Official Protocol Title:	A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study to Compare the Efficacy and Safety of Sotatercept (ACE-011) Versus Placebo When Added to Standard of Care for the Treatment of Pulmonary Arterial Hypertension (PAH)
NCT number:	NCT03496207
Document Date:	18-Jan-2022

Statistical Analysis Plan

Extension Period: A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study to Compare the Efficacy and Safety of Sotatercept (ACE-011) Versus Placebo When Added to Standard of Care for the Treatment of Pulmonary Arterial Hypertension (PAH)

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Investigational Product:	Sotatercept (ACE-011)
Protocol Number:	A011-09 Extension Period
EudraCT Number:	2017-004738-27
Version Number:	1.2
Date:	18 January 2022

ACCELERON PHARMA SIGNATURE PAGE

The undersigned have approved this Statistical Analysis Plan Version 1.2 for use in this study.

PPD

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SAP SUMMARY OF CHANGES TABLE

The changes from Extension Period SAP Version 1.1 (30 April 2021) to Extension Period SAP Version 1.2 (18 January 2022) are detailed below. Minor edits are not included.

Location	Description of Change	Brief Rationale
Section 5.6.1.4. Supportive Analysis	Added analysis with Month-6 window for Placebo-controlled period.	Added to support the End of Period analysis.
Section 5.6.4. Subgroup Analysis	Added subgroup analysis for the subgroups of Baseline Cardiac Index (< 2.5 or >= 2.5 L/min/m^2 at baseline)	Baseline Cardiac Index < 2.5 represents an important intermediate/high risk category and Baseline Cardiac Index > = 2.5 L/min/m^2 represents an important low risk category.

TABLE OF CONTENTS

SAP SUMMARY OF CHANGES TABLE 3
1. INTRODUCTION 7
2. STUDY OBJECTIVES 7
3. OVERALL STUDY DESIGN 8
3.1. Extension Period Study Design 8
3.2. Rerandomization 8
3.3. Treatment Discontinuation 9
3.4. Sample Size and Power Calculation 9
4. ANALYSIS POPULATIONS 10
4.1. Full Analysis Set for the Extension Period (FAS-E) 10
4.2. Safety Population for the Extension Period 10
4.3. PK Population for the Extension Period 10
4.4. Per Protocol Set for the Extension Period (PPS-E) 10
5. STATISTICAL METHODOLOGY 11
5.1. General Considerations 11
5.2. Disposition of Patients 11
5.3. Demographic, Baseline Characteristics, and Disease History 11
5.4. Study Drug Exposure 11
5.5. Prior and Concomitant Medication and Procedures 11
5.5.1. Prior and Concomitant Medication 11
5.5.2. Non-Medication Procedures 12
5.6. Efficacy Analyses 12
5.6.1. Extension Period Analysis 12
5.6.1.1. Placebo-crossed Efficacy Analysis 13
5.6.1.2. Delayed-start Efficacy Analysis 14
5.6.1.3. Sensitivity Analysis 14
5.6.1.4. Supportive Analysis 14
5.6.2. Other Extension Period Analysis 15
5.6.2.1. Six-minute walk distance (6MWD) at 12-Months 15
5.6.2.2. WHO Functional Class Change at 12-Months 15
5.6.2.3. Other Secondary Efficacy Endpoints at 12-Months and aligned with 3rd RHC (Month 18-24) 16

5.6.3. Exploratory Endpoints 17
5.6.4. Subgroup Analysis 19
5.6.5. Additional Sensitivity Analysis 20
5.6.6. Special Handling for COVID-19 22
5.7. Safety Analysis 22
5.7.1. Adverse Events 22
5.7.2. Laboratory Evaluations 23
5.7.3. Vital Signs 24
5.7.4. Electrocardiogram (ECG) Results 24
5.7.5. Physical Examination 25
5.8. Pharmacokinetics 25
5.8.1. Pharmacokinetic Sampling Schedule 25
5.8.2. Pharmacokinetic Data Handling 26
5.8.3. Pharmacokinetic Analysis 26
5.9. Pharmacodynamics 26
5.10. Interim Analysis 26
5.11. Protocol Deviations 26
5.12. Data Handling 27
5.12.1. Analysis Visit Window 27
5.12.2. Handling of Missing Data 27
5.12.2.1. Missing Dates for Adverse Event and Concomitant Medication 27
5.12.2.2. Missing Dates for Disease Diagnosis Date 29
5.12.3. Handling of Data Limits 29
5.13. Changes in Conduct or Planned Analyses from the Protocol 29
6. REFERENCES 30
7. APPENDICES 31
7.1. Appendix 1 - List of Abbreviations 31
7.2. Appendix 2 - Schedule of Events (SoE) 33

LIST OF TABLES

Table 1: Notation: Efficacy Measurement at Different Time Points 12
Table 2: Patients Blood Sample Collection Schedule 25

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used for the analysis of Extension Period of Acceleron Protocol A011-09. This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol amendment 07A dated 17 July 2020. Any further changes to the protocol may necessitate updates to the SAP.

This SAP will be signed off before the study database lock of the Extension period. Any deviations from the SAP will be described and justified in the final clinical study report (CSR).

2. STUDY OBJECTIVES

The primary objectives of the Extension period are:

- To compare the efficacy endpoints between the continued sotatercept treatment group and placebo-crossed treatment group in the extension period using delayed-start efficacy analysis.
- To compare post-baseline (Month 18-24) vs baseline (Month 0) values of efficacy endpoints within the placebo-crossed treatment group using placebo-crossed efficacy analysis.
- To evaluate the long-term safety and tolerability of sotatercept in WHO functional class II-III PAH patients

The secondary objectives for the extension periods are:

- To assess the long-term effects on patients with PAH continuing sotatercept plus SOC on functional and pharmacodynamic endpoints compared with those transitioning from placebo plus SOC to sotatercept plus SOC.
- To assess the Pharmacokinetics (PK) of sotatercept in patients with PAH

The exploratory objectives for the extension periods are:

- To assess relevant biomarkers for PAH
- To assess efficacy parameters in patients with PAH

3. OVERALL STUDY DESIGN

This is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group study of sotatercept plus SOC versus placebo plus SOC in participants with PAH of WHO functional class II-III with an extension period where the placebo participants are rerandomized to one of the dose groups of sotatercept plus SOC.

3.1. Extension Period Study Design

In this study, 106 participants were randomly assigned in a 3:3:4 ratio to one of the 3 treatment groups in the Placebo-Controlled Treatment Period with 32 participants in Arm 1: Placebo SC every 21 days plus SOC for 24 weeks, 32 participants in Arm 2: Sotatercept (0.3 mg/kg, SC) every 21 days plus SOC for 24 weeks and 42 participants in Arm 3: Sotatercept (0.7 mg/kg, SC) every 21 days plus SOC for 24 weeks. Out of the 32 participants originally randomized to Placebo, 30 participants entered the Extension period with 15 of the participants rerandomized to 0.3 dose group and 15 participants rerandomized to 0.7 dose group. Out of the 32 participants originally randomized to 0.3 dose group, 31 participants entered the Extension period and out of the 42 participants originally randomized to 0.7 dose group, 36 participants entered the Extension period. Study duration for the extension period is up to 30 months with a 8-week Follow-Up Period after the last dose of study drug.

Participants who have not discontinued early from the Placebo-Controlled Treatment Period will continue directly into the Extension Period. Participants who have been on sotatercept will continue to receive sotatercept at their current dose level SC plus SOC. Participants who were in the placebo arm will be re-randomized to receive sotatercept 0.3 or 0.7 mg/kg SC plus SOC. Study drug will be administered subcutaneously every 21 days for up to 30 months.

Follow-Up Period

Participants will enter into a Follow-Up Period for 8 weeks after the last dose of study treatment during the Extension Period.

Participants who discontinue the study early (including during either the Placebo-Controlled Treatment Period or the Extension Period) will be asked to return for EOT and EOS visits. Additional safety assessments, including urinalysis and hematology, as determined by the investigator, may be done at this time.

The independent Data Monitoring Committee (DMC) used during Placebo-controlled period will continue monitoring at 6-month intervals during the extension period. A detailed charter will outline all activities of the DMC (including, but not limited to, type of data to be reviewed, DMC responsibilities, and frequency of meetings).

The main analysis including Delayed-start efficacy analysis and Placebo-crossed efficacy analysis of the extension period will be performed on the primary and secondary endpoints after the last patient has completed the third right-heart catheterization or has passed the Month 18-24 window for the 3rd RHC or has an early EOT.

3.2. Rerandomization

Following the completion of the 24-week Placebo-Controlled Treatment Period, placebo participants will be re-randomized 1:1 to treatment with sotatercept 0.3 mg/kg plus SOC or

sotatercept 0.7 mg/kg plus SOC through the computerized system, provided by the Interactive Response Technology (IRT), and sotatercept-treated participants will continue on their current dose in the Extension Period in a blinded manner.

3.3. Treatment Discontinuation

Reasons that may lead to discontinuation of study treatment include:

- Completion of treatment
- Adverse event
- Participant request (withdrawal of consent)
- Loss of treatment effect
- Clinical worsening requiring rescue therapy with a PAH agent
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- QTcF > 500ms during treatment period

Reasons that may lead to a participant's withdrawal from the study include:

- Participant's request (withdrawal of consent)
- Screen failure
- Participant's unwillingness or inability to comply with the protocol
- Loss of treatment effect
- Death
- Lost to follow-up
- Study terminated by sponsor
- Adverse event

The sponsor may terminate study treatment or a dose level after consultation with the investigator and the DMC at any time for safety or administrative reasons. The sponsor will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the participants.

If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

3.4. Sample Size and Power Calculation

For the delayed-start efficacy analysis of the extension period, with 30 participants in the placebo arm transition to sotatercept (out of the 32 participants randomized to placebo, two participants

discontinued early and did not reach the Extension period) and about 60 participants continuing on the sotatercept treatment with values after third right heart catheterization, with an assumed difference in PVR of 100 dyn·sec/cm^5 (-150 dyn·sec/cm^5 in placebo transitioning to sotatercept arm and -250 dyn·sec/cm^5 in continuing sotatercept arm) and a standard deviation of 220, there is a power of about 40% to detect the difference at 2-sided alpha = 0.025 level in PVR between the arms.

And with an assumed difference in 6MWD of 30 meters (30 meters in placebo transitioning to sotatercept arm and 60 meters in continuing sotatercept arm) and a standard deviation of 50, there is a power of about 65% to detect the difference at 2-sided alpha = 0.025 level in 6MWD between the arms.

For the Placebo-crossed efficacy analysis of the extension period, with 30 participants in the placebo arm transition to sotatercept, with an assumed change from baseline in PVR of -220 dyn·sec/cm^5 that is sustained after third right heart catheterization in the Extension period and a standard deviation of 220, there is a power > 99% to at 2-sided alpha = 0.025 level in PVR.

4. ANALYSIS POPULATIONS

4.1. Full Analysis Set for the Extension Period (FAS-E)

The Full Analysis Set consists of all randomized participants treated with correct treatment assignment who transitioned to extension period.

4.2. Safety Population for the Extension Period

All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received who transitioned to extension period.

All ACE-011-treated is the set of all participants who received sotatercept at any time. This set is also used to study the overall safety of sotatercept.

4.3. PK Population for the Extension Period

PK population will include all participants who have received at least 1 dose of sotatercept and have sufficient pharmacokinetic samples collected and assayed for PK analysis who transitioned to extension period.

4.4. Per Protocol Set for the Extension Period (PPS-E)

PPS includes all participants in the Full Analysis Set (FAS-E) who transitioned to extension period and had their Extension Period PVR assessment, with no failure to perform key procedures (RHC and 6MWT) during the 3rd RHC window (Month 18-24), without missing 3 consecutive doses immediately before 3rd RHC, and with no other deviations that also have major impacts on the efficacy of the study treatment.

5. STATISTICAL METHODOLOGY

5.1. General Considerations

Unless otherwise noted, continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (STD), minimum, median, and maximum. Categorical data will be summarized with frequencies (n) and percentages (%). In cases where missing data cause percentages sum to less than 100, a missing data row will be provided. Percentages will use column totals as the denominator unless otherwise indicated.

All study data will be included in study data listings. Missing data will generally be treated as missing, not imputed, unless otherwise stated.

5.2. Disposition of Patients

The number and percentage of patients receiving study treatment who completed the treatment period and study period along with the associated reasons for discontinuation from treatment and/or withdrawal from study will be presented.

5.3. Demographic, Baseline Characteristics, and Disease History

Baseline and demographic characteristics will be summarized by descriptive statistics for all the randomized patients as randomized by treatment groups. Partially missing diagnosis dates will be imputed based on the rules mentioned in the Data Handling section.

Demographic and baseline data, medical history, and disease history data will be listed for each patient.

5.4. Study Drug Exposure

Study drug exposure will be descriptively summarized for safety population and will present the duration of exposure, the number of treatment cycles, the total dose administered, and the number of patients with dose delay and reduction.

The duration of exposure will be calculated as (last dose date – first dose date) + 21.

The total number of cycles will be summarized by presenting the number and percentage of patients in each category.

The total dose administered is the total amount in mg a patient received during the treatment period.

Study drug administration details will be listed for each patient.

5.5. Prior and Concomitant Medication and Procedures

5.5.1. Prior and Concomitant Medication

The prior and concomitant medications are coded with WHO dictionary. The medications will be summarized for the safety population.

Medications will be assigned as prior or concomitant based on the following rules with the partial missing dates imputed based on the rules mentioned in the Data Handling section below:

- If both the start and stop date exist and are before the first dose date of study drug, the medication will be counted as prior.
- If the start date is on or after the first dose date of study drug, the medication will be counted as concomitant.
- If the start date is before the first dose date of study drug and the stop date is after the first dose date of study drug or the medication is ongoing, the medication will be counted as concomitant.
- If the start date is missing and the stop date is before the first dose of study drug, the medication will be counted as prior.
- If the start date is missing and the stop date is after the first dose of study drug or the medication is ongoing, the medication will be counted as concomitant.
- If the start and stop dates are missing, the medication will be counted as concomitant.

All prior and concomitant medications will be listed for each patient.

5.5.2. Non-Medication Procedures

Non-medication procedures will be coded using MedDRA. All non-medication procedures will be listed for each patient.

5.6. Efficacy Analyses

All efficacy endpoints in the extension period will be analyzed using Full Analysis Set for the Extension Period (FAS-E) and Per Protocol Set for the Extension Period (PPS-E) population unless otherwise specified. Analysis on Full Analysis Set for the Extension Period (FAS-E) will be considered as primary for the extension period analysis.

5.6.1. Extension Period Analysis

Participants will have a total of three PVR assessments over the course of the study: PVR at Baseline (PVR0), PVR following completion of the 6-month Placebo-Controlled Treatment Period (PVR6), and PVR from 3rd Right Heart Catheterization done at Month 18-24 window post baseline (PVR-ext.). The 6MWD and WHO Functional Class (FC) measurements taken at or closest around the same timepoint as PVR within the Month 18-24 window or the first measurement within the Month 18-24 window if no PVR measurement are also analyzed similarly. Table 1 provides notation for efficacy measurements at different time points.

Table 1: Notation: Efficacy Measurement at Different Time Points

	PVR	6MWD	FC	FC numeric version
Month 0 (baseline)	PVR0	6MWD0	FC0	FCn0
Month 6	PVR6	6MWD6	FC6	FCn6
Month 18-24	PVR-ext	6MWD-ext	FC-ext	FCn-ext

6MWD = 6-minute-walk distance; FC = functional class; PVR = pulmonary vascular resistance.

Two Analysis Treatment Groups in the Extension Period:

- Continued sotatercept treatment group: Participants randomized to either dose group (0.3 mg/kg and 0.7 mg/kg) of sotatercept at the beginning of the Placebo-Controlled Period. They continued to receive sotatercept in the Extension Period.
- Placebo-Crossed treatment group: Participants randomized to Placebo at the beginning of Placebo-Controlled Period and then randomized to either 0.3 mg/kg or 0.7 mg/kg of sotatercept in the Extension Period.

Two Statistical Efficacy Analyses:

- Delayed-start efficacy analysis: Compare the efficacy endpoints between the two treatment groups in the Extension Period.
- Placebo-crossed efficacy analysis: Compare post-baseline (Month 18-24) vs baseline (Month 0) values of efficacy endpoints within the Placebo-Crossed treatment group.

The overall type I error rate will be 2-sided 0.05. Recycle method will be used to control the overall type I error rate.[1]

The set of Placebo-crossed efficacy analyses will be tested first at 2-sided 0.025 level. Gate keeping method will be used to sequentially test each efficacy endpoint. PVR will be tested first at 0.025 level. If successful, 6MWD will be tested second at 2-sided 0.025 level. If both PVR and 6MWD are successfully tested, FC improvement will then be tested at 2-sided 0.025 level.

If all three efficacy endpoints in the Placebo-crossed efficacy analyses are statistically significant, then the type I error rate of 0.025 will be recycled. The set of Delayed-start efficacy analysis will be tested at 0.025 + 0.025 = 0.05 2-sided level. Otherwise, if at least one of the three tests is not significant, they will be tested sequentially at 2-sided 0.025 level. Each endpoint in Delayed-start efficacy analysis will be tested similarly as the sotatercept placebo-crossed efficacy analyses.

The sotatercept 0.3 mg/kg group and 0.7 mg/kg group will be pooled into one sotatercept group Extension Period analysis.

5.6.1.1. Placebo-crossed Efficacy Analysis

The primary analysis is to evaluate PVR-ext - PVR0 in Placebo-Crossed treatment group with type I error rate of 2-sided 0.025. ANCOVA will be used to test the intercept with PVR0-average (PVR0) as the covariate. Normality will be tested using Shapiro-Wilk test. If normal distribution is rejected, a non-parametric Wilcoxon signed rank test will be used. Multiple imputation method will be used to handle the missing data.

The key secondary analysis is to evaluate 6MWD-ext - 6MWD0 in Placebo-Crossed treatment group after the successful testing on primary PVR analysis, with type I error rate of 2-sided 0.025. ANCOVA will be used to test the intercept with 6MWD0-average (6MWD0) as the covariate. The normality check and missing data handling method will be similar to primary analysis.

The other secondary analysis is to evaluate FCn-ext – FCn0 in the Placebo-Crossed treatment group after the successful testing on primary PVR and key secondary 6MWD analysis, with type I error rate of 2-sided 0.025. ANCOVA will be used to test the intercept with FCn0-average

(FCn0) as the covariate. The FC categories are converted to numerical values, I = 1, II = 2, III = 3 and IV = 4. The numerical values will be used in this analysis. This conversion is made in order to increase statistical power of the ANCOVA analysis.

5.6.1.2. Delayed-start Efficacy Analysis

The primary analysis is to compare the change from baseline (PVR-ext – PVR0) between the Continued sotatercept treatment group and the Placebo-Crossed treatment group to evaluate disease modifying effect with type I error rate of 2-sided 0.025. ANCOVA will be used with PVR0 and FC0 as covariates. Normality will be tested using Shapiro-Wilk test. If normal distribution is rejected, a non-parametric Wilcoxon rank sum test stratified by FC0 will be used. Multiple imputation method will be used to handle the missing data.

The key secondary analysis is to compare change from baseline (6MWD-ext – 6MWD0) between the Continued sotatercept treatment group and Placebo-Crossed treatment group after the successful testing on primary PVR analysis with type I error rate of 2-sided 0.025. ANCOVA will be used with 6MWD0 and FC0 as covariates. The normality check and missing data handling method will be similar to primary analysis.

The other secondary analysis is to compare FC-ext improvement from baseline (FC0) between the Continued sotatercept treatment group and Placebo-Crossed treatment group after the successful testing on primary PVR and key secondary 6MWD analysis, with type I error rate of 2-sided 0.025. Cochran-Mantel-Haenszel (CMH) test will be used with FC0 as the stratum.

5.6.1.3. Sensitivity Analysis

For the participants who missed the third right heart catheterization during the Month 18-24 but was performed later, the Delayed-start Efficacy Analysis and Placebo-crossed Efficacy Analysis will be repeated with those out-of-window visit values as a sensitivity analysis.

5.6.1.4. Supportive Analysis

The Placebo-crossed Efficacy Analysis will also be repeated with Month-6 (Cycle 9) as baseline in order to analyze the effect of sotatercept on participants after transitioning from placebo to sotatercept at Month-6 (Cycle 9). A similar analysis with Month-6 (Cycle 9) as baseline will also be conducted on the continued sotatercept (combined and by dose arms) in order to evaluate the continued effect of sotatercept in the long term.

In order to characterize the combined difference between sotatercept treatment arms and placebo after the placebo participants crossing over to sotatercept, aligned supportive analysis will be performed by combining the results of change from baseline after 6 months for participants on the original sotatercept treated arms with the results of change from baseline at Month-12 for additional placebo to sotatercept participants after 6 months in sotatercept and comparing with the results of change from baseline after first 6 months for participants originally randomized to placebo group. This analysis will be done on the secondary endpoints of Six-minute walk distance (6MWD), WHO Functional Class, NT-proBNP and Multi-component improvement endpoints.

In addition, because of the same participants being present in the placebo group and also in the placebo-crossed sotatercept group, and there is also correlation between the repeated

measurements on participants at baseline and Month-6, and at Month-12, additional supportive analysis to explore the treatment difference in continuous secondary endpoints of Six-minute walk distance (6MWD), and NT-proBNP will be performed using MMRM model (proc mixed in SAS with repeated statement) and binary enpoints of WHO Functional Class Improvement and Multi-component Improvement endpoint are analyzed using GEE logistic regression (proc genmod in SAS with repeated statement), with just the values from baseline, Month-6 and Month-12 for all the participants.

Additional placebo-controlled period supportive analysis is performed on 6MWD using a Month-6 window defined as follows. Month-6 measurement is defined as one occurring in a window of Day 147-189 excluding any measurements after a subject has crossed over from Placebo to Sotatercept in the extension period. If there are multiple measurements, then the closest measurement to Day 168 is used. The Month-6 window supportive analysis is performed on Full Analysis Sets using an ANCOVA model with standard multiple imputation. Normality distribution assumption is tested using Shapiro-Wilk method and if significant, a non-parametric stratified Wilcoxon-rank sum test is performed. In addition, a Worst Rank Analysis method is performed, in which, for the participants who missed the measurement due to death, their missed post-baseline measurement will be imputed as -2000. And for those participants who missed the measurement due to clinical worsening, their missed post-baseline measurement will be imputed as -1000.

5.6.2. Other Extension Period Analysis

5.6.2.1. Six-minute walk distance (6MWD) at 12-Months

The average of the distance in the two-screening measurement will be used as the baseline.

The Delayed-Start analysis and Placebo-Crossed analysis performed after third right heart catheterization as described in the sections above will also be performed for 6MWD at 12-months in the Full Analysis Set for the Extension Period (FAS-E). In addition, the above exploratory analysis will be performed for each dose group separately.

In addition, several methods for missing value handling will be explored as described in the Additional Sensitivity Analysis section below.

5.6.2.2. WHO Functional Class Change at 12-Months

The average of the distance in the two-screening measurement will be used as the baseline.

The Delayed-Start analysis and Placebo-Crossed analysis performed after third right heart catheterization as described in the sections above will also be performed for WHO Functional Class at 12-months in the Full Analysis Set for the Extension Period (FAS-E). In addition, the above exploratory analysis will be performed for each dose group separately.

In addition, several methods for missing value handling will be explored as described in the Additional Sensitivity Analysis section below.

5.6.2.3. Other Secondary Efficacy Endpoints at 12-Months and aligned with 3rd RHC (Month 18-24)

Change in NT-ProBNP from Baseline

The Delayed-Start analysis and Placebo-Crossed analysis performed after third right heart catheterization will also be performed for NT-proBNP at 12-months and aligned with 3rd RHC (Month 18-24) in the Full Analysis Set for the Extension Period (FAS-E). In addition, the above exploratory analysis will be performed for each dose group separately.

In addition, several methods for missing value handling will be explored as described in the Additional Sensitivity Analysis section below.

Simplified French Risk Score

The simplified French risk scoring system is based on the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. In this study, the noninvasive parameters will be used to determine the score. "Low risk" is defined as attaining or maintaining all 3 low-risk criteria: WHO FC I or II, 6MWD > 440 m, and NT-proBNP < 300 ng/L. The proportion of participants who attain low risk is analyzed.

Echo Parameters

The Echo parameters of interest are Change from baseline in the following parameters: Tricuspid Annular Plane Systolic Excursion (TAPSE), Pulmonary Artery Pressure (PAP), Pulmonary Artery Systolic Pressure (PASP), Right Ventricular Pulmonary Artery contractile-pressure coupling (RV-PA coupling), Right Ventricular End Systolic Area (RVESA), Right Ventricular End Diastolic Area (RVEDA) and Right Ventricular Fractional Area Change (RVFAC).

Clinical Worsening

Clinical worsening will be assessed by the investigator at each visit and recorded on the CRF. Assessments are:

- Death
- Worsening-related listing for lung and/or heart transplant
- Need to initiate rescue therapy (see below), with an approved PAH SOC therapy
- Need for atrial septostomy
- PAH-specific hospitalization (> 24 hours)
- Functional deterioration as defined by both of the below events occurring together at any time, even if they began at different times, as compared to their screening values:
  - Worsened WHO functional class (II to III, III to IV, II to IV, etc.)

  and

  - Decrease in 6MWD by ≥ 15% (confirmed by two 6MWTs)

Clinically significant abnormal findings will be reported as adverse events.

Number of patients and percentages with clinical worsening will be summarized by visit and overall during the treatment period.

Time to clinical worsening will be summarized using Kaplan-Meier estimates (median and its 95% confidence interval). Participant who has no clinical worsening will be censored at the last visit on treatment. Stratified log-rank test will be used to test the treatment difference of each active treatment arm versus placebo arm separately. Cox proportional hazard model stratified by randomization factors will be used to estimate the hazard ratio and its 2-sided 80% and 95% CIs will be provided.

Change in QoL (CAMPHOR, SF-36) at 12-Months and aligned with 3rd RHC (Month 18-24) vs. Baseline

QoL will be measured using CAMPHOR and SF-36. Change in individual subscale scores and total scores comparing to baseline will be summarized by visit and treatment. The change in all the three components of CAMPHOR score: Symptom (impairment) score, Activity (disability) score and Quality of life (QoL) score and the overall score, which is the sum of the above three component scores will be analyzed using stratified Wilcoxon's rank-sum test stratified by randomization factors. The change in SF-36 score and the individual component scores (Physical Component Scores (PCS) and Mental Component Scores (MCS)) will be formally analyzed using ANCOVA model with randomization factors as covariates.

Population PK Parameters of Sotatercept

Sotatercept concentration data will be summarized per Section 5.8.

5.6.3. Exploratory Endpoints

Multi-component Improvement Endpoint

Improvement in the lives of PAH patients will be assessed at each visit using Multi-component improvement endpoint.

Multi-component Improvement Endpoint is defined by the number of patients who exhibit all three of the following criteria:

- Any Improvement in WHO Functional Class or maintenance of WHO Functional Class II
- Improvement in NT Pro-BNP by at least 30% (≤-30% from baseline)
- Improvement in 6MWD by at least 30 meters (≥ 30m from baseline)

The Multi-component Improvement Endpoint is compared in each of the treatment groups. Multi-component Improvement Endpoint defined by the number of patients who exhibit at least two of the above criteria is also analyzed as an additional analysis. Missing values will be treated as non-responder by default unless special handling rule for COVID-19 as mentioned in Section 5.6.6 applies.

Other Exploratory Endpoints

In addition to the clinical improvement endpoints, the following exploratory endpoints will be summarized by visit for each treatment group using descriptive statistics.

- Change from baseline in TGF-β ligands (e.g., activin A) and other PAH-related biomarkers (GDF15, TGFB1, VEGRF1 and MMP2) as well as variance in related genes and transcript expressions of BMPR2

- Mortality Risk Assessment
- Renal Risk Assessment using Estimated Glomerular Filtration Rate (eGFR)
- Change in ECHO parameters other than the one listed above (TAPSE, PAP, PASP, RV-PA coupling, RVESA, RVEDA and RVFAC), if any
- Change in Cardiac Index calculated using the following formula[2]:

$$Cardiac\ Index\ =\ Cardiac\ Output\ (CO)\ /\ Body\ Surface\ Area\ (BSA)$$

$$Body\ Surface\ Area\ (BSA) = \sqrt{\left(\frac{height\ (cm)\ *\ weight\ (kg)}{3600}\right)}$$

The details of PAH related biomarkers and PK/PD analysis will be described in detail in separate analysis plans.

Mortality Risk Assessment

Different approaches will be explored to assess risk in PAH[3] such as the use of risk variables according to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines with 1-year mortality risk classified as Low risk < 5%, Intermediate risk 5–10% and High risk > 10% based on the available parameters, and the use of a risk score such as the simplified REVEAL 2.0 (Registry to Evaluate Early And Long-term PAH Disease Management) registry risk score with the available parameters and REVEAL Lite 2.0 scores.

Renal Risk Assessment using eGFR

Estimated Glomerular Filtration Rate (eGFR) is used to measure the condition of renal functionality with respect to any effect due to the treatment. The eGFR is calculated from four inputs - Serum Creatinine (SerumCr), Gender, Race (Black or Not) and Age as follows:

$$eGFR\ in\ mL/min\ per\ \ 1.73m^2 = 175 * SerumCr^{-1.154} * Age^{-0.203} * 1.212(if\ patient\ is\ black) * 0.742\ (if\ female)$$

Compare the improvement in eGFR from baseline for patients who have eGFR < 60 mL/min per 1.73 m^2 at baseline, in each of the treatment groups. Compute the number of patients for whom there is an improvement of at least 20 points.

Hematocrit Adjusted PVR

In order to study the effect of hemoglobin increase on PVR, the analysis on the primary endpoint is repeated on Hematocrit adjusted PVR, which is calculated using the following formula:[5]

$$[adjusted\ PVR] = \frac{mPAP}{CO * e^{[2(\varphi_{measured} - \varphi_{ref}]}} - \frac{PAWP}{CO}$$

$[adjusted\ PVR]$: $Pulmonary\ Vascular\ Resistance\ (Wood\ Units)$

$\varphi_{ref}(Hematocrit\ reference\ level) = 0.45, i.e.\ 45\%$

$\varphi_{measured}$: $Hematocrit\ measured$

$mPAP$: $mean\ Pulmonary\ Artery\ Pressure\ (mmHg)$

$PAWP$: $Pulmonary\ Artery\ Wedge\ Pressure\ (mmHg), equivalent\ to$

$PCWP$: $Pulmonary\ Capillary\ Wedge\ Pressure\ (mmHg)$

CO: $Cardiac\ Output\ (L/min)$

5.6.4. Subgroup Analysis

Subgroup analyses of change of the Primary and Secondary Endpoints at 3rd RHC and applicable endpoints at 12 months and 18 months might be performed with the following baseline factors if the sample size in the subgroup category is ≥ 10:

- Sex (male and female)
- Known pathological mutations (including BMPR2 mutation) vs Wild Type at baseline

- PAH Etiological Subgroups (iPAH, hPAH (heritable PAH), Drug/Toxin, Connective Tissue Disease, congenital heart disease with s/p Shunt Repair)
- Monotherapy vs Double vs. Triple combination therapy at baseline
- Prostacyclin Infusion Therapy vs. Non-Prostacyclin Infusion at baseline
- WHO functional class (II or III)
- Baseline PVR (≤ 800 or > 800 dyn*sec/cm^5 at baseline)
- Baseline Cardiac Index (< 2.5 or > = 2.5 L/min/m^2 at baseline)

Subgroup analyses of change of the Primary and Secondary Endpoints for the above subgroups including baseline Cardiac Index < 2.5 and >= 2.5 L/min/m^2 are also performed for the Placebo-controlled period at 24 weeks.

5.6.5. Additional Sensitivity Analysis

Several methods for missing value handling including the following techniques will be explored to conduct sensitivity analysis on the primary, key secondary endpoints and other secondary endpoints as appropriate:

- Standard Multiple Imputation
- Pattern Mixture Model
- Tipping Point Analysis

For the comparison between the treatment arms of the change from baseline for the primary endpoint, ANCOVA with the randomization stratification factor as the covariate will be used. For the secondary endpoints, ANCOVA with the randomization stratification factor as the covariate model and a Mixed effect Model Repeat Measure (MMRM) model will be used. The MMRM model includes the baseline endpoint value and the randomization stratification factor as covariate; treatment group, time point, and treatment group-by-time point interaction as fixed effects. An unstructured covariance structure will be used to model the within-patient covariance across visits.

Standard Multiple Imputation

Missing at Random (MAR) assumption is made to perform standard Multiple Imputation (MI). For missing points, monotonous regression is used to fill in the missing points in the order of time points using values calculated at the previous time points. The analysis involves the following steps:

1. The missing data are filled in m times to generate m complete data sets using monotonous regression model accounting for baseline value, randomization stratification factor, and if necessary, additional covariates such as age and other secondary endpoints at different visits in the imputation model.
2. The m complete data sets are analyzed by using standard procedures. ANCOVA with the randomization stratification factor and baseline value as the covariate and Mixed effect Model Repeat Measure (MMRM) model as mentioned above will be used for analysis here.

3. The results from the m complete data sets are combined for the inference.

Pattern Mixture Model

Pattern Mixture Model with control-based pattern imputation will be used to perform sensitivity analysis, if the p-value is highly significant at a 1-sided alpha of 0.025. The analysis includes the following steps:

1. When imputing missing values for time-point t, the input dataset should include all placebo participants, and only those participants from the experimental arm that have values at time-point t missing (only those that need imputation at time-point t). Imputation model will be estimated using placebo participants only. This way, participants from experimental arm will be imputed based on the control participants' model. Note that treatment arm should not be included as an effect in this model. The missing data are filled in m times using monotonous regression model accounting for baseline value, randomization stratification factor, and if necessary, additional covariates such as age and other secondary endpoints at different visits in the imputation model to generate m complete data sets using this Pattern Mixture Model.
2. The m complete data sets are analyzed by using standard procedures. ANCOVA with the randomization stratification factor as the covariate and Mixed effect Model Repeat Measure (MMRM) model as mentioned above will be used for analysis here.
3. The results from the m complete data sets are combined for the inference.

Tipping Point Analysis

Tipping point analysis will be used to perform sensitivity analysis, if the p-value is highly significant at a 1-sided alpha of 0.025. Tipping point analysis include the following steps. The first three steps are the standard multiple imputation (MI) steps:

1. The missing data are filled in m times to generate m complete data sets using the Pattern Mixture model as mentioned above.
2. The m complete data sets are analyzed by using standard procedures. ANCOVA with the randomization stratification factor and baseline value as the covariate and Mixed effect Model Repeat Measure (MMRM) model as mentioned above will be used for analysis here.
3. The results from the m complete data sets are combined for the inference.
4. Repeat the step 1 to generate multiple imputed data sets, with a specified shift parameter that adjust the imputed values for observations in the treatment group, not the placebo group).
5. Repeat the step 2 for the imputed data sets with shift parameter applied.
6. Repeat the step 3 to obtain the p-value and check statistical significance.
7. Repeat the steps 4-6 with more stringent shift parameter applied until the p-value becomes not significant.

5.6.6. Special Handling for COVID-19

Several methods for missing value handling of visits missed due to COVID-19 are applied as follows: For the main analysis after 3rd Right Heart Catheterization, the participants who missed assessments in the Month 18-24 window due to COVID-19 will be taken out of the denominator for binary endpoints such as WHO Functional Class improvement and Multi-component Improvement Endpoint. For the Multi-component Improvement Endpoint with three components, if a response could be established based on the components with available values, that response of responder or non-responder will be used for that participant. Otherwise, if a response could not be established based on the components with available values and some components are missing due to COVID-19 the participant will be taken out of the denominator. For the 12-Month analysis, for a subject who missed the 12-Month visit due to COVID-19, the values if available from the next available visit within a 12-week window may be used, otherwise will be taken out of the denominator for binary endpoints.

5.7. Safety Analysis

The safety endpoints will be summarized using the Safety Population. The safety endpoints include treatment emergent adverse events, changes in laboratory tests, vital signs, immunogenicity, and ECG's.

Severity of AEs will be coded using National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0).[4]

5.7.1. Adverse Events

All AEs and SAEs reported from C1D1 to the EOS visit are to be reported and documented on the AE CRF. All AEs worsened or started between C1D1 and 8 weeks safety follow-up visit after the last dose will be considered as treatment emergent adverse events (TEAE). Any partial dates will be imputed based on the rules in Data Handling section below. A drug-related TEAE is defined as any TEAE related to the study medication as assessed by the investigator or with missing assessment of the causal relationship.

The following summaries will be presented for all dosed:

- Number and percentage of patients reporting each TEAE, categorized by System Organ Class (SOC) and Preferred Term (PT)
- Number and percentage of patients reporting each TEAE experienced by ≥ 5% and ≥ 10% of patients in all patients by PT
- Number and percentage of patients reporting SAE, categorized by SOC and PT
- Number and percentage of patients reporting Grade ≥ 3 TEAE, categorized by SOC and PT
- Number and percentage of patients reporting related TEAE, categorized by SOC and PT
- Number and percentage of patients reporting related SAE, categorized by SOC and PT

- Number and percentage of patients reporting TEAE leading to drug withdrawal, categorized by SOC and PT
- Number and percentage of TEAE of special interest (AESI)
- Number and percentage of TEAE by severity
- Number and percentage of TEAE categorized by Monotherapy vs Double vs Triple combination therapy at baseline
- Number and percentage of TEAE categorized by Prostacyclin Infusion Therapy vs Non-Prostacyclin Infusion at baseline
- All AEs will also be summarized by last dose received prior to the event.

Note that counting will be by patient, not event, and patients are only counted once within each SOC or PT. If a patient experiences the same AE at more than one severity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. Any missing severity, causality, or outcome will not be imputed and classed as unknown.

Events to be considered adverse events of special interest (AESI) in this study, according to National Cancer Institute-Common Toxicity Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0)[4], are SMQ fertility disorders, Hepatic disorders (SMQ) (Narrow and broad), Ischemic heart disease (SMQ) Embolic and thrombotic events (SMQ) and the following:

- Leukopenia
- Neutropenia (including febrile neutropenia)
- Thrombocytopenia

All AEs will be listed. The following listings will also be provided:

1. patients with SAEs;
2. patients with Grade ≥ 3 AEs;
3. patients with AEs leading to study drug discontinuation;
4. patients with AEs leading to death;
5. Patients with AEs leading to dose modifications.

In addition, Time-at-risk Exposure-adjusted Incidence Rate[6] analysis will also be performed on the summarized AEs. Exposure Adjusted Incidence Rates (EAIRs) are calculated as number of participants with an AE divided by the sum of the individual times at risk for the first occurrence of an AE of all participants in the safety set from start of treatment during Extension period to first onset of AE during Extension period before switch (or end of Extension period if no switch), date of switch, end of Extension period or death, whichever occurs first.

5.7.2. Laboratory Evaluations

The following laboratory parameters will be measured over time:

Hematology

Complete blood count (CBC) with differential: CBC includes RBCs, white blood cells (WBCs), platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC); reticulocyte count, platelet count.

Chemistry

Albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide, creatinine, glucose, phosphorus, potassium, sodium, total bilirubin, direct bilirubin.

Urinalysis

Urine Creatinine, urine albumin creatinine ratio (UACR).

Actual values and changes in laboratory values from baseline will be summarized by time point.

Shift tables for the following parameters comparing values above, within and below the normal reference range overtime will be presented using standard reference ranges:

Hematology: RBC, WBC, Platelets, Hemoglobin and Hematocrit

Chemistry: ALT, AST, BUN, Creatinine and Total Bilirubin

Urinalysis: UACR

All laboratory values will be listed for all patients.

5.7.3. Vital Signs

Vital signs parameters include temperature, pulse rate, respiratory rate, and blood pressure. For each parameter at each time point, the change from baseline to post baseline will be summarized. Vital signs will also be listed for all patients. This includes height at screening and weight at all dosing visits.

BMI will be calculated using the formula: BMI = weight (kg) / [height (m)]^2

5.7.4. Electrocardiogram (ECG) Results

The quantitative ECG assessments (ventricular rate, PR interval, QRS duration, QRS Interval and QTcF interval) will be summarized at each time point.

ECG overall interpretation (normal, abnormal not clinically significant and abnormal clinically significant) will be presented for actual values and changes from baseline to each post baseline visit [expressed as Improvement, No Change, and Deterioration].

Note:

- Improvement = Abnormal Clinically Significant (CS) to Abnormal Not Clinically Significant (NCS)/Normal, Abnormal NCS to Normal
- Deterioration = Normal to Abnormal NCS/CS, Abnormal NCS to Abnormal CS
- No change = Normal to Normal, Abnormal NCS to Abnormal NCS, Abnormal CS to Abnormal CS

If either result is missing or unknown for any patient, then the corresponding 'Missing'/ 'Unknown' category will also be presented.

ECG results will be listed for all patients.

5.7.5. Physical Examination

Physical exam details will be listed only.

5.8. Pharmacokinetics

5.8.1. Pharmacokinetic Sampling Schedule

Blood samples will be collected from all patients at the schedule presented in Table 2.

Table 2: Patients Blood Sample Collection Schedule

Visit	Study Day (± 3days)	Pre-dose or No dose	4-hourPost-dose
Cycle 1 Day 1	1	Yes	Yes
Cycle 1 Day 8	8	Yes	No
Cycle 2 Day 1	22	Yes	No
Cycle 2 Day 8	29	Yes	No
Cycle 3 Day 1	43	Yes	No
Cycle 5 Day 1	85	Yes	Yes
Cycle 8 Day 1	148	Yes	No
Cycle 9 Day 1	169	Yes	Yes
Cycle 9 Day 8	176	Yes	No
Cycle 10 Day 1	190	Yes	No
Cycle 10 Day 8	197	Yes	No
Cycle 13 Day 1	253	Yes	Yes
Cycle 17 Day 1	337	Yes	Yes
Cycle 21 Day 1	421	Yes	Yes
Cycle 25 Day 1	526	Yes	No
Cycle 29 Day 1	610	Yes	Yes
Cycle 34 Day 1	715	Yes	Yes
EOT	N/A	Yes	No
EOS	N/A	Yes	No

N/A = Not Applicable

5.8.2. Pharmacokinetic Data Handling

The following rules regarding concentration values below the limit of quantitation (BLQ) and other data handling rules regarding concentration data are only intended for listings and summary of concentration data. Data handling rules for population PK and population PK/PD analyses will be presented in a separate analysis plan.

Concentrations that are BLQ prior to the first dose will be assigned a numerical value of zero. Post-treatment concentrations that are BLQ will be treated as missing.

Concentrations assigned a value of missing will be omitted from the descriptive statistics. A concentration value of zero will be excluded from the computation of the geometric mean (geometric CV%). If any patients are found to be noncompliant with respect to dosing, have incomplete data, or encounter other circumstances that would affect the evaluation of pharmacokinetics, a decision will be made on a case-by-case basis as to their inclusion in the pharmacokinetic analysis. Data excluded from pharmacokinetic analysis will be included in the data listings, but not in the summaries.

In tables and listings for the derived pharmacokinetic data, there should be four decimal places for numerical values below 1, three decimal places for numeric values below 10 but above 1, and two decimal places for numeric values above 10. However, the listings of raw data should not have more decimal places than the actual data.

5.8.3. Pharmacokinetic Analysis

All sotatercept serum concentrations will be listed by patient and scheduled time (visit and study). Actual dosing/sampling time, sample time relative to first dosing time, visit, and concentration will be presented in the listing.

The sotatercept serum concentrations will be summarized by scheduled time, including N (number of observations), arithmetic mean, arithmetic standard deviation (SD), arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, minimum, median, and maximum. Mean (SD) serum concentration-time profiles will be presented on linear scales.

5.9. Pharmacodynamics

Venous blood samples will be collected for measurement of PD biomarkers including but not limited to activin A, NT-proBNP, estrogen (e2) 16-alpha-hydroxyesterone, 2-methoxyestradioal, 2-hydroestradiao, testosterone, FSH, and estradiol at timepoints listed in the SoE. PD biomarkers will be summarized using descriptive statistics by visits for each treatment group.

5.10. Interim Analysis

There are no Interim Analysis planned for the study. There are only planned DMC safety reviews.

5.11. Protocol Deviations

All major protocol deviations will be listed and summarized.

5.12. Data Handling

5.12.1. Analysis Visit Window

Baseline is defined as the last observation on or prior to the first dose of study drug, unless otherwise specified. For the purpose of Extension Period Analysis, the following rules will be followed:

1. Month 18-24 window corresponds to Day 548 – 730.
2. Enlarged window of Day 480-730 is used to include 3rd RHC PVR measurements.
3. 6MWD and WHO Functional Class measured on the same day or closest to the PVR measurement will be used.
4. If there is no 3rd RHC PVR measurement, then the first measurement of 6MWD and WHO Functional Class in the Day 548 – 730 window will be used.
5. Other efficacy parameters such as NT-proBNP and Multi-component Improvement endpoint will be handled similarly.

5.12.2. Handling of Missing Data

As a general principle, no imputation of missing data will be done unless otherwise specified. Exceptions are the start and stop dates of AEs and concomitant medication with the rules listed below. The imputed dates will be used to allocate the medication as prior or concomitant medications and to determine whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

In addition, partial disease diagnosis dates are imputed to calculate time since disease diagnosis. The listing will present the actual partial dates.

5.12.2.1. Missing Dates for Adverse Event and Concomitant Medication

Incomplete Start Date

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same, but the month of partial

date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.

- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same, but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed. The corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.

If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

5.12.2.2. Missing Dates for Disease Diagnosis Date

For disease diagnosis dates, the imputation rules are:

a. If day is missing, use 15th of the month
b. If both day and month are missing, impute as January 1st
c. If month is missing, impute as January
d. If year is missing, set to missing

5.12.3. Handling of Data Limits

All the PD values reported as less than Lower Limits of Quantification (LLOQ) will be assigned a value of LLOQ/2 during summarization. Percentage values reported as greater than 99% will be assigned a value of 99.5% during summarization.

5.13. Changes in Conduct or Planned Analyses from the Protocol

The text for the dose assignment in the Evaluable population is updated to refer to the dose received at least 6 times rather than the dose to which they were originally assigned.

6. REFERENCES

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5. Hematocrit-corrected Pulmonary Vascular Resistance, Rebecca R. Vanderpool and Robert Naeije, 2018, American Thoracic Society.
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7. APPENDICES

7.1. Appendix 1 - List of Abbreviations

Abbreviation or Specialist Term	Explanation
6MWD	Six-minute-walk distance
6MWT	Six-minute-walk test
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMP	Bone morphogenetic protein
BP	Blood Bone morphogenetic protein pressure
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CRF	Case report form
CxDy	Cycle x Day y
CO	Cardiac Output
DBP	Diastolic blood pressure
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	Estimated Glomerular Filtration Rate
ERA	Endothelin-receptor antagonist
EOS	End of study
EOT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FST	Follistatin
IgG2	Immunoglobulin G2
IP	Investigational product
mPAP	Mean Pulmonary Artery Pressure
MMRM	Mixed effect model repeat measurement

Abbreviation or Specialist Term	Explanation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal-prohormone of brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PAWP	Pulmonary Artery Wedge Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per Protocol Set
PVR	Pulmonary vascular resistance
RBC	Red blood cell
RHC	Right heart catheterization
RVEF	Right ventricular ejection fraction
RVFA	Right ventricular fractional area
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SOC	Standard of care
SoE	Schedule of Events
TAPSE	Tricuspid annular plane systolic excursion
TGF-β	Transforming growth factor-beta
UACR	Urine Albumin-to-Creatinine Ratio
ULN	Upper limit of normal
VAF	Variant allele frequency
WHO	World Health Organization

7.2. Appendix 2 - Schedule of Events (SoE)

Refer to A011-09 Protocol Amendment 07A, dated 17 April 2020, Section 2.