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Title:

An Open-Label Extension Study of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CPFE	Combined pulmonary fibrosis and emphysema
CSR	Clinical study report
DLCO	Lung diffusion capacity
DMC	Data Monitoring Committee
DSP	Distance saturation product
eCRF	Electronic Case Report Form
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ILD	Interstitial lung disease
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PFT	Pulmonary function test
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease
PT	Preferred Term
SAP	Statistical analysis plan
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SpO_2	Saturation of peripheral capillary oxygenation
TLC	Total lung capacity
WHO	World Health Organization

1 PREFACE

This plan provides further details of the planned analyses for the RIN-PH-202 study as presented in the study protocol. This plan, based on the original RIN-PH-202 study protocol dated 14 October 2015 and the subsequent study protocol amendment (latest version study protocol amendment 1 dated 18 August 2016), provides further details of the planned analyses stated in the study protocol and may include 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 primary objective of this study is to provide or continue to provide inhaled treprostinil for eligible subjects who participated in the RIN-PH-201 study.

Secondary objectives are to assess the long-term safety and efficacy of inhaled treprostinil in subjects with pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE).

2.2 ENDPOINTS

2.2.1 Efficacy

To evaluate the effect of continued long-term therapy with inhaled treprostinil, the efficacy endpoints are:

- Peak 6-Minute Walk Distance (6MWD)
- N-terminal pro-brain natriuretic peptide (NT-proBNP)
- Quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ)
- Optional evaluation of change in biomarkers from Baseline to Week 48 (or study discontinuation if prior to Week 48)
- Change in distance saturation product (DSP)

The changes in biomarkers from Baseline to Week 48 are an optional evaluation and their analysis will be detailed in a separate document and not covered in this SAP.

2.2.2 Safety

To evaluate the effect of continued long-term therapy with inhaled treprostinil, the safety endpoints are:

- Adverse events (AEs)
- Oxygenation
  - Pulse oximetry (saturation of peripheral capillary oxygenation [SpO_2])
  - Supplemental oxygen (L/min)
- Pulmonary function tests (PFTs)
  - Forced expiratory volume in 1 second (FEV_1)
  - Forced vital capacity (FVC)
  - Total lung capacity (TLC)
  - Lung diffusion capacity (DLCO)
- Clinical laboratory parameters
- Vital signs
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

3 STUDY DESIGN

This is a multicenter, open-label study. Subject visits will occur at Baseline, Weeks 4, 12, and every 12 weeks thereafter until Week 108. The study will continue until each subject has completed Week 108 or until inhaled treprostinil becomes commercially available for patients with pre-capillary pulmonary hypertension associated with interstitial lung disease (PH-ILD) including CPFE (whichever is sooner).

4 RANDOMIZATION

This study is not randomized. All subjects will receive inhaled treprostinil during this open-label study if they completed Week 16 of the parent study (RIN-PH-201). However, some analyses will be based on the treatment assignment in the parent study.

5 SEQUENCE OF PLANNED ANALYSES

Along with the safety information from the parent study, safety information from the RIN-PH-202 study will be provided to the Data Monitoring Committee (DMC) periodically for safety review.

After study completion and unblinding for the parent study, a data cut for the RIN-PH-202 study will be performed to facilitate the analyses for the RIN-PH-201 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. It is expected that approximately 266 subjects who completed protocol RIN-PH-201 will 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 inhaled treprostinil at any time during the 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 and will be organized by treatment group in the parent study. Listings will include assessment date, assessment time (if available), and study day. Study day is calculated as the assessment date minus the date of the first inhaled treprostinil dose in the RIN-PH-202 study + 1. For data collected on a fixed schedule, the assessment identifier will also be included in the listing.

In general, data will be summarized by visit window. The visit window is calculated based on the time from the first dosing date of inhaled treprostinil in the RIN-PH-202 study. For all presentations of the summary tables, the data will be presented by subjects in the inhaled treprostinil and placebo groups from the parent study (RIN-PH-201) and overall.

For continuous variables, 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.

8.1 EXAMINATION OF SUBGROUPS

Exploratory subgroup analyses may be performed as data permit.

8.2 PREMATURE DISCONTINUATION AND MISSING DATA

A subject 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 consistently deviated from the protocol.
- The subject's behavior is likely to undermine the validity of his/her results.
- The subject permanently initiates an infused prostacyclin therapy for >29 days.
- 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 the analyses of this study.

8.4 ASSESSMENT WINDOWS

For efficacy and safety assessments, Baseline is defined as the last measurement prior to the first dose of inhaled treprostinil in the RIN-PH-202 study.

The assessments will be mapped into the analysis visit windows based on Table 8-1.

Table 8-1 Assessment Windows for Scheduled Visits

Visit	Target Study Day	Study Day Interval
Baseline	1	Study Day ≤1
Week 4	29	1< Study Day ≤57
Week 12	85	57< Study Day ≤127
All other visits	169, 253, etc	Target Study Day ±42

Note: Study Day = (Assessment Date) - (First inhaled treprostinil Dosing Date) +1

8.4.1 Multiple Evaluations Within the Same Analysis Window

After all the observations have been assigned according to Table 8-1, if there are multiple valid observations for an assessment within an assigned analysis visit window, only one of these observations will be used for summary statistics. The observation to be used will be determined using the following hierarchy (in decreasing order):

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

8.5 DERIVED AND TRANSFORMED DATA

The time to event will be calculated for each of the following variables as detailed in Table 8-2:

- Hospitalization due to a cardiopulmonary indication
- Exacerbation of underlying disease
- Death

Table 8-2 Derivation of Time to Event

Parameter	Scenario	Formula	Status
Time to hospitalization (weeks)	Subjects with hospitalization during the study	= (Hospitalization date – first visit date +1)/7	0 (event)
	Subjects without hospitalization during the study	= (Last assessment date – first visit date +1)/7	1 (censored)
Time to exacerbation (weeks)	Subjects with exacerbation during the study	= (Exacerbation date – first visit date +1)/7	0 (event)
	Subjects without exacerbation during the study	= (Last assessment date – first visit date +1)/7	1 (censored)
Time to death (weeks)	Subjects who died during the study	= (Death date – first visit date +1)/7	0 (event)
	Subjects who completed or discontinued prematurely	= (Last assessment date – first visit date +1)/7	1 (censored)

9 STUDY POPULATION

9.1 SUBJECT ACCOUNTABILITY

A listing of subject disposition and inhaled treprostinil exposure will include subject number, treatment group in the parent study, first and last inhaled treprostinil dose date/time in the RIN-PH-202 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 inhaled treprostinil treatment by each visit achieved, the number of subjects who discontinued inhaled treprostinil treatment, and the reason for discontinuation. This summary will be provided by treatment group in the parent study and overall.

Inhaled treprostinil exposure and the total subject-years of inhaled treprostinil exposure will be summarized by treatment group in the parent study and overall.

In addition, for subjects who were in the inhaled treprostinil treatment group in the parent study (RIN-PH-201), their exposure to inhaled treprostinil in the parent study will be combined with the RIN-PH-202 study. The overall exposure to inhaled treprostinil across both the parent study and the RIN-PH-202 study will be summarized.

9.2 ELIGIBILITY CRITERIA

The listing of entry criteria for all subjects will include each subject's treatment group in the parent study, status regarding meeting all eligibility criteria (yes/no), and 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. Deviations will be reviewed by the clinical team prior to database lock and those that might affect subject safety or efficacy outcomes will be considered "Major." All other deviations will be classified as "Minor."

9.3 OTHER DESCRIPTIONS OF STUDY POPULATION

9.3.1 Demographics

The listing of subject demographics will include subject number, assessment date, date of birth, subject age (years), sex, ethnicity, race, height, weight, and body mass index (BMI). Age will be calculated based on the first inhaled treprostinil dose date in the RIN-PH-202 study. The summary of demographics will include descriptive statistics for age (years) at first dose of inhaled treprostinil and categorical summaries for age (<65 years of age, 65 to <80 years of age, and ≥80 years of age), sex, ethnicity, race, height, weight, and BMI, where weight is the measure before the first dose of inhaled treprostinil for the RIN-PH-202 study and height is obtained from the parent study.

9.3.2 Baseline Characteristics

Baseline characteristics will include 6MWD, 6MWD category (≤350 m versus >350 m and ≤median Baseline 6MWD versus >median Baseline 6MWD), DLCO percent predicted

(<40% versus ≥40%), NT-proBNP, and PFTs and will be summarized by treatment group in the parent study and overall. Baseline measurements are defined as the last measurement prior to the first inhaled treprostinil dose in the RIN-PH-202 study. Baseline characteristics will be included in the appropriate listings.

9.3.3 PH-ILD History

Information related to subjects' PH-ILD history will be listed. The listing will include the date of initial PH diagnosis, years since PH diagnosis, etiology of ILD (including idiopathic interstitial pneumonia subcategory), date of confirmatory computed tomography scan, and the date of confirmatory lung biopsy, if performed.

The current ILD diagnosis (ILD category) and time since PH diagnosis will be summarized by parent study treatment group and overall.

9.3.4 Concomitant Medications

All concomitant medications recorded on the eCRF will be mapped to a standard name and Anatomical Therapeutic Chemical (ATC) Levels 1 to 4 using the WHODrug Global. The ATC Levels 2 and 4 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 from parent study), date discontinued (or indication that drug was ongoing at end of study), and the condition(s) treated/indication(s). Summaries will be provided for medications ongoing from the parent study and for those added in the RIN-PH-202 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 by ATC Level 2 and Level 4. If ATC Level 4 is not available for a medication, ATC Level 3 will be substituted. If ATC Level 3 is not available, ATC Level 2 will be substituted. If ATC Level 2 is not available, ATC Level 1 will be substituted.

9.3.5 Inhaled Treprostinil Dosing

In the RIN-PH-202 study, inhaled treprostinil dosing information will be recorded whenever a change occurs in the dose. A listing and a summary will be provided for inhaled treprostinil dosing. The listing will include initial dose (number of breaths for each session and number

of breaths for the day), date of this initial dose, and dose and date of each dose change. Dosing at each analysis visit will be summarized. The summary will include both the numeric summaries and the categorical summaries for number of breaths per session as well as the number of breaths per day. If study drug is dosed differently across different sessions on the same day, the maximum number of breaths will be used for summarization. A summary of overall duration of exposure will be included, as well as the final dose (breath/session) and the maximum study drug dose (breath/session) reached for each subject (numerically and categorically).

For study treatment compliance, the number and percentage of days with dose >0 breaths will be calculated and summarized.

10 EFFICACY ANALYSES

10.1 6-MINUTE WALK TEST

The listing of the 6-Minute Walk Test (6MWT) will include subject number, analysis visit, assessment date/time (day), last inhaled treprostinil dose date/time (day), the last inhaled treprostinil dose (number of breaths), hours from last inhaled treprostinil dose to 6MWT, 6MWD results and associated changes from Baseline, use of supplemental oxygen, and any circumstances affecting the 6MWT. The summaries of 6MWD will be provided by treatment assignment in the parent study (inhaled treprostinil or placebo) and overall by visit. The summaries will include descriptive statistics for 6MWD at each analysis visit and the change from Baseline. Baseline is defined as the last 6MWD measured prior to the first dose of inhaled treprostinil in the RIN-PH-202 study. Additionally, a plot of mean change from Baseline in 6MWD at each study visit by parent study treatment group will be provided.

10.2 N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE

NT-proBNP values and associated changes from Baseline will be listed and the listing will include subject number, analysis visit, and assessment date (day). NT-proBNP values and change from Baseline values will be summarized by parent study treatment group and overall at each analysis visit. The summary will also include the geometric mean and geometric standard deviation. Baseline is defined as the last NT-proBNP value obtained prior to the first dose of inhaled treprostinil in the RIN-PH-202 study.

10.3 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

SGRQ total and domain scores will be listed and the listing will include subject number, analysis visit, assessment date (day), and parent study treatment group. SGRQ total and domain scores and the associated changes from Baseline values will be summarized by parent study treatment group at each analysis visit. Baseline scores will be calculated from the last SGRQ administered prior to the first dose of inhaled treprostinil in the RIN-PH-202 study.

10.4 DISTANCE SATURATION PRODUCT

DSP will be calculated as follows:

Parameter	Formula
DSP (m%)	= (Distance walked in meters) x (Lowest oxygen saturation recorded during the 6MWT)

Abbreviations: 6MWT, 6-Minute Walk Test; DSP, Distance Saturation Product

DSP values and associated changes from Baseline will be listed and the listing will include subject number, analysis visit, and assessment date (day). DSP values and change from Baseline values will be summarized by parent study treatment group at each analysis visit. Baseline is defined as the last DSP value obtained prior to the first dose of inhaled treprostinil in the RIN-PH-202 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 RIN-PH-201 are recorded as continuing AEs in the RIN-PH-202 study. All AEs with an onset date on or after the first dose of inhaled treprostinil in the RIN-PH-202 study or AEs ongoing from the parent study will be included in data listings 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) to categorize AEs. All 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

SOC and PT, 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 AEs leading to death, the number of subjects with any serious AEs, and the number of subjects with any study drug-related serious AEs.

The summaries of AEs by SOC and PT will be provided by parent study treatment group and overall. The summaries of AEs, serious AEs, non-serious AEs, AEs probably or possibly related to inhaled treprostinil, and AEs leading to permanent discontinuation of inhaled treprostinil will include the number of subjects (percent of subjects) and number of events for each reported PT.

The total number of AEs and the AE rates will be calculated and summarized for each display, as appropriate. The AE rate will be calculated as the total number of AEs divided by the total patient years of exposure to study drug per treatment group in the parent study.

11.2 DEATHS

All deaths will be listed (including those occurring within 30 days of the last inhaled treprostinil dose for subjects who discontinued prematurely) by subject, and will include the subject number, treatment group in the parent study, date of assessment (day), date of death (day), first and last inhaled treprostinil doses in the RIN-PH-202 study, and cause of death (including other, specify text [if applicable]). A summary of deaths will be presented by the parent study treatment group and overall and will include the number (percent) of subjects who died (including those occurring within 30 days of the last inhaled treprostinil dose for subjects who discontinued prematurely) and their causes of death.

Time to death will be summarized by parent study treatment group and overall 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 parent study treatment group and overall.

In addition, a Cox proportional hazards model may be fit for time to death to obtain the hazard ratio and its associated 95% confidence interval. The model will include parent study treatment group as an explanatory variable.

11.3 HOSPITALIZATIONS DUE TO CARDIOPULMONARY INDICATIONS

All hospitalizations will be listed including admission date, discharge date, and hospitalization status at the end of the study. Those hospitalizations due to cardiopulmonary indications will be flagged. This listing will be organized by parent study treatment group.

The number and percentage of subjects who experience any hospitalizations and any hospitalizations due to cardiopulmonary indications will be summarized by parent study treatment group and overall. Additionally, the total number of hospitalizations due to cardiopulmonary indications per subject will be categorized by parent study treatment group and overall.

Kaplan-Meier analyses and Cox regression as described in Section 11.2 will also be done.

11.4 EXACERBATIONS OF UNDERLYING LUNG DISEASE

All exacerbations of underlying lung disease will be listed including start date, end date, status at the beginning and end of the study, whether the exacerbation was considered serious, and if so, the date the event became serious.

The number and percentage of subjects who experience exacerbations of underlying lung disease will be summarized by parent study treatment group and overall. Additionally, the total number of exacerbations of underlying lung disease per subject will be categorized by parent study treatment group and overall.

Kaplan-Meier analyses and Cox regression as described in Section 11.2 will also be performed.

11.5 OXYGENATION

Oxygenation is measured by pulse oximetry (SpO_2 and supplemental oxygen requirement [L/min]) during each 6MWT. At each 6MWT, pulse oximetry (for SpO_2) will be measured at pre-walk, during walk, and post-walk. During walk, the lowest SpO_2 will be recorded. All pulse oximetry results along with the collection date/time (study day) will be listed. Heart rate will be listed for pre-walk and post-walk only.

Heart rate will be summarized by parent study treatment group and overall, by time point (pre-walk and post-walk) and visit. The summary will be provided for the original values, change from pre-walk for each visit, and change from Baseline values. For change from Baseline calculations, the measurements pre-walk and post-walk at post-Baseline visits will be compared with the measurements at corresponding pre-walk and post-walk at Baseline.

11.5.1 Pulse Oximetry

SpO2 will be summarized by parent study treatment group and overall at each time point (pre-walk, during walk, and post-walk) and analysis visit. The summary will be provided for the original values, change from pre-walk for each visit, and change from Baseline values. For change from Baseline calculations, the measurements pre-walk, during walk, and post-walk at post-Baseline visits will be compared with the measurements at corresponding pre-walk, during walk, and post-walk at Baseline. Baseline is defined as the last values obtained prior to the first dose of inhaled treprostinil in the RIN-PH-202 study.

In addition, for each time point at each visit, the number and percentage of subjects with SpO2 or lowest SpO2 <80%, ≥80% to <88%, and ≥88%, and with SpO2 dropping ≥10% during walk and/or post-walk from pre-walk, will be summarized by parent study treatment group and overall.

11.5.2 Supplemental Oxygen

At each visit, supplemental oxygen requirements will be collected at rest and during 6MWT. These data will be listed, including visit, 6MWT date/time, and oxygen use at rest and during walk. The number and percentage of subjects requiring supplemental oxygen use at rest and during the 6MWT will also be summarized by parent study treatment group and overall.

Supplemental oxygen level at rest at each visit and the corresponding changes from Baseline will be summarized by parent study treatment group and overall.

11.6 PULMONARY FUNCTION TESTS

The PFT parameters include:

- FEV_1 and percent predicted value,
- FVC and percent predicted value,
- TLC and percent predicted value, and
- DLCO for carbon monoxide and percent predicted value.

If the PFT is done both prior to and after a bronchodilator, only pre-bronchodilator values will be recorded and listed. The listing will include subject number, analysis visit, and assessment date (day) as well as each PFT result and the percent predicted values for each PFT. All PFT parameters (absolute values and percent predicted values) and their respective change from Baseline values will be summarized by parent study treatment group and overall at each visit.

11.7 CLINICAL LABORATORY TESTS

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
Calcium	mmol/L
Albumin	g/L

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

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

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 visit, and their corresponding changes from Baseline, will be descriptively summarized by parent study treatment group and overall.

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

Pregnancy test results for female subjects will be summarized by parent study treatment group and overall and listed by subject number, analysis visit, and pregnancy status.

11.8 VITAL SIGNS

Vital sign results will be mapped to analysis visit based on assessment date. The vital sign data will be listed by subject and parent study treatment group for each analysis visit by assessment date/time (day), weight, heart rate, blood pressure, respiration rate, and temperature. The original measures and their changes from Baseline (defined as the last measurement prior to the first inhaled treprostinil dosing in the RIN-PH-202 study) will be summarized for all analysis visits by the parent study treatment group and overall.

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14.3.1	Kaplan-Meier Plot of Time to Death
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14.3.4	Kaplan-Meier Plot of Time to Exacerbation of Underlying Lung Disease