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Title:

An Open-Label Extension Study of UT-15C in Subjects with Pulmonary Arterial Hypertension – A Long-Term Follow-up to Protocol TDE-PH-310

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
BMI	Body Mass Index
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ERA	Endothelin receptor antagonist
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PDE-5I	Phosphodiesterase type 5 inhibitor
PT	Preferred Term
SAP	Statistical analysis plan
sGC	Soluble guanylate cyclase
SOC	System Organ Class
SR	Sustained release
TID	3 times daily
UT-15C	Treprostinil diethanolamine
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 PREFACE

This document describes the planned analyses for the TDE-PH-311 study. This plan is based on the original TDE-PH-311 protocol dated 03 Feb 2012 and subsequent protocol amendments (latest version protocol amendment 6 dated 29 Sep 2016), and provides further details of the analyses presented in the protocol as well as 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

2.1 OBJECTIVES

The objectives of this study are to:

- Provide treprostinil diethanolamine (UT-15C) sustained-release (SR) tablets for eligible subjects who participated in study protocol TDE-PH-310
- Assess the long-term safety of oral UT-15C
- Assess the effect of continued long-term therapy with UT-15C on exercise capacity (6-Minute Walk Distance [6MWD]/Borg dyspnea score), World Health Organization (WHO) Functional Class, and plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) (at Week 48 only).

2.2 ENDPOINTS

The safety endpoints are as follows:

- Adverse events (AEs)
- Clinical laboratory parameters
- Vital signs

Concomitant medications, including PAH concomitant medications, also will be documented.

Efficacy will be assessed by:

- 6-Minute Walk Test (6MWT)
- Borg dyspnea score
- WHO Functional Class
- NT-proBNP

3 STUDY DESIGN

This is an open-label study. Subject visits will occur at Baseline, Weeks 6 and 12, and every 12 weeks thereafter. The study will continue until either oral UT-15C becomes available within the respective territories or the study is discontinued by the Sponsor. The Baseline Visit corresponds to the Study Termination Visit from the parent study (TDE-PH-310) and occurs prior to initiation of the open-label study.

4 RANDOMIZATION

This study is not randomized. All subjects will receive UT-15C during the open-label study if the subjects were randomized to UT-15C or placebo in the parent study. However, some analyses are based on the treatment assignment in the parent study.

5 SEQUENCE OF PLANNED ANALYSES

Along with the safety information from the parent study (TDE-PH-310), safety information from the TDE-PH-311 study will be provided to the Data Monitoring Committee (DMC) periodically for safety review.

At the time of study completion and unblinding for the parent study (TDE-PH-310), a data cut for the TDE-PH-311 study will be performed to facilitate the analysis for the TDE-PH-311 study. Analyses based on additional data cuts and the final analyses at the time of study closing will be performed separately.

6 SAMPLE SIZE CONSIDERATIONS

No formal sample size calculation has been conducted. All eligible subjects from the parent study (TDE-PH-310) may be enrolled into this open-label extension study.

7 ANALYSIS POPULATIONS

All available data from all subjects will be used as detailed in this analysis plan.

The safety population will include any subject who received UT-15C at any time during the course of the TDE-PH-311 study. All analyses are based on the safety population.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All data included in each data cut will be listed. In general, listings will be sorted by subject number and scheduled assessment (if applicable) or the visit date. Listings will include assessment date, assessment time (if available), and study day. The study day is calculated as the assessment date minus the date of the first UT-15C dose in the TDE-PH-311 study. For data collected on a fixed schedule, the assessment identifier will also be included on the listing.

In general, the data will be summarized by visit window. The visit window is calculated based on the time from the first dosing date of UT-15C in the TDE-PH-311 study. For all presentations of the summary tables, the data will be presented by subjects in the UT-15C and placebo groups from the parent study (TDE-PH-310) and overall.

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 in 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.

8.1 EXAMINATION OF SUBGROUPS

Exploratory subgroup analyses will be performed as data permit.

8.2 PREMATURE DISCONTINUATION AND MISSING DATA

A subject may voluntarily withdraw or be withdrawn from the study 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 deviated from the protocol.
- The subject's behavior is likely to undermine the validity of his/her results.

- The subject becomes pregnant

All available data from all subjects in the safety population, as defined in Section 7, will be used as detailed in this analysis plan.

Missing data will not be imputed.

8.3 MULTIPLE COMPARISONS AND MULTIPLICITY

No multiple comparison adjustments are planned for analysis of this study.

8.4 ASSESSMENT WINDOWS

For efficacy and safety assessments, Baseline is defined as the measurements prior to the first dose of UT-15C in the TDE-PH-311 study.

Summary analyses will be based on the scheduled (norminal) visits with no visit windows applied.

9 STUDY POPULATION

9.1 SUBJECT ACCOUNTABILITY

A listing of subject disposition and UT-15C exposure will include subject number, treatment group in the parent study, first and last UT-15C dose date/time in the TDE-PH-311 study, date completed/discontinued the study, cut off date, study drug exposure (weeks), reason for discontinuation, and any other details regarding reason for discontinuation. The summary of subject accountability will include the number (percent) of subjects by treatment group who completed the study without early termination, the number of subjects who completed UT-15C treatment by each visit acheived, number of subjects who discontinued UT-15C treatment, and the reason for discontinuation. This summary will be provided by treatment group in the parent study and overall.

UT-15C exposure and the total subject-years of UT-15C exposure will be summarized by the treatment group in the parent study and overall.

In addition, for subjects who were in UT-15C group in the parent study (TDE-PH-310), their exposure to UT-15C in the parent study will be combined into the TDE-PH-311 study. The

overall exposure to UT-15C across both the parent study and the TDE-PH-311 study will be summarized.

9.2 ELIGIBILITY CRITERIA

The listing of entry criteria for all subjects will include whether the subject rolled over from the previous study, each subject's treatment group in the parent study, status regarding meeting all eligibility criteria (yes/no), and will include an explanation if not all eligibility criteria are met. The summary of entry criteria will include the number and percent of subjects who did meet and the number and percent of subjects who did not meet all eligibility criteria by treatment group in the parent study and overall.

In addition, a listing will be provided for protocol deviations. The listing will include the subject number, deviation date, deviation type, deviation severity, and deviation description by treatment group in the parent study.

9.3 OTHER DESCRIPTIONS OF STUDY POPULATION

9.3.1 Demographics

The listing of subject demographics will be organized by treatment group in the parent study, and will include subject number, country, assessment date, date of birth, subject age (years), sex, ethnicity, race, height, weight, and body mass index (BMI). The age will be calculated based on the first UT-15C dose date in the TDE-PH-311 study. The summary of demographics will include descriptive statistics for age (years) at first dose of UT-15C and categorical summaries for age (<65 and ≥65 years), sex, ethnicity, race, height, weight, and BMI, where weight is the measure before the first dose of UT-15C for the TDE-PH-311 study and height is obtained from the parent study.

9.3.2 Baseline Characteristics

Baseline characteristics include 6MWD, 6MWD category (≤380 m versus >380 m), Borg dyspnea score, and WHO Functional Class, and will be summarized by treatment group in the parent study and overall. Baseline measures are defined as the last measurement prior to the first UT-15C dose in the TDE-PH-311 study.

9.3.3 PAH History

The listing of PAH history will be organized by treatment group in the parent study, and will include the subject number, the date of initial PAH diagnosis, number of years since PAH diagnosis, etiology, WHO Functional Class at Baseline, 6MWD at Baseline, Borg dyspnea score at Baseline, background PAH therapy (endothelin receptor antagonist [ERA] alone, phosphodiesterase type 5 inhibitor [PDE-5I] alone, or soluble guanylate cyclase [sGC] stimulator alone), and background PAH medication name. The number of years since PAH diagnosis will be calculated based on the first UT-15C dose date in the TDE-PH-311 study. The summary of PAH history will include descriptive statistics for years since PAH diagnosis and categorical summaries for etiology and background PAH therapy at randomization in the parent study.

9.3.4 Concomitant Medications

The listing of concomitant medications will be organized by treatment group in the parent study, and will include subject number, whether the subject has had any concomitant medications, and all concomitant medications (including PAH medications) that were reported on or after the date of the first UT-15C dosing in the TDE-PH-311 study. The concomitant medications will be listed by verbatim term, WHO Drug Dictionary (WHO-DD) standard name, start and stop dates, condition treated/indication, whether the concomitant medication is ongoing from parent study, and whether or not the concomitant medication is ongoing at the end of the study. Summaries will be provided for medications ongoing from the parent study and for those added in the TDE-PH-311 study. Each summary will be provided by treatment group in the parent study and overall, and will include the number (percent) of subjects reporting each medication (based on the WHO-DD medication name) and the number of records for each medication.

9.3.5 UT-15C Dosing

In the TDE-PH-311 study, UT-15C dosing information will be collected on a monthly basis. A listing and a summary will be provided for UT-15C dosing. The listing will be organized by treatment group in the parent study, and will include the subject number, dose recording date, and the actual dose (in milligrams) for morning, mid-day, and evening.

The UT-15C dose will be summarized by analysis visit. The summary will also include the number and percent of subjects in each dose category by treatment group in parent study and overall. The same summary table will be repeated by each background PAH therapy. The dose categories include UT-15C drug dose (3 times daily [TID]) <1 mg, 1 to <2 mg, 2 to <4 mg, 4 to <6 mg, 6 to <8 mg, 8 to <10 mg, 10 to <12 mg, and ≥12 mg.

10 EFFICACY ANALYSES

10.1 6-MINUTE WALK TEST

The listing of the 6MWT will be organized by treatment group in the parent study, and will include subject number, analysis visit, assessment date/time (day), last UT-15C dose date/time (day), the last UT-15C dose (in milligrams), hours from last UT-15C dose to 6MWT, 6MWD results, Borg dyspnea scores, use of supplemental oxygen, and any circumstances affecting the 6MWT. The summaries of 6MWD will be provided by treatment assignment in the parent study (UT-15C or placebo) by visit, PAH etiology (idiopathic, heritable, associated with connective tissue disease, and other), Baseline WHO Functional Class, and quartiles of the last UT-15C dose. The summaries will include descriptive statistics for 6MWD measure at each analysis visit and the change from Baseline. Baseline is defined as the last 6MWD measured prior to the first dose of UT-15C in the TDE-PH-311 study.

Achievement of a walk distance of at least 440 m by each analysis visit will be summarized by treatment group in the parent study and overall. Achievers and non-achievers will then be summarized based on their Baseline walk (<=440 m vs >440 m) by treatment group in the parent study and overall.

10.2 BORG DYSPNEA SCORE

Borg dyspnea score information will be listed as part of the 6MWD. The summary of the Borg dyspnea score will be provided by treatment group in the parent study. The summaries will include descriptive statistics for measurements at each analysis visit and the change from Baseline values. Baseline is defined as the last Borg dyspnea score measured prior to the first dose of UT-15C in the TDE-PH-311 study.

10.3 WHO FUNCTIONAL CLASS

WHO Functional Class information will be listed by treatment group in the parent study, and will include subject number, analysis visit, assessment date (day), and WHO Functional Class. The summaries of the WHO Functional Class will be provided by treatment group in the parent study. The summaries will include descriptive statistics for measurements at each analysis visit and the change from Baseline values. Baseline is defined as the last WHO Functional Class assessed prior to the first dose of UT-15C in the TDE-PH-311 study.

11 SAFETY ANALYSES

11.1 ADVERSE EVENTS

AEs are captured from the time the Informed Consent Form is signed. Any AEs that are ongoing at the Study Termination Visit from study TDE-PH-310 are recorded as continuing AEs in TDE-PH-311 study. All AEs with an onset date on or after the first dose of UT-15C in the TDE-PH-311 study or AEs ongoing from the parent study will be included in data listing and summaries.

The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and all summaries will utilize the Preferred Term (PT) and/or System Organ Class (SOC). All AEs and serious AEs will be organized by treatment group in the parent study, and listed by subject, including onset date (day), cessation date (day), verbatim term, corresponding PT and SOC, seriousness, date AE became serious, severity, frequency, relationship to study drug, action taken with study drug, and outcome.

The overall summary of AEs includes the number of subjects with any AE, the number of subjects with any study drug-related AEs, the number of subjects with AEs leading to study drug withdrawal, the number of subjects with any serious AEs, the number of subjects with any severe AEs, and the number of subjects with any study drug-related severe AEs.

The summaries of AEs by SOC and PT will be provided by treatment group in the parent study and overall. The summaries of AEs, serious AEs, severe AEs, AEs probably or possibly related to UT-15C, serious AEs probably or possibly related to UT-15C, and AEs

leading to permanent discontinuation of UT-15C will include the number of subjects (percent of subjects) and number of events for each reported PT.

The summary of AEs adjusted for UT-15C exposure will include the number of subjects (percent of subjects) and number of events for each reported PT, as well as the number of events per patient-year of exposure.

11.2 DISEASE-RELATED EVENTS

Disease-related events will be listed by the subject number, treatment group in parent study, and events (yes/no). The summary will include the number (percent) of subjects who reported each symptom by treatment group in the parent study and overall. Disease-related events include abdominal pain, anorexia, ascites, chest pain, cool extremities, cor pulmonale, cough, cyanosis, dizziness, dyspnea, general edema, hemoptysis, fatigue, hypoxia, loss of consciousness, nausea, orthopnea, pallor, palpitations/cardiac arrhythmia, paroxysmal nocturnal dyspnea, pulmonary hypertension exacerbation, syncope, tachycardia, weight loss/gain, vasovagal reaction, and vomiting.

11.3 DEATHS

All deaths will be listed (including those occurring within 30 days of the last UT-15C dose) by subject, and will include the subject number, treatment group in the parent study, date of assessment (day), whether subject died, date of death (day), and cause of death (including other, specify text [if applicable]). An additional listing of deaths will include the subject number, first UT-15C dose in TDE-PH-311 study, last UT-15C dose (day) in TDE-PH-311 study, date of death (day), and cause of death. The summary of deaths will be presented by the parent study and overall and will include the number (percent) of subjects who died (including those within 30 days of study participation) and their causes of death.

Time to death will be calculated as:

(the death date – the date of the first UT-15C dosing in TDE-PH-311 study)

The Kaplan-Meier (K-M) estimator will be provided for the time to death, and K-M plots will be provided by treatment group in the parent study.

11.4 CLINICAL LABORATORY TESTS

Laboratory results will be mapped into the analysis visit based on the assessment date. The laboratory data will be listed by subject and treatment group in the parent study, including all hematology and clinical chemistry parameters by analysis visit. The listings will include the collection date/times (day), laboratory test, and results. The normal laboratory reference ranges will be included in the listings. A designation for low (L) or high (H) will be included for those laboratory values that are outside the relevant normal range. The listing of urinalysis will also be presented by subject and the treatment group in the parent study, and will include each scheduled and unscheduled urinalysis assessment. The laboratory sample collection date/time (day), laboratory test, normal range, designation for high or low, and analysis visit will be provided for each assessment, as well as the result of the test.

For hematology and clinical chemistry parameters, the original values and their changes from Baseline (defined as the last measurement prior to the first dose of UT-15C in the TDE-PH-311 study) will be summarized for each analysis visit by the treatment group in the parent study and overall. Shift tables will also be provided. For urinalysis results, the number and percent of subjects within each category will be summarized for all analysis visits by treatment group in the parent study and overall.

Pregnancy test results for the female subjects will be organized by treatment group in the parent study, and listed by subject number, analysis visit, and did the subject become pregnant during the study (yes/no).

11.5 VITAL SIGNS

Vital sign results will be mapped into the analysis visit based on the assessment date. The vital sign data will be listed by subject and treatment group in the parent study for each analysis visit by assessment date/time (day), weight, heart rate, blood pressure, and respiration rate. The original measures and their changes from Baseline (defined as the last measurement prior to the first UT-15C dosing in the TDE-PH-311 study), and descriptive statistics, will be summarized for all analysis visits by the treatment group in the parent study and overall.

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Listing titles suggested here may be altered or edited as appropriate by the clinical data programmers while maintaining the original intent of the listing.

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Figure titles suggested here may be altered or edited as appropriate by the clinical data programmers while maintaining the original intent of the figure.

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