Protocol *B1791089*

AN OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE PHARMACOKINETICS OF SINGLE AND MULTIPLE INTRAVENOUS DOSES OF PANTOPRAZOLE IN TWO AGE COHORTS OF HOSPITALIZED PEDIATRIC SUBJECTS 1 TO 16 YEARS OF AGE WHO ARE CANDIDATES FOR ACID SUPPRESSION THERAPY

Statistical Analysis Plan (SAP)

Version: 2.0

SAP Author: PPD

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments

2.0	03OCT2022	PPD	• Removed a table of list of reviewers from current page.
			• Following updates are based on Protocol Amendment 3 (07NOV2018):
			  • Added text for flexible dosing duration (Section 2.1).
			  • Added text changing the PK sampling to Days 1 and 2 (Section 2.1).
			  • Updated both primary objectives and the first secondary objective (Sections 2.2.1 and 2.2.2) to align with the amended protocol.
			  • Removed Table 1 (Section 6.3.1) and replaced it with text from the amended protocol.
			  • Inserted pop PK modeling verbiage (Section 8.3).
			  • Updated the TOC.

1.0	17FEB2016	PPD	Original SAP

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

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LIST OF TABLES

No table of figures entries found. None.

LIST OF FIGURES

None.

APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

Pantoprazole sodium is a proton pump inhibitor indicated for oral use in adults and pediatric patients 12 years of age and above (5 years of age and above in the US) for treatment in the healing and symptomatic relief of erosive esophagitis (EE) associated with gastroesophageal reflux disease (GERD). The intravenous (IV) formulation is approved for use in adults for the same indication but is not approved for use in children.

The rationale for conducting this Post Authorization Safety Study (PASS) is to characterize the PK profile of single and repeated IV doses of pantoprazole in hospitalized pediatric subjects in age groups of 1 to less than 2 years, and 2 to 16 years who in the judgment of the investigator are candidates for acid suppression therapy. These data will fulfill the FDA Post Marketing Requirement (PMRs 145-1 and 255-6).

2.1. Study Design

This is a non-randomized, open-label, multicenter study to characterize the pharmacokinetics of single and multiple IV doses of pantoprazole in hospitalized pediatric subjects in two independent age cohorts of 1 to 16 years (1 to less than 2 years; 2 to 16 years old) who in the judgment of the investigator are candidates for acid suppression therapy. There will be approximately 12 subjects per age cohort and a total of approximately 24 subjects for this two-cohort study.

Eligible subjects will be assigned to the following main age cohorts:

- *Cohort 1: 1 to less than 2 years;*
- *Cohort 2: 2 to 16 years old.*

In Cohort 2, there will be approximately equal distribution across the age sub-cohorts of 2 to 5 years, 6 to 11 years and 12 to 16 years.

*All subjects will receive a fixed dose of IV pantoprazole according to weight. The maximum dose per 24 hour period will not exceed 40 mg. Pantoprazole will be administered IV over 15 minutes through a Y-site or dedicated line in the morning of Day 1 and once daily for 7 days (*fixed dosing, *every 24 hours for 7 days,* prior to Protocol Amendment 3, whilst flexible dosing will be used afterwards (4-7 days as needed)*). Guidance will be provided to the clinical site regarding preparation and administration instructions. PK samples will be collected, using the IV line, to measure plasma concentrations of pantoprazole on study Day 1 and Day 7* (prior to Protocol Amendment 3, whilst Days 1 and 2 afterwards). *A follow up post treatment telephone contact will occur approximately 31 days after the last dose.*

2.2. Study Objectives

2.2.1. Primary

- *To characterize the PK of single and multiple IV doses of pantoprazole in pediatric subjects aged 1 to less than 2 years old.*

- *To characterize the PK of single and multiple IV doses of pantoprazole in pediatric subjects aged 2 to 16 years old.*

2.2.2. Secondary

- *To determine the safety, tolerability, and PK of single and multiple IV dose pantoprazole in each of the two independent age cohorts.*

- *To assess the CYP2C19 genotype in pediatric subjects receiving IV pantoprazole, to determine the presence of the gene for the major enzyme responsible for metabolism of pantoprazole.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned. Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses are required.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population is defined as all subjects treated with pantoprazole who have at least 1 concentration.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all subjects treated with pantoprazole who have at least 1 of the PK parameters of primary interest.

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

5.4. Other Analysis Sets

None.

5.5. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are randomized but not treated.

If a subject takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

5.6. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.6.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.6.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of pantoprazole will be taken according to the Schedule of Activities given in the protocol.

PK parameters to be estimated from the population PK model:

Clearance (CL), volume of distribution (Vd), maximum plasma concentration (C_{max}), area under the plasma concentration-time profile from time zero to the 24 hour time post dose (AUC_{24}), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}) and terminal phase half-life ($T_{1/2}$) of pantoprazole following single and multiple IV doses.

6.3.2. PD Endpoints

None.

6.3.3. Pharmacogenomics

Buccal cell collection for CYP2C19 genotyping will be taken to determine the presence of the gene for the major enzyme responsible for metabolism of pantoprazole.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

7.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification).

7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample).

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular cohort with ≥3 evaluable measurements. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as shortened intravenous infusion), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

As this is a descriptive study only, no formal hypothesis testing will be performed. *No pooled analyses across the two independent age cohorts are planned.*

8.2. Population Pharmacokinetic Analyses

Pantoprazole concentration data will be analyzed using a population PK analysis approach (nonlinear mixed-effects models). Prior pediatric PK data may be used to guide and assist the model building and covariate selection. A two-compartment model with IV infusion will be used to describe pantoprazole concentrations, with clearance (CL) and volume of distribution (Vd) of the central compartment being the key population PK parameters in the model. The potential influence of covariates, including age and body weight, on these parameters will be explored during the model building phase of the analysis. Other covariates, including gender and baseline values, may also be explored using graphical approaches.

The final population PK model will also be used to estimate the following PK Parameters: maximum plasma concentration (C_{max}), area under the plasma concentration time profile from time zero to the 24 hour time post dose (AUC_{24}), area under the plasma concentration time profile from time zero extrapolated to infinite time (AUC_{inf}) and terminal phase half life ($T_{1/2}$) of pantoprazole following single and multiple IV doses.

Box and whisker plots for individual subject parameters (AUC_{24}, AUC_{last} and C_{max}) be presented by cohort and dosing and overlaid with geometric means.

A Population Modeling Analysis Plan (PMAP-EQDD-B179a-sNDA-1153) describing the details of the model building, covariate assessment, model validation and PK parameter estimation will be provided separately.

Presentations for pantoprazole concentrations will include:

- A listing of all concentrations sorted by cohort (present in heading), subject id, day and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by cohort, day and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by dosing (single dose (Day 1) and multiple dose (Days 2 & 7 combined) on the same plot per scale, based on the summary of concentrations by cohort, dosing (single dose and multiple dose) and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by dosing (single dose (Day 1) and multiple dose (Days 2 & 7 combined) on the same plot per scale, based on the summary of concentrations by cohort, dosing (single dose and multiple dose) and time postdose).

- Individual concentration time plots by cohort and dosing (single dose and multiple dose) (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each cohort and dosing per scale).

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each subject (containing both dosing (single dose and multiple dose)) per scale].

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

8.3. Safety Analysis

A set of summary tables split by age cohort will be produced to evaluate any potential risk associated with the safety and toleration of administering pantoprazole.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by cohort.

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic and Clinical Examination Data

A break down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by cohort.

Data will be reported in accordance with the sponsor reporting standards.

8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards by cohort.

8.3.5. Laboratory Data

Laboratory data will be listed in accordance with the sponsor reporting standards.

8.3.6. Vital Signs Data

The baseline measurement is the last predose measurement.

For each planned timepoint, baseline values and change from baseline values within each cohort will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

8.3.7. Other Safety Data

Primary diagnosis, including method of diagnostic confirmation, will be summary tabulated by cohort. These data will be listed in accordance with the sponsor reporting standards.

8.3.8. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.3.9. Screening and Other Special Purpose Data

- CYP2C19 genotyping data will be listed in accordance with the sponsor reporting standards.

- Serum B-hCG for all females of childbearing potential will be obtained at Screening. These data will not be brought in-house, and therefore will not be listed.

9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

Not applicable.