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Title:

An Open-label Extension Study of APD811-003 in Patients with Pulmonary Arterial Hypertension

Author: [redacted]

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
6MWT	6-Minute Walk Test
6MWD	6-Minute Walk Distance
AE	Adverse event
BNP	B-Type natriuretic peptide
ECG	Electrocardiogram
FC	Functional Class
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PT	Preferred Term
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
SAE	Serious adverse event
SOC	System Organ Class
WHO	World Health Organization

1 PREFACE

This document describes the planned analyses for Study APD811-007, as presented in the study protocol. This plan is based on the original APD811-007 protocol dated 17 June 2014 and subsequent protocol amendments (latest version Protocol Amendment 4 dated 15 May 2019), 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 may be performed. Such analyses will be documented in the Clinical Study Report.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

The study objectives are to:

- Evaluate the long-term safety and tolerability of ralinepag in subjects with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) who have completed Study APD811-003.
- Evaluate the effect of ralinepag in subjects with WHO Group 1 PAH who completed Study APD811-003, as determined by the incidence of clinical worsening.
- Evaluate changes from baseline in 6-Minute Walk Distance (6MWD), WHO/New York Hearth Association Functional Class (FC), and hemodynamics.

2.2 ENDPOINTS

The safety endpoints are as follows:

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

Efficacy will be assessed by:

- Clinical worsening
- 6-Minute Walk Test (6MWT)
- WHO FC
- Hemodynamics

- B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP)

3 STUDY DESIGN

APD811-007 is a Phase 2, multicenter, open-label extension study to determine the long-term safety and tolerability of ralinepag in subjects with WHO Group 1 PAH who have completed the Phase 2 study, APD811-003, or who were assigned to placebo and were discontinued for clinical worsening. Subjects must also meet eligibility criteria for participation in APD811-007. All subjects enrolled in the study will receive open-label treatment with ralinepag. Subjects on active treatment in the parent study (APD811-003) will remain on current dose and have onsite clinical assessments performed every 3 months until the subject is discontinued from the study. Subjects in the placebo treatment group of the parent study will undergo a dose-titration period until a stable, maximum tolerated dose is reached (up to 9 weeks). The titration will be followed by a treatment period during which monthly onsite clinic assessments will be performed for the first 3 months and then every 3 months until the subject is discontinued from the study or the study is terminated.

The APD811-007 Baseline Visit corresponds to the Study Termination Visit of the parent study and occurs prior to initiation of study drug.

Study APD811-007 is being discontinued by the Sponsor to combine all subjects still ongoing treatment across the program into 1 Phase 3, open-label, long-term extension study (ROR-PH-303).

4 RANDOMIZATION

Study APD811-007 is not randomized. All subjects will receive ralinepag during the open-label study, regardless if the subjects were randomized to and received ralinepag or placebo in the parent study. However, some analyses are based on the treatment group (ralinepag or placebo) in the parent study.

5 INTERIM ANALYSIS

An interim analysis was performed in September 2018 to evaluate the long-term safety and tolerability for all subjects who had received treatment in APD811-007 for at least 1 year. In addition, the objective of the interim analysis was to support proposed Phase 3 studies. Interim analysis was intended to take place in lieu of final study analysis; however, with the discontinuation of Study APD811-007, final analysis is being conducted to serve the protocol objectives with the entirety of study data.

6 SAMPLE SIZE CONSIDERATIONS

No formal sample size calculation has been conducted. All eligible subjects from the parent study may be enrolled into the 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 ralinepag at any time during the course of the APD811-007 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 ralinepag dose in the APD811-007 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 scheduled (nominal) visits. For all presentations of the summary tables, the data will be presented by treatment group of the parent study 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, and all categories represented on the electronic Case Report Form 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 the following:

- Clinical worsening
- Deviation/noncompliance with the protocol
- A serious or intolerable AE occurs
- The Sponsor or Investigator terminates the study, or
- Withdrawal of consent – any subject may withdraw his/her consent from the study at any time. The Investigator should make a reasonable attempt to document the specific reason why consent is withdrawn.

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 APD811-007.

8.4 ASSESSMENT WINDOWS

For efficacy and safety assessments, baseline is defined as the last measurement prior to the first dose of ralinepag in the APD811-007 study.

Summary analyses will usually be based on the scheduled (nominal) visits with no visit windows applied. If appropriate, hemodynamic parameters will only be summarized by the Baseline and post-Baseline Visits of APD811-007.

9 STUDY POPULATION

9.1 SUBJECT ACCOUNTABILITY

A listing of subject disposition and ralinepag exposure will include the subject number, treatment group in the parent study, first and last ralinepag dose date/time in the APD811-007 study, date completed/discontinued the study, 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 who completed the study without early termination, the number of subjects who completed ralinepag treatment by each visit achieved, number of subjects who discontinued ralinepag treatment, and the reason for discontinuation. This summary will be provided by treatment group in the parent study and overall.

Ralinepag exposure and the total patient-years of ralinepag exposure will be summarized by the treatment group in the parent study and overall. Duration of treatment will be further characterized by weeks on the immediate-release and extended-release formulations.

In addition, for subjects who were in the ralinepag group of the parent study, exposure to ralinepag in the parent study will be combined into the APD811-007 study. The overall exposure to ralinepag across both the parent study and the APD811-007 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 an explanation if all eligibility criteria are not met. The summary of entry criteria will include the number (percent) of subjects who met all eligibility criteria and the number (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, age (years), sex, ethnicity, race, height, weight, and body mass index. The age will be calculated based on the first ralinepag dose date in the APD811-007 study. The summary of demographics will include descriptive statistics for age (years), height, weight, and body mass index at first dose of ralinepag, where weight and height are obtained from the parent study; and categorical summaries for age (<65 and ≥65 years), sex, ethnicity, and race.

9.3.2 Baseline Characteristics

Baseline characteristics including 6MWD, 6MWD category (≤440 m versus >440 m), pulmonary vascular resistance (PVR), WHO FC, BNP, and NT-proBNP will be summarized by treatment group in the parent study and overall. Baseline measures are defined as the last measurement prior to the first ralinepag dose in the APD811-007 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, PAH classification, WHO FC at Baseline, 6MWD at Baseline, PVR at Baseline, PAH disease specific concomitant medication, and background PAH medication name. The number of years since PAH diagnosis will be calculated based on the first ralinepag dose date in the APD811-007 study. The summary of PAH history will include descriptive statistics for years since PAH diagnosis and categorical summaries for PAH classification and PAH disease specific concomitant medication 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 the verbatim term, WHO Drug Dictionary standard name, the date started, date discontinued, and the condition(s) treated/indication(s). Summaries will be provided for medications ongoing from the parent study and for those added in the APD811-007 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 WHO Drug Dictionary medication name.

9.3.5 Ralinepag Dosing

In the APD811-007 study, a listing and a summary will be provided for ralinepag dosing. The listing will be organized by treatment group in the parent study, and will include the subject number, visit date, titration action, actual dose, immediate-release or extended-release, and total daily dose.

The ralinepag dose will be summarized by analysis visit. The summary will also include the number (percent) of subjects in each dose category by treatment group in parent study and overall.

10 EFFICACY ANALYSES

10.1 TIME TO CLINICAL WORSENING

Time to the first event of clinical worsening will be calculated and listed. Time to clinical worsening is calculated from the treatment start date in APD811-007 to the first occurrence of clinical worsening. For subjects who do not experience clinical worsening, it will be censored at the last record date of clinical worsening assessment or end of study, whichever is latest.

Summaries and analyses will be performed for time to clinical worsening. Kaplan-Meier estimate will be provided along with the corresponding p-value using log-rank test. In addition, hazard ratio, 95% confidence interval, and p-value will be provided using the Cox proportional hazard model. A Kaplan-Meier plot will also be provided.

10.2 6-MINUTE WALK TEST

The listing of the 6MWT will be organized by treatment group in the parent study, and will include the subject number, visit, assessment date/time (day), last ralinepag dose date/time (day), the last ralinepag dose (micrograms), hours from last ralinepag dose to 6MWT, 6MWD results, and use of supplemental oxygen. The summaries of 6MWD will be provided by treatment group in the parent study for each visit. The summaries will include descriptive statistics for 6MWD and the change from baseline. Baseline is defined as the last 6MWD measured prior to the first dose of ralinepag in the APD811-007 study.

10.3 WHO FUNCTIONAL CLASS

WHO FC information will be listed by treatment group in the parent study and will include the subject number, visit, assessment date (day), and WHO FC. The summaries of the WHO FC will be provided by treatment group in the parent study. The summaries will include descriptive statistics for measurements at each visit and the shift from baseline. Baseline is defined as the last WHO FC assessed prior to the first dose of ralinepag in the APD811-007 study.

10.4 HEMODYNAMICS

Right heart catheterization (RHC) measurements will be obtained at 1 year (±3 months) after a subject enrolls into Study APD811-007. If the subject has been in Study APD811-007 beyond 1 year (±3 months) at the time of regulatory/ethics approval of Protocol Amendment 2, an RHC assessment will be conducted at 2 years (±3 months) instead. If a subject has been enrolled in Study APD811-007 more than 2 years at the time of regulatory/ethics approval, an RHC assessment will be performed at the time of those approvals.

Hemodynamic values will be listed by treatment group in the parent study. The summaries of the hemodynamic values will be provided by treatment group in the parent study. The summaries will include descriptive statistics for measurements at each visit and the change from baseline values. The summary statistics may include the geometric mean, interquartiles, and ratio to the baseline. Baseline is defined as the last hemodynamic values assessed prior to the first dose of ralinepag in the APD811-007 study. The mean plot of PVR may be generated across time with each parent treatment group.

10.5 BNP/NT-proBNP

BNP and NT-proBNP will be measured at Baseline and then every 3 months during the treatment period. BNP and NT-proBNP will be listed by treatment group in the parent study. The summaries of the BNP and NT-proBNP will be provided by treatment group in the parent study. The summaries will include descriptive statistics for measurements at each visit and the change from baseline values. The summary statistics may include the geometric mean, interquartiles, and ratio to the baseline. Baseline is defined as the last BNP and NT-proBNP assessed prior to the first dose of ralinepag in the APD811-007 study.

11 SAFETY ANALYSES

11.1 ADVERSE EVENTS

AEs are captured from the time the Informed Consent Form is signed. AEs that are ongoing at the parent study Termination Visit are recorded as continuing AEs in the APD811-007 study. All AEs with an onset date on or after the first dose of ralinepag in the APD811-007 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, and all summaries will utilize the Preferred Term (PT) and/or System Organ Class (SOC). All AEs and serious adverse events (SAEs) will be organized by treatment group in the parent study and listed by subject number, including onset date (day) and time, stop date (day) and time, verbatim term, corresponding PT and SOC, seriousness, severity, 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 SAEs, 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, SAEs, severe AEs, AEs related to ralinepag, SAEs related to ralinepag, and AEs leading to permanent discontinuation of ralinepag will include the number (percent) of subjects and number of events for each reported PT.

The summary of AEs adjusted for length of ralinepag exposure will include the number (percent) of subjects and number of events for each reported PT, as well as the number of events per patient-years of exposure.

11.2 DEATHS

All deaths will be listed (including those occurring within 30 days of the last ralinepag dose) by subject number and will include the first ralinepag dose date in Study APD811-007, last ralinepag dose date in Study APD811-007, date of death, 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.

11.3 CLINICAL LABORATORY TESTS

The laboratory data will be listed by subject number and treatment group in the parent study, including all hematology and clinical chemistry parameters by 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 and coagulation will also be presented by subject number and 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, clinical chemistry, and coagulation parameters, the original values and their changes from baseline (defined as the last measurement prior to the first dose of ralinepag in the APD811-007 study) will be summarized for each analysis visit by the treatment group in the parent study and overall. Shift tables for hematology and clinical chemistry will also be provided. For urinalysis results, the number (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 female subjects will be organized by treatment group in the parent study and listed by subject number and did the subject become pregnant during the study (yes/no).

11.4 VITAL SIGNS

The vital sign data will be listed by subject number and treatment group in the parent study for each visit by the assessment date/time (day), heart rate, systolic blood pressure, diastolic blood pressure, and respiratory rate. The original measures and their changes from baseline (defined as the last measurement prior to the first ralinepag dose in the APD811-007 study), and descriptive statistics will be summarized for all analysis visits by the treatment group in the parent study and overall.

11.5 SAFETY ECG

Individual ECG values will be listed by treatment group in the parent study and visit. They will be summarized using descriptive statistics. Intervals to be provided for each ECG are: respiratory rate, PR, QRS, QT, QT interval corrected, QT interval corrected for Bazett's formula, and QT interval corrected for Fridericia's formula. Post-baseline ECGs will be compared with the baseline ECG. Summary statistics will also be provided for change from baseline in ECG values. The baseline value is defined as the last measurement prior to the first ralinepag dose in APD811-007.

12 CHANGES FROM ANALYSIS PLANNED IN THE PROTOCOL

For the final analysis, the following changes have been made to the analyses that are described in the protocol:

- Safety Population will be used for all summaries (protocol Section 9.1 specifies modified Intent-to-Treat Population for efficacy analyses).
- The protocol separated the primary objective and secondary objectives. The analyses will be based on efficacy and safety, not specifically separating the primary and secondary objectives.
- Protocol Section 6.2 states medical and social history would be updated at Baseline in Study APD811-007. These updates were not collected.
- No imputation will be performed for missing efficacy values (protocol Section 9.1 specifies Last Observation Carried Forward imputation for efficacy missing values).
- Baseline for change from baseline in efficacy values will be the APD811-007 baseline value (protocol Section 9.2 specifies the Day 1 pre-dose measurement in Study APD811-003 as the main baseline, with Day 1 of Study APD811-007 as baseline for a secondary analysis).
- Follow-up vital status (mortality) was not collected.
- Local results of BNP/NT-proBNP are not available.

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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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