  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose of study treatment
  - The day of first dose of study treatment, if the month/year of the onset of AE is the same as month/year of the first dose of study treatment and month/year of the AE resolution date is different
  - The day of first dose of study treatment or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose of study treatment and month/year of the AE resolution date are the same
- If the onset date of an AE is missing both the day and month, it will be set to the earliest of:
  - 1 January of the year of onset, as long as this date is on or after the first dose of study treatment
  - Month and day of the first dose of study treatment, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the first dose of study treatment,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing the day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the date of death, if the death occurred in that month or EOT (EOT-DB, EOT-OL), if EOT occurred in that month.
- If the resolution date of an AE is missing both the day and month, it will be set to the earliest of December 31 of the year or the date of death, if the death occurred in that year or EOT (EOT-DB, EOT-OL), if EOT occurred in that year.
- Completely missing resolution dates will not be imputed.

If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study treatment based on partial onset date or resolution date.

2.7.2. Prior and Concomitant Medications

Partial prior and concomitant medication start dates will be imputed as follows:

- If the onset date of a medication is missing the day only, it will be set to:
  - First day of the month that the medication started, if month/year of the medication is different than the month/year of the first dose of study treatment,
  - First day of the month that the medication started, if an answer to the question “Was the medication/therapy taken prior to the study?” is “Yes”,
  - The day of first dose of study treatment if the month/year of the start of medication is the same as month/year of the first dose of study treatment and month/year of the medication

end date is different, and answer to the question "Was the medication/therapy taken prior to the study?" is "No" or missing.

  - The day of first dose of study treatment or day of medication end date, whichever is earliest, if month/year of the start of medication and month/year of the first dose of study treatment and month/year of the medication end date are the same, and answer to the question "Was the medication/therapy taken prior to the study?" is "No" or missing.

- If the start date of medication is missing both the day and month, it will be set to the earliest of:
  - 1 January of the year of start, as long as this date is on or after the first dose of study treatment,
  - 1 January of the year of start, if first dose of study treatment is the same year that the medication started, and answer to the question "Was the medication/therapy taken prior to the study?" is "Yes",
  - Month and day of the first dose of study treatment if this date is the same year that the medication started, and answer to the question "Was the medication/therapy taken prior to the study?" is "No" or missing,
  - Last day of the year if the year of the medication start is prior to the year of the first dose of study treatment,
  - The medication end date.
- Completely missing start dates will not be imputed and such medications will be flagged as concomitant unless medication end date is prior to first dose of study treatment.

Partial medication end dates not marked as ongoing will be imputed as follows:

- If the end date of a medication is missing the day only, it will be set to the earliest of the last day of the month of the end date or the date of death, if the death occurred in that month or EOT (EOT-DB, EOT-OL), if EOT occurred in that month.
- If the end date of a medication is missing both the day and month, it will be set to the earliest of December 31 of the year or the date of death, if the death occurred in that year or EOT (EOT-DB, EOT-OL), if EOT occurred in that year.
- Completely missing end dates will not be imputed and will be flagged as concomitant unless medication start date is after EOT-DB.

2.7.3. Hospitalizations

Partial hospitalization admission dates will be imputed as follows:

- If the admission date of a hospitalization is missing the day only, it will be set to:
  - First day of the month that the hospitalization occurred, if month/year of the admission is different than the month/year of the first dose of study treatment
  - The day of first dose of study treatment, if the month/year of the admission is the same as month/year of the first dose of study treatment and month/year of the discharge date is different

  - The day of first dose of study treatment or day of discharge date, whichever is earliest, if month/year of the admission and month/year of the first dose of study treatment and month/year of the discharge date are same

- If the admission date of a hospitalization is missing both day and month, it will be set to the earliest of:
  - 1 January of the year of admission, as long as this date is on or after the first dose of study treatment
  - Month and day of the first dose of study treatment, if this date is the same year that the hospitalization occurred
  - Last day of the year if the year of the admission is prior to the year of the first dose of study treatment,
  - The discharge date.
- If subject is hospitalized due to an AE, AE onset date is available and partial admission date was imputed to earlier date than AE onset date or is missing then AE onset date will be imputed as hospitalization start date instead. In case there are more AEs for the same hospitalization, the earliest AE onset date after treatment start date will be used.
- Completely missing admission dates without corresponding AE will be imputed as min(first dose of study treatment, discharge date).

Partial hospitalization discharge dates not marked as ongoing will be imputed as follows:

- If the discharge date of a hospitalization is missing day only, it will be set to the earliest of the last day of the month of the discharge or the date of death, if the death occurred in that month or EOT (EOT-DB, EOT-OL), if EOT occurred in that month.
- If the discharge date of a hospitalization is missing both day and month, it will be set to the earliest of 31 December of the year or the date of death, if the death occurred in that year or EOT (EOT-DB, EOT-OL), if EOT occurred in that year.
- Completely missing discharge dates will be imputed as the latest resolution date of corresponding AEs, if available. In all other cases the discharge date will be kept missing.

2.7.4. Other Partial or Missing Dates

Death Date

If subject has partial death date, the first day of the month/year will be imputed if day/month is missing. If subject has a later date in the database for any assessment, the last known date will be imputed. Completely missing death date will not be imputed and such a death will be considered on-treatment.

Date of diagnosis

Partial date of diagnosis will be imputed with the first day of the month/year if day/month is missing. Completely missing date of diagnosis will not be imputed.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Timing of study analyses

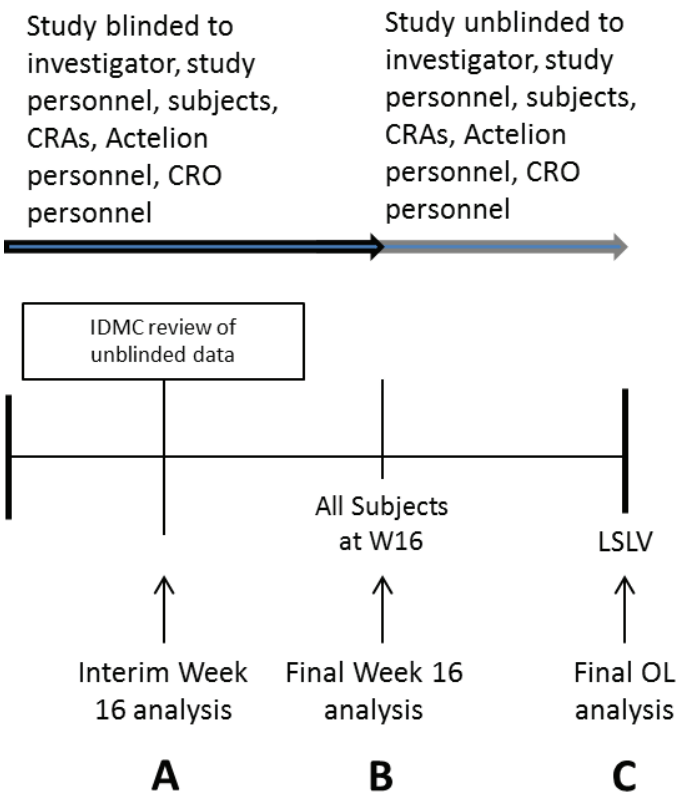
The data will be analyzed at 3 time points during the study [see Figure 3]:

A. The IA will be performed when information fraction for the primary endpoint is at least 50% for each stratum by an independent statistical support group (SSG) for the IDMC The details about the decision rules and sample size re-estimation are presented in Section 3.3.2.
B. Unless the study is stopped prematurely during the IA, the final analysis of the DB period will occur when all subjects have reached Week 16 or prematurely discontinued from the study. The final analysis of the DB period will be performed by the sponsor.
C. The final analysis of the study will occur when all subjects have performed their EOS visit (once the last subject has completed the OL treatment period). The final analysis of the study will be performed by the sponsor. [Not covered in this SAP Part 1].

Furthermore, periodic IDMC meetings will be scheduled to review interim safety and efficacy data. The first meeting will take place approximately 6 months after the first subject is randomized into the trial. Subsequent meetings will occur every 6 months or every 30 randomized subjects, whichever comes first until completion of the DB phase of the study. In addition, one meeting will be scheduled to review the data package for the IA. Hence a minimum of 6 review meetings and one IA will take place. Other meetings or data reviews may be scheduled at the discretion of the IDMC or upon request by the Sponsor Committee.

Measures for the protection of Study Integrity and Control of Operational Bias are described in section 7.2 of the DMC charter, and unblinding considerations are covered in Section 3.2 of this SAP. Section 3.3 covers the specifics of the IA, Section 3.4 includes considerations for the creation of outputs for the IDMC meetings, and Section 3.5 describes specific data-handling rules for ongoing subjects at the time of the data cut-off either for the IDMC reviews, the IA or at the time of the final analysis of the DB period.

Figure 3 Study analyses



CRA = Clinical Research Associate; CRO = Contract Research Organization; EOS = End-of-Study; DB = double-blind; IDMC = Independent Data Monitoring Committee; SSG = statistical support group; FSFV = First Subject First Visit; LSLV = Last Subject Last Visit; M/T FDC = macitentan / tadalafil FDC; OL=open-label; W = week

A Conducted by the independent SSG and interpreted by the IDMC when the information fraction is at least 50% for each stratum.
-Analysis for efficacy or futility and sample size re-estimation

B When all subjects have reached Week 16 or prematurely discontinued from the study
-Analysis of primary endpoint, secondary endpoints, and "other" endpoints for the double blind treatment period, conducted by the Sponsor

C When all subjects have performed their EOS visit
-Final analysis of the study conducted by the Sponsor

3.2. Unblinding

3.2.1. Unblinding for IDMC meetings

An independent SSG, not otherwise involved in the design, conduct, or analysis of the study, will have access to the randomization code in order to prepare unblinded reports for review by the IDMC, as described in the DMC charter. The independent SSG will be represented by an independent statistician. The randomization code will be made available to the independent SSG in accordance with the Janssen process for unblinding.

At the time of the IA, the independent SSG will have access to full randomization information for all subjects randomized. In accordance with the DMC charter, the IDMC will review the entire

data package, including the primary endpoint results, and will provide a recommendation on early study termination for efficacy or futility or on sample-size adjustments.

If the study is terminated for efficacy, further recruitment into the study will be stopped and unblinding will occur after all randomized subjects have completed Week 16 assessments or prematurely discontinued the study.

3.2.2. Unblinding for the final Week 16 analysis (double-blind treatment period)

Full randomization information will be made available to the sponsor for data analysis [see Figure 3] only after the last randomized subject has completed 16 weeks of DB treatment or has prematurely discontinued from the study, the database is cleaned, and the data extraction is performed, in accordance with sponsor Quality System documents.

Following each subject's completion of the DB treatment period, they will enter the OL treatment period. In order to preserve the blind of each individual subject until the final DB analysis, all subjects will enter a 2-week blinded titration period prior to initiating their M/T FDC treatment.

3.3. Interim analysis and adaptive sample size re-estimation

3.3.1. IA timing

The IA will be conducted when the information fraction for the primary endpoint is at least 50% for each stratum. This ensures that there will be at least a 50% information fraction for each pairwise comparison.

The information fraction is defined as the proportion of subjects included in the IA divided by the total number of planned subjects for each pairwise comparison.

For the M/T FDC vs macitentan 10 mg comparison, the information fraction is calculated as:

$t_1 = (N_{IA\ ERA}+N_{IA\ Naive1}) /102,$
where $N_{IA\ ERA}$ is the number of subjects in the prior-ERA stratum who are randomized and have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment at the time of the IA,
and $N_{IA\ Naive1}$ is the number of subjects in the treatment-naïve stratum who are randomized to either macitentan 10 mg or M/T FDC and have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment at the time of the IA.

For the M/T FDC vs tadalafil 40 mg comparison, the information fraction is calculated as:

$t_2 = (N_{IA\ PDE\text{-}5i}+N_{IA\ Naive2}) /102,$
where $N_{IA\ PDE\text{-}5i}$ is the number of subjects in the prior-PDE-5i strata who are randomized and have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment at the time of the IA,

and $N_{IA\ Naive2}$ is the number of subjects in treatment-naïve strata who are randomized to either tadalafil 40 mg or M/T FDC and have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment at the time of the IA.

Subjects are counted once they are randomized and have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment.

Given the specificity of the design regarding the randomization ratio in each stratum and the grouping of subjects for each pairwise comparison (see Figure 1), it can be estimated that the total number of subjects to be included in the:

- M/T FDC vs macitentan 10 mg comparison is $N_1=0.75\times N_{Naive}+N_{ERA}$
- M/T FDC vs tadalafil 40 mg comparison is $N_2=0.75\times N_{Naive}+N_{PDE\text{-}5i}$

where N_{Naive} is the number of treatment-naïve subjects, N_{ERA} the number of prior-ERA subjects and $N_{PDE\text{-}5i}$ the number of prior-PDE-5i subjects.

Under the protocol assumptions for sample size (see Section 1.4), each pairwise comparison requires a maximum of 102 subjects at the final analysis leading to pre-planned N_{ERA}, $N_{PDE\text{-}5i}$ and N_{Naive} of 51, 51 and 68, respectively, and an overall total of 170 subjects (which guarantees 50% naïve subjects for each pairwise comparison).

The earliest the IA can be conducted is when both N_1 and N_2 ≥51 subjects and when a minimum of 34 treatment-naïve subjects, 26 prior-ERA subjects, and 26 prior-PDE-5i subjects are randomized and either reach Week 16 or discontinue early (86 subjects in total).

3.3.2. IA decision rules

The primary endpoint will be tested on the FAS using 2 analysis of covariance (ANCOVA) models separately comparing the combination group to each monotherapy as described in Section 5.2.3.3. The 2 p-values obtained for both pairwise comparisons will be used to implement the following statistical decision rules.

The independent SSG will make unblinded results available to the IDMC. The IDMC will review the interim results and make corresponding recommendations in line with the DMC charter.

The IDMC may recommend, based on the unblinded interim data, that the sponsor:

1. Stop the study for efficacy if the interim test for PVR is positive for both pairwise comparisons at the two-sided $\alpha_1(t)$ (alpha level for statistical testing at the interim analysis for an information fraction t, different for each pairwise comparison, as described in ATTACHMENT 3),
2. Continue the study with reassessed sample size to a total between 120 <N ≤250 subjects if either of the interim tests for PVR is negative at the two-sided α_1 (t) and conditional success probability of both pairwise comparisons ≥20%.
   a. Decrease if both pairwise comparisons are ≥**88%**

b. Increase if either pairwise comparison is <**88%**

3. Continue unchanged if the conditional success probability of both pairwise comparisons ≥2.5% and <20% in either pairwise comparison

4. Stop for futility if the conditional success probability is <2.5% in either pairwise comparison

Detailed guidelines for interim decision-making are presented in Figure 4. The boundaries to be used for the IA will depend on the actual information fraction and will be re-calculated by the independent SSG. Formulae to determine alpha level for statistical testing and conditional power are presented in ATTACHMENT 3.

For each hypothesis, the information fraction is calculated individually based on the number of subjects entering the test of the respective null hypothesis at the IA and on the number of subjects originally planned for the final analysis. The earliest the IA can be performed is when the information fraction is 50% for each pairwise comparison. In this case (with $N_1=N_2=51$ subjects), the alpha to be used will be 0.01345, using the Hwang, Shih and De Cani (Hwang 1990) alpha spending function for both pairwise comparisons. Any departure from the assumptions may lead to different stopping boundaries and decision-making rules.

In case the study is stopped for efficacy (IDMC recommendation 1), subject recruitment will be stopped, but subjects enrolled so far will remain on trial treatment as planned and unblinding will occur after all randomized subjects have completed Week 16 assessments or prematurely discontinued the study. In that scenario, the primary efficacy analysis will be based on the set of subjects used for the decision-making process, ie, using the same data extract as for the IA. An analysis including overrun subjects and extra follow-up data will be performed by the sponsor after database lock (DBL) and unblinding as a sensitivity analysis.

If the study is not terminated early (IDMC recommendations 2 and 3), the inverse normal combination method will be utilized to combine first- and second-stage p-values for the control of the type-1 error rate (Lehmacher 1999) in the final Week 16 analysis performed by the sponsor. The guideline for calculating the combination weights is included in ATTACHMENT 3 and will be based on the available individual information fractions at the time of the IA. Combination weights will not be adjusted based on the IA decision.

If the study is declared positive at either interim or final Week 16 analysis, the secondary efficacy endpoints will be analyzed at the same alpha level used for the primary endpoint using a hierarchical testing procedure following the order of the endpoints as listed in protocol section 5.1.2. This testing strategy controls the overall type I error in a conservative way (Hung 2007, Glimm 2009, Tamhane 2010)

Methods for the sample size re-estimation are described in Section 0.

A rule to guide the calculation of the new strata sizes after the new target sample size has been established for each pairwise comparison can be defined as:

- $N_{ERA}=N_{PDE\text{-}5i}=N$

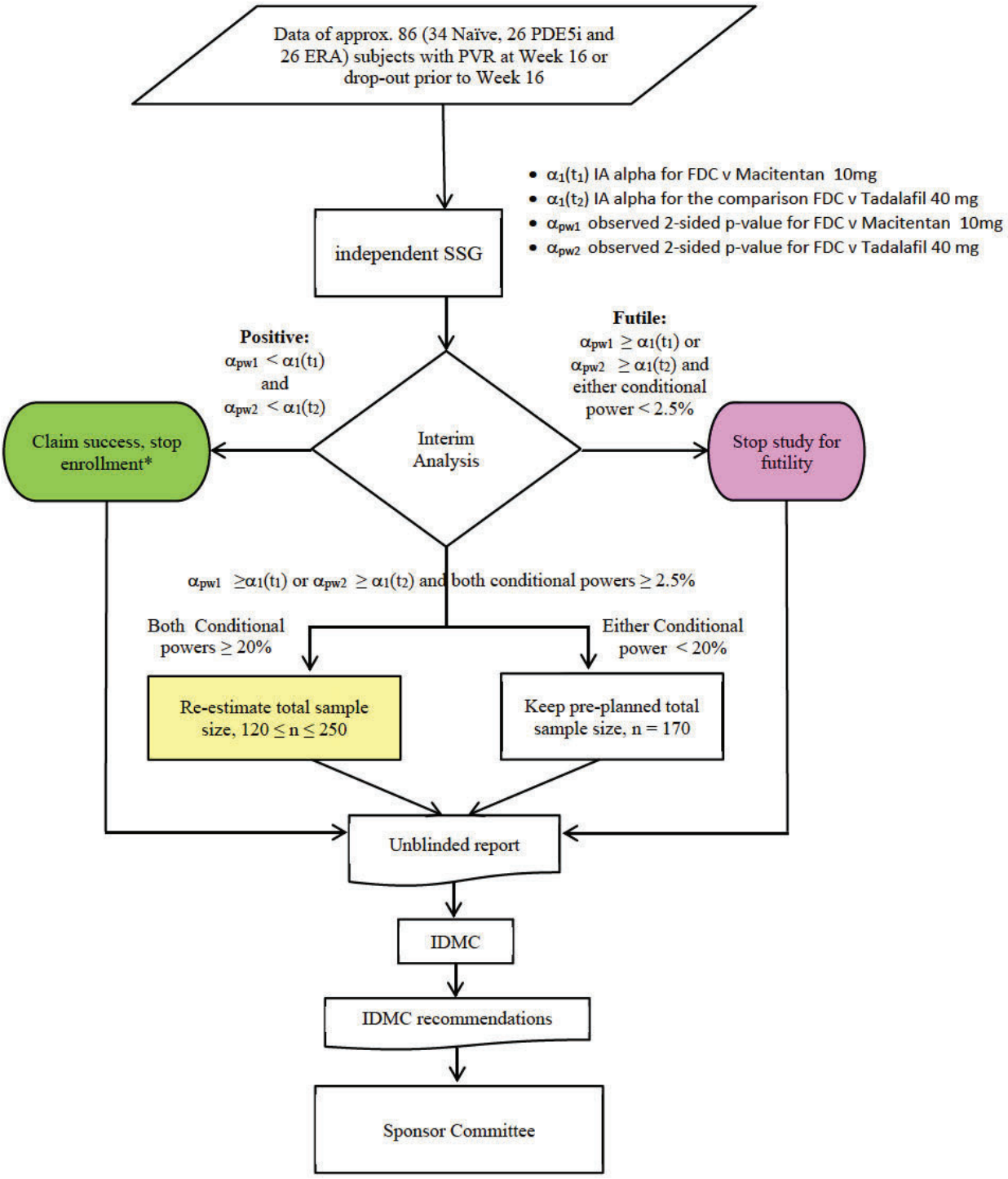
- $0.75 \times N_{Naive} + N = new\_pairwise\_sample\_size$
- $0.75 \times N_{Naive} = N$ (guarantees 50% naïve in each pairwise comparison)

Which can be resolved as:

- $N_{ERA} = N_{PDE\text{-}5i} = new\_pairwise\_sample\_size / 2$ (and should be rounded to the closest whole number that can be divided by 3)
- $N_{Naive} = 0.75 \times new\_pairwise\_sample\_size$ (and should be rounded to the closest whole number that can be divided by 4)

where N_{Naive} is the number of treatment-naïve subjects, N_{ERA} is the number of prior-ERA subjects and $N_{PDE\text{-}5i}$ is the number of prior-PDE-5i subjects.

Figure 4 **Flowchart of decision making on interim and final analysis of PVR**



3.3.3. Final Week 16 analysis if the study is not terminated early

If the study is not terminated early (IDMC recommendations 2 and 3), to control the type I error and adjust for the IA, the final Week 16 analysis of the primary and secondary efficacy endpoints will be conducted by the sponsor using the inverse normal combination method with pre-specified weights to combine first- and second-stage p-values (Lehmacher 1999).

The first-stage set of subjects constitutes all subjects who have contributed to the IA. The remaining subjects required to reach the total sample size based on the IA decision constitute the second-stage set of subjects.

- The separate first-stage analysis will be based on the first-stage set of subjects.
  - For the primary efficacy endpoint, the first-stage p-values from the ANCOVA models (as described in Section 5.2.3.3) will be used in the final Week 16 analysis in the weighted inverse-normal combination (INC) test statistic (as detailed in ATTACHMENT 3). The models and p-values will be based on the same data extract as used at the time of the IA.
  - For the secondary efficacy endpoints, the first-stage p-values from the models described in Sections 5.3.1.2.3 and 5.3.2.2.3 will be used to contribute first-stage data to the INC test statistic for the final Week 16 analysis. Since these analyses will not have been performed at the time of the IA in the scenario where the study is not terminated early, the first-stage p-values will be derived based on the data extract available at the time of the final Week 16 analysis.
- The separate second-stage analysis will be based on the second-stage set of subjects. Due to the population-wise splitting, no subjects contributing to the separate first-stage test statistics are included into the separate second-stage analysis. The second-stage p-values will be calculated in the same way as the first-stage p-values of the corresponding endpoint.
- The primary and secondary endpoints will be tested by combining p-values from the separate first and second stage analyses using the INC function with prefixed weights.

The final adjusted p-value, median unbiased parameter estimates and repeated confidence intervals (RCIs) will be presented in the final Week 16 analysis of both the primary and secondary endpoints using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company).

If data are presented separately for the first-stage and second-stage results, the stage of the subjects will be indicated in the data presentation.

Table 2 presents an overview of the set of subjects in each stage and pre-defined weights for the inverse normal method for the final Week 16 analysis of primary and secondary efficacy endpoints for the hypothetical scenario, where the number of subjects entering each pairwise comparison at the interim (time point A) is 52 ($\boldsymbol{n_{11} = n_{12} = 52}$ stated differently, $N_{IA\ ERA} + N_{IA\ Naive1} = N_{IA\ PDE\text{-}5i} + N_{IA\ Naive2} = 52$) and at the final analysis (time point B) the number equals per pairwise comparison $n_{11} + n_{21}$ and $n_{12} + n_{22}$.

Table 2: Significance Level, Set of Subjects and Weights for Inverse Normal Combination Method at Final Week 16 Analysis for the Hypothetical Scenario Where the Number of Subjects Entering Each Pairwise Comparison at the Interim (Time Point A) is 52 ($n_{11} = n_{12} = 52$) and at the final analysis, (time point B) equals per pairwise comparison $n_{11} + n_{21}$ and $n_{12} + n_{22}$

Endpoint	Analysis time point	Pairwise comparison	Significance level for one sided $\alpha = 0.025$		Inverse normal combination method			
			Information fraction*	Critical value for 1-sided Z and corresponding α-level	Stage 1		Stage 2	
					Subjs	Weight	Subjs	Weight
Primary endpoint: Change in PVR expressed as the ratio of EDBT to baseline	A	FDC vs. Macitentan 10 mg	$t_1 = n_{11}/102$	$c_{11} = -2.460657$ $\alpha_1(t_1) = 0.00693415$	n_{11}	100 %	NA	NA
		FDC vs. Tadalafil 40 mg	$t_2 = n_{12}/102$	$c_{12} = -2.460657$ $\alpha_1(t_2) = 0.00693415$	n_{12}	100 %	NA	NA
	B	FDC vs. Macitentan 10 mg	100%	$c_{2,1} = -2.026$ $\alpha_{2,1} = 0.021$	n_{11}	$\sqrt{t_1}$	Remaining n_{21}	$\sqrt{1-t_1}$
		FDC vs. Tadalafil 40 mg	100%	$c_{2,2} = -2.026$ $\alpha_{2,2} = 0.021$	n_{12}	$\sqrt{t_2}$	Remaining n_{22}	$\sqrt{1-t_2}$
Secondary endpoint: Change from baseline to EDBT in 6MWD	A	FDC vs. Macitentan 10 mg	$t_1 = n_{11}/102$	$c_{11} = 2.460657$ $\alpha_1(t_1) = 0.00693415$	n_{11}	100 %	NA	NA
		FDC vs. Tadalafil 40 mg	$t_2 = n_{12}/102$	$c_{12} = 2.460657$ $\alpha_1(t_2) = 0.00693415$	n_{12}	100 %	NA	NA
	B	FDC vs. Macitentan 10 mg	100%	$c_{2,1} = 2.026$ $\alpha_{2,1} = 0.021$	n_{11}	$\sqrt{t_1}$	Remaining n_{21}	$\sqrt{1-t_1}$
		FDC vs. Tadalafil 40 mg	100%	$c_{2,2} = 2.026$ $\alpha_{2,2} = 0.021$	n_{12}	$\sqrt{t_2}$	Remaining n_{22}	$\sqrt{1-t_2}$

Secondary endpoint: Proportion of subjects with absence of worsening in WHO FC from baseline to EDBT	A	FDC vs. Macitentan 10 mg	$t_1 = n_{11}/102$	$c_{11} = 2.460657$ $\alpha_1(t_1) = 0.00693415$	n_{11}	100 %	NA	NA
		FDC vs. Tadalafil 40 mg	$t_2 = n_{12}/102$	$c_{12} = 2.460657$ $\alpha_1(t_2) = 0.00693415$	n_{12}	100 %	NA	NA
	B	FDC vs. Macitentan 10 mg	100%	$c_{2,1} = 2.026$ $\alpha_{2,1} = 0.021$	n_{11}	$\sqrt{t_1}$	Remaining n_{21}	$\sqrt{1-t_1}$
		FDC vs. Tadalafil 40 mg	100%	$c_{2,2} = 2.026$ $\alpha_{2,2} = 0.021$	n_{12}	$\sqrt{t_2}$	Remaining n_{22}	$\sqrt{1-t_2}$

* The actual information fractions for each comparison will depend on the recruitment in the three strata and will be calculated by SSG based on actual treatment assignment. The corresponding critical values will be updated accordingly by SSG.

$Z_{INC,final}$: Weighted inverse-normal combination (INC) test statistic at final Week 16 analysis.

n_{11}: Actual number of subjects in either prior-ERA or treatment-naïve strata and randomized to either FDC or macitentan 10 mg who have completed Week 16 RHC assessment (or have discontinued from the study prior to their Week 16 RHC assessment) at data cutoff (randomized at least 16 weeks prior to cutoff) for analysis time point A.

n_{12}: Actual number of subjects in either prior-PDE-5i or treatment-naïve strata and randomized to either FDC or tadalafil 40 mg who have completed Week 16 RHC assessment (or have discontinued from the study prior to their Week 16 RHC assessment) at data cutoff (randomized at least 16 weeks prior to cutoff) for analysis time point A.

n_{21}: $n_1^* - n_{11}$ where n_1^* is the actual total number of subjects in either prior-ERA or treatment-naïve strata and randomized to FDC or macitentan 10mg.

n_{22}: $n_2^* - n_{12}$ where n_2^* is the actual total number of subjects in either prior-PDE-5i or treatment-naïve strata and randomized to FDC or tadalafil 40 mg.

The secondary efficacy endpoints will be formally evaluated according to the testing hierarchy (conditional to conclusive outcome of the primary efficacy endpoint results at final Week 16 analysis).

3.4. Outputs for IDMC Meetings

For periodic data reviews performed by the IDMC, summary tables will be created by the independent SSG using SAS (SAS Institute Inc.) and R (R Core Team (2012) and based on the SDTM and Analysis Data Models (ADaMs) provided by the sponsor to include presentation of the following data:

- Subject disposition
- Demographic data
- Baseline characteristics (including medical history)
- AEs, AEs of special interest, serious adverse events (SAEs), hospitalization, and deaths
- Selected laboratory parameters (hemoglobin, liver tests), vital signs / body weight
- Treatment exposure
- Concomitant treatments, procedures
- Protocol deviations
- Efficacy data (hemodynamic, 6MWD, WHO FC)

Separate summaries will be created for the data from the DB period only and for the OL data available at the time of the IDMC data cut-off.

For the DB outputs, data will be derived and presented as described in this CSR SAP in Sections 2, 4, 5 and 6. For the OL outputs, considerations for data derivations and presentations are described in Section 3.4.1. Data handling rules are also described in section 8.2 of the DMC charter.

The summary tables in the IDMC data package will be displayed with real treatment identity. A separate data package may be created for the open session, only presenting data for the overall population (not by treatment group) and only containing data that could not cause operational bias.

For protection of data integrity and minimization of potential operational bias in the study, which features an unblinded adaptive sample size re-estimation, some measures have been put in place and are described in attachment 8 of the DMC charter. Relevant aspects for the creation of outputs for the IDMC open session are:

- The outcome of the sample size re-assessment (new target sample size overall and by stratum) will not be communicated to anyone directly involved in running the study, including the study team, local monitors, investigators, or site staff;
- Individual subject-level stratum information from Interactive Web Response System and/or previous ERA or PDE-5i use from the electronic case report form (eCRF) concomitant medications page will not be not communicated to the study team;
- Aggregated number of subjects per strata will not be communicated to the study team after the IA.

For the first IDMC meeting, only limited data will be available so the open session package may only contain data listings.

3.4.1. Open-label Treatment Period Considerations

3.4.1.1. Visit Windows

Any available data from the OL period will be presented by nominal visits only and no visit windowing will be performed for the IDMC.

3.4.1.2. Analysis Sets for open-label treatment period

In addition to analysis sets described in Section 2.3, the Open-label Set (OLS) will be used to assess data from the OL period for the IDMC.

The OLS includes all subjects who receive at least one dose of OL study treatment in the OL period.

OL data will be presented by treatment received in the DB period and by strata, as described in Section 2.3.7.

3.4.1.3. Study Day

Safety assessments performed for the OLS will have Study Day 1 defined as the start of the first administration of macitentan 10 mg and tadalafil (20 mg or 40 mg) in the OL treatment period.

3.4.1.4. Baseline and Treatment-Emergent Period

The baseline value for the OL treatment period is defined as the last assessment obtained prior to the first intake of macitentan 10 mg and tadalafil (20 mg or 40 mg) in the OL treatment period.

The OL treatment-emergent period is defined from first intake of macitentan 10 mg and tadalafil (20 mg or 40 mg) in the OL treatment period up to EOT-OL+30 days.

3.4.1.5. Specific data handling

The following additional variables will be derived to describe OL data:

- OL Compliance=[(number of tablets dispensed at all visits−number of tablets returned at all visits)/total number of tablets that should have been taken from the first dose of study treatment in OL to EOT-OL×100]
- OL Study treatment duration (weeks) is defined as (date of EOT-OL–date of first dose of OL study treatment+1)/7.

3.5. Ongoing Subjects

Some definitions will be modified for data from subjects ongoing (in the DB or OL treatment period) at the time of the data cut-off either for the IDMC reviews, the IA or at the time of the final analysis of the DB period.

Generally, if an assessment start date (including imputed start dates) is after the cut-off date, such assessment will not be included in the datasets or outputs. If the end date of an event that started before or on the cut-off date is after the cut-off date, such event will be considered as ongoing, unless specified otherwise.

If a partial or missing date should be imputed based on imputation rules after the cut-off date, the cut-off date will be used for imputation instead.

Specific date-handling rules will be described in a separate data cut-off planning document.

4. SUBJECT INFORMATION

Unless otherwise specified, data in this section will be summarized by treatment as described in Section 2.3.7. The number of subjects in each analysis set will be summarized and listed for the All randomized analysis set. Number of subjects excluded from each analysis set and reason for exclusion will be summarized and listed as well. In addition, the distribution of subjects by strata and country will be presented for demographics, baseline characteristics and disposition tables. An overall table with frequency of subjects in each country and site will be prepared.

4.1. Demographics and Baseline Characteristics

Table 3: presents a list of the demographic variables that will be summarized for the FAS.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Categorical Variables:	
Age (18-25 years, 26-50 years, 51-64 years, and ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race (American Indian or Alaska Native, Asian [if Asian, Japanese or Other Asian]|, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, not reported)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported)	
Region (US, non-US)	
Geographical region (North America, Latin America, Asia, Eastern Europe, South and Western Europe, Oceania)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

The following baseline characteristics variables will be summarized for the FAS:

- WHO FC (I, II, III, IV).
- PAH etiology (idiopathic, heritable, drug- and toxin- induced, PAH associated with other conditions [connective tissue disease, HIV infection, portal hypertension, congenital heart

disease, schistosomiasis], long-term responders to calcium channel blockers, with overt features of venous/capillaries involvement)

- Time since diagnosis (in years). For each subject time since diagnosis will be derived as:
  - (Date of the first study treatment administration–date of diagnosis+1)/365.25
- Baseline RHC results (this will include a summary of the PVR results used for randomization as calculated by the central reader [WCC] together with the proportion of assessments based on Fick cardiac output [CO] and thermodilution CO).
- Medical history by System Organ Class (SOC) and Preferred Term (PT)

Demographics, baseline characteristics and medical history will also be listed on the FAS.

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized overall.

The number of subjects in the following disposition categories will be summarized throughout the DB period for the All randomized analysis set:

- Subjects randomized
- Subjects receiving study treatment
- Subjects completing the study DB period
- Subjects who terminated study DB period prematurely
- Reasons for premature termination of study DB period

The number of subjects in the following treatment disposition categories will be summarized for the FAS:

- Subjects receiving different than randomized treatment throughout the whole DB period
- Subjects completing DB study treatment
- Subjects who discontinued DB study treatment prematurely
- Reasons for premature discontinuation of DB study treatment
- Subjects entering OL treatment period

A subject will be counted as completing DB study treatment if CRF question “Did the subject take study drug until this visit?” at Visit 8 is answered as “Yes”. Otherwise the subject will be considered to have discontinued DB study treatment prematurely.

A subject will be counted as completing the study DB period if the subject underwent Visit 8.

A subject entering the OL treatment period is defined as a subject receiving at least one dose of OL study treatment in the OL period.

The distribution of the time to premature DB study treatment discontinuation will be displayed with Kaplan-Meier curves for the FAS. Subjects who terminate DB treatment prematurely at any

time in the DB period will be considered an 'Event' and their date of DB study treatment discontinuation will be used in the time to event calculation. Subjects who complete the DB study treatment will be censored and the date of EOT-DB will serve as the time of censoring.

Listings will be provided for the following categories of subjects, for the All randomized analysis set:

- Subjects who discontinued DB study treatment prematurely
- Subjects who terminated the DB study prematurely
- Subjects who were unblinded during the DB study period
- Subjects who were randomized yet did not receive DB study treatment
- Subjects who started the DB study treatment after but not on the randomization day

4.3. Treatment Compliance

Study treatment compliance is based on study treatment accountability. Compliance will be calculated for the SS separately within each treatment and strata group, as defined in Section 2.3.7, from the first dose of study treatment to EOT-DB.

Compliance=[(number of tablets dispensed at all visits−number of tablets returned at all visits)/Total number of tablets that should have been taken from the first dose of study treatment to EOT-DB×100

The total number of tablets that should have been taken is calculated as follows:

Table 4: Number of tables that should have been taken

	Titration phase		**Maintenance phase**
	Week 1	**Week 2**	
M/T FDC	Not applicable		EOT-DB date − First dose of study treatment date
Tadalafil 20 mg	Last dose of study treatment date in Week 1 − First dose of study treatment date	2 × (EOT-DB date − First dose of study treatment date in Week 2)*	
Macitentan 10 mg	EOT-DB date − First dose of study treatment date		

* if subject does not tolerate tadalafil 40 mg and receives only 20 mg dose, the number of tables that should have been taken is calculated as follows: (EOT-DB date − First dose of study treatment date in Week 2).

Study treatment compliance will be summarized descriptively. Compliance to randomized treatment versus actual treatment will be presented in a summary table.

The number and percentage of subjects who have:

- <80%

- 80–100%
- >100–120%
- >120%

overall study treatment compliance will be summarized by treatment group.

4.4. Extent of Exposure

Exposure summaries will be presented on the SS for the DB treatment period.

Study treatment duration (weeks) is defined as (date of EOT-DB–date of first dose of study treatment+1)/7.

Study treatment duration considering treatment interruptions will be derived and summarized as well. Study treatment duration with interruptions (weeks) is calculated as (date of EOT-DB–date of first dose of study treatment – days without study treatment administration +1)/7.

The number and percentage of subjects who receive study treatment will be summarized by treatment group. For subjects in the M/T FDC and tadalafil group, the number and percentage of subjects who received a dose of 40 mg of tadalafil at least once will be summarized.

Descriptive statistics for study treatment duration (N, mean, standard deviation [SD], median, and range [minimum, maximum]) will be presented in weeks by treatment group.

Duration of exposure to treatment will be summarized in the following duration categories: <4 weeks, 4-<8 weeks, 8-<12 weeks, 12-<16 weeks, ≥16 weeks by treatment group and presented graphically in a histogram.

Cumulative treatment ≥4 week, ≥8 weeks, ≥12 weeks and ≥16 weeks will be summarized.

For subjects in the M/T FDC and tadalafil group, the duration the subject was taking tadalafil 20 mg will be summarized. This will be calculated by adding up all intervals where tadalafil 20 mg was taken. Duration of such intervals is defined as (date of last dose of tadalafil 20 mg in the interval–date of first dose of tadalafil 20 mg in the interval)+1. Similarly, it will be derived for tadalafil 40 mg.

The number (%) of subjects with a tadalafil dose adjustment (summarized separately as increase from 20 mg to 40 mg and as decrease from 40 mg to 20 mg) will be summarized by treatment group. The number (%) of tadalafil dose adjustments per subject will be summarized by treatment group as well.

Individual subject listings will be provided for exposure data broken down by treatment group, stratum, site, and subject number.

4.5. Protocol Deviations

All major protocol deviations (MPDs) for the DB treatment period will be reported in the CSR. The protocol deviations will be identified by medically trained staff before DBL for the final analysis of the DB period.

MPDs may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. The MPD criteria are described in a separate document: the MPD criteria list. Subjects with MPDs will be summarized by category and listed.

There is no Per Protocol Set (PPS) so no MPDs lead to exclusion from the PPS.

4.6. Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the SS.

Definitions

A previous medication is any treatment for which the end date is prior to the first dose of study treatment.

A medication that is concomitant is any treatment that is either ongoing at the start of study treatment or initiated during the treatment period up to EOT-DB.

Prior and Concomitant medications will be coded using the latest version of WHO Drug Dictionary at the DBL.

Summaries of concomitant medications will be presented by Anatomic and Therapeutic Class (ATC) level 4 term, strata and treatment group. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least 1 concomitant medication. In addition, concomitant and prior medications of special interest will be presented. This includes PAH-specific medications; if they are summarized as concomitant, the category will be called Prohibited PAH-specific medications. (see ATTACHMENT 1 for list of medications).

Additional summaries of medications starting between EOT-DB and EOT-DB+7 days will be provided for all medications.

Prior medications will be summarized by treatment group within strata group and ATC term.

All medications will be listed including flag indicating if medication is prior or concomitant.

5. EFFICACY

This study implements an adaptive group-sequential design with early futility and efficacy stopping rules and sample size re-estimation. It includes an IA (according to group-sequential design methodology) when approximately 86 (≥34 treatment-naïve, ≥26 prior-ERA, and ≥26 prior-PDE-5i) subjects have completed their EDBT assessment or have prematurely discontinued from the study.

If the study is not stopped early for futility or efficacy, a final analysis will be carried out when approximately 120–250 subjects (based on conditional power considerations on PVR) have completed their EDBT assessment or prematurely discontinued from the study. The DB part of the study will then be reported.

In all models that include the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) as a covariate, the value of the strata recorded at randomization will be used (rather than the corrected strata value if an error was discovered post randomization). A listing will be created to display the strata at randomization and the actual strata together with DB treatment information if any subjects have been assigned to an incorrect strata at randomization.

Conditional to positive outcome of the interim PVR results, all secondary endpoints will be formally evaluated according to the testing hierarchy. In case of negative outcome of the interim PVR results, ie, if the study is not stopped early for efficacy, secondary endpoints will only be evaluated at the final analysis according to the testing hierarchy.

Individual subject listings will be provided for efficacy endpoints. Each listing will be broken down by treatment group, stratum, site, subject number, and assessment date, where appropriate.

5.1. Analysis Specifications

5.1.1. Level of Significance

The overall Type I error is 5% two-sided.

The primary endpoint will be tested using 2 models separately, comparing the combination group to each monotherapy. Only if both tests are statistically significant and M/T FDC is shown to be superior to both monotherapies will the study be declared to show conclusive evidence of efficacy.

Each null hypothesis will be tested (and family wise error rate preserved) during the IA using a Hwang, Shih and DeCani alpha spending function with gamma (γ) = –2:

$$\alpha_1(t) = \alpha\ (1-\exp(-\gamma t))/(1-\exp(-\gamma)),$$

where t is the information fraction for a given pairwise comparison.

The alpha to be spent at the IA depends on the fraction of available information at the timing of the IA for each pairwise comparison. The earliest the IA can be performed is when the information fraction is 50% for each pairwise comparison. In this case (with N_1=N_2=51 subjects), the alpha to be used will be 0.01345 for both pairwise comparisons.

If the study is not terminated early, the INC method will be utilized to combine first- and second-stage p-values for the control of the type-1 error rate (Lehmacher 1999).

If the study is declared positive at either interim or final Week 16 analysis, secondary efficacy endpoints will be analyzed at the same alpha level used for the primary endpoint using a hierarchical testing procedure following the order of the endpoints as listed in Section 5.3.

Long-term efficacy data from the OL phase will be analyzed descriptively.

5.1.2. Data Handling Rules

Depending on the efficacy endpoint and estimand, not all data collected on the subjects will be used in the analyses. For both the primary and secondary endpoints, the estimand section describes how this is handled and in particular rules for using only on-treatment data and/or data prior to the introduction of prohibited PAH-specific medication.

For data not collected (missing) or excluded from the assessment of a given estimand, specific data imputation rules are defined for each endpoint.

For other efficacy endpoints, no missing data imputation will be performed and observed data will be used for analysis as described in the analysis method section for each endpoint.

Baseline definitions are provided in Section 2.6.

5.2. Primary Efficacy Endpoint(s)

- Change in PVR expressed as the ratio of EDBT to baseline.

5.2.1. Definition

PVR (dyn.sec/cm^5) is based on the results of the RHC assessment. CCI [redacted].

Completion of baseline and follow-up RHC will be confirmed by the site staff in the eCRF, and the raw data (traces) will be made available to the central reading facility (WCC).

Inclusion of the subjects in the trial will be based on central reader evaluation of RHC data collected within 5 weeks prior to Randomization.

The site will enter the following variables into the eCRF at baseline and EDBT:

- Date and time of the RHC,
- Date and time of last dose of study treatment intake prior to RHC,
- Heart rate (HR) during RHC,
- Systolic systemic artery pressure (s-SAP),
- Diastolic systemic artery pressure (d-SAP),
- Mean right atrial pressure (mRAP),
- Systolic pulmonary artery pressure (sPAP),
- Diastolic pulmonary artery pressure (dPAP),
- Mean pulmonary artery pressure (mPAP),
- Pulmonary artery wedge pressure (PAWP),

- Left ventricular end diastolic pressure (LVEDP), if available/measured,
- Arterial oxygen saturation,
- Mixed venous oxygen saturation,
- CO (calculated by thermodilution and/or Fick),
- Hemoglobin value used to calculate Indirect Fick CO,
- PVR.

The central reader evaluates the raw data according to the independent review charter in a blinded fashion and provides the following assessments:

- mRAP,
- sPAP
- dPAP,
- mPAP,
- PAWP,
- LVEDP, if available,
- Indirect Fick CO,
- Thermodilution CO,
- PVR.

For the analysis of the primary endpoint, the PVR values will be derived by the sponsor using the assessments provided by the central reader (WCC) CCI [redacted]

PVR (dyn·sec·cm-5): PVR=((mPAP−PAWP)/CO)×80

- If a valid PAWP cannot be obtained and a valid LVEDP is available then LVEDP will be used instead of PAWP
- If PAWP and LVEDP are missing at post-baseline, the available baseline PAWP (or LVEDP) for the subject is used as a substitute for the missing post-baseline PAWP.
- If the thermodilution CO is not obtainable or available, then this value will be imputed from the indirect Fick CO.

The primary endpoint is the ratio of EDBT to Baseline PVR, ie, $\left(\frac{PVR\ at\ EDBT}{PVR\ at\ baseline}\right)$. It is assumed to follow a log-normal distribution. Consequently, the statistical analysis will be performed on the log of this ratio, and the primary endpoint is the absolute change from baseline to EDBT visit of the log-transformed PVR values. The results will be presented on the original scale (geometric means [GMs]) after exponentiation of the absolute mean changes obtained on the log scale.

If PVR value is missing (or excluded due to the occurrence of intercurrent events) at EDBT, it will be imputed according to the rules described in Section 5.2.2.

5.2.2. Estimand

The primary PVR estimand is described according to the following 4 attributes:

A. **Treatment:** 2 treatment comparisons of interest: FDC of macitentan 10 mg and tadalafil 40 mg (M/T FDC) compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg; treatments as randomized.

B. **Population:** FAS, as randomized.

C. **Variable:** As defined in Section 5.2.1.

D. **Intercurrent events** (events that preclude observation of the variable or affect its interpretation):

- Death occurring prior to the EDBT visit,
- Prohibited PAH-specific medication (see Section 4.6) received for any reason prior to EDBT visit,
- Study treatment discontinuation/interruption for more than 2 days immediately prior to the EDBT visit,
- Study treatment(s) dose adjustments at any time prior to the EDBT visit except from the planned up-titration in Weeks 1 and 2.

E. **Population-level summary:** Ratio of the geometric means between the M/T FDC group and each monotherapy group (macitentan 10 mg and tadalafil 40 mg) separately. Based on the INC of the stage-wise test statistics to control for the adaptive design, the main estimator at final analysis will be the median unbiased estimator for the overall treatment effect and corresponding RCIs based on the stage-wise ordering (see ATTACHMENT 3, Section 6).

Intercurrent events will be handled as follows:

- "Death occurring prior to the EDBT visit" will be addressed by imputing the EDBT PVR value using the rules defined in Section 5.2.3.2.
- "Prohibited PAH-specific medication received for any reason prior to EDBT visit" will be addressed by disregarding the PVR assessments obtained at the EDBT visit and imputing them with the rules defined in Section 5.2.3.2.
- "Study treatment discontinuation/interruption for more than 2 days immediately prior to the EDBT visit" will be addressed by disregarding the PVR assessments obtained more than 2 days after study treatment discontinuation/interruption and imputing them with the rules defined in Section 5.2.3.2.
- "Study treatment(s) dose adjustments at any time prior to the EDBT visit" will not lead to exclusion of on-treatment PVR assessments obtained at EDBT, and those values, if available, will be used in the primary analysis, otherwise they will be imputed with the rules defined in Section 5.2.3.2.

This estimand targets the effect of treatment initiation on the variable measurement prior to the occurrence of death or introduction of prohibited PAH-specific medication and follows a "while on treatment" strategy. For purposes of the primary endpoint, on-treatment is defined as up to 2 days after last DB treatment intake.

5.2.3. Analysis Methods

5.2.3.1. Hypotheses and statistical model

GM_{FDC} denotes the geometric mean of the ratios of EDBT to Baseline PVR values for subjects randomized to the M/T FDC group.

$GM_{macitentan\ 10\ mg}$ denotes the geometric mean of the ratios of EDBT to Baseline PVR values for subjects randomized to the macitentan 10 mg group.

$GM_{tadalafil\ 40\ mg}$ denotes the geometric mean of the ratios of EDBT to Baseline PVR values for subjects randomized to the tadalafil 40 mg group.

The global null hypothesis (H_O) is the union of 2 null hypotheses:

H_O: $H_{O1} \cup H_{O2}$,

where:

H_{O1} is "$GM_{FDC} / GM_{macitentan\ 10\ mg} = 1$" in the combined treatment-naïve and prior-ERA strata,

H_{O2} is "$GM_{FDC} / GM_{tadalafil\ 40\ mg} = 1$" in the combined treatment-naïve and prior-PDE-5i strata.

The global alternative hypothesis (H_1) is the intersection of 2 alternative hypotheses:

H_1: $H_{11} \cap H_{12}$,

Where:

H_{11} is "$GM_{FDC} / GM_{macitentan\ 10\ mg} \neq 1$" in the combined treatment-naïve and prior-ERA strata,

H_{12} is "$GM_{FDC} / GM_{tadalafil\ 40\ mg} \neq 1$" in the combined treatment-naïve and prior-PDE-5i strata.

5.2.3.2. Handling of missing data for the main analysis

By design, only 1 post-Baseline PVR measurement must be taken at the time of the scheduled EDBT visit. In some instances, the EDBT assessment may be missing with no other post-Baseline assessment available.

If PVR cannot be calculated due to missing PAWP, the following conventions will be applied for the calculation at a visit at which both mPAP and CO are assessed and not missing:

1. If PAWP is missing, LVEDP will be used.
2. If PAWP and LVEDP are missing at post-Baseline, the available baseline PAWP (or LVEDP) for the subject is used as a substitute for the missing post-baseline PAWP.

In the case of a completely missing PVR assessment at EDBT, the following missing data imputation rules will be used:

- If the subject dies prior to Week 16, the highest observed individual ratio of the last on-treatment PVR to the baseline PVR in the FAS, amongst all subjects in the same stratum is imputed (or a value of 1 [ie, no change from baseline] is imputed if this worst observed value is an improvement [ie, decrease] from baseline).
- If the subject has a disease progression/worsening as confirmed by the adjudication committee prior to Week 16, the 75th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all subjects in the same stratum will be used to impute the on-treatment PVR value.
- If the subject does not die and does not experience a disease progression/worsening as confirmed by the adjudication committee prior to Week 16, the 50th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all subjects in the same stratum and treatment group will be used to impute the on-treatment PVR value.

5.2.3.3. Main analysis

The null hypotheses will be tested by means of two ANCOVA models on the $\log_e$ transformed ratios of EDBT to Baseline PVR values. Model covariates will include randomized treatment, the $\log_e$ transformed Baseline PVR value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i). The resulting least squares (LS) means and 95% CLs obtained in each treatment group, and the LS-means differences (95% CLs) for M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg will be inversely transformed using the exponential function and multiplied by 100 to provide:

1. the adjusted geometric mean of the ratios of EDBT to Baseline PVR values and corresponding 95% CLs, expressed in percent, in each treatment group, and
2. the adjusted GMRs and corresponding 95% CLs for M/T FDC vs macitentan 10 mg (GMR1) and for M/T FDC vs tadalafil 40 mg (GMR2).

The 2 p-values obtained from the tests of GMR1 and GMR2 (ie, the p-values for the LS-means differences) will be used to determine the superiority of M/T FDC vs macitentan 10 mg and tadalafil 40 mg.

At the time of the IA, the 2 p-values obtained for the pairwise comparisons will be used to implement the statistical decision rules described in Section 3.3.2.

The final Week 16 analysis of the primary efficacy endpoint will be conducted using the INC method with pre-specified weights to combine first and second stage p-values (see ATTACHMENT 3).

Final interpretation of the results will then be based on the final adjusted p-value, median unbiased estimator for the overall treatment effect and corresponding RCIs obtained by ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company). Refer to Section 0 for details.

At the final Week 16 analysis, the global null hypothesis will be rejected if both tests are significant at the appropriate alpha level according to the testing strategy detailed in Section 5.1.1 and Section 3.3.2.

For each analysis/supportive analysis, absolute values at baseline and at EDBT as well as absolute pre to post changes from baseline to EDBT in PVR will be summarized using descriptive statistics in addition to the analysis results. This will provide summary statistics for EDBT and change to EDBT for each imputation rule defined by the use of the intercurrent events. In addition, the number of subjects in the different intercurrent event scenarios, and with missing or imputed PVR values, will be described. All available RHC data for the DB treatment period will also be listed.

Absolute values at baseline and at EDBT as well as absolute pre to post changes from baseline to EDBT in PVR as reported by the sites on the eCRF will also be summarized using descriptive statistics.

5.2.3.4. Supportive/sensitivity analyses

For the primary estimand, the following sensitivity analyses will be performed. The sensitivity estimators obtained will not control for the adaptive design and will not be based on the stage-wise splitting as applied for the main analysis.

i. Sensitivity analyses to assess the impact of missing values and their imputation

To assess the robustness of the model towards possible stratum or treatment-arm-related drop-out patterns, the following 3 sensitivity analyses for the primary endpoint will be conducted:

Sensitivity analysis 1: Repeat the primary imputation rule with the exceptions that the values to be imputed in case of death or disease progression must be determined regardless of stratum instead of within the same stratum as defined for the primary analysis.

Sensitivity analysis 2: Use of multiple imputation where each missing value is replaced with a set of plausible values that represent the uncertainty about the right value to impute. Each one of the imputed data sets is analyzed using the same model as for the primary analysis and eventually aggregated using Rubin's rule.

Sensitivity analysis 3: A tipping-point analysis will be performed where missing data are replaced with a range of values to see how extreme the imputed value of the missing data must be for the results of the study to tip from significant to not significant.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

Sensitivity analysis 4: An observed case analysis applying the main ANCOVA model without any imputation (see Section 5.2.3.3).

ii. Sensitivity analyses for potential deviations from the normality assumptions

Sensitivity analysis 5: To address the impact of potential deviations from the assumption of normality of the residuals from the primary ANCOVA models, a non-parametric test (stratified rank analysis of covariance) will be performed as follows:

- Missing EDBT values will be imputed as specified for the primary analysis in Section 5.2.3.3.
- Ranking will be performed by stratum (regardless of treatment group) on the primary variable ($\log_e$-transformed ratios of EDBT to baseline PVR values) and the $\log_e$-transformed baseline PVR value.
- A stratified (by stratum) Wilcoxon-Mann-Whitney test will be performed on the residuals from the linear regression of the response variable ranks on the baseline ranks.

iii. Other sensitivity analyses

Sensitivity analysis 6: The primary endpoint analysis (ANCOVA) will be repeated without adjustment for the stratification factors.

Sensitivity analysis 7: The primary endpoint analysis (ANCOVA) will be repeated without adjustment to control for the adaptive design. The analysis will be carried out on the total sample size (without the stage-wise splitting approach).

iv. Other estimands

Five additional estimands will also be assessed (based on the INC of the stage wise test statistics to control for the adaptive design as for the primary estimand):

- same as the primary estimand except that "prohibited PAH-specific medication received prior to EDBT visit" will not be considered as an intercurrent event and PVR assessments obtained after such an event will not be excluded from the analysis for that reason,
- same as the primary estimand except that on-treatment is defined as up to 7 days after last DB treatment intake instead of 2 days for the primary estimand,
- same as the primary estimand except that:
  - "prohibited PAH-specific medication received prior to EDBT visit" will not be considered as an intercurrent event and PVR assessments obtained after such an event will not be excluded from the analysis for that reason,
  - on-treatment is defined as up to 7 days after last DB treatment intake instead of 2 days for the primary estimand,
- same as the primary estimand except for the variable of interest, which is the absolute change from baseline to EDBT in PVR instead of the ratio of EDBT to baseline PVR.
- same as the primary estimand except that in the population definition and for the treatment attribute, subjects are analyzed according to treatment received as opposed to treatment assigned.

- same as the primary estimand except that the population definition will be changed to FAS excluding subjects with major deviation to the inclusion and exclusion criteria that could impact the assessment of the primary endpoint.

5.3. Secondary Endpoints

The secondary efficacy endpoints are listed here according to the hierarchical order that will be statistically tested:

- Change from baseline to EDBT in 6MWD.
- Proportion of subjects with absence of worsening in WHO FC from baseline to EDBT.

The primary estimands for each of the secondary endpoint variables defined in Section 5.3 follow the same approach as the primary endpoint estimand with the following exceptions:

- On-treatment is defined as up to 7 days after last DB treatment intake,
- Assessments obtained in subjects receiving prohibited PAH-specific medication for any reason prior to EDBT visit are *not* excluded from the analysis.

The rationale for handling intercurrent events differently for the secondary endpoint estimands compared to the primary endpoint is to minimize missing data. We allow a slightly wider window before exclusion of assessments, as an immediate impact of prohibited PAH medication / study drug discontinuation on the values being measured is not expected.

The primary endpoint estimand strategy will also be applied to the secondary endpoints as a sensitivity analysis.

The sensitivity estimators obtained for the secondary endpoints will not control for the adaptive design and will not be based on the stage-wise splitting as applied for the main analysis.

5.3.1. Change from baseline to EDBT in 6MWD

5.3.1.1. Definition

This secondary efficacy endpoint is the change from baseline to EDBT in 6MWD (in meters), defined as:

6MWD (m) at EDBT−6MWD (m) at baseline.

5.3.1.2. Analysis Methods

5.3.1.2.1. Estimand

The estimand defining the treatment effect on the secondary endpoint, change from baseline to EDBT in 6MWD, has the following attributes:

A. **Treatment:** 2 treatment comparisons of interest: FDC of macitentan 10 mg and tadalafil 40 mg (M/T FDC) compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg; treatments as randomized

B. **Population:** FAS, as randomized, subjects with non-missing baseline 6MWD value

C. **Endpoint:** As defined in Section 5.3.1.1.

D. **Intercurrent event:**
   - Death occurring prior to the EDBT visit,
   - Prohibited PAH-specific medication received for any reason prior to EDBT visit,
   - Study treatment discontinuation/interruption for more than 7 days immediately prior to the EDBT visit,
   - Study treatment(s) dose adjustments at any time prior to the EDBT visit except from the planned up-titration in Weeks 1 and 2.

E. **Population-level summary measure**: Difference in means of change from baseline 6MWD between the M/T FDC group and each monotherapy group (macitentan 10 mg and tadalafil 40 mg) separately. Based on the INC of the stage-wise test statistics to control for the adaptive design, the main estimator at final analysis will be the median unbiased estimator for the overall treatment effect and corresponding RCIs based on the stage-wise ordering (see ATTACHMENT 3, Section 6)

Intercurrent events will be handled as follows:

- "Death occurring prior to the EDBT visit" will be addressed by imputing the EDBT 6MWD value using the rules defined in Section 5.3.1.2.2.
- "Prohibited PAH-specific medication received for any reason prior to EDBT visit" will not lead to exclusion of on-treatment 6MWD assessments obtained at EDBT, and those values, if available, will be used in the primary analysis, otherwise they will be imputed with the rules defined in Section 5.3.1.2.2.
- "Study treatment discontinuation/interruption for more than 7 days immediately prior to the EDBT visit" will be addressed by disregarding the 6MWD assessments obtained more than 7 days after study treatment discontinuation/interruption and imputing them with the rules defined in Section 5.3.1.2.2.
- "Study treatment(s) dose adjustments at any time prior to the EDBT visit" will not lead to exclusion of on-treatment 6MWD assessments obtained at EDBT, and those values, if available, will be used in the primary analysis, otherwise they will be imputed with the rules defined in Section 5.3.1.2.2.

This estimand targets the effect of treatment initiation on the variable measurement prior to the occurrence of death and follows a "while on treatment" strategy.

5.3.1.2.2. Handling of missing data for the main analysis

In the main analysis, if an EDBT assessment is missing for subjects with a post-Baseline 6MWD measurement obtained before EDBT, the (last) post-Baseline 6MWD measurement will be carried forward unless this imputation would lead to an improvement, in which case a change of 0 m (no change) will be imputed. For subjects without a post-Baseline 6MWD measurement, a change of 0 m (no change) will be imputed. If the subject dies before Week 16, the lowest (worst

deterioration) change from Baseline recorded amongst all subjects in the same treatment group will be imputed.

5.3.1.2.3. Main analyses

The change from Baseline to EDBT in 6MWD will be analyzed for each comparison of interest by means of an ANCOVA model that will include treatment group, Baseline 6MWD value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) as covariates. LS-mean estimates for each treatment group and for the treatment effects (M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg) will be displayed with means, 95% CLs, and p-value.

The 2 p-values obtained from each test (ie, the p-values for the LS-means differences) will be used to determine the superiority of M/T FDC vs macitentan 10 mg and tadalafil 40 mg. The global null hypothesis will be rejected if both tests are significant at the appropriate alpha level according to the testing strategy detailed in Section 5.1.1 and Section 3. Median unbiased parameter estimates and repeated CLs will be presented in the final analysis using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company). The assumptions of the ANCOVA model (normality of the residuals and homogeneity of variance) will be investigated graphically (eg, Q-Q plot and residual plots). If there are major deviations from the assumptions, alternative non-parametric tests will be conducted.

For each analysis/supportive analysis, absolute values at baseline and at EDBT as well as absolute pre to post changes from baseline to EDBT in 6MWD will be summarized using descriptive statistics in addition to the analysis results. This will provide summary statistics for EDBT and change to EDBT for each imputation rule defined by the use of the intercurrent events. In addition, the number of subjects in the different intercurrent event scenarios, and with missing or imputed 6MWD values, will be described. All available 6MWD data for the DB treatment period will also be listed.

Supportive data collected on Borg dyspnea index or oxygen saturation will be listed only.

5.3.1.2.4. Supportive/sensitivity analyses

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- An observed case analysis, applying the main ANCOVA without any imputation of missing EDBT assessments.
- An analysis applying the main ANCOVA without adjustment for the stratification factors.
- A mixed model repeated measure model performed on the FAS using the “on-treatment” observed data up to Week 16, ie, at baseline, Week 8 and Week 16. For this analysis, the assessment will be windowed, eg, for Week 8, any measurement between study Day 2 and study Day 84 will be considered and for Week 16, any measurement between study Day 85 and min(EOT-DB+7 days, start of OL treatment) will be considered. If a subject has 2 or more measurements during the window, the closest to the target day (Day 57 for Week 8 and Day 113 for Week 16) will used for the analysis. If 2 measurements are equidistant from the target

day, the later one is used. In addition, absolute values at baseline and by visit as well as absolute changes from baseline during the DB period will be summarized by treatment on the FAS using descriptive statistics. This will be done for "on-treatment" data and repeated when also including off-treatment measurements up to Week 16 (Visit 8).

- An analysis applying the main ANCOVA but using the primary endpoint estimand strategy.

5.3.2. Proportion of subjects with absence of worsening in WHO FC from baseline to EDBT

5.3.2.1. Definition

Absence of worsening in WHO FC level at EDBT as compared to baseline is characterized based on the following dichotomous variable:

- Worsening: X=0 if (difference between EDBT and baseline in WHO FC) >0
- No worsening: X=1 if (difference between EDBT and baseline in WHO FC) ≤0

The secondary endpoint is the proportion of subjects who remained stable or improved (no worsening) (X=1) between baseline and EDBT.

5.3.2.2. Analysis Methods

5.3.2.2.1. Estimand

The estimand defining the treatment effect on the secondary endpoint, change from baseline to EDBT in WHO FC, has the following attributes:

A. **Treatment:** 2 treatment comparisons of interest: FDC of macitentan 10 mg and tadalafil 40 mg (M/T FDC) compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg; treatments as randomized.

B. **Population:** FAS, as randomized, subjects with non-missing baseline WHO FC value.

C. **Endpoint:** As defined in Section 5.3.2.1.

D. **Intercurrent event:**
   - Death occurring prior to the EDBT visit,
   - Prohibited PAH-specific medication received for any reason prior to EDBT visit,
   - Study treatment discontinuation/interruption for more than 7 days immediately prior to the EDBT visit; study treatment(s) dose adjustments at any time prior to the EDBT visit, except from the planned up-titration in Weeks 1 and 2.

E. **Population-level summary measure:** odds ratio (OR) of the proportions of subjects with absence of worsening in WHO FC between the M/T FDC group and each monotherapy group (macitentan 10 mg and tadalafil 40 mg) separately. Based on the INC of the stage-wise test statistics to control for the adaptive design, the main estimator at final analysis will be the median unbiased estimator for the overall treatment effect and corresponding RCIs based on the stage-wise ordering (see ATTACHMENT 3, Section 6).

Intercurrent events will be handled as follows:

- "Death occurring prior to the EDBT visit" will be addressed by imputing the absence of worsening in WHO FC level at EDBT value using the rules defined in Section 5.3.2.2.2.
- "Prohibited PAH-specific medication received for any reason prior to EDBT visit" will not lead to exclusion of on-treatment WHO FC assessments obtained at EDBT, and those values, if available, will be used in the primary analysis, otherwise they will be imputed with the rules defined in Section 5.3.2.2.2.
- "Study treatment discontinuation/interruption for more than 7 days immediately prior to the EDBT visit" will be addressed by disregarding the WHO FC assessments obtained more than 7 days after study treatment discontinuation/interruption and imputing them with the rules defined in Section 5.3.2.2.2.
- "Study treatment(s) dose adjustments at any time prior to the EDBT visit" will not lead to exclusion of on-treatment WHO FC assessments obtained at EDBT, and those values, if available, will be used in the primary analysis, otherwise they will be imputed with the rules defined in Section 5.3.2.2.2.

This estimand targets the effect of treatment initiation on the variable measurement prior to the occurrence of death and follows a "while on treatment" strategy.

5.3.2.2.2. Handling of missing data for the main analysis

In the main analysis, if an EDBT assessment is missing, subjects will be assumed to have worsened at EDBT.

5.3.2.2.3. Main analyses

The proportion of subjects who improved or remained stable (absence of worsening) from baseline to EDBT in WHO FC (ie, a change ≤0) will be analyzed for each comparison of interest as a binary variable (no worsening vs worsening) by means of a logistic regression model. The model for the decrease from baseline to EDBT 'Yes/No' in WHO FC, representing a shift to a lower FC, will include treatment group, baseline WHO FC, and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) as covariates. The adjusted OR for the treatment effects (M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg) will be displayed with 95% CLs and p-value. An OR above 1 can be interpreted as a larger improvement in WHO FC (or stable) occurring in the M/T FDC group compared to the reference group.

The null hypothesis will be rejected upon achieving a statistically significant difference at the appropriate alpha level (according to the testing strategy detailed in Section 5.1.1 and Section 3) in favor of the FDC vs each of monotherapy arm (macitentan 10 mg and tadalafil 40 mg). Median unbiased parameter estimates, and repeated CLs will be presented in the final analysis using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company).

For each analysis/supportive analysis, the number of subjects in the different intercurrent scenarios, and with missing, imputed or as collected WHO FC values, will be described.

5.3.2.2.4. Supportive/sensitivity analyses

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- An observed case analysis without any imputation of missing EDBT assessments.
- In subjects with a post-baseline WHO FC measurement obtained before Week 16, the post-baseline WHO FC measurement will be carried forward. This imputation will be performed unless the following occurs:
  - If a subject dies without a prior EDBT WHO FC assessment, then the EDBT WHO FC is imputed by class IV.
- An analysis using the primary endpoint estimand strategy.
- The proportion of subjects who improved or remained stable (absence of worsening) from baseline to EDBT in WHO FC (ie, a change ≤0) will also be summarized by visit and treatment, on the FAS using the "on-treatment" observed data up to Week 16, ie, at baseline, Week 8 and Week 16. For this analysis, the assessments will be windowed, eg, for Week 8, any measurement between study Day 2 and study Day 84 will be considered and for Week 16, any measurement between study Day 85 and min(EOT-DB+7 days, start of OL treatment) will be considered. If a subject has 2 or more measurements during the window, the closest to the target day (Day 57 for Week 8 and Day 113 for Week 16) will used for the analysis. If 2 measurements are equidistant from the target day, the later one is used. This will be repeated when also including off-treatment measurements up to Week 16 (Visit 8).

5.4. Other Efficacy Endpoints

For other efficacy endpoints, statistical testing, if performed, will be descriptive only. The estimators obtained for these endpoints will not control for the adaptive design and will not be based on the stage-wise splitting as applied for the main analysis of the primary and secondary endpoints.

Other efficacy endpoints for the DB treatment period are:

- Change from baseline to EDBT in PAH-SYMPACT™ Cardiopulmonary symptom domain score.
- Change from baseline to EDBT in PAH-SYMPACT™ Cardiovascular symptom domain score.
- Change from baseline to EDBT in PAH-SYMPACT™ Physical impact domain score.
- Change from baseline to EDBT in PAH-SYMPACT™ Cognitive/emotional impact domain score.
- Time to first M/M event occurring between baseline and EDBT, defined as any of the following:
  - Death (all causes).
  - Non-planned PAH-related hospitalization.

- Initiation of intravenous or subcutaneous prostacyclin or prostacyclin analog for worsening PAH.
- Clinical worsening defined as:
  - Deterioration in exercise testing, confirmed by two 6-minute walk tests (6MWTs) performed on different days within 2 weeks, showing at least 15% decrease in 6MWD from baseline.

AND

  - Worsening of PAH symptoms, defined as at least 1 of the following
    - Increase in WHO FC.
    - Appearance or worsening of signs/symptoms of right heart failure that do not respond to optimized oral diuretic therapy.

- Time to death due to PAH or hospitalization for PAH occurring between baseline and EDBT:
  - Death due to PAH, or onset of a treatment-emergent AE (TEAE) that led to permanent discontinuation of study treatment with a fatal outcome due to PAH occurring within 4 weeks of study treatment discontinuation.

  OR
  - Non-planned PAH-related hospitalization.
- Change from baseline to EDBT in N-terminal pro B-type natriuretic peptide (NT-proBNP).
- Change from baseline to EDBT in QoL, assessed by the EQ-5D-5L.
- Change from baseline to EDBT in work productivity and activity impairment, assessed by the WPAI©: GH.
- Changes from baseline to EDBT in the following hemodynamic variables:
  - Right atrial pressure.
  - Right ventricular stroke work index (RVSWI).
  - Right atrial pressure / PAWP ratio.
  - Stroke volume index (SVI).
  - Pulmonary artery pulsatility index (PAPi).
  - Pulmonary artery compliance.
- Proportion of subjects who achieve a right atrial pressure of $\leq$8 mmHg at EDBT.
- Proportion of subjects who needed additional diuretics (higher doses or added diuretics) by EDBT.
- Number per year of all-cause and PAH-related hospitalizations, from baseline up to EDBT.
- Number per year of in-patient hospital days for all causes and PAH-related causes, from baseline up to EDBT.
- Number per year of emergency room (ER) visits for all causes and PAH-related causes that do not result in hospital admittance from baseline up to EDBT.

5.4.1. Change from baseline to EDBT in PAH-SYMPACT™ domain scores

5.4.1.1. Definition

The PAH-SYMPACT™ consists of 2 parts: Symptoms and Impacts.

The Symptoms part has two domains: Cardiopulmonary Symptoms Domain and Cardiovascular Symptoms Domain, which contain 6 and 5 items, respectively. The Symptoms part also contains questions about oxygen use. The Impacts part has 2 domains: Physical Impacts Domain and Cognitive/Emotional Impacts Domain, which contain 7 and 4 items, respectively.

Scores for the individual items and domains range from 0–4, with higher scores indicating greater symptom severity or worse impact. Mean weekly symptom item scores are calculated as an average of the daily item scores, and mean symptom domain score is then calculated as the average of the mean weekly scores for its included items (excluding oxygen use). The mean impact domain scores are calculated as the average of the mean impact item scores.

Item scores are set to missing if more than 3 item scores per week are missing. Domain scores are set to missing if more than half of the respective item scores are missing. For more details on scoring algorithm including handling of missing item responses, see Appendix 5 of the protocol.

The 4 main variables for the analysis of the secondary endpoint, change from baseline to EDBT in PAH-SYMPACT™ Symptoms and Impact domains scores, are the absolute changes from baseline to EDBT visit, defined as:

- Domain score at EDBT visit − Domain score at baseline.

5.4.1.2. Analysis Methods

Change from baseline to EDBT in PAH-SYMPACT™ Symptom and Impact domain scores will be analyzed on the PAH-SYMPACT™ Analysis Set for each comparison of interest by means of ANCOVA, as described in Section 5.3.1.2.3. In the main analysis, missing EDBT visit scores will be imputed using the last observation carried forward (including the baseline score).

Absolute values at baseline and at EDBT visit as well as absolute changes from baseline to EDBT visit will be summarized by treatment on the FAS using descriptive statistics. Additionally, it will be summarized how many subjects had the domain score used as collected and how many subjects had imputed value together with the reason for imputation.

5.4.2. Time to First M/M Event Occurring Between Baseline and EDBT

5.4.2.1. Definition

Time to first M/M event occurring between baseline and EDBT is defined as any of the following:

- Death (all causes).
- Non-planned PAH-related hospitalization.
- Initiation of intravenous or subcutaneous prostacyclin or prostacyclin analog for worsening PAH.

- Clinical worsening defined as:
  - Deterioration in exercise testing, confirmed by two 6MWTs performed on different days within 2 weeks, showing at least 15% decrease in 6MWD from baseline.

AND

- Worsening of PAH symptoms, defined as at least 1 of the following
  - Increase in WHO FC.
  - Appearance or worsening of signs/symptoms of right heart failure that do not respond to optimized oral diuretic therapy.

An independent Clinical Events Committee (CEC) of PAH experts will review and confirm all reported M/M events, including start date of the event, in a blinded fashion. All cases confirmed by the CEC will be included in the analysis of the endpoint.

The time to M/M event is determined as the time from baseline (defined as the first dose of study treatment) to the first occurrence of a M/M event confirmed by the CEC.

Subjects without the endpoint event (confirmed by the CEC) in the DB period (between baseline and up to EDBT visit) are right censored at EDBT visit date.

5.4.2.2. Analysis Methods

FAS will be used to analyze this endpoint. Time to first M/M will be tested for each comparison of interest by logrank test comparing M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg.

The time to occurrence of the first CEC confirmed M/M event will be estimated by Kaplan-Meier method. The hazard ratio of M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg from Cox modeling with 95% CLs will also be computed.

Causes of M/M events confirmed by CEC will be summarized in frequency table (as first event and also all events per subject).

Additionally, a sensitivity analysis will be performed on all M/M events up to the EDBT visit regardless of the adjudication by CEC.

5.4.3. Time to death due to PAH or hospitalization for PAH occurring between baseline and EDBT

5.4.3.1. Definition

Time to death due to PAH or hospitalization for PAH occurring between baseline and EDBT is defined as:

- Death due to PAH, or onset of a TEAE that led to permanent discontinuation of DB study treatment with a fatal outcome due to PAH occurring within 4 weeks of study treatment DB discontinuation.

OR

- Non-planned PAH-related hospitalization.

The time to death/hospitalization due to PAH event is determined as the time from baseline (defined as the first dose of study treatment) to the first occurrence of an event specified above.

Subjects without the endpoint event in the DB period (between baseline and up to EDBT visit) are right censored at EDBT visit date unless they died beforehand for reasons not related to PAH, in which case they are censored at the date of death.

5.4.3.2. Analysis Methods

FAS will be used to analyze this endpoint. The time to death/hospitalization due to PAH will be analyzed for each comparison of interest by means of logrank and Cox regression, as described in Section 5.4.2.2.

Death and hospitalizations due to PAH will be summarized in a frequency table (as first event and also all events per subject).

5.4.4. Change From Baseline to EDBT in NT-proBNP

5.4.4.1. Definition

NT-proBNP samples will be processed through the central laboratory, and the results will be sent electronically to Actelion. Results will be reported in conventional units (ng/L).

Change from baseline to EDBT in NT-proBNP will be calculated as:

- NT-proBNP value at EDBT visit−NT-proBNP value at baseline.

5.4.4.2. Analysis Methods

Absolute values at baseline and at EDBT visit as well as absolute changes from baseline to the EDBT visit will be summarized by treatment on the FAS using descriptive statistics.

In addition, the NT-proBNP data will be analyzed in the same way as the primary endpoint, as described in Section 5.2.3.3 using 2 ANCOVA models on the $\log_e$ transformed ratios of EDBT to Baseline values. Model covariates will include randomized treatment, the $\log_e$ transformed Baseline value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i). The resulting LS means and 95% CLs obtained in each treatment group, and the LS-means differences (95% CLs) for M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg, will be inversely transformed using the exponential function and multiplied by 100 to provide:

- the adjusted geometric mean of the ratios of EDBT to Baseline values and corresponding 95% CLs, expressed in percent, in each treatment group, and
- the adjusted GMRs and corresponding 95% CLs for M/T FDC vs macitentan 10 mg and for M/T FDC vs tadalafil 40 mg.

P-values will be descriptive only and no p-value adjustment will be performed.

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.4.5. Change From Baseline to EDBT in Quality of Life, Assessed by the EQ-5D-5L

5.4.5.1. Definition

The EQ-5D-5L consists of a descriptive system (the questionnaire), and the Euro Quality of Life visual analogue scale (EQ VAS):

- The questionnaire assesses health status according to 5 dimensions (Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression). Each dimension is divided into 5 levels (I have no problem, I have slight problem, I have moderate problem, I have severe problem, I am unable to perform the described activity).
- The EQ VAS is a vertical scale, with endpoints of 100 (best imaginable state) at the top and 0 (worst imaginable state) at the bottom, which offers a simple method for obtaining a self-rating of current health-related QoL.

Index score will be computed from the 5 dimensions. A mapping function between EQ-5D-5L and EQ-5D-3L is available for some countries for the index score to be computed (see euroqol.org). For countries where the crosswalk value set is not available, United Kingdom (UK) crosswalk value set will be used. If any of the dimensions is missing, index score is not computed and is set to missing.

A sample of the EQ-5D-5L questionnaire (English version for the UK) and EQ VAS is provided in Appendix 6 of the protocol.

5.4.5.2. Analysis Methods

Absolute values at baseline and at EDBT visit as well as absolute changes from baseline to EDBT visit will be summarized for the EQ VAS and index score by treatment on the EQ-5D-5L Analysis Set using descriptive statistics. Each dimension will be summarized separately at baseline and at EDBT as a categorical variable with number and percentage of subjects in each level.

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.4.6. Change from baseline to EDBT in work productivity and activity impairment assessed by WPAI: GH

5.4.6.1. Definition

The WPAI©: GH (Appendix 9 of the protocol) is a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to general health (Reilly 1993). It has a recall period of 1 week. The WPAI©: GH will not be administered to illiterate subjects, defined as subjects who were unable to sign the ICF for themselves, or subjects for whom the questionnaire is not available in a language that can be easily understood and read by them.

The questionnaire contains 6 questions reflecting situations in the past 7 days prior to filling the questionnaire:

- Q1: Are you currently employed? (Yes/No)
- Q2: Number of hours missed due to health problems
- Q3: Number of hours missed due to other reasons
- Q4: Number of hours actually worked
- Q5: How much health problems affected productivity while you were working? (0 [best] to 10 [worst] scale)
- Q6: How much health problems affected your ability to do regular daily activities, other than work at a job? (0 [best] to 10 [worst] scale)

The following scores will be computed:

- Percent work time missed due to health:

  100 * Q2 / (Q2 + Q4)
- Percent impairment while working due to health:

  100 * Q5 / 10
- Percent overall work impairment due to health:

  100 * Q2 / (Q2 + Q4) + [(1 – (Q2 /(Q2 + Q4)))*(Q5 / 10)]
- Percent activity impairment due to health:

  100 * Q6 / 10

Higher scores indicate greater impairment and less productivity. Scores are calculated only if all individual questions included in the score computation are collected. For more information on the scoring method see (reillyassociates.net).

5.4.6.2. Analysis Methods

Absolute values at baseline and at EDBT visit as well as absolute changes from baseline to EDBT visit in the computed scores will be summarized by treatment on the WPAI© Analysis Set using descriptive statistics.

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.4.7. Change from baseline to EDBT in hemodynamic variables

5.4.7.1. Definition

The study endpoint are changes from baseline to EDBT in the following hemodynamic variables:

- Right atrial pressure.
- RVSWI.
- Right atrial pressure / PAWP ratio.

- SVI.
- PAPi.
- Pulmonary artery compliance.

In addition, other hemodynamic variables are collected in the study. All of the hemodynamic variables are based on RHC results and RHC methodology as described in Section 7.2.2.1 of the protocol CCI [redacted]. Some of the data are entered by the sites in the eCRF while a central reader (WCC) will also evaluate the data and provide an independent assessment of the hemodynamic variables as described in the WCC Independent review charter.

Table 5 provides of list of the hemodynamic variables, their source (main and secondary) and derivation rules (if applicable).

Notes:
- If a valid PAWP cannot be obtained and a valid LVEDP is available then LVEDP will be used instead of PAWP.
- If PAWP and LVEDP are missing at post-baseline, the available baseline PAWP (or LVEDP) for the subject is used as a substitute for the missing post-baseline PAWP.
- If the thermodilution CO is not obtainable or available, then this value will be imputed from the indirect Fick CO.

Table 5: Overview of hemodynamic variables

Hemodynamic variable	Primary Source	Primary Derivation	Secondary Source	Secondary Derivation
Right atrial pressure (mRAP)	WCC	As transferred	eCRF	As collected
Pulmonary artery wedge pressure (PAWP)	WCC	As transferred	eCRF	As collected
Left ventricular end diastolic pressure (LVEDP)	WCC	As transferred, if available	eCRF	As collected, if available
Diastolic pulmonary artery pressure (dPAP)	WCC	As transferred	eCRF	As collected

Table 5: Overview of hemodynamic variables				
Hemodynamic variable	**Primary Source**	**Primary Derivation**	**Secondary Source**	**Secondary Derivation**
Systolic pulmonary artery pressure (sPAP)	WCC	As transferred	eCRF	As collected
Mean pulmonary artery pressure (mPAP)	WCC	As transferred, based on sPAP and dPAP also derived by WCC	eCRF	As collected
Right ventricular stroke work index (RVSWI)	Sponsor derived	RVSWI (gram/m^2/beat) = (stroke volume [SV] / body surface area [BSA]) × (mPAP − mRAP) × 0.0136 Using mPAP and mRAP as transferred by WCC, BSA as derived by the sponsor and SV as derived by the sponsor using WCC CO and HR as collected in the eCRF,	Sponsor derived	Using eCRF data instead of WCC
Cardiac index (CI)	Sponsor derived	CI (l·min-1.m-2): CI = CO / BSA Using CO as transferred by WCC and BSA as derived by the sponsor	Sponsor derived	Using eCRF data instead of WCC
Fick Cardiac output (CO)	WCC	As transferred based on eCRF/site data on: - Subjects age, sex, height (cm), and weight (kg) - HR during RHC (bpm) - Hemoglobin (g/dL) - Mixed Veneous Oxygen Saturation (%) (Acquired from distal port of the pulmonary artery catheter).	eCRF	As collected

Table 5: Overview of hemodynamic variables				
Hemodynamic variable	**Primary Source**	**Primary Derivation**	**Secondary Source**	**Secondary Derivation**
		- Arterial Oxygen Saturation (%) (Acquired using oximeter) And on oxygen consumption (ml/min) calculated by WCC based on gender, age, HR and BSA.		
Thermodilution Cardiac output (CO)	WCC	As transferred	eCRF	As collected
Body Surface Area (BSA)	Sponsor derived	BSA (m^2)= 0.007184 × $weight^{0.425}$ × $height^{0.725}$ (with weight expressed in kg and height in cm), based on eCRF/site data on: - Subjects height (cm), and weight (kg) at the same visit as the RHC assessment		
Right atrial pressure / PAWP ratio	Sponsor derived	Ratio = mRAP / PAWP, Using mRAP and PAWP as transferred by WCC	Sponsor derived	Using eCRF data instead of WCC
Stroke volume index (SVI)	Sponsor derived	SVI (ml/m^2/beat) = SV / BSA, based on CO as transferred by WCC and BSA as derived by the sponsor	Sponsor derived	Using eCRF data instead of WCC
Stroke volume (SV)	Sponsor derived	SV (ml) = CO × 1000 / HR, based on CO as transferred by WCC and HR as collected in the eCRF	Sponsor derived	Using eCRF data instead of WCC
Pulmonary artery	Sponsor derived	PAPi = (sPAP − dPAP) / mRAP, Using sPAP,	Sponsor derived	Using eCRF data instead of WCC

Table 5: Overview of hemodynamic variables				
Hemodynamic variable	**Primary Source**	**Primary Derivation**	**Secondary Source**	**Secondary Derivation**
pulsatility index (PAPi)		dPAP and mRAP as transferred by WCC		
Pulmonary artery compliance	Sponsor derived	Pulmonary artery compliance (ml/mmHg) = SV / (sPAP - dPAP), based on sPAP, dPAP and CO as transferred by WCC and HR as collected in the eCRF	Sponsor derived	Using eCRF data instead of WCC
Mixed venous oxygen saturation	eCRF	As collected		
Arterial oxygen saturation	eCRF	As collected		
Systolic Systemic Arterial Pressure (s-SAP)	eCRF	As collected		
Diastolic Systemic Arterial Pressure (d-SAP)	eCRF	As collected		
Total pulmonary resistance (TPR)	Sponsor derived	TPR (dyn·sec·cm-5) = (mPAP /CO) × 80, based on mPAP and CO as transferred by WCC	Sponsor derived	Using eCRF data instead of WCC
Cardiac efficiency (CE)	Sponsor derived	CE (ml/mmHg) = SV / mPAP, based on CO and mPAP as transferred by WCC and HR as collected in the eCRF	Sponsor derived	Using eCRF data instead of WCC

Table 5: Overview of hemodynamic variables				
Hemodynamic variable	**Primary Source**	**Primary Derivation**	**Secondary Source**	**Secondary Derivation**
Right ventricular work (RVW)	Sponsor derived	RVW (l × min−1 × mmHg) = CO × mPAP × 0.0144, based on CO and mPAP as transferred by WCC	Sponsor derived	Using eCRF data instead of WCC
Right ventricular work index (RVWI)	Sponsor derived	RVWI (l·min−1.m−2 × mmHg) = CI × mPAP × 0.0144. Using Janssen derived CI based on CO as transferred by WCC and mPAP as transferred by WCC.	Sponsor derived	Using eCRF data instead of WCC
Right ventricular power	Sponsor derived	Right ventricular power (l·min−1.m−2 × mmHg) = CI × mPAP. Using Janssen derived CI based on CO as transferred by WCC and mPAP as transferred by WCC.	Sponsor derived	Using eCRF data instead of WCC
Pulmonary artery elastance	Sponsor derived	Pulmonary artery elastance (mmHg/mL) = sPAP / SV. based on CO and sPAP as transferred by WCC and HR as collected in the eCRF	Sponsor derived	Using eCRF data instead of WCC

5.4.7.2. Analysis Methods

Absolute values at baseline and at EDBT visit as well as absolute changes from baseline to EDBT visit will be summarized by treatment on the FAS using descriptive statistics. In addition, the data will be listed. Summaries and listings will be produced for all hemodynamic parameters described in Table 4 and for both derivations methods if 2 methods are described in the table.

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.4.8. Proportion of Subjects Who Achieve a Right Atrial Pressure of ≤8 mmHg at EDBT

5.4.8.1. Definition

Right atrial pressure is based on RHC results. If a subject does not have right atrial pressure measurement or it was done after EDBT visit date such subject will be considered as not achieving the right atrial pressure of ≤8 mmHg.

5.4.8.2. Analysis Methods

FAS will be used to analyze this endpoint. The proportion of subjects achieving atrial pressure of ≤8 mmHg will be presented together with the 2-sided 95% CLs based on the exact binomial distribution. The p-values from Fisher's test will also be presented for the comparison between M/T FDC and macitentan 10 mg and between M/T FDC and tadalafil 40 mg. In addition, the 95% CLs for the risk ratio will be presented for both comparisons.

5.4.9. Proportion of Subjects Who Needed Additional Diuretics by EDBT

5.4.9.1. Definition

Proportion of subjects who needed additional diuretics (higher doses or added diuretics) by EDBT. Diuretics will be based on the Concomitant Therapy CRF page. Subject will be marked as "needed additional diuretics by EDBT" if the first diuretics dose increase or added diuretics is identified between the first dose of study treatment and EDBT visit.

5.4.9.2. Analysis Methods

FAS will be used for the analysis. The proportion of subjects will be analyzed in the same way as described in Section 5.4.8.2.

5.4.10. Number Per Year of All-cause and PAH-related Hospitalizations and In-patient Hospital Days, From Baseline up to EDBT.

5.4.10.1. Definition

All hospitalizations starting between the first dose of study treatment and up to EDBT visit will be used for number per year of hospitalizations and in-patient hospital days. The following medical encounters are considered hospitalizations:

- Intensive care unit
- Hospice/palliative care unit
- Hospital in-patient department
- Long-term care facility
- Rehabilitation center

Hospitalizations will be identified as PAH-related based on the investigator's assessment of the hospitalization.

Subject's time on study (in years) for hospitalization endpoints will be derived as follows:

(EDBT visit date–Date of first dose of study treatment+1)/365.25.

Subject-years on study in a treatment group will be computed as the total subject's time on study for all subjects in the treatment group.

The number of days for a hospitalization will be counted as:

Min(hospitalization discharge date, EDBT visit date)−hospitalization admission date+1.

In case of missing discharge date of a hospitalization that is not ongoing, the number of days for the hospitalization will be imputed as a median hospitalization length in the geographical region. If the median hospitalization length in the geographical region cannot be computed or the hospitalization is ongoing, the length of the hospitalization will be computed from the admission date up to the EDBT visit date.

5.4.10.2. Analysis Methods

This endpoint will be analyzed for FAS.

The total number of hospitalizations will be added up by treatment group. This number will then be divided by subject-years on study in the treatment group to obtain the number per year of hospitalizations.

The same approach as for the number per year of hospitalizations will be done for the number per year of in-patient hospitalization days.

5.4.11. Number per Year of Emergency Room Visits From Baseline up to EDBT.

5.4.11.1. Definition

All ER medical encounters between the first dose of study treatment and up to EDBT visit will be used for the number per year of ER visits. If an ER visit results in a hospital admittance (ie, subject has other hospitalization, as defined in Section 5.4.10.1 reported on the same day), such an encounter will not be considered for this endpoint.

ER visits will be identified as PAH-related based on the investigator's assessment of the encounter.

Subject's time on study and subject-years on study in a treatment group are derived in the same way as described in Section 5.4.10.1.

5.4.11.2. Analysis Methods

This endpoint will be analyzed for the FAS. The total number of ER visits will be added up by treatment group and divided by subject-years on study in the treatment group to obtain the number per year of ER visits.

6. SAFETY

All safety analyses will be based on the SS and reported by actual treatment received, unless otherwise specified. Summaries will be displayed by treatment and strata group as described in Section 2.3.7.

For all continuous safety variables, descriptive statistics will include the N, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

All safety data will be listed, with flags for treatment-emergent quantitative abnormalities. AEs in subjects who were screened but not treated will be listed.

Treatment-emergent period

Treatment-emergent period is defined from first intake of study treatment in the DB period up to min(EOT-DB+30 days, start date of OL treatment)

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) at the DBL. All reported TEAEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. No formal testing between treatment groups will be done.

If severity of AE is missing the worst severity, ie, “Severe” will be imputed. If AE relationship to the study treatment is missing, “Related” will be imputed.

An overall summary table of TEAEs will be provided, containing number of subjects with at least 1:

- AE
- AE related to study treatment
- SAE
- SAE related to study treatment
- AE leading to premature discontinuation of study treatment
- Fatal AE

Summary tables will be provided by SOC and PT within each SOC, in descending order of incidence for:

- AEs
- SAEs
- AEs leading to premature discontinuation of study treatment

- Fatal AEs
- AEs by intensity
- AEs by relationship to study treatment

Additionally, summary tables will be provided by PT, in descending order of incidence for:

- AEs
- SAEs
- AEs leading to premature discontinuation of study treatment
- Fatal AEs
- AEs by intensity
- AEs by relationship to study treatment
- AEs of special interest (hypotension, anemia, edema and fluid retention, and hepatic disorders)

AEs of special interest are defined in ATTACHMENT 2.

In addition to the summary tables, listings will be provided for subjects who experienced at least 1:

- AE
- SAE
- AE leading to premature discontinuation of study treatment

Frequencies for the following treatment-emergent deaths and all deaths in the DB period and corresponding parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study treatment (yes/no/unknown)

The summary will be based on the Death Information CRF page, and relationship to the study treatment will be mapped through corresponding AE, if available. A listing of subjects who died will be provided.

6.2. Clinical Laboratory Tests

All laboratory data will be reported in International System (SI) units. All laboratory data provided by central laboratory will be taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled visits. Local laboratory data will be included in listings and used only to find marked abnormalities.

If value below limit of quantification (LOQ) is recorded, the LOQ value itself will be used in the summaries instead. It will be clearly noted in the listings if value is below LOQ.

List of parameters:

Hematology

- Hemoglobin (g/L).
- Hematocrit (L/L).
- Erythrocyte count (reticulocyte count) (10^{12}/L).
- Leukocyte count with differential counts (10^9/L).
- Platelet count (10^9/L).

Clinical chemistry

- Alanine aminotransferase (ALT) (U/L).
- Aspartate aminotransferase (AST) (U/L).
- Alkaline phosphatase (U/L).
- Total and direct bilirubin (µmol/L).
- Creatinine (µmol/L).
- Blood urea nitrogen (mmol/L).
- Uric acid (µmol/L).
- Glucose (mmol/L).
- Sodium, potassium, chloride, calcium, magnesium (mmol/L).
- Total protein, albumin (g/L).
- Albumin/globulin ratio.
- Estimated glomerular filtration rate (mL/min/1.73 m^2)

Coagulation tests

- Prothrombin time and/or international normalized ratio.
- Activated partial thromboplastin time.

Abnormalities

A postbaseline marked abnormality (abnormality based on criteria defined in Table 6 and Table 7 below) will be considered treatment emergent if it is worse than the baseline abnormality (ie, worsening in category). If the baseline abnormality is missing, the abnormality is always considered treatment emergent. If the postbaseline value is above the upper limit and the baseline value is below the lower limit, then the postbaseline abnormality will be considered treatment-emergent. The same applies to the postbaseline value being below the lower limit with the baseline value being above the upper limit.

Table 6: Blood chemistry marked abnormalities (SI Units)				
Laboratory test name (CDISC Synonym[s])	**LL**	**LLL**	**HH**	**HHH**
Alanine aminotransferase	NA	NA	> 3 × ULN	> 5 × ULN
Aspartate aminotransferase	NA	NA	> 3 × ULN	> 5 × ULN
Alkaline phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Bilirubin; Total bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Creatinine	NA	NA	> 1.5 × ULN	> 3 × ULN
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
Creatinine clearance	< 60 ml/min	< 30 ml/min	NA	NA

CDISC=Clinical Data Interchange Standards Consortium; NA = not applicable; ULN = upper limit of normal.

Table 7: Blood chemistry marked abnormalities (SI Units)				
Laboratory test name (CDISC Synonym[s])	**LL**	**LLL**	**HH**	**HHH**
Hemoglobin	< 100 g/L	< 80 g/L	> 20 g/L above baseline	> 40 g/L above baseline
Hematocrit; EVF; PCV (male)	< 0.32 L/L	< 0.20 L/L	> 0.60 L/L	> 0.65 L/L
Hematocrit; EVF; PCV (female)	< 0.28 L/L	< 0.20 L/L	> 0.55 L/L	> 0.65 L/L
Platelets (assuming no platelet cluster)	$< 75 \times 10^9$/L	$< 50 \times 10^9$/L	$> 600 \times 10^9$/L	$> 999 \times 10^9$/L
Leukocytes; white blood cells	$< 3.0 \times 10^9$/L	$< 2.0 \times 10^9$/L	$> 20.0 \times 10^9$/L	$> 100.0 \times 10^9$/L
Neutrophils (Abs)	$< 1.5 \times 10^9$/L	$< 1.0 \times 10^9$/L	NA	NA
Eosinophils (Abs)	NA	NA	$> 5.0 \times 10^9$/L	NA
Lymphocytes (Abs)	$< 0.8 \times 10^9$/L	$< 0.5 \times 10^9$/L	$> 4.0 \times 10^9$/L	$> 20 \times 10^9$/L

CDISC= Clinical Data Interchange Standards Consortium; EVF = erythrocyte volume fraction; NA = not applicable; PCV = packed cell volume.

Treatment-emergent marked laboratory abnormalities will be summarized for each laboratory variable for which marked abnormalities are defined providing their incidence and frequency.

In addition, the proportion of subjects with the following treatment-emergent liver abnormalities will be summarized:

- ALT ≥3× upper limit of normal (ULN), ALT ≥5×ULN, ALT ≥8×ULN
- AST ≥3×ULN, AST ≥5×ULN, AST ≥8×ULN
- ALT or AST ≥3×ULN, ALT or AST ≥5×ULN, ALT or AST ≥8×ULN
- ALT or AST ≥3×ULN and concomitant (collected on the same day) bilirubin ≥2×ULN and both (ALT or AST and bilirubin) increased compared to baseline

Descriptive statistics will be presented for all chemistry, hematology, and coagulation laboratory tests at all specified analysis visit windows.

Change from baseline to all time points specified by analysis visit windows will be summarized for chemistry, hematology and coagulation tests and displayed by treatment group.

An evaluation of drug-induced serious hepatotoxicity (e-DISH) plot of the maximum treatment-emergent ALT (in multiples of ULN) by maximum treatment-emergent bilirubin (in multiples of ULN) will be presented to detect possible cases of drug-induced liver toxicity up to EOT-DB+30 days. Reference lines of 3×ULN for ALT and 2×ULN for bilirubin will be drawn and number and percentage of subjects in each quadrant will be displayed.

All laboratory data will be listed together with derived marked abnormality flag. A separate listing of marked abnormality laboratory values will be provided.

6.3. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including weight, pulse, blood pressure (systolic and diastolic) and BMI will be summarized at each specified analysis visit window. Height will be summarized only at baseline. Change from baseline will be summarized for the treatment-emergent period at each study visit. Descriptive statistics (mean, SD, median, minimum and maximum) will be presented. A listing of all vital sign measurements will be presented together with marked abnormality flag.

Incidence of treatment-emergent markedly abnormal vital signs, as defined in Table 8, will be summarized for subjects who had at least 1 postbaseline assessment for that vital sign. If a subject is missing a baseline assessment, any postbaseline assessment is considered to be an increase/decrease from baseline (ie, any assessment meeting the first part of the abnormality criteria is considered as treatment emergent markedly abnormal vital sign).

Table 8: Blood chemistry marked abnormalities (SI Units)

Vital Sign	Criteria
Pulse	>120 bpm and with >30 bpm increase from baseline
	<50 bpm and with >20 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >40 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline

Table 8: Blood chemistry marked abnormalities (SI Units)	
Vital Sign	Criteria
Diastolic blood pressure	>105 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline

7. BIOMARKERS

Optional biomarker assessments are described in Section 7.2.2.7 of the protocol.

The biomarker analysis will be performed after study closure and will not be included in the study report.

8. CHANGES FROM THE PROTOCOL

The All randomized analysis set was added in the SAP.

The FAS definition was clarified as follows:

From "The FAS includes all randomized subjects who received at least one dose of study treatment." to "The FAS includes all randomized subjects who received at least one dose of at least one study treatment."

A PPS was planned in the protocol but this population will not be defined or used for the analyses. This is because the protocol deviations that could have an impact on the treatment effect are the same as the intercurrent events already handled via the estimands and sensitivity analyses, eg, insufficient exposure, non-availability of measurements, use of prohibited medications.

In the protocol, a sensitivity analysis was planned to be performed on subjects in the PPS for the primary and most relevant secondary variables. This will not be performed since no PPS is defined for the study.

The QoL analysis sets definitions were modified to require at least 1 baseline value to be available for the specific questionnaire of interest for inclusion of the subjects in the analysis set instead of requiring at least 1 post baseline value.

In the protocol, it is specified that subject disposition will be summarized for the Screened analysis set. This was changed and the All randomized analysis set will be used for a summary of study disposition, and FAS will be used to summarize treatment disposition. The reason for this change is that subjects not randomized cannot be summarized by treatment group. Number of screened subjects will be still summarized together with screen failure subjects.

It is specified in the protocol that baseline for efficacy endpoints is the last assessment obtained prior to randomization. However, an on-treatment estimand is defined for the primary and secondary endpoints and therefore the baseline definition is revised in the SAP to more appropriately use the last assessment prior to the first dose of study treatment. Additionally, it is not expected for many subjects to have different randomization and start of treatment dates. Such

subjects will be listed together with their randomization date, first dose of study treatment date and the difference in days between these two dates.

In the protocol, study concomitant and study treatment concomitant medications are defined. It is of interest to identify medications that subjects used during the treatment period; for that reason only one definition of concomitant medications is used in the SAP as follows:

A medication that is concomitant is any treatment that is either ongoing at the start of study treatment or initiated during the treatment period up to EOT-DB.

This corresponds to a change to the prior medication definition in the protocol to use the first dose of study treatment instead of the ICF date as a reference date. The modified definition is as follows:

A previous medication is any treatment for which the end date is prior to the first dose of study treatment.

In the protocol, it is specified that subgroup analyses are carried out for the primary endpoint and the 6MWD secondary endpoint. In addition, in the SAP, subgroup analyses are also planned for the WHO FC secondary endpoint.

As per the protocol, all protocol deviations will be reported in the CSR. As per the SAP, in order to align with the Janssen process, only major protocol deviations will be reported in the CSR.

The description of the primary endpoint is clarified in the SAP as “Change in PVR expressed as the ratio of EDBT to baseline”. This corrects an inconsistency in the protocol where it is described as “Change in PVR expressed as the ratio of geometric means of EDBT to baseline” in Section 6.1.1 and in the synopsis while it is correctly described as “the ratio of EDBT to baseline PVR” in Section 10.2.1.

In order to align with the finalized ICH guideline on estimands, the treatment attribute was added as attribute “A” in the estimand description of the primary and secondary endpoints. All other attributes as described in the protocol are therefore re-labelled B-E in the SAP.

For the estimand of the secondary endpoints 6MWD and WHO FC, an extra condition had been specified in the SAP to select the population requiring that the population only includes subjects with non-missing baseline value. Missing baseline is independent from treatment allocation and exclusion of those subjects from the estimand population should not lead to selection bias.

It is clarified in the SAP that for all endpoints for which statistical analyses are performed, separate models will be used for each comparison of interest as is done for the primary endpoint. For example for the secondary endpoint 6MWD, the protocol text for the analysis is changed from:

“The change from baseline to EDBT in 6MWD will be analyzed by means of an ANCOVA model and will include treatment group, baseline 6MWD value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) as covariates.”

to:

"The change from Baseline to EDBT in 6MWD will be analyzed for each comparison of interest by means of an ANCOVA model that will include treatment group, Baseline 6MWD value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) as covariates."

For the secondary endpoints 6MWD and WHO FC, it is clarified in the analysis sections in the SAP that the "The 2 p-values obtained from each test (ie, the p-values for the LS-means differences) will be used to determine the superiority of M/T FDC vs macitentan 10 mg and tadalafil 40 mg. The global null hypothesis will be rejected if both tests are significant at the appropriate alpha level according to the testing strategy."

This is a correction to the text used in the protocol Sections 10.3.3.1 and 10.3.3.2 that stated "The null hypothesis will be rejected upon achieving a statistically significant difference at a two-sided significance level of $\alpha = 0.05$ in favor of the FDC vs each monotherapy arm (macitentan 10 mg and tadalafil 40 mg)." but was not consistent with the protocol text in Section 10.3.1 about the overall testing strategy that specified "Secondary efficacy endpoints will be analyzed at the $\alpha 1(t)$ level using a hierarchical testing procedure following the order of the endpoints."

For the secondary endpoints 6MWD and WHO FC, it is clarified in the analysis sections in the SAP that "Median unbiased parameter estimates, and repeated CLs will be presented in the final analysis using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company)." This is consistent with the control of the type-1 error that is also planned for the primary endpoint.

Definition of time to death due to PAH or hospitalization for PAH occurring between baseline and EDBT was changed to consider only the DB period treatment discontinuation for the TEAEs as this SAP deals with analysis of the DB period only.

REFERENCES

(D-19.237) Clinical Protocol AC-077A301: A DUE, Version 2. Prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy. Actelion Pharmaceuticals Ltd. (12 Aug 2019).

(euroqol.org) EQ-5D-5L | Valuation | Crosswalk Index Value Calculator. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/. Accessed 25 March 2020.

(Glimm 2009) Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine. 2010; 29:219-228.

(Hung 2007) H.M. James Hung, Sue-Jane Wang, Robert O'Neill. Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. Journal of Biopharmaceutical Statistics, 17: 1201-1210, 2007

(Hwang 1990) Hwang, I. K., Shih, W. J., DeCani, J. S. (1990). Group sequential designs using a family of Type I error probability spending functions. Statistics in Medicine 9: 1439–1445. 361

(Lehmacher 1999) Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics. 1999 Dec; 55(4):1286-90.

(Reilly 1993) Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a Work Productivity and Activity Impairment Instrument. PharmacoEconomics 1993, 4(5):353-65.

(reillyassociates.net) WPAI Scoring. Reilly Associates. http://www.reillyassociates net/WPAI_Scoring.html. Accessed 25 March 2020.

(Tamhane 2010) Tamhane AC, Mehta CR, Liu L. Testing a Primary and a Secondary Endpoint in a Group Sequential Design. Biometrics. 2010; 66:1174-1184.

(unstats.un.org) Standard country or area codes for statistical use (M49). United Nations Statistics Division website. https://unstats.un.org/unsd/methodology/m49/overview/. Accessed 23 March 2020.

(Wassmer 2016) Wassmer G, Brannath W. Estimation and p-Values for Two-Stage Adaptive Designs. In: Group Sequential and Confirmatory Adaptive Designs in Clinical Trials. 2016;189-219. Springer Series in Pharmaceutical Statistics. Springer, Cham.

ATTACHMENTS

ATTACHMENT 1 MEDICATIONS OF SPECIAL INTEREST

Concomitant and prior medications of special interest are defined as follows:

Concomitant/Prior Medication Special Interest Category	**Standard ATC Name**	**Note**
PAH-specific medications	Sildenafil	Medications with ATC name containing any of the listed standard ATC names are considered as PAH-specific medications.
PAH-specific medications	Tadalafil	
PAH-specific medications	Vardenafil	
PAH-specific medications	Iloprost	
PAH-specific medications	Epoprostenol	
PAH-specific medications	Beraprost	
PAH-specific medications	Treprostinil	
PAH-specific medications	Selexipag	
PAH-specific medications	Riociguat	
PAH-specific medications	Macitentan	
PAH-specific medications	Bosentan	
PAH-specific medications	Ambrisentan	

ATTACHMENT 2 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest are defined as follows:

AE Special Interest Category	**Standardised MedDRA query (SMQ)**	**Preferred Term**	**Note**
Hypotension		Blood pressure ambulatory decreased	
Hypotension		Blood pressure decreased	
Hypotension		Blood pressure diastolic decreased	
Hypotension		Blood pressure immeasurable	
Hypotension		Blood pressure orthostatic decreased	
Hypotension		Blood pressure systolic decreased	
Hypotension		Blood pressure systolic inspiratory decreased	
Hypotension		CT hypotension complex	
Hypotension		Diastolic hypotension	
Hypotension		Hypotension	
Hypotension		Mean arterial pressure decreased	
Hypotension		Neonatal hypotension	
Hypotension		Orthostatic hypotension	
Hypotension		Postoperative hypotension	
Hypotension		Procedural hypotension	
Anemia	Haematopoietic erythropenia (narrow and broad)		
Anemia	Haematopoietic cytopenias affecting more than one type of blood cell (narrow and broad)		Excluding PTs: Blood disorder Blood count abnormal
Anemia			PTs containing "anaemia"
Oedema and Fluid Retention			PTs containing "Pulmonary congestion"
Oedema and Fluid Retention	Haemodynamic oedema, effusions and fluid overload (broad and narrow)		Excluding PTs containing "site"
Hepatic Disorders	Hepatic disorders		Exclude sub-SMQ: Liver-related coagulation and bleeding disturbances Exclude PTs: Ascites Bacterascites Biliary ascites Haemorrhagic ascites

ATTACHMENT 3 STATS APPENDIX

1. Critical Values & Inverse-Normal Transformed Test Statistics

Let $p_{ki(2)}$ denote the separate stagewise 2-sided p-value of the test for δ_i, the natural logarithm of the treatment effect as the treatment effect is defined in SAP Section 5.

The index *k* refers to the timing of the analysis:

- $k = 1$ denotes the first stage, i.e. at the interim analysis (IA)
- $k = 2$ denotes the second stage, i.e. at the time of the final analysis, in case the trial is not stopped early. This p-value is calculated at the time of the final analysis using data of subjects who were not included into the interim analysis.

The index i refers to the comparison of interest:

- $i = 1$ denotes the comparison of FDC vs. MMT
- $i = 2$ denotes the comparison of FDC vs. TMT

For $i = 1, 2$; and for $k = 1, 2$, define the 1-sided p-values as:

$$p_{ki(1)} = \begin{cases} p_{ki(2)}/2 & \text{if the treatment effect indicates superiority of FDC} \\ 1 - p_{ki(2)}/2 & \text{otherwise} \end{cases}$$

For notational convenience and to facilitate the description of the method, the one-sided upper-tail of the distribution of the test statistic will be considered further, unless stated differently.

Let $\alpha_1(t_i)$ denote the 2-sided significance level for the i^{th} pairwise comparison at the IA, with information fraction t_i. The latter is defined as $t_i = n_{1i}/n_{pi}$, where n_{1i} is the number of subjects included into the IA and n_{pi} is the pre-planned total sample size for the comparison i. Under the proposed design, $n_{p1} = n_{p2} = 102$ for both pairwise comparisons. The significance levels are derived in the following way using the Hwang, Shih and DeCani error spending function [Hwang *et al.*, 1990] with fixed $\gamma = -2$, hereinafter denoted as HSD(-2). That is, for $i = 1, 2$,

$$\alpha_1(t_i) = \alpha \frac{1 - e^{+2t_i}}{1 - e^{+2}} \quad , \quad \text{for HSD(-2) error spending function ,} \qquad (1)$$

with overall 2-sided significance level $\alpha = 0.05$ and information fraction t_i at the IA.

The interim inverse-normal transformed 1-sided test statistic Z_{1i} and critical value c_{1i} are given by:

$$Z_{1i} = \Phi^{-1}\left[1 - p_{1i(1)}\right] \quad \text{and} \quad c_{1i} = \Phi^{-1}[1 - \alpha_1(t_i)/2], \qquad (2)$$

where Φ^{-1} is the inverse of the cumulative density of the standard normal distribution.

To illustrate, suppose that for each pairwise comparison, 52 subjects are observed at the IA. Then, $n_{11} = n_{12} = 52$ and $t_1 = t_2 = 52/102 = 0.5098039$. For HSD(-2) in (1), this results in $\alpha_1(t_1) = \alpha_1(t_2) = 0.0138683$, with corresponding critical value $c_{11} = c_{12} = 2.460657$.

Let Z_{2i} denote the stage-2 inverse-normal transformed 1-sided test statistic for the i^{th} pairwise comparison, i.e. $Z_{2i} = \Phi^{-1}[1 - p_{2i(1)}]$.. Then, the weighted inverse-normal combination test statistic, $Z_{INC,i}$, (Lehmacher 1999) , per comparison i, is defined as:

$$Z_{INC,i} = C_i(p_{1i(1)}, p_{2i(1)}) = \sqrt{t_i}\, Z_{1i} + \sqrt{1 - t_i}\, Z_{2i}. \quad (3)$$

Note that, at the time of the IA, Z_{2i} , and hence $Z_{INC,i}$, are not yet observed and are not needed for the calculation of conditional power.

2. Conditional Power

If, at the IA, $p_{1(1)} \geq \alpha_1(t_1)$ or $p_{2(1)} \geq \alpha_1(t_2)$or equivalently, $Z_{11} \leq c_{11}$ or $Z_{12} \leq c_{12}$, the conditional power, CP_i, for the respective pairwise comparison and for the pre-planned stage-2 sample size, $n_{2i} = n_p - n_{1i}$, will be calculated. The unblinded estimates for the treatment effect and for the standard deviation, as observed at the IA (via Z_{1i}), are used to calculate the conditional power as follows:

$$CP_i = 1 - \Phi\left(q_i - \frac{\sqrt{n_{2i}}}{\sqrt{n_{1i}}} Z_{1i}\right), \quad (4)$$

where:

- Φ is the cumulative density of the standard normal distribution
- $q_i := \frac{c_{2i} - \sqrt{t_i}\, Z_{1i}}{\sqrt{1 - t_i}}$
- $c_{2,i}$ is the group-sequential critical value at stage 2 for the combination test statistic $Z_{INC,i}$ calculated using the considered α spending rule:

$$\frac{[\alpha - \alpha_1(t_i)]}{2} = Pr\{Z_{1i} \leq c_{1i}, Z_{INCi} > c_{2,i}\} \quad (5)$$

For example, if $t_1 = t_2 = \frac{52}{102} = 0.5098039$, then for $\gamma = -2$, $c_{21} = c_{22} = 2.026$.

3. Sample Size Re-Estimation

Let M denote the pairwise comparison having the minimum observed conditional power and let CP_M denote the corresponding minimum conditional power:

$$CP_M = \min_{i=1,2}(CP_i).$$

The sample size will only be re-estimated if the minimum conditional power $CP_M \geq \lambda_R$. λ_R thus defines the lower bound of the conditional power for sample size increase.

For a given target conditional power λ_{crit} (e.g., $\lambda_{crit} = 88\%$), the required stage-2 sample size $n_{2\lambda}$ is determined by CP_M via expression (2). Specifically, the required stage-2 sample size $n_{2\lambda}$ is determined iteratively as the minimum integer fulfilling the condition $CP_M > \lambda_{crit}$ and guaranteeing an overall 2:1 treatment allocation per pairwise comparison (and hence, per stratum).

The required stage-2 sample size will be re-estimated, if the minimum conditional power $CP_M$with the originally planned size exceeds the threshold λ_R:

$$n_{2MR} = \max\left\{\max\left(n_{min,M}\,, \max_{i}(n_{enr,i})\right) - n_{1M}\ ,\ \min\left(n_{2\lambda}, n_{max,M} - n_{1M}\right)\right\}, \quad (6)$$

where:

- $n_{min,M}$ is the pre-specified minimum total sample size in case the study is not stopped early for efficacy or futility for comparison M,
- $n_{max,M}$ is the pre- specified maximum total sample size, and
- $n_{enr,i}$ is the number of subjects who have been enrolled to the study at the time of the IA for comparison i, ,
- n_{1M} the number of subjects in the first stage (at IA) for the comparison M,
- $n_{2\lambda}$ is the required sample size for a minimum conditional power of λ_{crit}.

The stage-2 sample size n_{2MR} for the pairwise comparison with the minimum CP will also be used as the stage-2 sample size for the other pairwise comparison, i.e. the one with a larger CP.

Example

Suppose that for the M^{th} pairwise comparison, the planned sample size is $n_p = 102$ subjects, with $n_{min,M} = 72$ and $n_{max,M} = 150$. Suppose further that at the time of the IA, $n_{1M} = 52$ subjects are observed. If the first step of the sample size re-estimation yield $n_{2\lambda} = 26$ required stage-2 subjects, then a total of $n_M = n_{1M} + n_{2\lambda} = 52 + 26 = 78$ subjects would suffice for 88% conditional power. Assuming $\max_{i}(n_{enr,i}) = 80$ subjects are already enrolled, then the re-estimated stage-2 sample size would be:

- $n_{2MR} = \max\left\{\max(72\,, 80) - 52\ ,\ \min(26, 150 - 52)\right\}$
- $n_{2MR} = \max\{28\ ,\ 26\} = 28$

The re-estimated total sample size for the final analysis per comparison would be

$$n_{1M} + n_{2MR} = 52 + 28 = 80 = \max_{i}(n_{enr,i})$$

Note that in the above example, it does not matter which contrast $\max_i(n_{enr,i})$ is based on .

Hence, depending on the actual enrollment, $n_{enr,i}$ per comparison, and hence per stratum, the effective number of subjects to recruit after the IA might be different, while the newly determined final sample size per comparison will be identical.

The sponsor will aim to ensure, via adequate monitoring, that half of the recruitment in each strata will be achieved approximately around the same time so that the distributions of naïve vs. non-naïve can be guaranteed to be similar at the IA and at the final analysis with around 50% naïve subjects for each pairwise comparison. This is illustrated in Section 3.3.2 in the SAP.

If $n_{1M} + n_{2MR} > n_{enr,M}$, the re-estimated total sample size per strata should be determined.

4. Interim (Stage-1) Analysis for PVR

Based on the accumulated data at the time of the IA, the test statistics $Z_{1i}, i = 1,2$ are constructed using the inverse normal method (2). One of the following 2 decisions will be made:

1. If $Z_{11} > c_{11}$ and $Z_{12} > c_{12}$, then enrollment is stopped and early study success is claimed, as both comparisons are significant, and hence H_0 is rejected.

2. If $Z_{11} \leq c_{11}$ or $Z_{12} \leq c_{12}$, the study proceeds to stage 2 and the CP for each pairwise comparison will be calculated under the planned total sample size as described in the SAP Section 1.4, and CP_M will be determined.

   Let λ_F, λ_R and λ_{crit} respectively denote the conditional power thresholds for early futility, sample size re-estimation, and the targeted power for sample size re-estimation.

   - If $CP_M < \lambda_F$, then the study is stopped for futility and early study failure is concluded.
   - If $\lambda_F \leq CP_M < \lambda_R$, then the study proceeds with the pre-planned total sample size n_p.
   - If $\lambda_R \leq CP_M < \lambda_{crit}$, then the study proceeds with an increased re-estimated stage-2 sample size (Section 10.3.3).
   - If $CP_M \geq \lambda_{crit}$, then the study proceeds with a decreased re-estimated stage-2 sample size in accordance with the procedure laid out in Section 10.3.3.

5. Final Analysis

If the study is not stopped early, then the final test for the i^{th} pairwise comparison is conducted by comparing the weighted inverse-normal combination test statistic $Z_{INC,i}$with the corresponding critical value $c_{2,i}$

The study is claimed successful in any of the following cases:

- $Z_{11} > c_{11}$ and $Z_{12} > c_{12}$ (Early success in both comparisons)
- $Z_{INC,1} > c_{21}$ and $Z_{INC,2} > c_{22}$ (Late success in both comparisons)
- $Z_{11} > c_{11}$ and $Z_{12} < c_{12}$ and $Z_{INC,2} > c_{22}$ (Early success in one comparison and late success in second comparisons)
- $Z_{11} < c_{21}$ and $Z_{INC,1} > c_{21}$ and $Z_{12} > c_{12}$ (Early success in one comparison and late success in second comparisons)

Even though early success in a single comparison could be declared, the confirmation of superiority in the second comparison will be required. The study will continue in this case in both comparisons (if not stopped for futility) to confirm success in the second comparison. Success in both comparisons may in this situation only be declared in the final analysis.

6. Confidence Intervals and Effect Estimation

Adjusted confidence intervals and parameter estimates will be calculated. Exact confidence intervals at study end will be calculated (see section 8.2.1 in Wassmer 2016) and the median unbiased estimate (MUE) $\hat{\delta}_i^{MUE}$ of the effect will be calculated based on the exact confidence intervals (see section 8.3.3 in Wassmer 2016). Repeated confidence intervals (RCI) will be calculated in the interim analysis and at study end (see section 8.2.2 in Wassmer 2016).

The software package ADDPLAN™ will be used to calculate the adjusted confidence limits and MUE, based on the estimates and standard errors from the respective models per contrast and endpoint.

6.1 Exact Confidence Intervals

Exact 95% confidence internals (CIs) will be calculated at study end based on the principles of stage wise ordering.

The trial enters the second stage, if there was

- no stopping for futility in the first stage: $\max p_{1i(1)} \leq \alpha_0$, with α_0, the critical boundary for futility, expressed as a boundary on the *p*-value **and**
- no stopping for success: $\max\left(p_{1i(1)}\right) \geq \frac{\alpha(t_i)}{2}$.

The critical boundary for futility is derived via formula (2). Assume for simplicity, that for both comparisons, the same information at the interim analysis is collected, so we can drop the index *i* here. α_0 is then calculated as follows by solving for Z_1:

- $\lambda_f = 1 - \Phi\left(\frac{c_2 - \sqrt{t}\,Z_1}{\sqrt{1-t}} - \frac{\sqrt{n_2}}{\sqrt{n_1}}Z_1\right) \Leftrightarrow Z_1 = \frac{c_2 - \sqrt{1-t}z_{1-\lambda_f}}{\sqrt{t}+\sqrt{1-t}\sqrt{\frac{n_2}{n_1}}} \mathrel{\widehat{=}} z_{1-\alpha_0}$
- As a result: $\alpha_0 = 1 - \Phi\left(\frac{c_2 - \sqrt{1-t}z_{1-\lambda_f}}{\sqrt{t}+\sqrt{1-t}\sqrt{\frac{n_2}{n_1}}}\right)$

Also, without loss of generality, $\frac{\alpha_1(t_i)}{2}$ will be further referred to as α_1, the critical boundary for early success. According to the stage-wise ordering principle, the sample point x' to provide more evidence against H_0 than the sample point x if

1. $p_1 \leq \alpha_1$ or $p_1 > \alpha_0$ $p_1' \leq p_1$ or
2. $\alpha_1 < p_1 \leq \alpha_0$ and $p_1' \leq \alpha_1$, or
3. $\alpha_1 < p_1 \leq \alpha_0$ and $\alpha_1 < p_1{}' \leq \alpha_0$ and $C(p_1{}', p_2{}') \leq C(p_1, p_2)$

Let

- $p_{k,\delta} = 1 - \Phi(\frac{\hat{\theta}_k - \delta}{se_1})$,
- $\alpha_{1,\delta} = 1 - \Phi(\Phi^{-1}(1-\alpha_1) - \frac{\delta}{se1})$ and
- $\alpha_{0,\delta} = 1 - \Phi\left(\Phi^{-1}(1-\alpha_0) - \frac{\delta}{se1}\right)$,

this allows to express $P_\delta(x' \geq_\delta x) = Q_\delta(p_{1,\delta}, p_{2,\delta})$ using the following p-value function:

$$Q_\delta(p_{1,\delta}, p_{2,\delta}) = \begin{cases} p_{1,\delta} & \text{if } p_1 \leq \alpha_1 \text{ or } p_1 > \alpha_0 \\ \alpha_{1,\delta} + \int_{\alpha_{1,\delta}}^{\alpha_{0,\delta}} \int_0^1 1_{\{C(x,y) \leq C(p_{1,\delta'}, p_{2,\delta'})\}} dxdy & \text{if } \alpha_1 < p_1 \leq \alpha_0 \end{cases}$$

(equation 8.8 in Wassmer 2016).

The two sided $(1-\alpha) * 100\%$ CI equals the confidence region $(l_2^e; r_2^e)$, where l_2^e satisfies $P_\delta(x' \geq_\delta x) = 1 - \frac{\alpha}{2}$ in δ, l_2^e satisfies $P_\delta(x' \geq_\delta x) = \frac{\alpha}{2}$ in δ, both are derived via numerical integration and numerical root finding.

If the trial is stopped after the first stage, either for futility or for success, the exact $(1-\alpha) * 100\%$ CI, $(l_1^e; r_1^e)$ corresponds with the unadjusted $(1-\alpha) * 100$ % CI.

Exact confidence intervals are only valid if the interim termination decisions follow the original plan. Due to the 2 treatment comparisons, situations may occur, in which the plan per comparison is not followed. This is the case in the following situations:

1. Early termination for futility in case that only one comparison meets $p_{1i(1)} > \alpha_0$
2. Early termination for success in one comparison only: $p_{1i(1)} < \alpha_1$.

A valid exact confidence interval for the successful comparison *i* in situation 2 is given by the exact confidence interval disregarding second stage data, which is the unadjusted $(1-\alpha) * 100$ % CI based on first stage data only.

6.2 Repeated Confidence Intervals

For the approximate repeated confidence bounds for combination tests, consider the above introduced shifted p-value, i.e. $p_{k,\delta}$. The 2-sided confidence interval is set up by considering 2 one-sided null hypotheses: $H_0^-: \delta \leq 0$ and $H_0^+: \delta \geq 0$, respectively for the computation of the lower bound and the upper bound. These null hypotheses will result respectively in 2 one-sided confidence regions, respectively $(l_k^r; +\infty)$ and $(-\infty; u_k^r)$.

The respective $H_{0\delta}^-$ is rejected in the first stage if $p_{1,\delta} \leq \alpha(t_1)$, in this case the lower bound of the RCI, $l_{1,\delta}^r = \hat{\delta}_1 - \Phi^{-1}(1-\alpha(t_1)) \times \text{se}_1$.

At the second stage, $H_{0\delta}$ is rejected if $p_{1,\delta} \leq \alpha_0$ and $Z_{inc} \leq c_2$. Using $\alpha_0 < 1$, define for the 1-sided lower bound first $\tilde{l}_0 = \hat{\delta}_1 - \Phi^{-1}(1-\alpha_0) \times \text{se}_1$; and secondly, define $\tilde{l}_2$ as the smallest δ resulting in $C(p_{1,\delta}, p_{2,\delta}) = c_2$ (leading to the rejection of $H_{0\delta}^-$).

The lower bound of the second stage 95% RCI is defined as $l_k^r = min(\tilde{l}_2, \tilde{l}_0)$.

Similarly, for the upper boundary of the RCI, consider for this purpose $H_{0\delta}^{+}$. If in the first stage, the null hypothesis $H_{0\delta}^{-}$ is rejected, the upper bound of the RCI is $u_1^r = \hat{\delta}_1 + \Phi^{-1}(1-\alpha(t_1)) \times \mathrm{se}_1$. In the second stage, the upper bound is defined via the u_1^r, the largest δ resulting in $C(p_{1,\delta}, p_{2,\delta}) = c_2$ (leading to the rejection of $H_{0\delta}^{+}$).

6.3 Median Unbiased Estimate

The MUE, $\hat{\delta}_i^{MUB}$ is calculated using methods for the exact confidence intervals and results as the maximum value satisfying $P_\delta(x' \geq_\delta x) = 0.5$. It is derived via numerical integration. If the trial is stopped after the first stage, the MUE simplifies to the $\widehat{\delta_i}$ as observed from the model.

Actelion Pharmaceuticals Ltd
(a Janssen Pharmaceutical Company of Johnson & Johnson)

Statistical Analysis Plan - Part 2

A DUE Prospective, multi-center, double-blind, randomized, active-controlled, triple dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy

Protocol AC-077A301; Phase 3

JNJ-68150420/ACT-064992D (Macitentan/Tadalafil fixed dose combination)

Status:	Approved
Date:	31 January 2023
Prepared by:	Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutical
Document No	EDMS-RIM-657334, 3.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	17 February 2022	Not Applicable	Initial release
2	16 September 2022	Exposure adjusted AE analysis is added.	To account for differences in the duration of treatment exposure among participants.
		In addition to tables, plan for graphical displays for selected laboratory parameters	For easier visualization of results.
		Details on summaries of AEs with onset during the tadalafil 20 mg titration phase added.	To add clarity.
		Remove planned sensitivity analysis of M/M per investigator assessment.	This endpoint is listed only summary tables are removed due to expected low number of events.
		Minor corrections and clarifications.	To add clarity.
3	26 January 2023	Minor clarifications and changes to improve layout and display of analyses. Small updates to safety data displays (including addition of liver function test outlier categories, layout of AE subgroup tables and tables of AEs during week 1/tadalfil up-titration). Editorial updates and corrections have been applied.	To improve clarity.

1. INTRODUCTION

This Statistical Analysis Plan (SAP) Part 2 describes the planned statistical data analyses for the Clinical Study Report (CSR) at the end of the open-label (OL) period of study AC-077A301. It also includes the planned analysis of combined double-blind (DB) and OL data available after the end of the DB period of study AC-077A301, which will be included in submission summary documents. These analyses will be referred to as 'final DB analysis/submission' in this SAP. The analyses of the DB data planned at the end of the DB period of the study are described in a separate document, the AC-077A301 CSR SAP Part 1 (EDMS-RIM-657335). Definition of variables and analyses in this SAP Part 2 will refer to the SAP Part 1 document, where applicable.

This SAP is based on the AC-077A301 protocol Version 7 dated 21 November 2022, the AC-077A301 COVID-19 Appendix to the Clinical Protocol dated 27 April 2021, the case report form (CRF) Version 16.01 dated 27 January 2022, and the Clinical Event Committee (CEC) Charter Version 5.0 dated 7 April 2022.

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM). All descriptive or formal statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise specified.

1.1. Objectives and Endpoints

1.1.1. Trial Objectives

The primary and secondary objectives of the study are related to the DB part of the trial and are described in SAP Part 1. These objectives are not covered in SAP Part 2, which focuses on the other objectives for the 24-month OL treatment period that are defined in the protocol.

Other objectives for the 24-month OL treatment period are:

- To evaluate the long-term safety of the M/T FDC (macitentan 10 mg and tadalafil 40 mg fixed dose combination).
- To evaluate the long-term effect of the M/T FDC on:
    - Exercise capacity.
    - WHO FC.
    - Time to first morbidity/mortality event.
    - Time to death due to PAH or PAH-related hospitalization.
    - Pharmacoeconomic measures.
    - Time to death (all causes).

1.1.2. Trial Endpoints

The primary and secondary endpoints of the study are related to the DB part of the trial and are described in the SAP Part 1. Other efficacy endpoints for the DB period are also described in SAP Part 1.

Other efficacy endpoints for the OL treatment period (as listed in the protocol) are:

- Change from baseline up to EOLT, by visit, in exercise capacity, as measured by the 6MWD.
- Change from baseline up to EOLT, by visit, in WHO FC.
- Time to first morbidity or mortality event occurring between baseline and EOLT, defined as any of the following:
    - Death (all causes).
    - Non-planned PAH-related hospitalization.
    - Initiation of IV or subcutaneous prostacyclin or prostacyclin analog for worsening PAH.
    - Clinical worsening defined as:
        - Deterioration in exercise testing, confirmed by two 6MWTs performed on different days within 2 weeks, showing at least 15% decrease of 6MWD from baseline.

      AND
        - Worsening of PAH symptoms, defined as at least one of the following
            - Increase in WHO FC.
            - Appearance or worsening of signs/symptoms of right heart failure that do not respond to optimized oral diuretic therapy.

- Time to death due to PAH or hospitalization for PAH occurring between baseline and EOLT:
    - Death due to PAH, or onset of a treatment-emergent AE that led to permanent discontinuation of study treatment with a fatal outcome due to PAH occurring within 4 weeks of study treatment discontinuation

    OR
    - Non-planned PAH-related hospitalization.

- Time to death (all causes) occurring between randomization and open-label database lock. (This endpoint is clarified in Section 5.5.5).
- Change from baseline up to EOLT, by visit, in NT-proBNP (analyzed on log scale).
- Number per year of all-cause and PAH-related hospitalizations, from baseline up to EOLT.
- Number per year of in-patient hospital days for all causes and PAH-related causes, from baseline up to EOLT.
- Number per year of emergency room visits for all causes and PAH-related causes that do not result in hospital admittance from baseline up to EOLT.

The safety endpoints are:

- Treatment-emergent AEs.
- SAEs.
- Deaths.
- AEs leading to premature discontinuation of study treatment.
- Change in vital signs (SBP, DBP, and pulse rate) and body weight from baseline to all assessed time points during the study.
- Treatment-emergent marked laboratory abnormalities as detailed in section 14.4 of the protocol.

- Proportion of participants with a treatment-emergent ALT and/or AST abnormality (≥3, ≥5, and ≥8 × ULN).
- Proportion of participants with a treatment-emergent ALT and/or AST abnormality (≥3 × ULN) associated with total bilirubin ≥2 × ULN (and increased as compared to baseline).
- Proportion of participants with a treatment-emergent hemoglobin abnormality (<100 g/L, and <80 g/L).
- Treatment-emergent AEs of special interest (hypotension, anemia, edema, liver events).

1.2. Study Design

This is a prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study with a treatment period duration of 16 weeks followed by a 24-month single-arm open-label treatment period.

In total, 170 participants are planned to be randomized into the study (range 150–250) to receive either M/T FDC, macitentan 10 mg, or tadalafil 40 mg given once daily. Participants will also receive matching placebos for the two other study treatments to maintain the blind. Treatment allocation will be stratified by treatment status at baseline, ie, treatment-naïve or treated by an ERA or a PDE-5i as a monotherapy:

- treatment-naïve participants will be randomized in a 2:1:1 ratio to M/T FDC, macitentan, or tadalafil.
- participants on allowed ERA monotherapy will be randomized in a 2:1 ratio to M/T FDC or macitentan.
- participants on allowed PDE-5i monotherapy will be randomized in a 2:1 ratio to M/T FDC or tadalafil.

In the double-blind treatment period, the FDC of macitentan 10 mg and tadalafil 40 mg is compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg given once daily.

After completion of the DB treatment period, participants will continue the study in an open-label treatment period for 24 months, during which all participants will receive M/T FDC. All EDBT assessments must be completed before the participant enters the open-label treatment period.

Participants who have discontinued double-blind study treatment prematurely will continue participation until Week 120 but will not receive open-label treatment.

Regardless of length of study treatment, all participants will be followed until Week 120.

The study will be conducted at approximately 150 sites in approximately 25 countries.

1.2.1. Study periods

The study comprises the following consecutive periods as depicted in Figure 1.

Screening period: Lasts up to 30 days; starts with the signature of the Informed Consent Form (ICF; Visit 1) and ends the day prior to randomization (Visit 2).

Double-blind treatment period: Starts on the day of randomization (Visit 2) and ends on the day of the EDBT visit (Visit 8). The DB treatment period consists of the titration phase (the first 2 weeks) and the maintenance phase (Week 3 through Week 16):

- **Titration phase:** Starts on the day of randomization (Visit 2, Day 1) and lasts 2 weeks, ending on Day 14 (end of Week 2).
  - Week 1: Loose combination (LC) 10/20: Participants are treated with an LC of macitentan 10 mg and/or tadalafil 20 mg and relevant placebos, depending on treatment arm, for 7 days from randomization (Visit 2, Day 1) to the end of Week 1 (Day 7).
  - Week 2: LC 10/40 Up-titration: Participants are treated with an LC of macitentan 10 mg and/or tadalafil 40 mg and relevant placebos depending on treatment arm from Day 8 to the end of Week 2 (Day 14).
  - Note: If a participant is already receiving a stable dose of PDE-5i within pre-specified dose ranges at baseline (ie, 40 mg tadalafil, 60–120 mg sildenafil, or 10 mg vardenafil daily), no up-titration is needed, and they will receive 40 mg tadalafil from Day 1.
- **Maintenance phase:** Participants are treated with macitentan 10 mg, tadalafil 40 mg, M/T FDC, or their respective placebos, depending on treatment arm. The period starts on Day 15 and lasts until EDBT (Visit 8).
  - Note: If a participant cannot tolerate 40 mg tadalafil during the titration period, the participant will remain on 20 mg tadalafil. The participant is allowed to be up-titrated once again to 40 mg tadalafil during the first 2 weeks of the maintenance phase of the DB treatment period (ie, between Visits 4 and 5).
  - Note: if a participant prematurely discontinues DB study treatment, they will be asked to return for an EDBT visit (within ±2 days of the time of treatment discontinuation and before initiation of new PAH-specific therapy), a safety follow-up (S-FU) visit 30 days after last treatment administration, and all remaining visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw consent for study participation and regular visits to the site are not possible, telephone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these telephone calls, M/M, adverse event (AE), vital status and concomitant medication information will be collected.

Open-label treatment period: For those participants who complete 16 weeks of DB treatment, the OL treatment period starts with the first dose of the OL study treatment. In case interim analysis results in early stopping of the DB period due to efficacy, participants may start OL study treatment prior to completing 16 weeks of DB treatment. All participants will have a titration phase of 2 weeks, during which the two drugs will be given as a loose combination. The OL treatment period lasts at least 24 months and ends with the End-of-Open-Label-Treatment (EOLT) visit. Participation in the open-label treatment period may be prolonged beyond 24 months until macitentan and tadalafil are accessible at the required doses, through other options according to local regulations.

The OL period of the study comprises the following consecutive phases:

- **Titration phase**: Starts on the first day of OL treatment and lasts for 2 weeks. The OL titration phase treatment assignment will be done through Interactive Response Technology (IRT) to maintain blinding of the DB treatment period treatment.

  - First week OL titration: Begins the first day of OL treatment and ends the 7th day of OL treatment. Participants who received macitentan monotherapy, or could not tolerate 40 mg tadalafil, in the DB treatment period will receive the loose combination of macitentan 10 mg and tadalafil 20 mg. Participants who had received the M/T FDC or tadalafil monotherapy treatment and could tolerate 40 mg tadalafil in the DB treatment period, will receive the loose combination of macitentan 10 mg and tadalafil 40 mg during this week.

  - Second week OL titration: Begins the 8th day of OL treatment and ends on the 14th day of OL treatment. All participants are treated with the loose combination of macitentan 10 mg and tadalafil 40 mg. Participants who cannot tolerate 40 mg tadalafil are not eligible to proceed to the OL treatment period maintenance phase and should complete a premature End of OL treatment (EOLT) visit.

- **Maintenance phase**: Begins the 15th day of open-label treatment and ends with the EOLT. All participants are treated with M/T FDC.

  - Note: if a participant prematurely discontinues study treatment, they will be asked to return for an EOLT visit within ±7 days of the time of treatment discontinuation and a safety follow-up visit 30 days after last treatment administration. If the participant did not withdraw consent for study participation, regular contacts will be conducted thereafter, at the scheduled visits until the Week 120 visit. If regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, morbidity and mortality events (M/M) AE, vital status and concomitant medication information will be collected.

End-of-Treatment (EOT): For an individual participant is the end of all study treatment.

Safety follow-up (S-FU) period: Starts on the day after the last dose of study treatment and ends at the Safety Follow-up Visit 30–35 days thereafter.

For participants who completed the 24-months of open-label treatment and who are eligible for a continued access program (post-trial access program or other open-label extension study) the S-FU period will be waived. In such case enrollment into the continued access program should occur on the same day as the last visit in this study, ie, EOS visit.

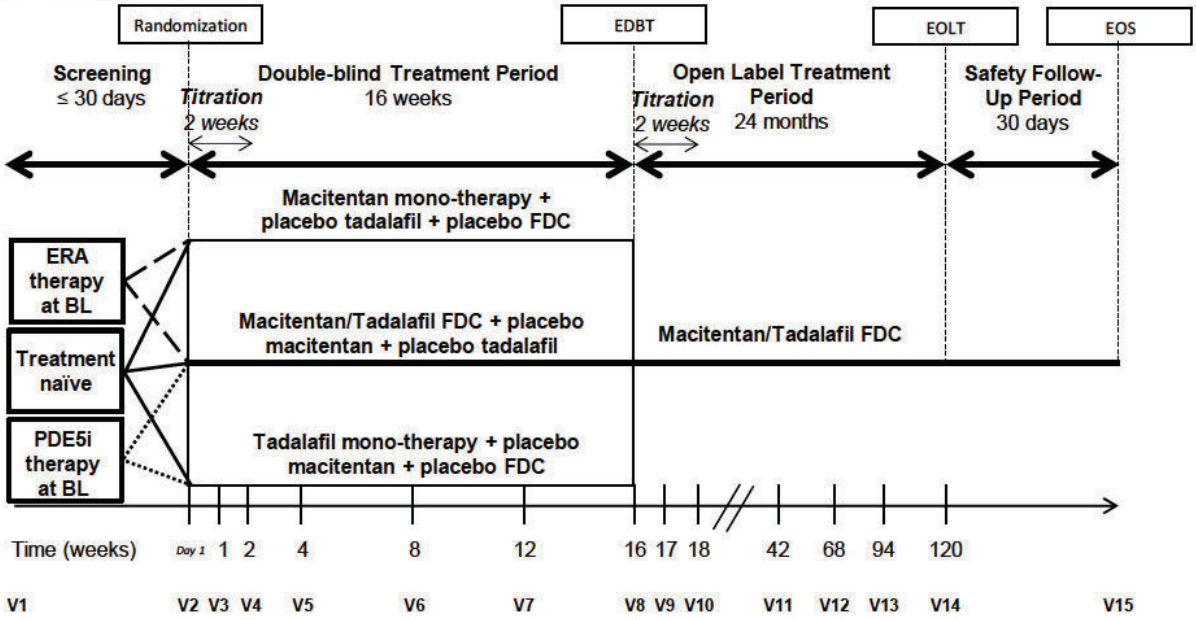
End of Study (EOS): EOS is reached when all participants have completed their EOS visit, died, or are lost to follow-up.

For an individual participant, EOS visit is defined as follows:

- For participants who complete treatment and do not enter a continued access program, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake.
- For participants who complete treatment and who are eligible for a continued access program (post-trial access or other open-label extension study) the EOS visit is defined as the EOLT visit.
- For participants who prematurely discontinue study treatment, EOS visit is defined as either the safety follow-up visit 30–35 days after last study treatment intake or the Week 120 visit, whichever comes last.

Survival Follow-up: For all participants including those who prematurely discontinue the study at any time (except those who withdrew consent), survival information will be collected starting at the time of double-blind database lock (announced) and thereafter approximately yearly until death or study closure (ie, within 2 months prior to the last participants last visit [announced]).

Figure 1 – Study Design



BL = baseline; EDBT = End of Double Blind Treatment; EOLT = End of Open Label Treatment; EOS = End of Study; ERA = endothelin receptor antagonist; FDC = fixed dose combination; PDE5i = Phosphodiesterase type-5 inhibitor; V = visit.

The schedule of visits and assessments can be found in Table 4 and Table 5 of the protocol.

1.2.2. Timing of analyses

The database of the study (including open-label part) will be cleaned, and the data extracted and analyzed at 3 time points during the study:

Timepoint A: The IA will be conducted when approximately 100 participants have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment and will only include data from countries in which the global amendment 5 (protocol version 6) has been approved. This analysis can allow for early termination for efficacy or futility, or unblinded reassessment of sample size required for the primary endpoint. Following the IA, recruitment will be stopped if futility or superiority is demonstrated. In the event the study is stopped for futility, all participants will be requested to return for an EOT visit and be transitioned to Standard of Care. In the event the study is stopped for efficacy, all participants in the double-blind treatment period will be requested for a EDBT visit and transitioned to the OL treatment, participants already enrolled in the OL period of the study will be allowed to continue through the end of the open-label treatment period. [Full details are covered in SAP Part 1]

Timepoint B: Unless the study is stopped prematurely following the IA outcome, the final analysis of the DB period will occur after all participants have reached Week 16 or prematurely discontinued from the study. [Full details are covered in SAP Part 1]

Timepoint C: The final analysis of the study will occur when all participants have performed their EOS visit (once the last participant has completed the OL treatment period or discontinued prematurely).

At or after the time of the final analysis of the DB period (occurring either at timepoint A if study is stopped prematurely during IA or at timepoint B) the open-label data will be analyzed together with the double-blind data. All available open-label data will be cleaned and analyzed up to an overall cut-off date defined for the submission. The results of these analyses will be reported in submission summary documents.

2. STATISTICAL HYPOTHESES

Formal hypothesis testing is performed only for the DB part of the study and is described in the SAP Part 1. No formal hypothesis testing is performed for the OL part of the study; hence no p-value is presented for the OL period. All analyses described in the SAP Part 2 are considered exploratory.

3. SAMPLE SIZE DETERMINATION

The sample size calculation for the study is described in detail in SAP Part 1. The sample size for the open-label period will be up to the number of randomized subjects in the DB period.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The Screened analysis set, all randomized analysis set, full analysis set, safety set and QoL analysis sets are defined in SAP Part 1 since they are used for the reporting of the DB period results. Analysis sets used to assess OL and combined DB and OL periods are described in the table below.

Table 2 – Analysis Sets

Analysis Sets	Description
Open-label Set (OLS)	The Open-label Set (OLS) includes all participants who receive at least one dose of OL study treatment in the OL period. Only data from the OL period are considered with the exception of baseline data which may origin from DB period. Analyses will be presented overall and by randomized DB treatment group.
Combination Safety Set (CSS)	The Combination Safety Set (CSS) includes all participants randomized to M/T FDC in the DB period and who received at least one dose of M/T FDC DB study treatment (ie, at least one dose of macitentan and tadalafil) and all participants who received at least one dose of M/T FDC study treatment (ie, at least one dose of macitentan and tadalafil) in the OL period. For participants treated with M/T FDC study treatment in DB period, data from DB and OL period are considered. For participants treated with monotherapy in DB period, only data from the OL period are considered with the exception of baseline data which may origin from DB period. Analyses will be presented overall and by actual DB treatment group.
Long-term M/T FDC Set (LTFDCS)	The Long-term M/T FDC Set (LTFDCS) includes all participants randomized to M/T FDC in the DB period. Data from DB and OL period are considered. Treatment arm is based on randomized treatment
Full analysis Set (FAS)	As defined in the SAP Part 1. It includes all randomized participants who received at least one dose of study treatment (for participants on FDC at least one dose of either macitentan or tadalafil). Data from DB and OL period are considered. Analyses will be presented by randomized DB treatment group.

4.1. Usage of the Analysis Sets

Table 3 summarizes the usage of the analysis sets.

Table 3 – Usage of analysis Sets

	Analysis Sets			
Endpoints	OLS *	LTFDCS	CSS	FAS
Change in 6MWD	√	√		√
Change in WHO FC	√	√		√
Time to first M/M event	√	√		√
Time to PAH death or PAH hospitalization	√	√		√
Time to death				√
Fold change in NT-proBNP	√	√		√
Health economics	√	√		
AE			√	
AESI			√	
Clinical laboratory tests			√	
Vital signs			√	

* only for OL final analysis
OLS = Open-label Set; LTFDCS = Long-term Macitentan/Tadalafil fixed dose combination Set; CSS = Combination Safety Set; FAS = Full analysis Set; 6MWD = 6-minute walk distance; WHO FC = World Health Organization Functional class; M/M Morbidity/Mortality; NT-proBNP = N-terminal pro B-type natriuretic peptide

4.2. Presentation based on strata/treatment groups

Data collected on participants who did not tolerate up-titration to tadalafil 40 mg and remained on tadalafil 20 mg or tadalafil 20 mg + macitentan 10 mg as separate tablets will be kept in the statistical analysis under the tadalafil 40 mg and M/T FDC arms, respectively.

Treatment groups for each section will be presented in the following way:

For the OLS, outputs will show 4 columns, one including all participants included in the OLS (Total column) and 3 columns by randomized DB treatment group. Treatment arms

"DB-Macitentan", "DB-M/T FDC", "DB-Tadalafil" follow the randomized treatment in DB. An example of treatment header for such a display is as follows:

All Strata			
DB-Macitentan	DB-Tadalafil	DB-M/T FDC	OL M/T FDC (Total)

For LTFDCS outputs, 4 columns will be presented as follows:

DB-M/T FDC			
Prior-ERA	Prior-PDE-5i	Treatment-naïve	All strata

For analyses on the FAS, data are presented without the strata as follows:

All Strata		
DB-Macitentan	DB-Tadalafil	DB-M/T FDC

For the CSS, actual DB treatment groups will be displayed. For participants who received monotherapy during DB, treatment arms will be labeled "DB-Macitentan", "DB-Tadalafil" and follow the actual treatment received in DB as defined in SAP Part 1. For participants who received M/T FDC during DB, the treatment arm is the actual treatment received in DB, it is labeled "DB-M/T FDC". In addition, a total column with all participants included in the CSS will be labeled "DB/OL M/T FDC (Total)".

An example of treatment header for such a display is as follows:

OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
DB-Macitentan	DB-Tadalafil	DB-M/T FDC	DB/OL M/T FDC (Total)

This display will be used for disposition, safety, treatment exposure and compliance, and concomitant medications outputs.

5. STATISTICAL ANALYSES

5.1. General Considerations

At or after the time of the final analysis of the DB period, all available OL data will be cleaned and analyzed together with the DB data up to an overall cut-off date defined for submission. Analyses to be performed at the time of the final analysis of the DB will be identified in the DPS Part 1 of this SAP (column "use for what effort", keyword "NDA/MAA submission"). The results of these analyses will be reported in submission summary documents.

For the final analysis of the OL period, all OL data will be cleaned and analyzed together with the DB data and also separately. Except where specified, all analyses listed in the DPS Part 1 of this

SAP are to be performed at the time of the final analysis of the OL. The results of these analyses will be reported in the CSR.

End of treatment in the DB treatment period (**EOT-DB**) is defined as the date of last intake of study drug in the DB period.

"**EDBT visit**" is defined as the last visit in the DB treatment period; this is Visit 8/Week 16 for participants who complete the DB treatment period or the premature EDBT visit for participants that prematurely discontinue study treatment during the DB treatment period.

End of treatment in the OL treatment period (**EOT-OL**) is defined only for participants treated in OL as the date of last intake of study drug in the OL treatment period. At the time of the final DB analysis/submission, it is defined as minimum (the last intake of study drug in the OL treatment period, cut-off date). Participants for whom the EOT-OL is imputed by the cut-off date are considered as ongoing in the OL treatment period.

EOT is defined as the date of last study drug intake in the study, ie, max (EOT-DB and EOT-OL).

"**EOLT visit**" is only defined for participants treated in OL and is defined as the last visit in the OL treatment period. EOLT visit date is Visit 14/Week 120 date for participants who complete the OL treatment period or premature EOLT visit date for participants who discontinue study treatment prematurely in the OL treatment period. At the time of final DB analysis/submission, it is the minimum of (Visit 14/Week 120, cut-off date) for participants who complete the OL treatment period or the minimum of (premature EOLT visit, cut-off date) for participants who discontinue study treatment prematurely in the OL treatment period. For participants considered as ongoing in the OL period (with EOT-OL imputed by the cut-off date), EOLT visit is imputed as the cut-off date.

Participants who have completed the 24 months of the OL period and are benefiting from the study intervention, as determined by their investigator, will be able to continue participation in the OL period beyond 24-months until alternative continued access is available in the participant's country and as per local regulations. These participants are to be followed through regular 6-monthly visits. For these participants EOLT visit may happen later than Visit 14 / Week 120. As only a very low number of participants is expected to continue treatment in the OL period beyond 24-months, in general by-visit displays will stop at the week 120 visit. However, the data collected after the week 120 visit are included in listings and in summary tables that present treatment-emergent safety events.

EOS visit is defined as the EOS visit as reported in the eCRF. At the time of the DB final analysis/submission, it is the minimum of (date of EOS visit as reported in the eCRF, cut-off date). Participants for whom the EOS is imputed by the cut-off date are considered as ongoing in the study.

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is described in Section 5.1.2. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

If more than one assessment falls on the same date, the worst assessment will be considered for categorical variables. For continuous variables the mean value of such assessments will be used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point. Listed below (Table 4, Table 5, Table 6) are the analysis visit windows and the target days for each visit defined in the protocol; there are different visit window assignment depending on the analysis population, as described in the table.

Table 4 – Visit Windows for OL period on OLS

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Time Interval (OL Day)*	Target Time Point (OL Day)
6MWT, WHO FC, NT-proBNP	DB/OL	8	OL Baseline	<=1	1
	OL	11	OL Month 6	2 to 272	182
	OL	12	OL Month 12	273 to 454	364
	OL	13	OL Month 18	455 to 636	546
	OL	14	OL Month 24	>=637	728

* OL Study day is defined in Section 5.1.2.
Note: Efficacy assessments are assigned to visit windows as specified in the table, however on-treatment summaries will be done only up to EOT+7 days.

Table 5 – Visit Windows for combined DB/OL period on LTFDCS and FAS

Parameter		Scheduled Visit Number	Time Interval (label on output)	Time Interval (Study Day)*	Target Time Point (Study Day)
6MWT, WHO FC		2	Baseline	<=1	1
		6	Week 8	For LTFDCS: 2 to Min(84, OL Day 1)** For FAS: 2 to 84	57
		8	Week 16	For LTFDCS: 85 to Min(203, OL Day 1)** For FAS: 85 to 203	113
		11	Week 42/OL Month 6	For LTFDCS: Min(204, OL Day 1 +1)** to 385	295

Parameter		Scheduled Visit Number	Time Interval (label on output)	Time Interval (Study Day)*	Target Time Point (Study Day)
				For FAS: 204 to 385	
		12	Week 68/OL Month 12	386 to 567	477
		13	Week 94/OL Month 18	568 to 749	659
		14	Week 120/OL Month 24	>=750	841
NT-proBNP		2	Baseline	<=1	1
		8	Week 16	For LTFDCS: 2 to Min(203, OL Day 1)** For FAS: 2 to 203	113
		11	Week 42/OL Month 6	For LTFDCS: Min(204, OL Day 1 +1)** to 385 For FAS: 204 to 385	295
		12	Week 68/OL Month 12	386 to 567	477
		13	Week 94/OL Month 18	568 to 749	659
		14	Week 120/OL Month 24	>=750	841

*Study day is defined in Section 5.1.2.
** For analysis based on LTFDCS, assessments will be assigned to DB visits Week 8 and 16 only up to day date of first dose in OL (as participants may start OL prior to week 16 in case interim analysis resulted in early stopping of the DB period for efficacy). Assessments from day 204 or date of first dose in OL+1 day up to day 385 will be assigned to Week 42 visit window.
Min = minimum.
Note: Efficacy assessments are assigned to visit windows as specified in the table, however on-treatment summaries will be done only up to EOT+7 days.

Table 6 – Visit Windows for combined DB/OL period on CSS

Parameter	Analysis Visit (label on output)	Time Interval (M/T FDC Day)*	Target Time Point (M/T FDC Day)
Laboratory tests (central lab, including liver tests, excluding hematology tests), vital signs	FDC Baseline	<=1	1
	FDC Week 21 (16/26)	2 to 238	148
	FDC Week 47 (42/52)	239 to 420	330
	FDC Week 73 (68/78)	421 to 602	512
	FDC Week 99 (94/104)	603 to 766	694
	FDC Week 120	>= 767	841
Hematology laboratory tests	FDC Baseline	<=1	1
	FDC Week 4	2 to 42	29
	FDC Week 8	43 to 101	54
	FDC Week 21 (16/26)	102 to 238	148
	FDC Week 47 (42/52)	239 to 420	330
	FDC Week 73 (68/78)	421 to 602	512
	FDC Week 99 (94/104)	603 to 766	694

Parameter	Analysis Visit (label on output)	Time Interval (M/T FDC Day)*	Target Time Point (M/T FDC Day)
	FDC Week 120	>= 767	841
Liver tests (AST and ALT, central lab)	FDC Baseline	<=1	1
	FDC Month 1	2 to 46	30
	FDC Month 2	47 to 76	61
	FDC Month 3	77 to 107	91
	FDC Month 4	108 to 137	122
	FDC Month 5	138 to 168	152
	FDC Month 6	169 to 198	183
	FDC Month 7	199 to 229	213
	FDC Month 8	230 to 259	244
	FDC Month 9	260 to 319	274
	FDC Month 12	320 to 411	365
	FDC Month 15	412 to 503	457
	FDC Month 18	504 to 594	548
	FDC Month 21	595 to 685	639
	FDC Month 24	686 – 786	731
	FDC Month 28 (Week 120)	>= 787	841
	FDC Baseline	<=1	1

* M/T FDC Study day is defined in Section 5.1.2.
Note: Safety assessments for treatment visits will be assigned to the visit windows only up to and including EOT+30 days.

5.1.2. Study Day

Study Day 1 or Day 1 refers to the start of the first DB study treatment administration.

OL Day 1 refers to the start of the first OL study treatment administration.

M/T FDC Day 1 refers to the start of the first M/T FDC study treatment administration (ie, loose combination of macitentan [10 mg] and tadalafil [20 mg or 40 mg] or as fixed dose combination) either in DB or OL period. For participants from the actual DB M/T FDC group, it is the DB treatment start date (Study Day 1 as defined above). For OL treatment participants from the actual DB monotherapy group (tadalafil 40 mg or macitentan 10 mg as received) it is the OL treatment start date (OL Day 1).

All efficacy and safety assessments at all visit/events will be assigned a day relative to these dates.

Study day for a visit/event is defined as:

- Visit/event date - (date of Day 1) +1, if visit/event date is ≥ date of Day 1
- Visit/event date - Date of Day 1, if visit/event date < date of Day 1

OL day for a visit/event is defined as:

- Visit/event date - (date of OL Day 1) +1, if visit/event date is ≥ date of OL Day 1
- Visit/event date - Date of OL Day 1, if visit/event date < date of OL Day 1

M/T FDC day for a visit/event is defined as:

- Visit/event date - (date of M/T FDC Day 1) +1, if visit/event date is ≥ date of M/T FDC Day 1
- Visit/event date - Date of M/T FDC Day 1, if visit date < date of M/T FDC Day 1

There is no 'Day 0'.

Study Day is used for presentation of data from the combined DB/OL period on the LTFDCS and on the FAS.

OL Day is used for presentation of data from the OL period on the OLS.

M/T Day is used for presentation of data from the combined DB/OL period on the CSS.

5.1.3. Baseline

For the LTFDCS and FAS analysis population, baseline is defined as the last observation prior to the first DB study treatment administration (same definition as in the SAP Part 1).

For the OLS analysis population, baseline is defined as the last assessment obtained prior to the first intake of OL study treatment.

For the CSS analysis population, baseline is defined as the last assessment prior to the first intake of M/T FDC study treatment either in DB or OL period. The first M/T FDC intake can be either loose combination of macitentan and tadalafil or M/T FDC tablet.

If the assessment is collected on the same day as the first study treatment, such assessment will be considered pre-dose and will be used for derivation of the baseline. The exceptions are AEs, concomitant medications and hospitalizations. If such events start on Study Day 1 (or OL Day 1 or M/T FDC Day 1) they will be considered treatment-emergent/concomitant.

If more than one assessment falls on the same date, the worse assessment will be considered as baseline for categorical variables. For continuous variables the mean value of such assessments will be chosen as a baseline.

5.1.4. Imputation Rules for Missing and Partial Dates

General rules for an imputation of missing and partial dates for AEs, prior and concomitant medications, hospitalizations, death date and date of diagnosis are described SAP Part 1. Partial and missing dates of assessments not described in SAP Part 1 will not be imputed and will be used as collected.

In order not to miss any treatment-emergent or concomitant records in OL for participants switching from monotherapy in DB to M/T FDC in OL, the following rules will be followed for this subset of participants:

Adverse Events

If the onset date of an AE is missing the day only, it will be set to:

- The day of first dose of OL study treatment, if the month/year of the onset of AE is the same as month/year of the first dose of OL study treatment and month/year of the AE resolution date is different
- The day of first dose of OL study treatment or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose of OL study treatment and month/year of the AE resolution date are the same

If the onset date of an AE is missing both the day and month, it will be set to:

- Month and day of the first dose of OL study treatment or the AE resolution date, whichever is earliest, if year of the onset of AE and year of the first dose of OL study treatment and year of the AE resolution date are the same.

All other imputation rules for AE onset and resolution dates will follow rules in SAP Part 1.

Prior and Concomitant Medications

If the onset date of a medication is missing the day only, it will be set to:

- The day of first dose of OL study treatment, if the month/year of the start of medication is the same as month/year of the first dose of OL study treatment and month/year of the medication end date is different
- The day of first dose of OL study treatment or day of medication end date, whichever is earliest, if month/year of the start of medication and month/year of the first dose of OL study treatment and month/year of the medication end date are the same

If the onset date of a medication is missing both the day and month, it will be set to:

- Month and day of the first dose of OL study treatment or the medication end date, whichever is earliest, if year of the start of medication and year of the first dose of OL study treatment and year of the medication end date are the same.

Completely missing end dates will not be imputed and will be flagged as concomitant unless medication start date is after EOT (rule will be applied to all participants).

All other imputation rules for medication start and end dates will follow rules in SAP Part 1.

Hospitalizations

If the admission date of a hospitalization is missing the day only, it will be set to:

- The day of first dose of OL study treatment, if the month/year of the admission is the same as month/year of the first dose of OL study treatment and month/year of the discharge date is different

- The day of first dose of OL study treatment or day of discharge date, whichever is earliest, if month/year of the admission and month/year of the first dose of OL study treatment and month/year of the discharge date are the same

If the admission date of a hospitalization is missing both the day and month, it will be set to:

- Month and day of the first dose of OL study treatment or the discharge date, whichever is earliest, if year of the admission and year of the first dose of OL study treatment and year of the discharge date are the same.

If participant is hospitalized due to an AE, AE onset date is available and partial admission date was imputed to earlier date than AE onset date or is missing then AE onset date will be imputed as hospitalization start date instead. In case there are more AEs for the same hospitalization, the earliest AE onset date after OL treatment start date will be used.

Completely missing admission dates without corresponding AE will be imputed as min (first dose of OL study treatment, discharge date).

All other imputation rules for hospitalization admission and discharge dates will follow rules in SAP Part 1.

M/M Components Event Date

All imputation rules for M/M event dates will follow rules in SAP Part 1.

5.2. Participant Disposition

The number of participants in the following disposition categories will be summarized throughout the study by DB treatment group and overall as described in Section 4.2 for each of the analysis set (OLS, LTFDCS and CSS):

- Participants entering the OL period
- Participants receiving OL study treatment
- Participants receiving M/T FDC DB study treatment
- Participants receiving M/T FDC DB and OL study treatment
- Participants completing DB study treatment [except for OLS]
- Participants who discontinued DB study treatment prematurely [except for OLS]
- Reasons for premature discontinuation of DB study treatment [except for OLS]
- Participants ongoing in OL study treatment [only for analyses at time of final DB analysis/submission]
- Participants completing OL study treatment
- Participants who discontinued OL study treatment prematurely
- Reasons for premature discontinuation of OL study treatment

- Participants completing the DB study period [except for OLS]
- Participants who terminated study DB period prematurely [except for OLS]
- Reasons for premature termination of study DB period [except for OLS]
- Participants ongoing in OL study period [only for analyses at time of final DB analysis/submission]
- Participants completing the OL study period
- Participants who terminated study OL period prematurely
- Reasons for premature termination of study OL period

Listings of participants will be provided for the following categories:

- Participants who discontinued OL study treatment prematurely, based on OLS
- Participants who terminated OL study prematurely, based on FAS

A participant will be counted as completing DB study treatment if CRF question "Did the subject take study drug until this visit?" at Visit 8 is answered as "Yes". Otherwise the participant will be considered to have discontinued DB study treatment prematurely.

A participant will be counted as completing the study DB period if the participant underwent Week 16 visit/Visit 8.

A participant entering the OL treatment period is defined as a participant receiving at least one dose of OL study treatment in the OL period.

A participant entering the OL period (with or without being treated in OL treatment period) is defined as a participant who underwent at least one visit between Visit 9 and Visit 14 (included).

A participant will be counted as completing the study OL period if the participant underwent week 120 Visit/Visit 14.

5.3. Primary Endpoint Analysis

Not applicable.

5.4. Secondary Endpoints Analysis

Not applicable.

5.5. Other Efficacy Endpoints Analysis

All other efficacy endpoints for the OL period will be analyzed for the OLS and LTFDCS. Selected efficacy endpoints will be analyzed for the FAS. Listings with data for each endpoint will be produced for the FAS, and as indicated also for OLS. Listing for OLS will contain all data from the OL period and OL baseline (where applicable). Listing for FAS will contain all data collected

throughout the study (DB and OL period). Each value will be flagged as assessed during DB or OL period.

It is allowed per protocol for participants to continue study treatment after the 24-month OL period is completed. EOLT visit in this case will be beyond 24 months. Therefore, the analyses specified below will include mainly data up to 24 months but also data beyond 24 months. The selection of assessments used for the summaries of efficacy is described for each endpoint in the sections below. All collected assessments will be presented in the corresponding listings.

5.5.1. Change from Baseline in 6MWD

5.5.1.1. Definition

This endpoint is change from baseline, by visit, in exercise capacity as measured by the 6MWD (in meters), defined as:

Post-baseline 6MWD (m) at scheduled timepoint − 6MWD (m) at baseline.

Assignment to visit windows is described in Section 5.1.1. For analyses based on OLS and LTFDCS, only assessment up to EOT+7 days will be summarized. For analyses based on FAS, all available data will be included.

5.5.1.2. Analysis Methods

Absolute values at baseline and by visit, as well as absolute changes from baseline to all scheduled timepoints will be summarized by treatment on the OLS, FAS and LTFDCS using descriptive statistics.

For the LTFDCS and FAS, a plot of the mean changes (± SE) in 6MWT from baseline overtime will be displayed. A reference line is included at zero change and baseline is added to the time axis to visualize an initial change from zero. When based on FAS, a reference line is displayed to separate DB from OL-treatment period.

In addition, for the FAS, the following analyses of the change from baseline in 6MWT will be performed considering all the observed values (from scheduled or unscheduled assessments) and the actual assessment day:

- Spaghetti plots will be presented by treatment arm to explore the longitudinal pattern of observed values.

- A parametric longitudinal mixed-effects model, with a (fixed-effects) mean structure that is quadratic over time (based on analysis visit, with time corresponding to the target assessment day of the corresponding analysis visit) and with a random intercept and a random slope will be considered for the change from baseline to each post-baseline assessment. The model will include time, time-by-treatment interaction term, time-by-time-by-treatment quadratic interaction term, treatment and the baseline value. Random intercept and slope at the level of the participant will be considered. Estimates by treatment

arm at analysis visits Week 8, Week 16, Week 42, Week 68, Week 94 and Week 120 will be presented along with 95% confidence intervals from the model. Graphical presentation of model estimates along with 95% confidence regions will be overlayed to the observed values of the change from baseline. In case of missing data, no imputation will be performed and only observed data will be summarized.

All available 6MWD data will also be listed as described in Section 5.5.

Supportive data collected on Borg dyspnea index (including the type of Borg scale used by the participant) or oxygen saturation will be listed only.

5.5.2. Change from Baseline in WHO FC

5.5.2.1. Definition

The change from baseline, by visit, in WHO FC will be categorized as worsening or no worsening that is assessed in the following way:

- Worsening: X=0 if (difference between post-baseline WHO-FC and baseline WHO-FC) >0
- No worsening: X=1 if (difference between post-baseline WHO-FC and baseline WHO-FC) ≤0.

WHO-FC assessments will be assigned to visit windows as described in Section 5.1.1. For analyses based on OLS and LTFDCS, only assessment up to EOT+7 days will be summarized. For analyses based on FAS, all available data will be included.

5.5.2.2. Analysis Methods

The proportion of participants who improved or remained stable (absence of worsening from baseline) in WHO FC (ie, a change ≤0) will be summarized by visit and treatment, on the OLS, FAS and LTFDCS.

In addition, at the time of OL final analysis and based on the FAS, a marginal weighted longitudinal generalized estimating equation will be considered for the absence of worsening at each post-baseline assessment. The model will include time (based on analysis visit, with time corresponding to the target assessment day of the corresponding analysis visit), time-by-treatment interaction term, and treatment. Estimates by treatment arm at analysis visits Week 8, Week 16, Week 42, Week 68, Week 94, and Week 120 will be presented along with 95% confidence intervals from the model.

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.5.3. Time to First M/M Event Occurring Between Baseline and EOT + 7 days and Between Baseline and Week 120 visit

5.5.3.1. Definition

Time to first M/M event is defined as any of the following:

- Death (all causes).
- Non-planned PAH-related hospitalization.
- Initiation of intravenous or subcutaneous prostacyclin or prostacyclin analog for worsening PAH.
- Clinical worsening defined as:
  - Deterioration in exercise testing, confirmed by two 6MWTs performed on different days within 2 weeks, showing at least 15% decrease in 6MWD from baseline (ie, Day 1 in DB).

  AND

  - Worsening of PAH symptoms, defined as at least 1 of the following:
    - Increase in WHO FC.
    - Appearance or worsening of signs/symptoms of right heart failure that do not respond to optimized oral diuretic therapy.

The sponsor will identify participants with a mortality event, and/or a morbidity event (including clinical worsening) through end of study. The adjudication package will be reviewed by two CEC members (CEC 1 and CEC 2) and a CEC adjudicator, if applicable (see details in the CEC Charter).

All cases reviewed and confirmed by the CEC will be included in the analysis of the endpoint. The onset date as assessed in the CEC review will be used. In case a partial or missing date is recorded by the CEC, then rules as specified in Section 5.1.4 will be applied.

The time to M/M event is defined as the time from baseline (Day 1) to the first occurrence of a M/M event confirmed by the CEC up to either EOT + 7 days or Week 120 visit. For participants without Week 120 Visit, Week 120 Visit is imputed by minimum (cut-off date, EOS date). Only events up to and including the cutoff date are considered.

Participants without the event (confirmed by the CEC) in the corresponding period are right censored

- at minimum (EOT+7 days, EOS, cutoff date) for analysis up to EOT+7 days
- at (imputed) Week 120 visit for analysis up to Week 120 visit.

5.5.3.2. Analysis Methods

LTFDCS will be used to assess this endpoint up to EOT+7 days. The FAS will be used to assess this endpoint up to EOT+7 days and up to Week 120 visit. The time to occurrence of the first CEC

confirmed M/M event will be estimated by Kaplan-Meier method, providing estimates for each treatment arm and corresponding 95% two-sided CLs at Week 16 (Day 113), Month 6 (Day 183), Month 12 (Day 365), Month 18 (Day 548), Month 24 (Day 730). The CLs are constructed using Greenwood's formula (Collett 2003) for the standard error of the Kaplan-Meier estimate and are added to the plot. The number of participants at risk, censored and with events will be computed and displayed at each time point for each group. Data will be summarized in tables or figures including number of events, number of censored observations, number of participants at risk and KM estimates of the survival function for time to event variables. The graph of the estimates survival function of the time to first M/M event for each treatment arm obtained from the Kaplan-Meier product-limit method will be displayed up to the time at which at least 10% of all participants remain at risk of an event. The graphical presentation follows the recommendations from (Pocock 2002).

Based on OLS (up to EOT+7 days), LTFDCS (up to EOT+7 days) and FAS (up to EOT+7 days and up to Week 120 visit), causes of M/M events confirmed by CEC will also be summarized in frequency tables as first event and also all events per participant. If a participant experiences several first events as assessed by the CEC (i.e. multiple events with the same onset date), the cause of the first event corresponds to the most severe event documented, using the following hierarchy: 1) Death, 2) Non-planned PAH-related hospitalization, 3) Initiation of IV or Subcutaneous prostacyclin or prostacyclin analog for worsening PAH, 4) Clinical worsening.

5.5.4. Time to Death Due to PAH or Hospitalization for PAH Occurring Between Baseline and EOT + 7 days or Between Baseline and Week 120 Visit

5.5.4.1. Definition

Time to death due to PAH or hospitalization for PAH is defined as:

- Death due to PAH, or onset of a TEAE that led to permanent discontinuation of study treatment with a fatal outcome due to PAH occurring within 4 weeks of study treatment discontinuation.

  OR
- Non-planned PAH-related hospitalization.

The PAH relatedness for death or hospitalization will be based on the investigator's assessment of the event as reported on the eCRFs. The following eCRF forms will be used:

- The "Death Information" form for death due to PAH ("Was death due to PAH?" eCRF question answered as "Yes"),

- The "Adverse Event" form for onset of TEAE leading to study treatment discontinuation (DB or OL) with fatal outcome due to PAH occurring within 4 weeks of study treatment discontinuation (date of DB or OL study treatment discontinuation is picked as the last date with dose administered on the "Study Drug Administration" form). The death due to PAH information will be based on the "Death Information" form,

- The "Suspected M/M event" form for non-planned PAH-related hospitalization.

The time to death/hospitalization due to PAH event is determined as the time from baseline (Day 1) to the first occurrence of an event specified above up to either EOT+7 days or Week 120 visit. For participants without Week 120 Visit, Week 120 Visit is imputed by minimum (cut-off date, EOS date). Only events up to and including the cutoff date are considered.

Participants without the endpoint event in the corresponding period are right-censored:

- at minimum (EOT+7 days, EOS, date of death for reason not related to PAH, cutoff date) for analysis up to EOT+7 days
- at minimum ([imputed] Week 120 visit, date of death for reason not related to PAH) for analysis up to Week 120 visit.

5.5.4.2. Analysis Methods

LTFDCS will be used to assess this endpoint up to EOT+7 days. The FAS will be used to assess this endpoint up to EOT+7 days and up to Week 120 visit. The time to death/hospitalization due to PAH will be estimated by Kaplan-Meier method as detailed in Section 5.5.3.2.

Based on OLS (up to EOT+7 days), LTFDCS (up to EOT+7 days) and FAS (up to EOT+7 days and up to Week 120 visit), death and hospitalizations due to PAH will be summarized in a frequency table as first event and also all events per participant. If a participant experiences several events, all events are counted separately unless the participant experiences the events at the same time (eg. if a participant dies during hospitalization, this is counted only as one event, the most serious one).

5.5.5. Time to Death (All Causes) Occurring Between First Dose in double-blind period and last available survival follow-up

5.5.5.1. Definition

Time to death (all causes) is defined as any death event reported by the investigator in the CRF.

The time to death is determined as the time from first dose of study treatment in DB to the participant's death up to last available follow-up date as collected in the Survival Follow up eCRF form.

Participants without the endpoint event between first dose of study treatment in DB and up to study closure are right censored last available follow-up date. Participants without the endpoint event who withdrew consent are right-censored at EOS date.

5.5.5.2. Analysis Methods

FAS will be used to analyze this endpoint. At the time of final DB analysis/submission, this endpoint includes all survival data collected up to the cut-off date. At the time of OL final analysis, this endpoint includes all survival data collected at the time of OL database lock.

The time to death will be estimated by Kaplan-Meier method as detailed in Section 5.5.3.2, providing estimates at 6-monthly intervals [Months 6 (Day 183), 12 (Day 365), 18 (Day 548), 24 (Day 730), 30 (Day 913), 36 (Day 1095), …].

Reasons for death will also be summarized in a frequency table.

5.5.6. Change from Baseline in NT-proBNP

5.5.6.1. Definition

NT-proBNP samples will be processed through the central laboratory, and the results will be sent electronically to the sponsor. Results will be reported in conventional units (ng/L). NT-proBNP values will be assigned to visit windows as described in Section 5.1.1. For OLS and LTFDCS, only assessment up to EOT+7 days will be summarized. For the FAS all available assessments are included.

Change from baseline, by visit, in NT-proBNP will be calculated as:

- Post-baseline NT-proBNP value at scheduled timepoint−NT-proBNP value at baseline.
- Percent of baseline calculated as: $\frac{\text{Post−baseline NT−proBNP value at scheduled timepoint}}{\text{NT−proBNP value at baseline}} \times 100$

5.5.6.2. Analysis Methods

Absolute values at baseline and by visit as well as absolute changes from baseline to all scheduled timepoints will be summarized by treatment on the OLS, LTFDCS, and FAS using descriptive statistics. Percent of baseline will also be summarized at each scheduled post-baseline timepoint using geometric means and two-sided 95% confidence intervals of the geometric means, assuming normal distribution of the log transformed NT-proBNP.

Based on the FAS, a plot of percent of baseline NT-proBNP over time will be displayed by means of geometric mean and 95% CL. A reference line is included at 100% and baseline is added to the time axis to visualize an initial change.

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.5.7. Number Per Year of All-cause and PAH-related Hospitalizations and In-patient Hospital Days, From Baseline up to EOLT

5.5.7.1. Definition

All hospitalizations starting between Day 1 (for LTFDCS) or OL Day 1 (for OLS) and up to EOLT visit will be used for number per year of hospitalizations and in-patient hospital days. The following medical encounters are considered hospitalizations:

- Intensive care unit
- Hospice/palliative care unit

- Hospital in-patient department
- Long-term care facility
- Rehabilitation centers

Hospitalizations will be identified as PAH-related based on the investigator's assessment of the hospitalization.

Participant's time on study (in years) for hospitalization endpoints will be derived as follows:

(EOLT visit date – (Day 1 or OL Day 1 for LTFDCS and OLS, respectively) + 1)/365.25,

Participant-years on study in a treatment group will be computed as the total participant's time on study for all participants in the treatment group.

The number of days for a hospitalization will be counted as:

Min(hospitalization discharge date, EOLT visit date)–hospitalization admission date+1.

In case of missing discharge date of a hospitalization that is not ongoing, the number of days for the hospitalization will be imputed as a median hospitalization length in the geographical region. If the median hospitalization length in the geographical region cannot be computed or the hospitalization is ongoing, the length of the hospitalization will be computed from the admission date up to the EOLT date.

In case participant was not enrolled in OL then EDBT visit will be used in place of EOLT visit.

5.5.7.2. Analysis Methods

This endpoint will be analyzed for OLS and LTFDCS.

The total number of hospitalizations will be added up by DB treatment group for OLS and overall for LTFDCS. This number will then be divided by participant-years on study in the DB treatment group for OLS (or overall for LTFDCS) to obtain the number per year of hospitalizations.

The same approach as for the number per year of hospitalizations will be done for the number per year of in-patient hospitalization days.

5.5.8. Number per Year of Emergency Room Visits From Baseline up to EOLT

5.5.8.1. Definition

All emergency room (ER) medical encounters between Day 1 (for LTFDCS) or OL Day 1 (for OLS) and up to EOLT visit will be used for the number per year of ER visits. If an ER visit results in a hospital admittance (ie, participant has other hospitalization, as defined in Section 5.5.7.1 reported on the same day), such an encounter will not be considered for this endpoint.

ER visits will be identified as PAH-related based on the investigator's assessment of the encounter.

Participant's time on study and participant-years on study in a treatment group are derived in the same way as described in Section 5.5.7.1.

5.5.8.2. Analysis Methods

This endpoint will be analyzed for the OLS and LTFDCS. The total number of ER visits will be added up by DB treatment group for OLS and overall for LTFDC and divided by participant-years on study in the DB treatment group for OLS (or overall for LTFDCS) to obtain the number per year of ER visits.

5.6. Safety Analyses

All safety analyses will be based on the CSS based on actual DB treatment received in the DB period, unless otherwise specified. Summaries will be displayed overall and by DB treatment group as described in Section 4.2.

For all continuous safety variables, descriptive statistics will include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Treatment-emergent period

The combined treatment-emergent period is defined from first intake of M/T FDC treatment [ie, loose combination of macitentan and tadalafil] in DB or OL treatment period up to EOT (EOT-DB or EOT-OL) + 30 days. For participants who completed the 24-months of OL treatment and who are eligible for continued access program (post-trial access program or other open-label extension study), the observation period will be shorter as these participants are not required to perform the 30 days safety follow up period.

5.6.1. Extent of Exposure

The number and percentage of participants who receive M/T FDC treatment (as loose combination of macitentan and tadalafil or as fixed dose combination) will be summarized for OLS and CSS.

Descriptive statistics for duration of M/T FDC treatment (N, mean, SD, median, and range (minimum, maximum)) will be summarized.

Duration of M/T FDC treatment will be summarized in the following duration categories: <4 weeks, 4-<16 weeks, 16-<42 weeks, 42-<68 weeks, 68-<94 weeks, 94-<120 weeks and ≥120 weeks overall and for each DB treatment group and presented graphically in a histogram.

Cumulative duration of M/T FDC treatment ≥4 weeks, ≥16 weeks, ≥42 weeks, ≥68 weeks, ≥94 weeks and ≥120 weeks will be summarized.

M/T FDC treatment duration (weeks) is defined as (date of EOT – date of first dose of M/T FDC treatment +1)/7. M/T FDC treatment duration with interruptions (weeks) is calculated as (date of

EOT – date of first dose of M/T FDC treatment – days without study treatment administration + 1)/7.

For the OLS, M/T FDC treatment duration (weeks) is defined as (date of EOT-OL – date of first dose of OL study treatment +1)/7. M/T FDC treatment duration with interruptions (weeks) is calculated as (date of EOT-OL – date of first of first dose of OL study treatment – days in OL without study treatment administration + 1)/7.

Individual participant listings will be provided for exposure data broken down by actual DB treatment group, stratum, site, and participant number. In case interim analysis results in early stopping of the DB period for efficacy, a listing of all DB and OL exposure is provided for participants in the FAS who enter OL period after premature discontinuation of DB study treatment.

M/T FDC treatment compliance will be summarized descriptively. See Appendix 7 for further details.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of DBL.

For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized overall and by actual DB treatment group. No formal testing between treatment groups will be done.

If severity of AE is missing the worst severity, ie, “Severe” will be imputed. If AE relationship to the study treatment is missing, “Related” will be imputed. If seriousness information of AE is missing the “Serious” will be imputed.

The same summary tables as described for the DB period in the SAP Part 1 section 6.1 will be done for the combined DB-OL period. AEs leading to premature study treatment discontinuation will include AEs that led to premature DB or OL study treatment discontinuation.

In order to account for differences in the duration of treatment exposure among participants, incidence rates of any treatment emergent AE, any treatment-emergent SAE, any AE leading to discontinuation, treatment-emergent AEs of special interest (AESI) and treatment-emergent fatal AEs will be presented as a rate adjusted for subject-years exposure (SYE).

Based on the CSS, the subject-observation time will be calculated, for each participant, as follows:

- For participants without event: by considering the treatment duration as EOT – Date of first dose of M/T FDC + 1
- For participants with event: by considering the M/T FDC treatment duration up to the start date of first event (min [date of first event, EOT] – Date of first dose of M/T FDC + 1).

The SYE will be calculated by first summing the subject-observation time for all participants and then dividing it by 365.25 days.

Then the Exposure Adjusted Incidence Rate (EAIR) for an event category, per 100 subject-years will be calculated by dividing the number of subjects with at least one event by the SYE and multiplying by 100:

Exposure Adjusted Incidence Rate (EAIR) = 100 * Number of participants with the event/SYE.

The exposure adjusted incidence rate is interpreted as the number of events occurring in 100 subject-years (SY). 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 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.

The following information will be displayed:

n = The number of participants with at least one event. Participants with multiple events will be counted only once.

T = The total of the participants time on M/T FDC treatment (in years). It is the duration of treatment.

Exposure Adjusted Rate = The exposure adjusted event incidence rate per 100-SY including 95% CL. It is interpreted as the number of events occurring in 100-SY.

In addition to the summary tables, specific AE type listings will be provided for participants who experienced at least 1:

- AE
- SAE
- AE leading to premature discontinuation of OL study treatment
- AESI (one listing for each AESI type as defined in SAP Part 1)

All AEs throughout the study will be included in the listings for all participants in the CSS, the listing on all AEs will also be provided based on the FAS. The listings will contain information about tadalafil and macitentan dose at the onset of the AE as well as the day of the last dose intake prior to the onset of the AE.

Separate summaries are provided on AEs with an onset during the first week of combination treatment when participants who are not on an allowable dose of PDE-5i (40 mg tadalafil, 60–120 mg sildenafil, or 10 mg vardenafil daily) undergo the tadalafil 20 mg titration phase (week 1 of M/T FDC). All treatment emergent AEs up to the day prior to start of tadalafil 40 mg (or up to FDC day 7 if no up-titration was mandated) are included in the analysis. Participants from the CSS are grouped by prior stratum and DB treatment group

The following displays are provided for AEs with an onset during the first week of combination treatment (tadalafil 20 mg titration phase):

- Overall summary table of TEAEs, containing number of participants with at least one: AE, AE related to study treatment, SAE, SAE related to study treatment, AE leading to premature discontinuation of study treatment, Fatal AE)
- TEAE table by SOC and PT within each SOC, in descending order of incidence in the overall group
- Listing of AEs

Deaths will be displayed by actual DB treatment received. For treatment-emergent deaths and all deaths, frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death
- Relationship to study treatment (related to study treatment/relationship unknown)

The summary will be based on the Death Information CRF page, and relationship to the study treatment will be mapped through corresponding AE, if available. A listing of participants who died during the study will be provided based on CSS and FAS. The listing will contain information about the last tadalafil and macitentan dose as well as the day of the last dose intake.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the CSS.

The analysis of the clinical laboratory tests will be the done in the same way as described in the SAP Part 1 in section 6.2 including the same definitions of marked liver and hemoglobin abnormalities. The following marked liver categories are added to the ones already defined in SAP part 1: ALT and/or AST >= 3xULN and <5xULN; ALT and/or AST >= 5xULN and <8xULN; ALT and/or AST >= 3xULN and bilirubin >= 2xULN at any time (and both, ALT or AST and bilirubin increased compared to baseline). All tables and figures defined for the DB treatment-emergent period will be repeated for the combined DB and OL treatment-emergent period.

In addition, a plot of the mean change from baseline (± SE) for parameters hemoglobin, leukocyte count, and platelet count over time will be displayed. A reference line is included at zero change and baseline is added to the time axis to visualize an initial change from zero.

All laboratory data throughout the study will be included in the listings for all participants in the CSS and the FAS.

5.6.3.2. Vital Signs and Physical Examination Findings

Vital signs parameters will be displayed for the participants included in the CSS.

The analysis of the vital signs parameters will be the done in the same way as described in the SAP Part 1 in section 6.3 including the definition of markedly abnormal vital signs. A further category of markedly abnormal vital signs is added as follows: 'Increase in body weight from baseline > 5 kg'. All tables and figures defined for DB treatment-emergent period will be repeated for the combined DB and OL treatment-emergent period.

All vital signs data throughout the study will be included in the listings for all participants in the CSS and the FAS.

5.7. Other Analyses

5.7.1. Biomarkers

Optional biomarker assessments are described in section 7.2.2.7 of the protocol.

The biomarker analysis will be performed after study closure and will not be included in the CSR.

5.7.2. Health Economics

Please refer to Sections 5.5.7 and 5.5.8 for the definition and analysis of health economics endpoints.

5.7.3. Definition of Subgroups

Summary of 6MWD, WHO FC and time to M/M event, will be performed by prior-strata subgroups (prior-ERA stratum, prior-PDE-5i stratum, treatment naïve stratum) on the FAS.

Based on the CSS, summary tables of treatment-emergent AE (by SOC and PT), SAE (by PT), and AESI (by SOC and PT) are provided for the following subgroups: Region (US, non-US), Prior-strata (treatment naïve, not treatment naïve), Age group, Sex, and Race. Overall summary table of treatment-emergent AEs (containing number of participants with at least one: AE, AE related to study treatment, SAE, SAE related to study treatment, AE leading to premature discontinuation of study treatment, Fatal AE) are provided for the following subgroups: Age group, Sex, and Race. Subgroups are defined in SAP Part 1.

6. DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

6MWD	6-minute walk distance
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
CEC	Clinical event committee
CL	confidence limit
CRF	case report form
CSR	Clinical Study Report
CSS	Combination safety set
DB	Double-blind
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
eCRF	electronic case report form
EDBT	End of Double-blind Treatment
EAIR	Exposure Adjusted Incidence Rate
EOLT	End of Open-label Treatment
EOS	End-Of-Study
EOT	End-Of-Treatment
ER	Emergency Room
ERA	Endothelin receptor antagonist
FAS	full analysis set
FC	Functional Class
FDC	Fixed dose combination
KM	Kaplan-Meier
LTFDCS	Long-term M/T FDC set
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
M/M	Morbidity /Mortality
M/T	Macitentan / Tadalafil
NT pro-BNP	N-terminal pro B-type natriuretic peptide
OL	Open-label
OLS	Open label Set
PAH	Pulmonary arterial hypertension
PD	Protocol deviation
PDE-5	Phosphodiesterase type-5
PDE-5i	Phosphodiesterase type-5 inhibitor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
S-FU	Safety follow-up
SMQs	standardised MedDRA queries
SOC	System organ class
SS	Safety set
SY	Subject-Year
SYE	Subject-Years Exposure
TEAE	treatment-emergent adverse event
US NCI	United States National Cancer Institute
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

It is clarified that the available OL data are analyzed together with the double-blind data at the time of final DB analysis/submission. An overall cut-off date will be applied for the analyses run at that time.

The protocol defines the baseline value for the combination treatment period as the last valid assessment obtained prior to the first intake of macitentan and tadalafil (double-blind or open-label). As there is no definition of "valid", the baseline definition was changed as follows:

For the CSS analysis population, baseline is defined as the last assessment prior to the first intake of M/T FDC study treatment either in DB or OL period. The first M/T FDC intake can be either LC of macitentan and tadalafil or M/T FDC.

The time to first M/M event is also analyzed as a separate endpoint up to Week 120 visit in order to include events collected after premature EDBT/EOLT.

It is clarified that the protocol endpoint time to death (all causes) from randomization until OL database lock is the time to death from first dose of study treatment up to last available survival follow-up at the time of OL database lock. The protocol endpoint time to death (all causes) from randomization until DB database lock is the time to death from first dose of study treatment up to last available survival follow-up at the time of final DB analysis/submisson (ie, up to the cut-off date). Both analyses are described in Section 5.5.5 of this SAP. 'Randomization' is changed to 'first dose in double-blind' to align with other efficacy endpoints which are analyzed from baseline (ie, first dose in DB period).

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants will be summarized and listed by strata group and DB treatment group, and overall as described in Section 4.2. In addition, the distribution of participants by stratum and geographical region will be presented unless otherwise noted.

Table 7 presents a list of the demographic variables that will be summarized by DB treatment group and overall for all the analysis sets (OLS and CSS).

Table 7 – Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (18-25 years, 26-50 years, 51-64 years, and >=65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian [if Asian, Japanese or Other Asian], Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, not reported)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported)	
Region (US, non-US)	
Geographical region (North America, Latin America, Asia, Eastern Europe, South and Western Europe, Oceania, Africa)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2])	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

Countries will be assigned to geographical region based on the Standard Country or Area Codes for Statistical Use (M49) standard (unstats.un.org).

Demography variables will be summarized as collected at the DB screening with an exception of body weight and BMI, these will be re-derived for baseline as applicable for each analysis set.

The following baseline characteristics variables will be summarized for all the analysis sets (OLS, LTFDCS and CSS):

- WHO FC (I, II, III, IV), re-derived for baseline as applicable for each analysis set.
- PAH etiology (idiopathic, heritable, drug- and toxin- induced, PAH associated with other conditions [connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis], long-term responders to calcium channel blockers, with overt features of venous/capillaries involvement)
- Time since diagnosis (in years). For each participant time since diagnosis will be derived as:
  - (Date of the first study treatment administration as applicable for each analysis set–date of diagnosis+1)/365.25.
- Baseline RHC results (this will include a summary of the PVR results as calculated by the central reader [WCC] together with the proportion of assessments based on Fick cardiac

output [CO] and thermodilution CO, the CO results as well as the mPAP, PAWP and LVEDP values from the central reader), re-derived for baseline as applicable for each analysis set.

- Baseline 6MWD (in meters), re-derived for baseline as applicable for each analysis set.

Demographics and baseline characteristics will also be listed on the OLS.

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations (PD) may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the number and percentage of participants with major protocol deviations during the OL period will be summarized by category and PD criterion based on the OLS. A listing of all major PDs is provided for the FAS. PD will be flagged as occurring during DB or OL period.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

6.5. Appendix 5 Prior and Concomitant Medications

Prior medications are analyzed as part of the SAP Part 1.

Concomitant medications will be coded using the latest version of World Health Organization Drug Dictionary (WHO-DD) at the DBL.

For the CSS, study treatment-concomitant medications are defined as any therapy used on or after the same day as the first dose of M/T FDC study treatment (ie, loose combination of macitentan and tadalafil) in DB or OL period, including those that started before and continue on after the first dose of M/T FDC study treatment in DB or OL period, up to EOT (EOT-DB or EOT-OL).

Summaries of concomitant medications will be presented by ATC level 4 term and standardized medication name, overall and by DB treatment group for CSS. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. In addition, study treatment-concomitant medications categorized as PAH-specific medications will be presented in the same fashion, by category. See SAP Part 1 for list of medications in the category.

In addition, for the CSS, PAH-specific medications at baseline will be summarized by category, ATC level 4 and DB treatment group. Medication at baseline is any medication taken during the first day of M/T FDC study treatment (ie, loose combination of macitentan and tadalafil).

PAH-specific medications initiated after end of M/T FDC study treatment up to EOS will be summarized by category, ATC level 4 and DB treatment group.

Medications and Procedures will be listed for CSS and for FAS.

6.6. Appendix 6 Medical History

Not applicable for this SAP. Medical history is analyzed in the SAP Part 1 section 4.1

6.7. Appendix 7 Treatment Compliance

Compliance will be summarized descriptively for the OL study treatment overall and by DB treatment group for the OLS, from first OL study treatment up to EOT-OL.

Compliance = [(number of OL treatment tablets dispensed at all visits−number of OL treatment tablets returned at all visits)/Total number of OL treatment tablets that should have been taken from the first dose of OL study treatment to EOT-OL] × 100.

The total number of OL treatment tablets that should have been taken will be calculated knowing that 3 tablets should be taken each day during the OL titration phase (OL Day 1 to OL Day 14) and then 1 tablet each day during the OL maintenance phase (OL Day 15 to EOT-OL).

The number of tablets dispensed will be derived based on the kit types dispensed. Each kit type contains a fixed number of tablets of each type (including placebo tablets). The number of tablets returned will be based on the information collected in the eCRF.

The number and percentage of participants who have:

- <80%
- 80–100%
- >100–120%
- >120%

overall study treatment compliance will be summarized overall and by actual DB treatment group.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined in the Attachment 2 of SAP Part 1.

6.9. Appendix 9 Medications of Special Interest

Concomitant medications of special interest are defined in Attachment 1 of SAP Part 1.

6.10. Appendix 10 Laboratory Toxicity Grading

Not applicable. Marked laboratory abnormalities as detailed in section 14.4 of the protocol and in SAP Part 1 section 6.2.

6.11. Appendix 11 Estimands Examples

Not applicable.

7. REFERENCES

(EDMS-RIM-263896, 3.0) Clinical Protocol AC-077A301: A DUE, Version 6. Prospective, multi-center, double-blind, randomized, active-controlled, triple dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy. Actelion Pharmaceuticals Ltd. (27 Apr 2021).

(EDMS-RIM-264821, 3.0) Clinical Protocol COVID-19 Appendix AC-077A301: A-DUE. Prospective, multi-center, double-blind, randomized, active-controlled, triple dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy. Actelion Pharmaceuticals Ltd. (27 Apr 2021).

(unstats.un.org) Standard country or area codes for statistical use (M49). United Nations Statistics Division website. https://unstats.un.org/unsd/methodology/m49/overview/. Accessed 23 March 2020.

(Collett 2003) Modelling Survival Data in Medical Research, 2nd Edition. Chapman & Hall; 2003.

(Pocock 2002) Pocock SJ, Clayton TC, G Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet. 2002;359:1686–89.