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Title:

Intravenous Remodulin (Treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
CDH	Congenital diaphragmatic hernia
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal mechanical oxygenation
eCRF	Electronic Case Report Form
ERA	Endothelin receptor antagonist
FiO_2	Fraction of inspired oxygen
ICF	Informed Consent Form
ICU	Intensive care unit
iNO	Inhaled nitric oxide
ITT	Intent-to-Treat
IV	Intravenous
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-Terminal pro-brain natriuretic peptide
OI	Oxygenation index
PaO_2	Partial pressure of oxygen saturation
PDE-5I	Phosphodiesterase type 5 inhibitor
PH	Pulmonary hypertension
PK	Pharmacokinetic(s)
PPHN	Persistent pulmonary hypertension of the newborn
PT	Preferred term
P/F	Partial pressure of oxygen saturation/fraction of inspired oxygen ratio
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
SpO_2	Saturation of peripheral capillary oxygenation
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1 PREFACE

This plan provides further details of the planned analyses for the RIV-PN-201 study as presented in the study protocol. This plan, based on the original RIV-PN-201 study protocol dated 12 Aug 2013 and the subsequent study protocol amendments (latest version study protocol amendment 3 dated 15 Apr 2016), provides further details of the planned analyses stated in the study protocol and any additional planned analyses. Additional post-hoc or unplanned analyses that are not defined in this Statistical Analysis Plan (SAP) may be performed. Such analyses will be documented in the Clinical Study Report (CSR).

2 STUDY OBJECTIVES AND ENDPOINTS

The primary study objective is to explore the safety and treatment effect of intravenous (IV) Remodulin as add-on therapy in neonates with persistent pulmonary hypertension of the newborn (PPHN) compared to placebo. A secondary objective is to evaluate treprostinil pharmacokinetics (PK) in neonates with PPHN.

2.1 PRIMARY ENDPOINT

The primary endpoint is the composite endpoint of clinical worsening through Day 14 as defined by one of the following:

- Death
- Initiation of extracorporeal mechanical oxygenation (ECMO) per institutional policies
- Need for additional treatment (initiation of an additional targeted pulmonary
- vasodilator therapy [eg, phosphodiesterase type 5 inhibitor {PDE-5I}, endothelin receptor antagonist {ERA}, prostanoid, L-citrulline])

2.2 SECONDARY ENDPOINTS

The secondary endpoints are as follows:

- Change in oxygenation index (OI) from Baseline to Hours 12, 24, and 72, and Days 7 and 14 and/or prior to study drug discontinuation/weaning
- Change in partial pressure of oxygen saturation (PaO_2)/fraction of inspired oxygen (FiO_2) (P/F ratio) from Baseline to Hours 12, 24, and 72
- Change in pre- and post-ductal saturation of peripheral capillary oxygenation (SpO_2) from Baseline to Hours 6, 12, 24, and 72
- Time to discontinuation of inhaled nitric oxide (iNO)
- Time on mechanical ventilation

- Time to initiation of ECMO
- Time to clinical worsening
- Change in N-terminal pro-brain natriuretic peptide (NT-proBNP)

2.3 SAFETY ENDPOINTS

Safety endpoints are as follows:

- Adverse events (AEs)
- Clinical laboratory parameters
- Physical examinations

3 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multi-center, comparative study that will enroll neonates in the intensive care unit (ICU) with PPHN. Eligible subjects must have 2 consecutive OIs of 15 or greater, separated by at least 30 minutes, after having received iNO for at least 3 hours. Once enrolled, subjects will be randomized to receive Remodulin (treprostinil) or placebo.

This study is designed to evaluate the treatment effect of Remodulin as add-on therapy compared to placebo during a 14-day treatment period. However, to assess continued safety in this neonatal population, subjects with residual or chronic pulmonary hypertension (PH) that does not fully resolve within 14 days may continue to receive study drug for up to an additional 14 days (up to 28 days total) per the Investigator's discretion. Post-treatment data will be collected until death, time of hospital discharge, time of withdrawal from study, or for 4 weeks after last dose of study drug, whichever comes first. Subjects with ongoing AEs at the time of hospital discharge will continue to be followed for their AEs until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant, or until 4 weeks after last dose of study drug. All serious adverse events (SAEs) should be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing for more than 4 weeks after last dose of study drug.

4 SEQUENCE OF PLANNED ANALYSES

Interim Safety Analyses

A safety review will be conducted by a Data Safety Monitoring Board (DSMB) after the first 10 subjects have been randomized to receive study drug and have completed the 14-day treatment period. A second review will occur once 40 subjects have been enrolled and completed the 14-day treatment period. Ad hoc meetings may be scheduled at additional enrollment milestones or in response to events related to the safety of study treatment.

Interim Efficacy and Futility Analyses

Efficacy and futility will be assessed at the second formal data review. Details of the planned analyses and stopping rules are specified in the DSMB SAP. If the DSMB votes to stop the study at the second review, all analyses will be conducted as specified in this SAP on the 40 available subjects. Otherwise, these analyses will not be conducted until the study is completely enrolled.

Final Analysis after Database Lock and Study Unblinding

After the database has been quality assured and locked, the treatment assignments will be provided to the Sponsor's project statistician by the central randomization service and all planned analyses described in this document will be performed. By intent, no changes will be made to the clinical database after unblinding. However, any changes that are deemed necessary, after unblinding, will be clearly documented in the CSR.

5 SAMPLE SIZE CONSIDERATIONS

Based on the systematic review of use of nitric oxide for respiratory failure in infants by Finer and Barrington (2006), 57.9% (194/335) subjects in the control group had an outcome of death or requirement for ECMO (Finer 2006). In this study, assuming 60% of subjects in the placebo group and 30% of subjects in the Remodulin group with an outcome of death, requirement for ECMO, or need for additional PH therapy, we calculated that 66 subjects (33 subjects per treatment group) will have at least 80% power to show a significant difference in favor of Remodulin at alpha level 0.05 (1-sided test). Approximately 70 subjects are planned to be

randomized (1:1) to either receive treatment with Remodulin or placebo in addition to the standard of care.

6 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population is defined as all subjects randomized into the study who received at least 1 dose of study drug. All ITT subjects will be counted in the group to which they were randomized, regardless of the study drug they were given. All efficacy analyses will be performed on this ITT population, unless otherwise specified.

The Safety population is defined as all subjects enrolled into the study who received at least 1 dose of study drug. All Safety population subjects will be counted in the group corresponding to the study drug received, regardless of randomized assignment. All safety analyses will be performed on this Safety population, unless otherwise specified.

The Per-protocol population will include all subjects in the ITT population, excluding subjects with major protocol deviations that may have an impact on the primary efficacy analyses. The major protocol deviations and the subject's exclusion from the Per-protocol population will be reviewed at a blinded data review meeting and documented prior to the database lock and the study unblinding.

The PK population will include all subjects in the ITT population with evaluable PK data. All PK analyses will be performed on this PK population, unless otherwise specified.

7 INTERIM ANALYSES

A DSMB will be established for the study including physicians knowledgeable in the treatment of PPHN and a statistician. Throughout the course of the study the DSMB will meet on a regular basis to monitor the safety of the study. Meetings will occur as outlined in the DSMB Charter. All analyses will be prepared by an independent external consultant and reviewed only by the DSMB as defined in the DSMB Charter. The Sponsor will only have access to blinded study data during this process. The details regarding the interim efficacy and safety analysis are included in a separate SAP.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All the data collected in the electronic Case Report Form (eCRF) will be listed. In general, listings will be sorted by treatment group, subject number, and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), study day, and all relevant data collected in the eCRFs. For data collected on a fixed schedule, the assessment identifier or the nominal time point will also be included on the listing. Repeat or redundant observations within an assessment window and observations that do not fall within any predefined assessment window (and will, therefore, be excluded from summaries) will be flagged in these listings. Subjects who are not to be included in the analysis population (eg, Safety population, Per Protocol population) will be flagged.

In general, the data will be summarized by scheduled assessment (if applicable) within each treatment group. For continuous variables, summary statistics will include the mean, standard deviation, median, minimum, and maximum. For summaries of non-normal data, interquartile range (lower quartile, upper quartile) may also be included. Minimums and maximums will be expressed using the level of precision in which the variable was collected. All other statistics will be rounded, using an additional decimal place than was collected. For discrete variables, summaries will include the frequency and percentage in each category. Percentages will be rounded to 1 decimal place. For all inferential analyses and descriptive comparisons, p-values will be rounded to 4 decimal places. Values less than 0.0001 will be denoted as <0.0001, and values greater than 0.9999 will be denoted as >0.9999 whenever practical. Categories of discrete variables will be ordered and labelled as they appear in the eCRF, and all categories represented on the eCRF will be included in summaries, even when they do not apply to any subjects in the study.

Unless otherwise specified, all statistical tests will be 2-sided at alpha level 0.05. All statistical calculations will be completed using the SAS® Version 9.4 or above.

8.1 COVARIATES

There are no planned covariates.

8.2 EXAMINATION OF SUBGROUPS

If the data permit, analyses may be stratified by presence/absence of congenital diaphragmatic hernia (CDH).

8.3 PREMATURE DISCONTINUATION AND MISSING DATA

8.3.1 Missing Data Handling for Primary Efficacy Endpoint

Any subject with a missing value for clinical worsening will be assigned a value of "Yes."

8.3.2 Missing Data Handling for Secondary Efficacy Endpoints

For any continuous secondary endpoint, missing values will be imputed using last observation carried forward (LOCF). If an assessment is missing at Baseline, change from Baseline will not be calculated and the subject will not be included in the analyses of this assessment.

Time to event will be derived as detailed in Section 8.5.3.

8.4 MULTIPLE COMPARISONS AND MULTIPLICITY

The primary efficacy endpoint of clinical worsening through Day 14 will be tested at alpha level 0.05. If the primary efficacy endpoint is statistically significant at alpha level 0.05, the statistical tests for secondary efficacy endpoints will be performed. As these comparisons are exploratory, no adjustments for multiplicity are planned.

8.5 DERIVED AND TRANSFORMED DATA

8.5.1 Baseline Values

In general, Baseline is defined as the last value for an assessment prior to randomization. This value may be obtained at either the Screening or the Baseline visit, depending upon the visit schedule.

8.5.2 Change from Baseline Values

Change from Baseline for an assessment is defined as the difference between the observed value and its associated Baseline value.

8.5.3 Time to Event and Censor Status

Time to event and censor status will be calculated based on the rules in Table 8-1 for time to clinical worsening, time to initiation of ECMO, and time to discontinuation of iNO.

Table 8-1 Time to Event and Censor Status Rules

Parameter	Scenario	Formula	Censor Status
Time to Clinical Worsening (days)	Subject with clinical worsening or subject died between Baseline and Day 14	= minimum of (Worsening date, death date) - Randomization date	0 (event)
	Subject without clinical worsening between Baseline and Day 14	= minimum of (Last assessment date - Randomization date, 14)	1 (censored)
Time to initiation of ECMO (days)	Subject initiated ECMO between Baseline and Day 14	= Initiation date - Randomization date	0 (event)
	Subject did not initiate ECMO between Baseline and Day 14	= minimum of (Last assessment date - Randomization date, 14)	1 (censored)
Time to discontinuation of iNO (days)	Subject discontinued iNO between Baseline and Day 14	= iNO discontinuation date - Randomization date	0 (event)
	Subject did not discontinue iNO between Baseline and Day 14	= minimum of (Last assessment date - Randomization date, 14)	1 (censored)

ECMO, extracorporeal mechanical oxygenation; iNO, inhaled nitric oxide

8.6 ASSESSMENT WINDOWS

For some assessments, target study day and time have been specified in the protocol. These scheduled assessments, as recorded on the eCRFs, and the corresponding target days and times and study days and time intervals are specified in Table 8-2.

Table 8-2 Assessment Windows for Scheduled Assessments

Visit	Target Study Day/Time	Study Day/Time Interval
Echocardiograms:		
Day 7	Day 7	2 ≤ Study Day ≤ 9
Day 14	Day 14	10 ≤ Study Day
Vital signs, OI, FiO_2, Blood Gas/Lactate:		
Hour 6	Day 1/6 hours	1 ≤ Study Day 1, Hour 6 ≤ 9
Hour 12	Day 1/12 hours	10 ≤ Study Day 1, Hour 12 ≤ 15
Hour 18	Day 1/18 hours	16 ≤ Study Day 1, Hour 18 ≤ 21
Hour 24	Day 1/24 hours	22 ≤ Study Day 1, Hour 24 ≤ 27
Hour 30	Day 2/6 hours	28 ≤ Study Day 2, Hour 6 ≤ 33

Visit	Target Study Day/Time	Study Day/Time Interval
Hour 36	Day 2/12 hours	34 ≤ Study Day 2, Hour 12 ≤ 39
Hour 42	Day 2/18 hours	40 ≤ Study Day 2, Hour 18 ≤ 45
Hour 48	Day 2/24 hours	46 ≤ Study Day 2, Hour 24 ≤ 51
Hour 54	Day 3/6 hours	52 ≤ Study Day 3, Hour 6 ≤ 57
Hour 60	Day 3/12 hours	58 ≤ Study Day 3, Hour 12 ≤ 63
Hour 66	Day 3/18 hours	64 ≤ Study Day 3, Hour 18 ≤ 69
Hour 72	Day 3/24 hours	70 ≤ Study Day 3, Hour 24
PK Assessments		
After 24 hours of study drug dosing	Day 1	24 hours ± 12 hours

Abbreviations: FiO_2, fraction of inspired oxygen; OI, oxygenation index; PK, pharmacokinetic(s)
Note: Study Day = (Assessment Date) - (First Dosing Date) +1

For assessments that are not listed in Table 8-2, the nominal assessment name recorded in the eCRF will be used.

Multiple Evaluations Within the Same Analysis Window

After all the observations have been slotted based on the specifications above, if there are multiple valid observations for an assessment within an assigned analysis visit window, only 1 of these observations will be used for summary statistics and analyses. The observation to be used is determined using the following hierarchy (in decreasing order):

- The observation closest to the target study day and time
- The later observation if 2 observations are equally close to the target study day and time

For missing values where the LOCF algorithm is applied, it is always the last valid observation on treatment carried forward, even though this might not be the observation obtained by the above hierarchy and used in the summaries by visit window.

9 STUDY POPULATION

Unless otherwise specified, all efficacy analyses will be performed on the ITT population, all safety analyses will be based on the Safety population, and all PK analyses will be carried out based on the PK population. In the ITT population, the treatment assignment is based on the assignment upon randomization. In the Safety population, the treatment assignment is based on

the actual treatment the subject received. The PK population will be comprised of those subjects with PK data.

The comparability between the 2 treatment groups will be checked for demographic and baseline characteristics. The p-values from Fisher's exact test (for discrete variables) or Group t-test or Wilcoxon rank sum test (for continuous variables) will be included on summaries but are not intended to be used to test formal hypotheses. For these comparisons, missing or unknown values will be excluded from the calculations.

9.1 SUBJECT ACCOUNTABILITY

All subjects' disposition information will be listed, including the study population the subjects belong to, premature study drug discontinuation status, reason for premature study drug discontinuation, premature study discontinuation status, and primary reason for premature study discontinuation.

The listing of subject accountability will include dates of informed consent, randomization, first study drug dose, each study drug dose change, last study drug dose, and last assessment. Each of these assessments will be summarized by treatment group and overall.

Information regarding whether each subject is included in each analysis population will be listed. If a subject is not included in an analysis population, the reason for exclusion will be noted on the listing. Also noted on the listing will be the randomized treatment assignment and the actual treatment received. The summary will include the frequency and percentage of all subjects in each analysis population as well as summaries for reason for exclusion.

Status of the treatment blind and, if broken, date/time of blind broken and reason will be listed.

9.2 PROTOCOL DEVIATIONS

The status of the entry criteria will be listed for all subjects. The listing will include the date of the initial screening assessment and a list of any specific entry criteria not met. This listing will also include the protocol version that the subject was enrolled under. Entry criteria violations will be summarized by treatment group and overall.

Additional protocol deviations will be documented throughout the study. Protocol deviations will be listed, including the date of the deviation, the type of deviation, and the severity of the deviation. The protocol deviations will also be summarized by treatment group and overall.

9.3 OTHER DESCRIPTIONS OF STUDY POPULATION

9.3.1 Demographics

All demographic data will be listed for all subjects, including assessment date, date of birth, country, age (in days), sex, ethnicity, race, length, and weight. Age (in days), sex, ethnicity, race, length, and weight will be summarized. The summary will include p-values (2-sided) from Fisher's exact test (for sex, ethnicity, and race) and Group t-test or Wilcoxon rank sum test (for age, length, and weight) comparing treatment groups.

9.3.2 Medical History and PPHN and Neonatal History

All significant past or ongoing medical conditions will be listed for all subjects. The listing will include the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for each condition listed, and if the condition is ongoing at Baseline. These medical conditions will be summarized by PT within each SOC by treatment group and overall.

PPHN and neonatal history will be listed for all subjects. The listing will include current PPHN diagnosis; gestational age; birth weight; Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores at 1 and 5 minutes; and prior surfactant and prostaglandin therapy. Each of these assessments will also be summarized by treatment group and overall with appropriate summary statistics.

9.3.3 Concomitant Medications

All concomitant medications specified on the eCRF will be mapped to a standard name using the World Health Organization Drug Dictionary (WHO-DD).

The standard name and verbatim term of all concomitant medications will be listed for all subjects. This listing will include the date started (or indication that drug was ongoing at randomization), date discontinued (or indication that drug was ongoing at end of study), and the condition(s) treated/indication(s). If a subject received no medications, this will be indicated on

the listing. A summary of concomitant medications present at Baseline and a summary of concomitant medications added during the study will include the frequency and percentage of subjects in each treatment group receiving each drug (by coded standard name).

10 EFFICACY ANALYSES

Except where otherwise noted, all efficacy analyses will only be performed on the ITT population.

10.1 PRIMARY EFFICACY MEASURES

10.1.1 Primary Efficacy Analyses

10.1.1.1 Hypothesis

The primary efficacy endpoint of clinical worsening assesses if treprostinil reduces the incidence of clinical worsening through Day 14 over placebo in subjects with PPHN. The null and alternative hypotheses are:

$$H_0: p_1 = p_2$$
$$H_a: p_1 \neq p_2,$$

where p_1 and p_2 are the proportion of subjects who experience clinical worsening in the treprostinil and placebo treatment groups, respectively.

10.1.1.2 Primary Efficacy Analysis

The frequency and percentage of subjects who experience clinical worsening through Day 14 will be calculated for each treatment group. A chi-square test will be conducted to compare the incidence of clinical worsening between the treprostinil and placebo treatment groups.

The SAS Procedure FREQ will be used. The pseudo SAS statements are listed below:

```
proc freq;
     tables Treatment* Worsening / chisq;
run;
```

10.1.1.3 Sensitivity and Subgroup Analyses

To further support the robustness and assess the sensitivity of the primary efficacy analysis of clinical worsening through Day 14 (provided that the primary analysis yields significant results),

the above summary and chi-square test will be repeated using each of the following modifications (if data permit):

- The Per Protocol population will be used instead of the ITT population
- PPHN diagnosis (associated with unilateral CDH versus not associated with unilateral CDH)

10.2 SECONDARY EFFICACY MEASURES

The secondary endpoints are as follows:

- Change in OI from Baseline to Hours 12, 24, and 72, and Days 7 and 14 and/or prior to study drug discontinuation/weaning
- Change in PaO_2/FiO_2 (P/F ratio) from Baseline to Hours 12, 24, and 72
- Change in pre- and post-ductal SpO_2 from Baseline to Hours 6, 12, 24, and 72
- Time to discontinuation of iNO
- Time on mechanical ventilation
- Time to initiation of ECMO
- Time to clinical worsening
- Change in NT-proBNP

10.2.1 Change in OI

The secondary efficacy endpoint of change in OI assesses if treprostinil decreases the level of OI over placebo in subjects with PPHN. The null and alternative hypotheses are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2,$$

where μ_1 and μ_2 are the median change from Baseline in OI of the treprostinil and placebo treatment groups, respectively.

The OI values will be listed for all subjects, including the nominal time point and collection date/time. The values and their respective changes from Baseline will be summarized for all scheduled timepoints. The difference between treatment groups for the change from Baseline at Day 14 will be tested via a Group t-test at the following timepoints: Hour 12, Hour 24, Hour 72, Day 7, Day 14, and prior to study drug discontinuation/weaning.

If normality assumptions for the parametric test are violated, the nonparametric Wilcoxon rank sum test will be used. For subjects who do not have OI measurements at a timepoint, the LOCF imputation will be used. The analyses will also be performed for the data without imputation for the missing measures.

10.2.2 Change in PaO_2/FiO_2

PaO_2/FiO_2 and change from Baseline in PaO_2/FiO_2 will be analyzed in a similar manner as described in Section 10.2.1 at 12 hours, 24 hours, and 72 hours.

10.2.3 Change in SpO_2

Pre- and post-ductal SpO_2 and change from Baseline in pre- and post-ductal SpO_2 will each be analyzed in a similar manner as described in Section 10.2.1. Additionally, change from Baseline in pre- and post-ductal SpO_2 will be summarized by treatment group at 6 hours, 12 hours, 24 hours, and 72 hours.

10.2.4 Change in NT-proBNP

NT-proBNP and change from Baseline in NT-proBNP at Day 14 will be analyzed as described in Section 10.2.1 at Day 7 and Day 14. The listing will include normal range and high/low flags as well as all collected assessments of NT-proBNP.

10.2.5 Time to Clinical Worsening

Data on the clinical worsening assessment page of the eCRF will be used to determine clinical worsening status. Clinical worsening events including the date (study day) of the event and details of the clinical worsening event will be listed. The time to clinical worsening will be calculated according to the rules specified in Table 8-1.

Time to clinical worsening will be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method, and displayed graphically as Kaplan-Meier curves. A tabular summary of this analysis will include the number of subjects at risk (sample size), estimated median duration, and a 95% confidence interval for the median duration for each treatment group. The log-rank test will be used to calculate the p-value for treatment differences.

The SAS Procedure LIFETEST will be used. The pseudo SAS statements are listed below:

```
proc lifetest;
     time TimeToWorsening*Censor_Status(1);
     strata Treatment;
run;
```

In addition, the Cox proportional hazards model will be fit to obtain the hazard ratio. The model will include treatment as an explanatory variable. The SAS procedure PHREG will be used. The pseudo SAS statements are listed below:

```
proc phreg;
  Model TimeToWorsening*Censor_Status(1) = treatment
        / risklimits alpha=0.05 ties=efron;
run;
```

10.2.6 Time to Initiation of ECMO

Time to initiation of ECMO will be analyzed as described in Section 10.2.5.

10.2.7 Time to Discontinuation of iNO

Time to discontinuation of iNO will be analyzed as described in Section 10.2.5.

10.2.8 Time on Mechanical Ventilation

A listing that includes start date and time, stop date and time, and total time on mechanical ventilation will be prepared. Time on mechanical ventilation will be summarized by treatment group, as appropriate. A Wilcoxon rank sum test will be conducted to assess differences between treatment groups.

11 HEALTH OUTCOMES

No health outcome assessments will be collected in this study.

12 SAFETY ANALYSES

All safety analyses will be performed on the Safety population.

12.1 EXTENT OF EXPOSURE

A listing of study drug dosing will include route of administration (IV or subcutaneous); initial dose and date and time of initial dose; and dose, date, and time of each dose change. Overall

duration of exposure will be included as well as the final dose and the maximum study drug dose reached for each subject. Summaries of initial dose, final dose, and maximum dose will be provided by treatment group. If the data warrant, these summaries will also be produced by route of administration.

12.2 ADVERSE EVENTS

All AEs will be coded to PT and SOC using the latest version of the MedDRA coding dictionary. Treatment-emergent adverse events (TEAEs) are those AEs with onset date equal to or after the start date of the study drug. TEAEs will appear in listings and summaries. Non–treatment-emergent AEs (the AEs occurring after signing the Informed Consent Form (ICF), but before receiving study drug) will be listed, but will not be included in summary tables.

The AE listings will include the AE verbatim term and its corresponding PT and SOC, all eCRF details, and a treatment-emergent indicator flag. The following AE listings will be provided:

- All AEs
- Deaths
- SAEs
- AEs leading to permanent discontinuation of study drug

All AE summaries will be sorted by overall frequency and/or SOC and will include the number and percentage of subjects experiencing each type of AE, the total number of each type of AE, and the AE rate of each type of AE. AE rate will be calculated as the total number of AEs divided by the total patient days of exposure to study drug per treatment group.

The following AE summaries will be provided:

- AEs by SOC and PT
- AEs by PT
- Deaths
- SAEs by SOC and PT
- Non-serious AEs by SOC and PT
- AEs probably or possibly related to study drug by SOC and PT
- AEs leading to permanent discontinuation by PT
- AEs by SOC, PT, and severity (mild, moderate, severe)

12.3 CLINICAL LABORATORY EVALUATIONS

Blood samples will be taken at Baseline, Day 7, Day 14, immediately prior to study drug weaning or discontinuation, within 12 hours of study drug discontinuation, 48 hours after study drug discontinuation, and upon hospital discharge or 4 weeks after study drug discontinuation. All samples will be sent to the institutional laboratory for evaluation of clinical chemistry and hematology.

12.3.1 Clinical Chemistry

The following clinical chemistry parameters will be evaluated by the central laboratory:

Parameter	Units
Sodium	mmol/L
Potassium	mmol/L
Bicarbonate	mmol/L
Chloride	mmol/L
Total bilirubin	umol/dL
Alkaline phosphatase	U/L
Alanine aminotrasferase	U/L
Aspartate aminotransferase	U/L
Urea nitrogen	mmol/dL
Creatinine	umol/L
Glucose	mmol/L
Calcium	mmol/L
Albumin	g/L
Lactate	mg/dL
pH	

Values that are “high” or “low” with respect to the reference range provided by the central laboratory will be flagged with an “H” or an “L,” respectively. All parameters will be listed for all subjects and assessments, along with their respective “high/low” flags.

Values of these parameters at each scheduled timepoint and their corresponding changes from Baseline will be descriptively summarized.

For each parameter, the frequency and percentage of subjects within each treatment group who had “low,” “normal,” or “high” Baseline values, then subsequently had “low,” “normal,” or

"high" follow-up values at each scheduled timepoint will be presented in a shift summary at each scheduled timepoint.

12.3.2 Hematology

The following hematology parameters will be evaluated by the central laboratory:

Parameter	Units
Hemoglobin	g/dL
Hematocrit	%
Red blood cell count	10^6/uL
White blood cell count	10^3/uL
Platelet count	10^3/uL
Prothrombin time	sec

Values that are "high" or "low" with respect to the reference range provided by the central laboratory will be flagged with an "H" or an "L," respectively. All parameters will be listed for all subjects and assessments, along with their respective "high/low" flags.

Numeric values of these parameters at each scheduled timepoint and their corresponding changes from Baseline will be summarized.

For each parameter, the frequency and percentage of subjects within each treatment group who have "low," "normal," or "high" Baseline values, then subsequently have "low," "normal," or "high" follow-up values at each scheduled timepoint will be presented in a shift summary.

12.4 OTHER SAFETY MEASURES

12.4.1 Echocardiograms

Echocardiograms will be collected at Screening, Day 7, Day 14, immediately prior to study drug weaning or discontinuation, and 48 hours after study drug discontinuation. All echocardiogram assessments will be listed for all subjects. This listing will include the date and time of assessment, tricuspid regurgitant jet velocity, pulmonary regurgitant jet velocity, shunting details (through patent ductus arteriosus, through atrial septal defect or patent foramen ovale, and through ventricular septal defect), right ventricle dilation, and interventricular septal position.

The echocardiogram results will be descriptively summarized by treatment group at each planned assessment time.

12.4.2 Vital Signs

All vital sign assessments will be listed for all subjects. This listing will include weight, length, heart rate, systolic and diastolic blood pressures, respiration rate, temperature, and SpO_2. The vital sign results at each scheduled timepoint and the associated change from Baseline will be descriptively summarized by treatment group.

12.4.3 PPHN Disease-related Events

The number and percentage of subjects who experienced any PPHN disease-related event will be summarized by treatment group. Each category of disease-related event will also be summarized by treatment group. A listing of PPHN disease-related events will also be provided.

13 PHARMACOKINETICS

A listing that includes treprostinil plasma concentration, sample collection date and time, and nominal timepoint will be created. A separate listing will include the calculated PK parameters (if possible) for each subject.

Treprostinil plasma concentrations and PK parameters will be summarized by treatment group and nominal timepoint. The summary will include geometric mean and standard deviation in addition to arithmetic mean, standard deviation, minimum, and maximum.

Full details for the analysis of the PK data will be provided in a separate analysis plan.

14 REFERENCES

Finer N and Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term (review). *Cochrane Database of Systematic Reviews*. 2006; Issue 4. Art. No.: CD000399. DOI: 10.1002/14651858.CD000399.pub2.

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