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Title:

Protocol TDE-HF-301: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) in Heart Failure with Preserved Ejection Fraction (HFpEF)

Protocol TDE-HF-302: An Open-label Extension Study of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) Associated with Heart Failure with Preserved Ejection Fraction (HFpEF)- A Long-term Follow-up to Study TDE-HF-301

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
HFpEF	Heart failure with preserved ejection fraction
HR	Heart rate
IV	Intravenous
IVRS/IWRS	Interactive voice or web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PH	Pulmonary hypertension
PT	Preferred Term
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	System Organ Class
TID	3 Times daily
WHO	World Health Organization

1 PREFACE

This statistical analysis plan (SAP) provides further details of the planned interim deliverables for each Data Monitoring Committee (DMC) meeting for the TDE-HF-301 and TDE-HF-302 studies. The purpose of this SAP is to ensure that the statistical methodologies that will be used, and the data listings, summary tables, and figures which will be produced, are appropriate and complete to support valid interim safety reviews.

2 STUDY OBJECTIVES

The primary objective of the TDE-HF-301 study is to assess the effect of oral treprostinil compared with placebo on change in exercise capacity as measured by change in 6-Minute Walk Distance (6MWD) from Baseline to Week 24 in subjects with pulmonary hypertension (PH) associated with heart failure with preserved ejection fraction (HFpEF).

The secondary objectives of this study are to assess the effect of oral treprostinil compared with placebo on the following:

- Time to clinical worsening defined by at least 1 of the following:
  - Hospitalization due to a cardiopulmonary indication
  - Outpatient administration of intravenous (IV) diuretics
  - Decrease in 6MWD >15% from Baseline (or too ill to walk) directly related to disease under study at 2 consecutive visits on different days
  - Death (all causes)
- Change in N-Terminal pro-brain natriuretic peptide (NT-proBNP) levels from Baseline to Week 24
- Change in World Health Organization (WHO) Functional Class from Baseline to Week 24

The exploratory objectives of the TDE-HF-301 study are to assess the effect of oral treprostinil compared with placebo on the following:

- Change in 6MWD from Baseline to Weeks 6, 12, and 18
- Change in Borg dyspnea score from Baseline to Weeks 6, 12, 18, and 24
- Change in NT-proBNP levels from Baseline to Week 12
- Change in WHO Functional Class from Baseline to Weeks 6, 12, and 18
- Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) from Baseline to Week 24
- Optional evaluation of biomarkers (specific targets to be determined) from Baseline to Week 24
- Optional evaluation of pharmacogenomics

The primary objective of the TDE-HF-302 study is to evaluate the long-term safety of oral treprostinil in subjects with PH associated with HFpEF who completed Study TDE-HF-301. The secondary objective of the TDE-HF-302 study is to assess the effect of continued long-term therapy with oral treprostinil on the following:

- 6MWD
- Borg dyspnea score
- WHO Functional Class

- NT-proBNP at Weeks 24 and 48

3 STUDY DESIGN(S)

Study TDE-HF-301 is a multi-center, randomized, double-blind, placebo-controlled study in subjects with WHO Group 2 PH associated with HFpEF. Once randomized, subjects will return to the site for study visits every 6 weeks for a 24-week treatment period. If a subject completes the 24-week treatment period on study drug, they will be permitted to enter the open-label extension study (Study TDE-HF-302). If a subject prematurely discontinues the study for any reason, or discontinues study drug prematurely, they will not be permitted to enter Study TDE-HF-302.

Subjects will receive their first dose of study drug (0.125 mg) in the clinic on the day of randomization. Dosing of study drug will be continued at 0.125 mg 3 times daily (TID; every 6 to 8 hours) with food, up to an initial maximum dose of 2 mg TID. Based on the approval by the DMC, the dose will be slowly titrated throughout the study up to a maximum of 4 mg TID and then 6 mg TID, as safety data permit, in an effort to reach a tolerated dose that provides clinical benefit.

Study TDE-HF-302 is a multi-center, open-label study for eligible patients who completed Study TDE-HF-301. Once enrolled, subjects will return to the site for study visits at Weeks 6, 12, 18, 24, and every 12 weeks thereafter.

4 RANDOMIZATION

Study TDE-HF-301 will be randomized 1:1 oral treprostinil to placebo. All subjects will be randomly allocated to receive oral treprostinil or placebo through the interactive voice or web response system (IVRS/IWRS) using a centrally administered randomization. The randomization will be stratified by Baseline 6MWD (less than or equal to 350 meters and greater than 350 meters).

Study TDE-HF-302 is an open-label study of oral treprostinil. All subjects will receive oral treprostinil.

5 SEQUENCE OF PLANNED ANALYSES

Throughout the course of the TDE-HF-301 study, the DMC will meet on a regular basis to monitor the safety of the studies and make changes to maximum dosages of study drug to be used in accordance with the DMC charter. The DMC will meet for formal safety reviews after approximately 10, 30, 60, 100, and 200 subjects have been enrolled in the TDE-HF-301 study. Ad hoc meetings may be scheduled at additional enrollment milestones or in response to events related to the safety of study treatment.

For the TDE-HF-301 study, the DMC will review subject disposition, demographics and baseline characteristics, 6-Minute Walk Test (6MWT), WHO Functional Class, clinical worsening, diuretic dosing, selected clinical laboratory parameters, vital signs, study drug dosing, and safety data, including adverse events (AEs), serious adverse events (SAEs), and deaths for the safety population using all available data. Pertinent vital sign parameters, dosing, and clinical laboratory parameters will be plotted.

For the TDE-HF-302 study, the DMC will review subject disposition and safety data, including AEs, SAEs, and deaths.

Data to be reviewed for the TDE-HF-301 and TDE-HF-302 studies will include by-subject listings as well as tabular summaries of the above noted data. Any additional information deemed necessary to evaluate the continued safety of all enrolled subjects will also be provided.

6 ANALYSIS POPULATION

The safety population for Study TDE-HF-301 will be defined as all subjects who receive at least 1 dose of study drug (regardless of randomization status); all subjects will be counted in the group corresponding to the treatment that they actually received.

The safety population for Study TDE-HF-302 will be defined as all subjects who receive at least 1 dose of open-label study drug; all subjects will be counted in the oral treprostinil group.

The safety population will be utilized to produce all data listings, summaries, and figures for discussion at the DMC meetings for the TDE-HF-301 and TDE-HF-302 studies.

7 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All available data will be presented in a semi-unblinded (masked) fashion with no imputation for any missing data. Treatment groups will be labeled A or B for summarization purposes; however, the DMC may request the full unblinding information in the closed session.

Subjects will contribute the data available up to the point of study completion or study discontinuation for any reason for both studies. For continuous variables, the summary statistics will include the mean, standard deviation, median, minimum, and maximum. Minimums and maximums will be expressed using the level of precision to which the variable was collected. All other statistics will be rounded, using an additional decimal point. For discrete variables, summaries will include the frequency and percent in each category. Percentages will be rounded to 1 decimal point. Whenever practical, categories of discrete variables will be ordered and labeled as they appear in the electronic case report form (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.

7.1 PREMATURE DISCONTINUATION AND MISSING DATA

Subjects may voluntarily withdraw or be withdrawn from the study and/or study drug by the Investigator at any time for reasons including, but not limited to, the following:

- The subject wishes to withdraw from further participation.
- A serious or life-threatening AE occurs or the Investigator considers that it is necessary to discontinue study drug to protect the safety of the subject.
- The subject significantly deviates from the protocol.
- The subject becomes pregnant.

- The subject's behavior is likely to undermine the validity of his/her results.

All available data from all treated subjects will be used as detailed in this analysis plan. No imputation for missing data will be performed.

8 STUDY POPULATION

8.1 SUBJECT DISPOSITION

For the TDE-HF-301 study, the listing of subject disposition will include subject number, date of enrollment, date of randomization, date study drug initiated, date study drug discontinued, reason for study drug discontinuation, date completed/discontinued from study, and reason for study termination. The number of subjects enrolled, randomized, dosed with study drug (safety population), who discontinued study drug, and who discontinued from the study will be summarized by treatment and overall, as well as the reasons for study drug discontinuation and study discontinuation, and the descriptive statistics for weeks on study drug.

For the TDE-HF-302 study, the listing of subject disposition will include subject number, date of enrollment, date completed/discontinued from study, and reason for discontinuation. The number of subjects enrolled, dosed with study drug (safety population), who discontinued from the study, and the reasons for discontinuation will be summarized overall.

8.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The listing of subject demographics and baseline characteristics for Study TDE-HF-301 will include subject number, date of birth, age at randomization (years), sex, race, ethnicity, HFpEF diagnosis, and etiology. Age at randomization, sex, race, ethnicity, and etiology will be summarized by masked treatment group and overall.

9 EFFICACY ANALYSES

Efficacy parameters will be assessed as a surrogate for safety issues. The efficacy parameters to be included are the 6MWT, WHO Functional Class, and reports of clinical worsening.

9.1 SIX-MINUTE WALK TEST

The listing of the 6MWT data for Study TDE-HF-301 will include subject number, nominal time point, assessment date/time, date/time of last study drug dose, last study drug dose (mg), total distance walked (m), Borg dyspnea score, oxygen receipt (yes/no), amount of oxygen (L/min), unusual circumstances, and reason walk not attempted (if applicable) for each treatment arm. The total distance walked (m) and Borg dyspnea score will be summarized by masked treatment group at Baseline, Weeks 6, 12, 18, and 24/Early Termination, including changes from Baseline.

9.2 WHO FUNCTIONAL CLASS

The listing of WHO Functional Class for Study TDE-HF-301 will include subject number, nominal time point, assessment date, and WHO Functional Class (I, II, III, or IV) for each treatment arm. The WHO Functional Class will be summarized by masked treatment group

and overall at Baseline, Weeks 6, 12, 18, and 24/Early Termination, including shifts from Baseline.

9.3 CLINICAL WORSENING

Clinical worsening will be assessed continuously from randomization until 1 of the following criteria are met:

- Hospitalization due to a cardiopulmonary indication
- Outpatient administration of IV diuretics
- Decrease in 6MWD >15% from Baseline (or too ill to walk) directly related to the disease under study at 2 consecutive visits on different days
- Death (all causes)

A listing of clinical worsening data for Study TDE-HF-301 will include subject number, clinical worsening (yes/no), date of clinical worsening event, and type of clinical worsening event for each treatment arm. The number (percent) of subjects who experienced clinical worsening and the clinical worsening event types will be summarized by masked treatment group.

10 SAFETY ANALYSES

Safety will be assessed by treatment-emergent changes in physical examination findings, vital signs, assessment of heart failure signs and symptoms, clinical laboratory tests, and the development of AEs after treatment. Treatment emergence is defined as the time points on or after the first dose of study drug.

Treatment-emergent changes in vital signs, incidence of treatment-emergent AEs, and treatment-emergent changes in laboratory parameters will be evaluated. Statistical summaries of safety data will be descriptive and exploratory in nature, focusing on the incidence of adverse experiences. The vital signs, AEs, deaths, and clinical laboratory parameters collected in Study TDE-HF-301 will be listed and summarized. The safety data analysis for Study TDE-HF-302 will list and summarize the AEs SAEs, and deaths. No inferential statistical analyses are planned for safety data.

10.1 STUDY DRUG DOSING

The listing of study drug dosing for Study TDE-HF-301 will include the subject number, date of study drug dose, first study drug dose (mg), and the dates/times of any new doses, along with the new dose (mg). The summary of study drug dose will include the first study drug dose (mg) and the study drug doses (mg) at Weeks 6, 12, 18, and 24/Early Termination by masked treatment group. For summarization purposes, the study drug dose (mg) will be calculated as the sum of the doses administered during the study day that corresponds to each nominal time point divided by the number of doses administered on that given day. Study drug dosing will be plotted across time. For the first 2 DMC meetings, given the low number of subjects, the dosing figures will include a line for each individual subject (spaghetti plot), using a different line type for each masked treatment group. After the second DMC meeting, the number of subjects will be too great for a spaghetti plot to be informative, thus mean plots

will be generated across time with each treatment group being represented by its own unique line.

10.2 DIURETIC DOSING

The listing of diuretic dosing will include the subject number, name of generic drug, total daily dose, indication that drug was onging at randomization (yes/no), start date, end date, and indication that drug was onging at the end of study for each treatment arm (yes/no).

10.3 ADVERSE EVENTS

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) according to System Organ Class (SOC) and Preferred Term (PT). The listings of all AEs and SAEs, separately, will include the subject number, reported AE/SAE term (verbatim term and MedDRA coded PT), start and stop dates/time or ongoing, treatment emergent status (yes/no), seriousness (reason for seriousness/no), date event became serious, frequency (once/intermittent/continuous), severity (mild/moderate/severe), action taken with study drug, Investigator's assessment of relationship to study drug (not related/possible/probable), and outcome. The listings will be sorted by subject number and then in chronological order of start date of AEs/SAEs, with the masked treatment arm represented at the page level for Study TDE-HF-301. The listings for Study TDE-HF-302 will also be sorted by subject number and then in chronological order of start date of AEs/SAEs, but all subjects will be included in the same listing since there is 1 treatment group in this open-label study.

Adverse event/SAE summaries will be limited to include only treatment-emergent AEs/SAEs. Treatment-emergent AEs/SAEs are those that were not present prior to receiving study drug or those that increased in seriousness or intensity after receiving study drug. The summaries of treatment-emergent AEs/SAEs will include the number and percent of subjects experiencing each type of event (by PT) and the total number of each type of event by masked treatment group for Study TDE-HF-301. For Study TDE-HF-302, the summaries of treatment-emergent AEs/SAEs will include the number and percent of subjects experiencing each type of event (by PT) and the total number of each type of event overall. The order of AEs/SAEs by PT will be in decreasing frequency within the overall column. The first row on these 4 tables will present the data for "Any Adverse Event" or "Any Serious Adverse Event," respectively.

10.4 DEATHS

The listing of deaths for studies TDE-HF-301 and TDE-HF-302 will include subject number, date of death, and cause of death for all deaths occurring between first study drug dose and the end of study, or within 4 weeks after last study drug dose, if the subject prematurely terminates. The summary of deaths for Study TDE-HF-301 will include the number (percentage) of deaths, as well as causes of death by masked treatment group. The summary of deaths for Study TDE-HF-302 will include the number (percentage) of deaths, as well as causes of death overall.

10.5 VITAL SIGNS

The listing of vital signs for Study TDE-HF-301 will include subject number, nominal time point, date/time, diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), and weight for each treatment arm. All time points will be ordered chronologically by subject. Vital signs (excluding height) and their respective changes from Baseline will be summarized by masked treatment group at Baseline, Weeks 6, 12, 18, and Week 24/Early Termination. Vital signs, with the exception of height, will be plotted across time. For the first 2 DMC meetings, given the low number of subjects, the vital sign figures will include a line for each individual subject (spaghetti plot). After the second DMC meeting, the number of subjects will be too great for a spaghetti plot to be informative, thus mean plots will be generated across time with each treatment group being represented by its own unique line.

10.6 LABORATORY ASSESSMENTS

The listing of laboratory parameters for Study TDE-HF-301 will include subject number, nominal time point, date/time, and the laboratory parameters specified for each type, as shown in 10-1.

Table 10-1 Laboratory Parameters

Clinical Chemistry	**Hematology**
Sodium	Red blood cell count
Potassium	Hemoglobin
Chloride	Hematocrit
Bicarbonate/CO_2	Platelet count
Albumin	White blood cell count
Blood urea nitrogen/urea	
Total bilirubin	
Indirect bilirubin	
Direct bilirubin	
Alkaline phosphatase	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Creatinine	

These laboratory parameters will be summarized along with change from Baseline by masked treatment group at Baseline, Week 12, and Week 24/Early Termination. The laboratory parameters will be plotted across time. For the first 2 DMC meetings, given the low number of subjects, the laboratory figures will include a line for each individual subject (spaghetti plot) with 2 different line colors used to delineate the 2 treatment groups. After the second DMC meeting, the number of subjects will be too great for a spaghetti plot to be informative, thus mean plots will be generated across time with each treatment group being represented by its own unique line.

11 APPENDICES

Table, listing, and figure titles suggested here may be altered or edited as appropriate by the clinical data programmers while maintaining the original intent of the output.

11.1 LIST OF TABLES

11.2 LIST OF LISTINGS

Listing Number	Listing Title
1	Listing of Subject Disposition for Study TDE-HF-301
2	Listing of Demographics and Baseline Characteristics for Study TDE-HF-301
3	Listing of Six-Minute Walk Test Data for Study TDE-HF-301
4	Listing of WHO Functional Class for Study TDE-HF-301
5	Listing of Clinical Worsening for Study TDE-HF-301
6	Listing of Study Drug Dose for Study TDE-HF-301
7	Listing of Diuretic Dosing for Study TDE-HF-301
8	Listing of Adverse Events for Study TDE-HF-301
9	Listing of Serious Adverse Events for Study TDE-HF-301
10	Listing of Deaths for Study TDE-HF-301
11	Listing of Vital Signs for Study TDE-HF-301
12	Listing of Laboratory Parameters for Study TDE-HF-301
13	Listing of Subject Disposition for Study TDE-HF-302
14	Listing of Adverse Events for Study TDE-HF-302
15	Listing of Serious Adverse Events for Study TDE-HF-302
16	Listing of Deaths for Study TDE-HF-302

11.3 LIST OF FIGURES