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)

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

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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.

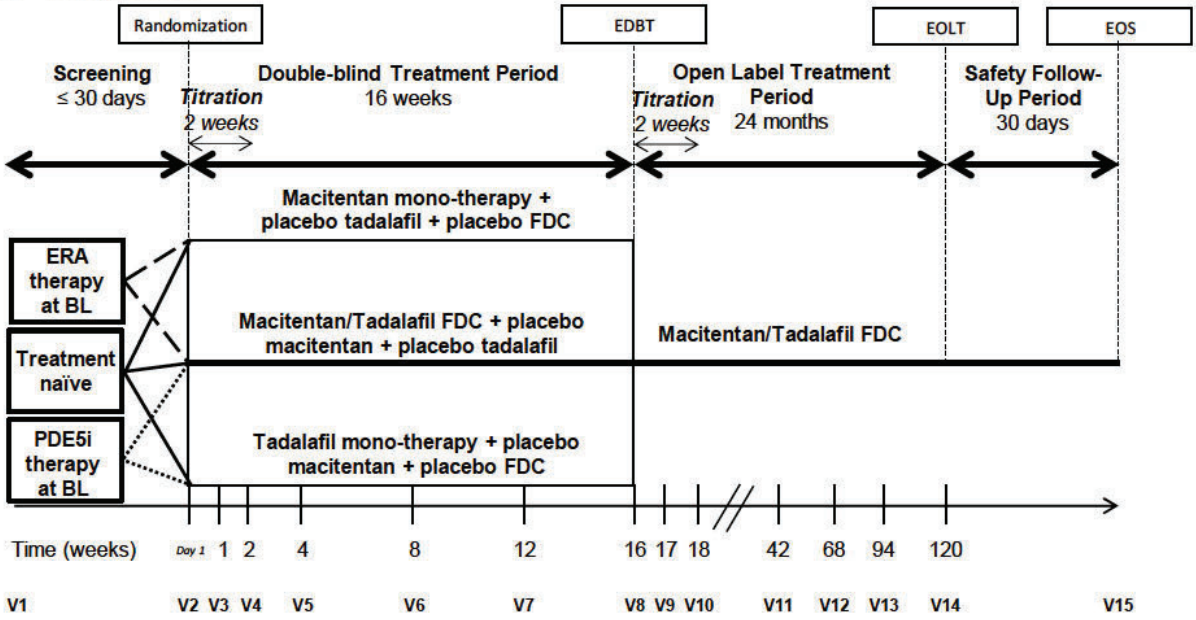
End of Study (EOS): EOS is reached when all participants have completed their EOS visit, died, or are lost to follow-up.

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

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