Official Title: Long-term Extension of a Phase 2, Open-Label Dose-Finding Study to Evaluate the Safety, Efficacy, and Tolerability of Multiple Subcutaneous Doses of rAvPAL-PEG in Subjects with PKU

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Statistical Analysis Plan

PAL-003

April 27, 2016

1 APPROVALS (SIGNATURE AND DATE)

Title: Long-term Extension of a Phase 2, Open-Label, Dose-Finding Study to Evaluate the Safety, Efficacy, and Tolerability of Multiple Subcutaneous Doses of rAvPAL-PEG in Subjects with PKU

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BUN	blood urea nitrogen
CDF	cumulative distribution function
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	electrocardiogram
HAE	hypersensitivity adverse event
Hg	mercury
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
Nab	neutralizing antibody
NCI	National Cancer Institute
NIAID/FAAN	National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
PAL	phenylalanine
PEG	polyethylene glycol
Phe	phenylalanine
PK	pharmacokinetics
PKU	phenylketonuria
PT	preferred term
rAvPAL-PEG	recombinant *Anabaena variabilis* phenylalanine ammonia lyase-PEG
SAP	Statistical Analysis Plan
SOC	system organ class
SMQ	Standardized MedDRA Queries
TEAE	treatment-emergent adverse event
Tab	total antibody
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

3 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis methods and data presentations to be included in the Clinical Study Report (CSR) for PAL-003, Long-term Extension of a Phase 2, Open-Label, Dose-Finding Study to Evaluate the Safety, Efficacy, and Tolerability of Multiple Subcutaneous Doses of rAvPAL-PEG in Subjects with PKU**.** This SAP includes the data summary methodologies for analysis of safety, efficacy, and pharmacokinetics (PK) data. Results obtained from the analyses described in this document will provide the basis of the CSR for this study. Analysis methods specified in this document take precedence over those described in the protocol should there be any differences.

3.1 Objectives of Study

The primary objective of the study is:

- To evaluate the effect of long-term administration of multiple doses of subcutaneous (SC) injections of pegvaliase (also described as rAvPAL-PEG or pegvaliase) on blood Phe concentrations in subjects with phenylketonuria (PKU).

The secondary objectives of the study are:

- To evaluate the safety and tolerability of long-term administration of SC injections of pegvaliase in subjects with PKU.
- To evaluate the immune response to long-term administration of SC injections of pegvaliase in subjects with PKU.

The exploratory objectives of the study are:

- To evaluate the long-term relationship of diet and change in blood Phe concentration following administration with pegvaliase in subjects with PKU.

The Substudy objectives are as follows:

- To evaluate steady-state PK of pegvaliase in subjects who have achieved and maintained target blood Phe concentration and for whom no further dose modifications are planned.

3.2 Study Design

This is a long-term extension of pegvaliase Phase 2 studies in subjects with PKU. The doses are planned to be in the same range as those tested in phase 2 (starting at 0.001 through 5.0 mg/kg/week or 2.5 mg through 375 mg/week), provided no dose-limiting toxicity is observed in a previous pegvaliase study.

Only subjects who completed a previous pegvaliase study will be enrolled into this study. Subjects enrolling into PAL-003 with no interruption in dosing from a previous pegvaliase

study may either continue their previous dosing regimen or begin this study at a higher dose level. Subjects who have had dosing interruptions between the previous pegvaliase study and PAL-003 must have their starting dose determined per the Sponsor's Medical Officer.

A PK substudy has been added to evaluate the steady-state PK of pegvaliase in up to 6 subjects who have achieved and maintained target blood Phe for at least 2 consecutive measurements and for whom no further dose modifications are planned. Subjects enrolled into the substudy will have additional pre-dose PK sampling performed.

3.3 Study Population

Only subjects who completed a previous pegvaliase study will be enrolled into this study.

3.4 Study Dosage and Administration

Pegvaliase will be provided in vials or prefilled syringes; subjects will be supplied with vials and syringes or prefilled syringes for administration in the clinic and self administration:

- Pegvaliase will be provided in 3 mL (milliliter) vials, each containing 1.5 ± 0.2 mL to deliver 15 mg of rAvPAL-PE per 1.0 mL (15 mg/mL protein concentration). Each vial is filled with 1.5 ± 0.2 mL to allow the withdrawal and delivery of up to 1.0 mL of the drug product.
- Or
- Pegvaliase will be provided in 3-mL vials, each containing 1.8 ±0.3 mL to deliver 20 mg of rAvPAL-PE per 1.3 mL (15 mg/mL protein concentration). Each vial is filled with 1.8 ± 0.3 mL to allow withdrawal and delivery of up to 1.3 mL.
- Or
- Pegvaliase will be provided in prefilled syringes in three sizes that deliver up to 1 mL. Syringe sizes are 2.5 mg (5 mg/mL protein concentration), 10 mg (20 mg/mL protein concentration), and 20 mg (20 mg/mL protein concentration).

Pegvaliase may be administered SC from 0.001 to a maximum weekly dose of 5.0 mg/kg or 375 mg/week.

3.5 Sample Size Determination

Subject who participated in a previous pegvaliase study may be enrolled into this study. No formal sample size calculation was conducted.

3.6 Blinding and Randomization Methods

This is an open-label study.

3.7 Interim Analysis

There is no formal interim analysis planned.

4 GENERAL ANALYSIS CONSIDERATION

Descriptive summaries of continuous variables will include the number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive summaries of categorical variables will include n and percent. Data from parent studies (PAL-002, PAL-004, 165-205) will be integrated together with data in PAL-003 for long term safety and efficacy analysis. The baseline value of an assessment is defined as the last available measurement prior to first administration of study drug from parent studies (PAL-002, PAL-004, 165-205), unless otherwise specified.

4.1 Analysis Populations

4.1.1 Efficacy

The efficacy population will consist of all subjects who receive at least one dose of study drug and have post-treatment blood Phe concentration measurements in any of the phase 2 studies (PAL-002, PAL-004, 165-205, PAL-003).

4.1.2 Safety

The safety population will consist of all subjects who receive at least one dose of study drug throughout the study duration of any of the phase 2 studies (PAL-002, PAL-004, 165-205, PAL-003).

4.1.3 PK

The PK population will consist of all subjects who receive any amount of study drug and have post-treatment plasma pegvaliase concentration measurements in any of the phase 2 studies (PAL-002, PAL-004, 165-205, PAL-003).

4.2 Treatment Group Presentation

Unless specified otherwise, analyses will be presented by parent Phase 2 studies (PAL-002, PAL-004, 165-205) combined, PAL-003, and all Phase 2 studies (PAL-002, PAL-004, 165-205, PAL-003) combined.

The following treatment groups may also be considered in the summary tables for corresponding assessments:

For [redacted], analyses will be presented by current [redacted] at each assessment visit in both parent studies (PAL-002, PAL-004, 165-205) and PAL-003. The weekly dose is defined as the [redacted] prior to each assessment.

[redacted]), analyses will be presented by daily [redacted] on or prior to AE onset date in both parent studies (PAL-002, PAL-004, 165-205) and PAL-003.

4.3 Pooling of Data from Sites with Small Enrollment

Due to small sample sizes at each site, separate analyses by site or pooled site will not be performed.

4.4 Study Day Derivation

Unless otherwise specified, the first study drug administration date for pegvaliase from parent studies (PAL-002, PAL-004, 165-205) is considered study day 1 and is used as the reference date for the derivation of study day in data displays. Study day is computed by subtracting study day 1 from a visit date plus 1 if the visit date occurs on or after the initial study drug start date. Otherwise, the study day will be the visit date minus the study day 1. There is no Study Day 0.

4.5 Visit Window for Analysis

An assessment for a subject will be classified according to the study day of the assessment where it falls within a visit window. The windows are designated for each scheduled visit with a target day. If there are two or more assessments within a designated window, the assessment that is closest to the target day will be used for analyses. If the two closest assessments to the target day are equidistant from the target day, then the average of the two assessments will be used for analyses. If the measurement is a laboratory categorical variable, however, then the worse of the 2 equidistant measurements will be used.

Table 1 lists the visits assigned for the analyses of all assessments and the corresponding range of treatment days (window) during which a visit may have occurred by analysis parameter.

Table 1: Visit Time Windows for the Treatment Period

Scheduled Time Point	Target Day	Visit Window
Baseline		Last measurement prior to pegvaliase administration from parent studies (PAL-002, PAL-004, 165-205)
Week 4	Day 22	Day 8 to Day 35
Week 8	Day 50	Day 36 to Day 63
Week 12	Day 78	Day 64 to Day 91
Week 16	Day 106	Day 92 to Day 119
Week 20	Day 134	Day 120 to Day 147
Week 24	Day 162	Day 148 to Day 175
…	…	…
Week 388	Day 2710	Day 2696 to Day 2723
Week 392	Day 2738	Day 2724 to Day 2751
Week 396	Day 2766	Day 2752 to Day 2779
Week 400	Day 2794	Day 2780 to Day 2807
Week 404	Day 2822	Day 2808 to Day 2835
Week 408	Day 2850	Day 2836 to Day 2863
Week 412	Day 2878	Day 2864 to Day 2891
Week 416	Day 2906	Day 2892 to Day 2919
Every 4 weeks		

Blood Phe concentration will also be summarized based on the data collected in PAL-003 and visits in Table 2. For this analysis, the first study drug administration date for pegvaliase from PAL-003 is considered as study day 1 and is used as the reference date for the derivation of study day in data displays.

Table 2: Visit Time Windows for the Treatment Period in PAL-003

Scheduled Time Point in PAL-003	Target Day in PAL-003	Visit Window in PAL-003
PAL-003 Baseline		Last measurement prior to pegvaliase administration from PAL-003
Week 4	Day 22	Day 8 to Day 35
Week 8	Day 50	Day 36 to Day 63
Week 12	Day 78	Day 64 to Day 91
Week 16	Day 106	Day 92 to Day 119
Week 20	Day 134	Day 120 to Day 147
Week 24	Day 162	Day 148 to Day 175
Every 4 weeks		

4.6 Handling of Dropouts and Missing Data

Subjects who discontinued prematurely will not be replaced. To investigate the primary objective, last observation carry forward (LOCF) imputation approach will be used as sensitivity analyses.

5 SUBJECT DISPOSITION

The number of subjects enrolled, the number of subjects who received study drug, the number of subjects who completed study, and the number of subjects in each analysis population (efficacy, safety, PK) will be summarized.

6 END OF STUDY

For subjects who prematurely discontinued the study, the primary reason for discontinuation will be summarized. A subject listing of completion and early termination will be provided.

7 PROTOCOL EXEMPTIONS AND DEVIATIONS

A major protocol deviation is defined as a departure from the approved study protocol that may impact the rights, safety, or welfare of the subjects or the integrity of the data, which will be summarized by deviation category.

A minor or administrative protocol deviation is defined as a departure from the approved study protocol that has minimum or no impact on the rights, safety, or welfare of the subjects or the integrity of the data. Minor protocol deviations will also be summarized by deviation category. For details regarding the classification of the deviations, please refer to the Study Specific Guideline for Managing Protocol Deviations.

Major and minor protocol deviations occurring during the parent studies (PAL-002, PAL-004, 165-205) and PAL-003 study will be summarized.

Subjects with protocol deviations during the parent studies (PAL-002, PAL-004, 165-205) and PAL-003 study will be provided in a listing. Subjects with inclusion or exclusion deviations during the parent studies (PAL-002, PAL-004, 165-205) and PAL-003 study will also be provided in a separate listing.

8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject characteristics and demographic information before the first dose of parent studies (PAL-002, PAL-004, 165-205) and the first dose of PAL-003 will be summarized. The demographics including age, age group (16 to <18 years of age, 18 to <66 years of age, ≥66 years of age), gender, race and ethnicity will be summarized using descriptive statistics.

Subject characteristics will include height, weight, blood Phe concentration, intake of protein and dietary Phe, body mass index (BMI), BMI group (<25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2), and immunogenicity status (positive, negative, or titer value).

9 MEDICAL HISTORY

Subject's past medical history and surgeries prior to parent studies (PAL-002, PAL-004, 165-205) and prior to PAL-003 were collected as general medical history. General medical history will be summarized by system organ class (SOC). A subject listing of each subject's medical history collected at the Screening Visit will also be provided.

10 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

Prior and concomitant medications taken prior to, on or after the first dose of pegvaliase will be summarized for all enrolled subjects. For analysis purposes, the following definitions will be used to determine prior and concomitant medications:

- Prior medications: any medications taken within 30 days prior to the screening and prior to the initial pegvaliase administration date
- Concomitant medications: any medications initially taken on or after the initial pegvaliase administration date
- Prior and concomitant medications: any medications taken both prior to the initial pegvaliase administration date and on or after the initial pegvaliase administration date will be reported both as prior and concomitant medications. Therefore, any medications taken prior to the pegvaliase first dose date where the stop date is reported as "continuing" will be considered both as prior and concomitant medications.

In the event the start date of a medication is completed missing, the start date will be imputed as the first dose date if the stop date is in the same year or later than the first dose date.

In the event the start date of a medication is partial, the following imputation rules will be applied:

- If only day is missing, then the start date will be imputed as the first day of the month, if the year and month is after the first dose year and month. If only day is missing, then the start date will be imputed as the last day of the month, if the year and month is prior to the first dose year and month. If month is the same as the month of first dose of pegvaliase then the start date will be imputed as the first dose date of pegvaliase.
- If only year is non-missing, then the start date will be imputed as the first day of the year if the year is after the year of first dose. If year is the same as the year of first dose of pegvaliase then the start date will be imputed as the first dose date of pegvaliase. If year is before the year of first dose of study drug then the start date will be imputed to the first day of July of the year.

In the event the stop date of a medication is partial, the following imputation rules will be applied:

- If only day is missing, then the end date will be imputed as the last day of the month.
- If only year is non-missing, then the end date will be imputed as the last day of the year.

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) dictionary (Sept. 2014). Prior and concomitant medication use will be summarized by Anatomical Therapeutic Chemical (ATC) medication class (Level 4) and preferred name (i.e., generic medication name) using descriptive statistics separately. A subject reporting the same medication more than once will be counted once when calculating the number and percentage of subjects who received that medication. A subject listing of prior and concomitant medications all subjects received will be provided.

11 EXTENT OF EXPOSURE TO STUDY DRUG

Exposure will be summarized using descriptive statistics such as n, mean, standard deviation, median, minimum, and maximum for the following variables:

- Average of daily doses (mg/day) received
- Average of dosing frequency (day) per week
- Total amount of study drug (mg) received
- Total duration of treatment in number of months, calculated by last dosing day minus first dosing day add 1 then divided by 30.
- Number of patients who had duration in different categories: less than 12 months, between 12 months and 24 months, between 24 months and 36 months, between 36 months and 48 months, longer than 48 months.
- Number of patients which had average daily dose in different categories: <20 mg/day, ≥20 mg/day to <40 mg/day, ≥40 mg/day to <60 mg/day, ≥60 mg/day.

When calculating the total exposure duration on study drug, any dose interruption longer than 28 days will be excluded from the calculation.

12 EFFICACY EVALUATIONS

Efficacy measurement (blood Phe concentration) from start of parent studies (PAL-002, PAL-004, 165-205) to 14 days after last dose of pegvaliase will be summarized using descriptive statistics for the CSR for PAL-003. Baseline blood Phe concentration is defined as the last available measurement prior to first administration of study drug from parent studies (PAL-002, PAL-004, 165-205). All efficacy data collected 14 days after the last dose in the study will not be included in the analysis.

As the measure of efficacy, observed blood Phe concentration at scheduled time point, change from baseline and percentage change from baseline in blood Phe concentration at scheduled time point, daily dose at which subject first had blood Phe values ≤600 µmol/L, daily dose at which subject first had blood Phe values ≤360 µmol/L, daily dose at which subject first had at least 20% blood Phe reduction from baseline using the average of 2 consecutive blood Phe assessments, time to when subject first had blood Phe values ≤600 µmol/L, time to when subject first had blood Phe values ≤360 µmol/L, and time to when subject first had two consecutive Phe values with at least 20% blood Phe reduction will be summarized using descriptive statistics for the efficacy population. Percent of subjects with blood Phe concentration ≤ 360 µmol/L and percent of subjects with blood Phe concentration ≤ 600 µmol/L over time will also be summarized and plotted.

To investigate the primary objective, last observation carry forward (LOCF) imputation approach will be used as sensitivity analyses.

The distribution of responses in blood Phe concentration will be evaluated using the cumulative distribution function (CDF) (McLeod 2011). The percentage of subjects responding at the beginning of PAL-003, the end of first year of PAL-003 and the end of PAL-003 will be plotted against the continuous range of responses. Thus, the CDF will show a continuous plot of the proportion of subjects at each time point along the continuum of Phe levels, an approach that offers a visual comparison of the separation among the three timepoints across all levels of change so that a variety of responder definitions can be considered simultaneously. In a rare disease setting, such as with PKU, this approach is proposed over applying a categorical responder definition due to the limitations in sample size.

A subject listing of blood Phe concentration will be provided. A summary table will be provided on the percent of subjects in each quartile of blood Phe concentration at each scheduled time point. Plots for mean blood Phe concentration, change from baseline and

percentage change from baseline in blood Phe concentration will also be generated for both observed values and values after LOCF imputation.

For the diet diary, standard descriptive statistics will be presented for the observed, change from baseline and percent change from baseline values of the three-day average of dietary protein, tyrosine and dietary phenylalanine at each visit. The three-day average diet diary results will also be listed. To explore the change in blood Phe concentration with respect to changes in subject diet, plots will be generated for mean blood Phe concentration with mean dietary protein and mean dietary Phe, mean change from baseline blood Phe concentration with mean change from baseline of dietary protein and dietary Phe.

13 PHARMACOKINETIC EVALUATIONS

A subject listing of plasma pegvaliase concentration and a listing of PK parameters will be provided. Scatter plots of dose-normalized trough plasma pegvaliase concentration at the last visit of PAL-003 vs. antibody measurements will also be provided. The PK analysis plan will be detailed in a separate document.

14 SAFETY EVALUATIONS

Safety will be assessed by examining the incidence, exposure adjusted event rate, severity grade, and relationship to study drug of all treatment-emergent adverse events (TEAEs) reported during the study period. In addition, changes in clinical laboratory results and vital signs from baseline values from parent studies (PAL-002, PAL-004, 165-205) will be assessed. All safety data collected 30 days after the last dose will not be included in the analysis.

AEs will be coded in accordance with the MedDRA version 18.0. Only treatment-emergent adverse events (TEAEs) occurring and reported during the study period will be included in the adverse event summaries. A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of the study drug administration till 30 days after last dose of the phase 2 studies (PAL-002, PAL-004, 165-205, PAL-003). If the onset date of an AE is missing, the AE will be considered treatment-emergent.

If the onset date or end date of an adverse event is partial, the same imputation rules described in section 10 will be applied:

The incidence and frequency of all treatment-emergent AEs will be summarized by SOC, preferred term (PT), and severity grade. For those AEs that occurred more than once during the study, the maximum severity will be used to summarize the AEs by severity. The SOCs and PTs will be displayed by descending order based on total population.

The treatment-emergent AEs will be summarized in the following categories:

- All AEs by SOC and preferred term
- All AEs by SOC, preferred term, and severity
- AEs assessed by the investigator as related to study drug by SOC and preferred term
- AEs assessed by the investigator as related by SOC, preferred term and severity
- Serious AEs (SAEs) by SOC and preferred term
- SAEs assessed by the investigator as possibly or probably related to study drug by SOC and preferred term
- All AEs by preferred term in descending frequency order
- Hypersensitivity AE by SOC and PT
- Hypersensitivity AE by SOC, PT and severity
- Neuropsychiatric AE by SOC, PT and severity

AE assessed by investigators as related to PFS/Device malfunction

- AEs leading to dose interruption or reduction by SOC and preferred term
- AEs leading to withdrawal from study by SOC and preferred term
- AEs leading to study drug discontinuation by SOC and preferred term
- Pregnancy
- Death

In addition to the standard summary tables and listings, the following information will also be summarized for AEs of special interest, and sponsor defined AEs of significance:

- Time to event onset from most recent dose for Anaphylaxis per NIAID/FAAN criteria and Anaphylaxis per NIAID/FAAN criteria meeting Brown's severe criteria
- Time to first event onset per subject from first dose
- Duration of the events
- Patient characteristics for subjects with special types of hypersensitivity AEs except for injection site reaction and arthralgia
- Actions related to study drug
- Common treatment
- Incidence rate over time

The AEs of special interest include:

- Anaphylaxis per NIAID/FAAN criteria
- Anaphylaxis per NIAID/FAAN criteria meeting Brown's severe criteria

The sponsor defined AEs of significance include:

- Hypersensitivity AEs
- Injection site reaction
- Generalized skin reaction with ≥ 14 day duration
- Injection site skin reaction with ≥ 14 day duration
- Arthralgia

The search strategy for AEs of special interest and sponsor defined AEs of significance is in Appendix 1.

In addition to standard AE listings, by subject listings of injection site reaction AEs, AEs of special interest, sponsor defined AEs of significance, and psychiatric AEs under each

identification strategies will be provided. Study drug dose level at onset date of each of the AE will be presented on the listings. AEs will be sorted by onset date, preferred term, and dose of study drug at event onset date. Number of Hypersensitivity AE will be plotted over time (1-6 month, 6-12 month, and once each year after).

Death information will also be displayed in a listing.

14.1 Immunogenicity

Immunogenicity testing will be performed using validated immunogenicity assays. Blood samples for routine immunogenicity testing will be collected prior to dosing as indicated in the protocol. Routine immunogenicity testing will include assays for anti-rAvPAL immunoglobulin G (IgG), anti-rAvPAL IgM, anti-PEG IgM, anti-PEG IgG, and neutralizing antibodies (NAb). In the event of a Hypersensitivity Reaction visit, sampling and testing will be performed for anti-rAvPAL-PEG IgE and anti-rAvPAL IgE as well as other potentially-related clinical laboratory tests, including CRP, C3/C4, and tryptase.

For immunogenicity analysis, an incidence table will be provided for PAL IgG, PAL IgM, PEG IgG, PEG IgM, and NAb. Titer summary statistics will also be provided for PAL IgG and PEG IgG, including mean, median, standard deviation, and minimum/maximum titer values at each study visit. The mean titers for PAL IgG and PEG IgG and percent positivity for PAL IgM, PEG IgM and NAb will be plotted over time. A listing of anti-rAvPAL-PEG IgE and anti-rAvPAL IgE test results will be provided by subject.

Anti-drug antibody impact on long-term safety will be evaluated. Plots and tables will be generated to explore the potential impact of anti-drug antibodies on hypersensitivity adverse event (HAE) frequency and severity. A listing will be provided of all hypersensitivity reaction visits with the most proximal antibody test result listed for each analyte, and when available, CRP, complement C3 and C4, and tryptase at the time of the event.

Anti-drug antibody impact on long-term efficacy will be evaluated. Plots and tables will be generated to explore the potential impact of anti-drug antibodies on blood Phe levels

14.2 Clinical Laboratory Tests

Standard descriptive statistics will be presented for clinical laboratory tests, including hematology, chemistry and urinalysis, at each scheduled visit and for change in laboratory values from baseline from parent studies (PAL-002, PAL-004, 165-205) to each scheduled visit. The proportion of subjects who experienced at least one laboratory test result with CTC grade as 3 or above and who experienced at least one laboratory test results outside the normal ranges will be presented for each measurement. Shift tables will be created for

selected laboratory parameters in clinical chemistry, hematology, and urinalysis (white blood cells [WBCs], neutrophils, eosinophils, basophils, erythrocyte sedimentation rate [ESR], serum creatinine, serum blood urea nitrogen [BUN], C3, C4, C-reactive protein [CRP], urine microalbumin, urine albumin/creatinine ratio, aspartate transaminase [AST], alanine transaminase [ALT], and total bilirubin, creatinine phosphokinase [CPK], hemoglobin decrease) to summarize the change in laboratory value from baseline to worst post-baseline value based on normal range (low, normal, and high) or National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading, where available. Results of complement 3, complement 4, C-reactive protein, micro albumin, urine albumin/creatinine ratio, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, serum creatinine, creatinine, and blood urea nitrogen (BUN) will be plotted overtime. A subject listing of laboratory test results for hematology, chemistry, urinalysis, and other laboratory tests will be provided separately. Values with CTC grade as 3 or above will be flagged in the listings. A listing of laboratory test results for subjects with ALT or AST ≥ 3x the upper limit of normal (ULN) and total bilirubin ≥ 2xULN will also be provided.

14.3 Vital Signs

Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C).

Standard descriptive statistics will be presented for the observed and change from baseline values from parents studies (PAL-002, PAL-004, 165-205) at each visit. A subject listing will also be provided.

14.4 12-lead Electrocardiogram

The frequency of abnormalities and clinically significant abnormalities in 12-lead electrocardiogram will be summarized at each visit. A subject listing of ECG findings will be provided.

14.5 Physical Examination

A subject listing for clinically significant findings at each visit will be provided.

14.6 Chest X-Ray

A subject listing for chest X-ray at each visit will be provided.

14.7 Pregnancy Test

A subject listing for pregnancy test at each visit will be provided.

14.8 Injection Site Inspection

A subject listing for injection site inspection at each visit will be provided.

15 REFERENCES

McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11:163-9.

16 SUMMARY OF CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
Amendment 1.0	April 27, 2016	12	To be consistent with phase 3 studies, the period of efficacy analysis data inclusion has been changed to from start of parent studies (PAL-002, PAL-004, 165-205) to 14 days after last dose of pegvaliase.
Amendment 1.0	April 27, 2016	12	To be consistent with phase 3 studies, the definitions of efficacy events have been changed to blood Phe values ≤600, blood Phe values ≤360, and at least 20% blood Phe reduction from baseline using the average of 2 consecutive blood Phe assessments.
Amendment 1.0	April 27, 2016	14	To be consistent with phase 3 study 165-302, serum sickness-like reaction and angioedema have been removed from AEs of special interest, and sponsor defined AEs of significance.
Amendment 1.0	April 27, 2016	14	To be consistent with phase 3 studies and due to the availability of NCI CTCAE grading, the parameters that would be included in the laboratory shift tables have been specified.
Amendment 1.0	April 27, 2016	15	The reference for cumulative distribution function has been added.
Amendment 1.0	April 27, 2016	17 (Appendices)	The searching strategies for AEs of special interest, and sponsor defined AEs of significance have been updated to be consistent with phase 3 study 165-302.

17 APPENDICES

Appendix 1: Searching Strategies for Adverse Event of Special Interest, and Sponsor Defined AEs of Significance

MedDRA version 18.0