105 Digital Drive

Novato, CA 94949

Statistical Analysis Plan

BMN165-303

February 29, 2016

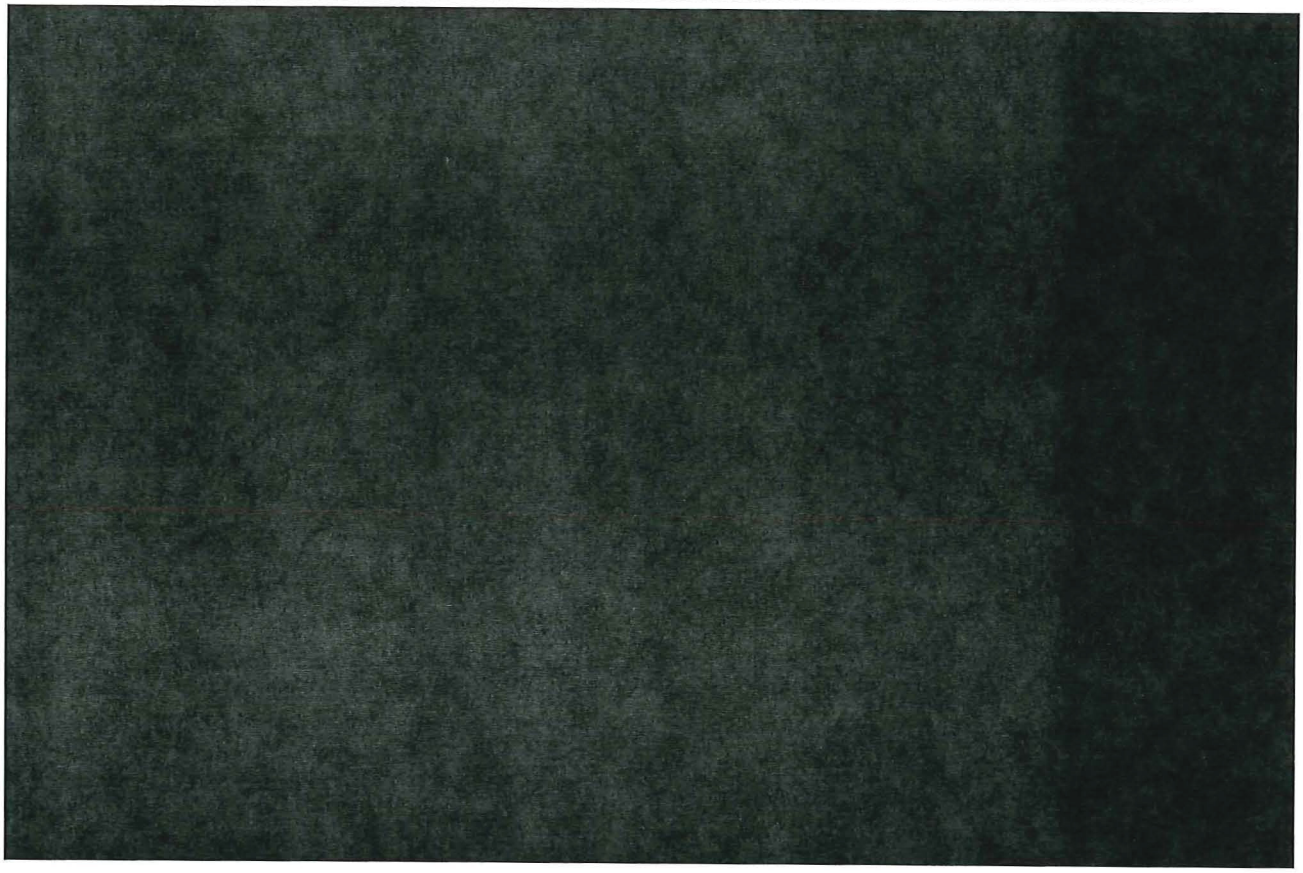
1 APPROVALS (SIGNATURE AND DATE)

Title: A Phase 3 Substudy to Evaluate Executive Function in Adults with Phenylketonuria Who Are Participating in the Phase 3 Study, 165-302

Protocol: BMN 165-303, Original

Date: February 29, 2016

Approvals



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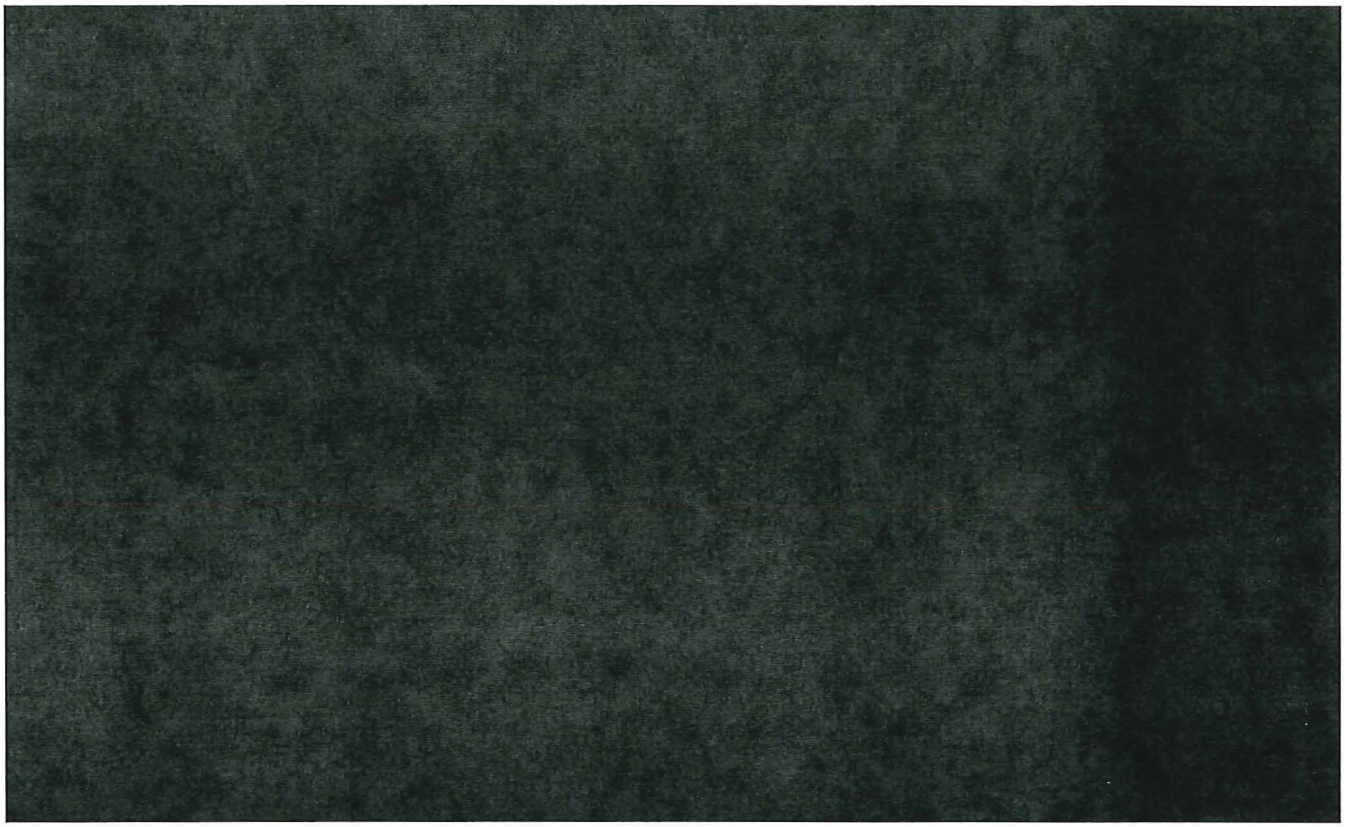

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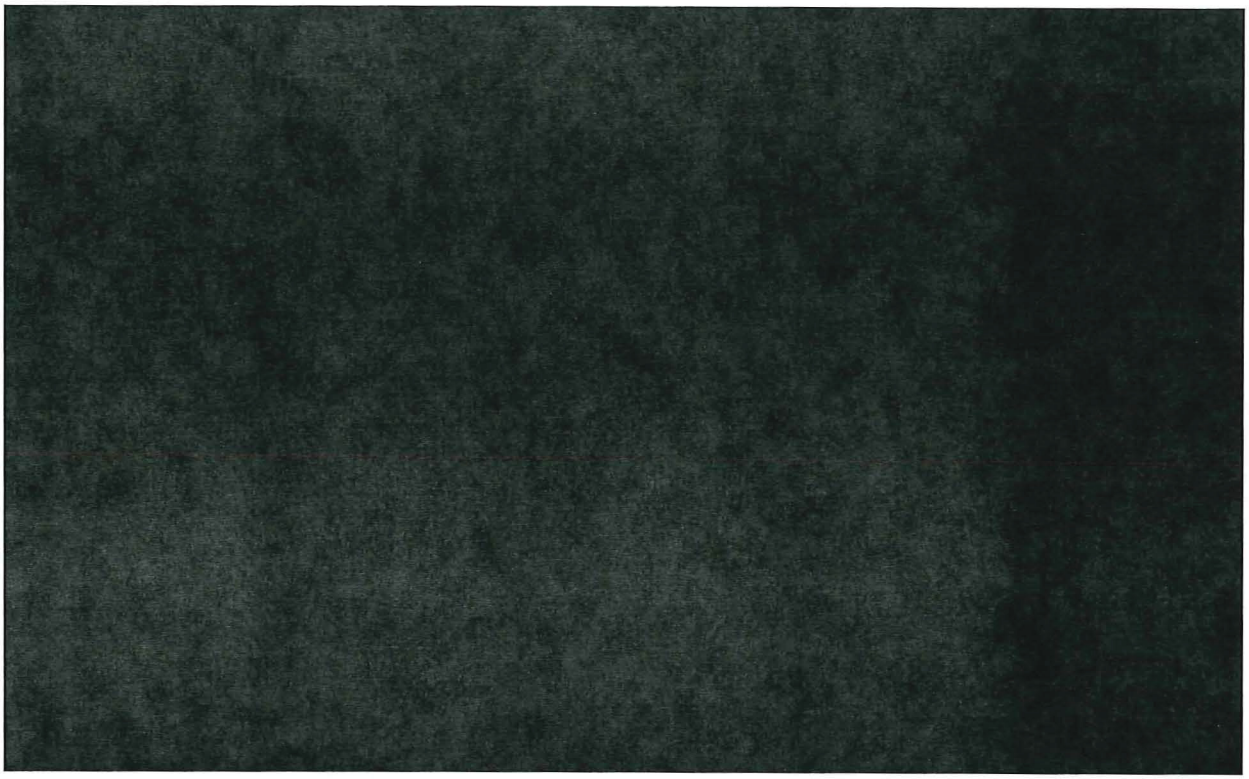

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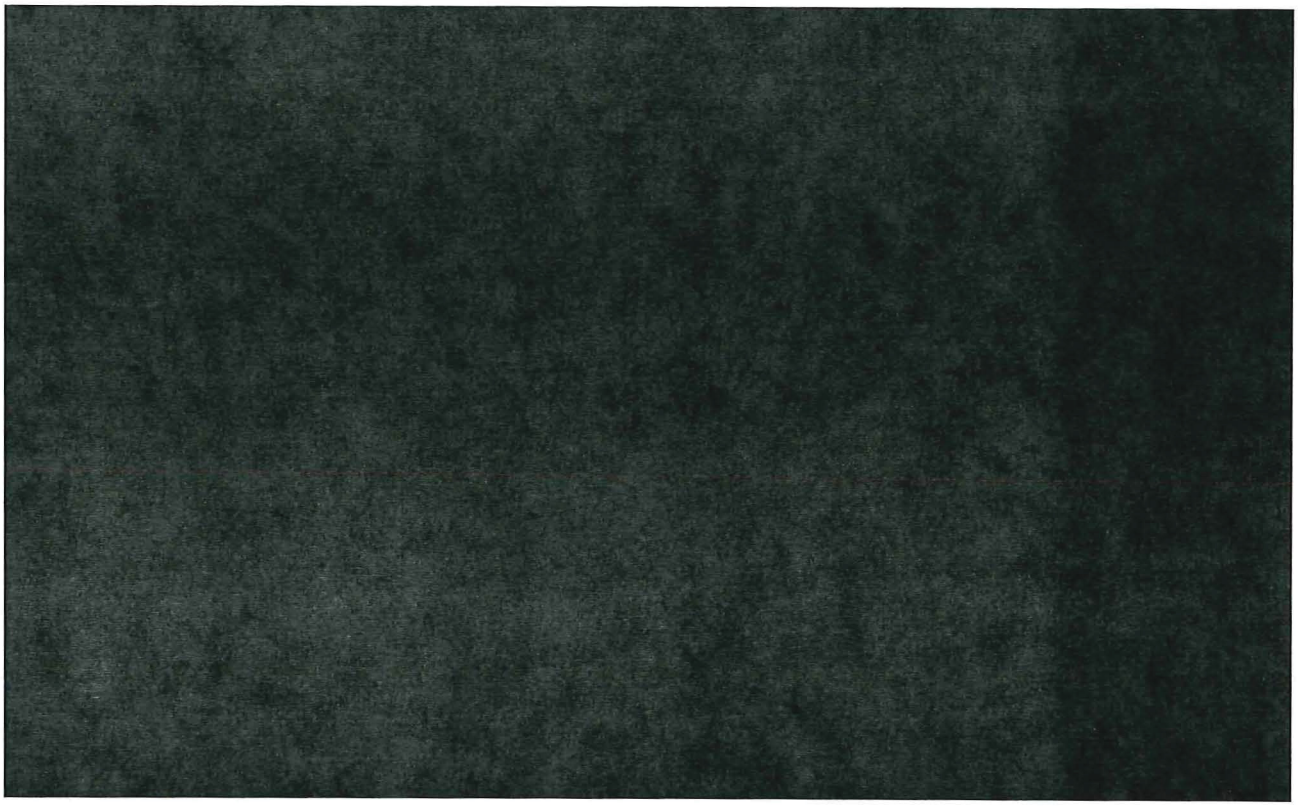

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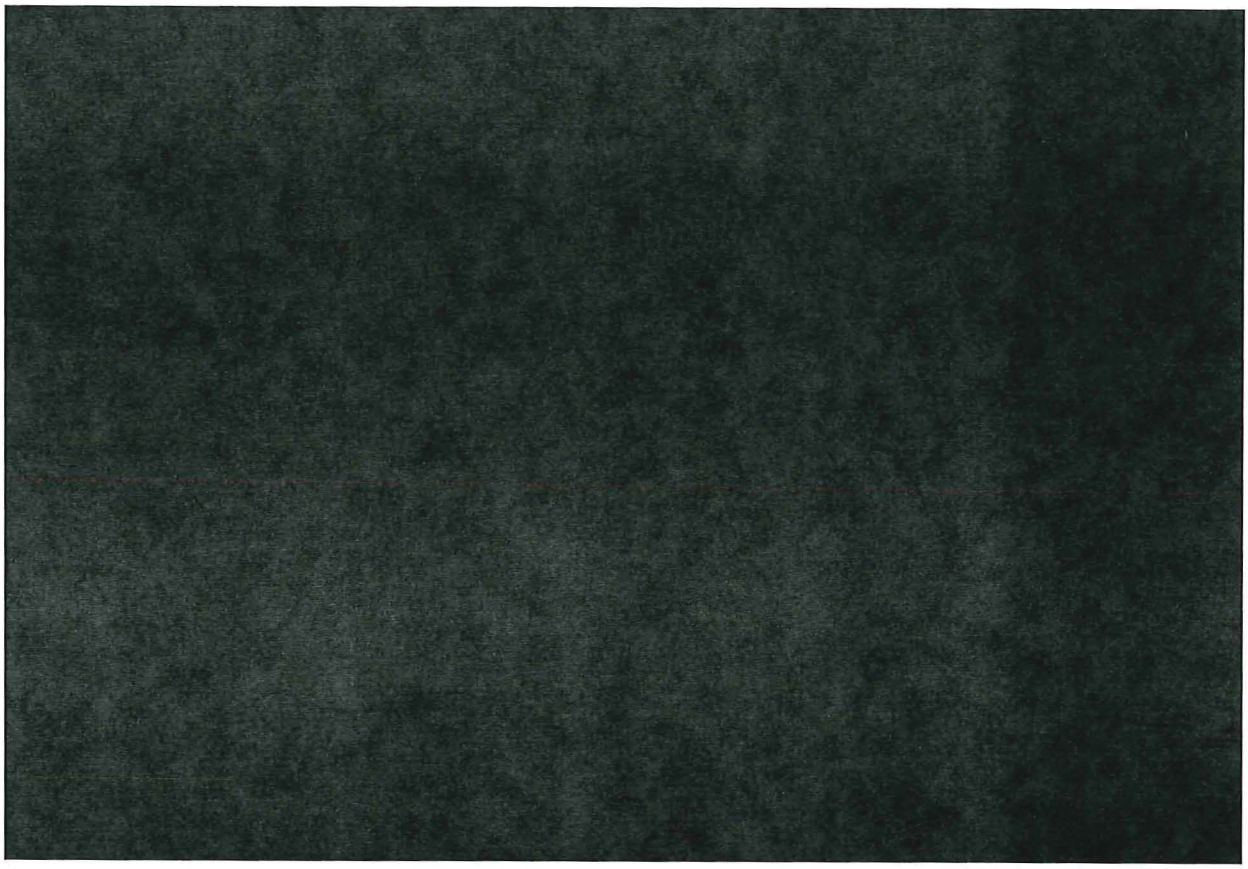

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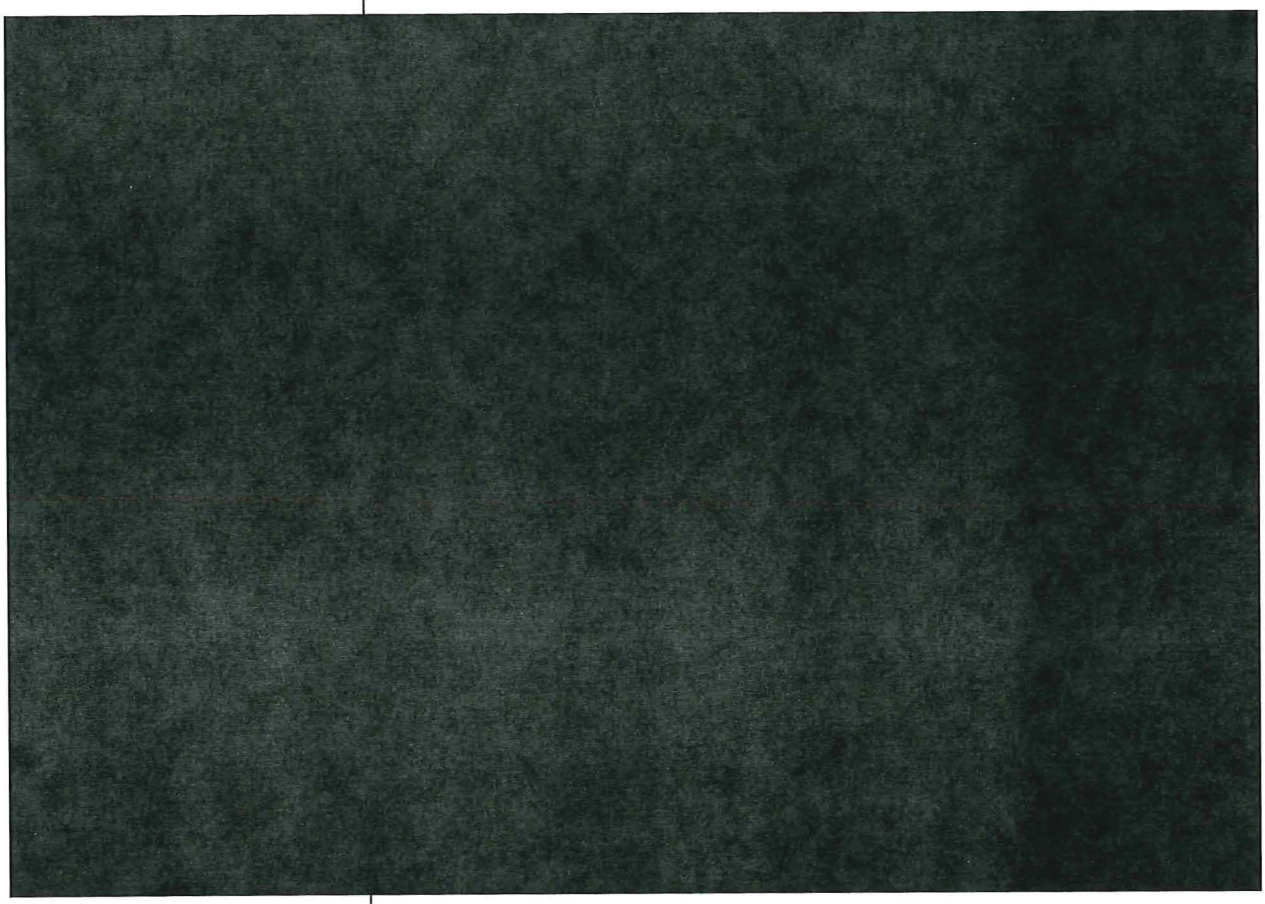

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CRF	Case Report Form
IA	Inattention
ITT	Intent-To-Treat
Phe	Phenylalanine
PKU	Phenylketonuria
POMS	Profile of Mood States
RVP	Rapid Visual Processing (CANTAB)
SAP	Statistical Analysis Plan
SD	Standard deviation
SST	Stop Signal Task (CANTAB)
SWM	Spatial Working Memory (CANTAB)

3 INTRODUCTION

Study BMN 165-303 is a Phase 3 substudy to BMN 165-302 to evaluate executive function in adults with phenylketonuria (PKU) who are participating in the pegvaliase Phase 3 Study, 165-302. The purpose of this Statistical Analysis Plan (SAP) is to provide a comprehensive description of methods of the data analyses outlined in the protocol (dated April 08, 2015).

If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

3.1 Objectives of Study

The primary objective of this study is to evaluate executive function in adult subjects with PKU who are participating in Study 165-302, as measured by selected Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks.

[redacted]

3.2 Study Design

This is a Phase 3 substudy which planned to enroll approximately 100 subjects, aged ≥ 18 to ≤ 70 years old, with PKU who are concurrently treated with pegvaliase or placebo in Part 2, followed by treatment with pegvaliase in Part 4 of Study 165-302. [redacted] No study drug is administered as part of this study. For this study, subjects will be asked to perform computer-based assessments (Cambridge Neuropsychological Test Automated Battery, or CANTAB) that assess executive function (specifically: attention, working memory, cognitive flexibility) using a selected set of three tasks from the CANTAB tool (Rapid Visual Processing [RVP], Spatial Working Memory [SWM] and Stop Signal Task [SST]) and to answer questions about their current state of self-perception (subject global assessment of attention (very poor, poor, fair, good, excellent), energy level (very low, low, moderate, high, very high), tiredness (extreme tiredness, a lot of tiredness, some tiredness, a little tiredness, no tiredness at all), confusion (extreme confusion, a lot of confusion, some confusion, a little confusion, no confusion at all), sadness (extreme sadness, a lot of sadness, some sadness, a little sadness, no sadness at all), anger (extreme anger, a lot anger, some anger, a little anger, no anger at all), and tension (extreme tension, a lot of tension, some tension, a little tension, no tension at all)).

After providing informed consent, subjects undergo screening evaluations to determine study eligibility. Study drug dosing should continue without interruption as part of subject

participation in Study 165-302. Screening assessments must be within 14 days before Day 1 of this study.

[redacted]. Subjects who discontinue from study drug in Part 2 or Part 4 of 165-302 will be asked to continue their participation in this study.

Assessments for this study must be performed at the same scheduled clinic visit of Part 2 and Part 4 of Study 165-302.

3.3 Study Population

Individuals eligible to participate in this study must meet all of the following criteria:

- Are currently participating in Part 1 of Study 165-302 and meet the criteria for participation in Part 2 of 165-302
- Are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to any research-related procedures.
- Have the ability to complete the CANTAB and subject global assessments.
- Are willing and able to comply with all study procedures.

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

- Any condition that, in the view of the investigator, places the subject at high risk of poor compliance or terminating early from the study

3.4 Sample Size Determination

[redacted]

3.5 Blinding and Randomization Methods

3.5.1 Blinding Method

No blinding was performed for this study. However, in Part 2 of Study 165-302, treatment assignment (pegvaliase or matching placebo) and blood Phe are blinded to subjects,

investigators, site personnel, and BioMarin. In addition, subjects, investigators, site personnel, and BioMarin remain blinded to treatment assignment until all randomized subjects in Part 2 complete or discontinue Part 2 of Study 165-302.

3.5.2 Randomization Method

Randomization does not occur in this study; however, subjects enrolling in this study are treated based on the randomization criteria in Part 2 of Study 165-302. In Study 165-302, subjects were randomized (2:1) to receive 20 mg/day pegvaliase (20mg/day Active Group) or a matching placebo (20 mg/day Placebo Group). Subjects were also randomized (2:1) to receive 40 mg/day pegvaliase (40mg/day Active Group) or a matching placebo (40mg/day Placebo Group).

3.6 Interim Analysis

Not applicable.

4 GENERAL ANALYSIS CONSIDERATION

Descriptive summaries of continuous variables will include the mean, standard deviation (SD), median, and range for the mean. Descriptive summaries of categorical variables will include n and percent.

The baseline value of an assessment is defined as the available measurement collected on Day 1 of Part 2 of Study 165-302, unless otherwise specified.

Data from Study 165-302 will be integrated in combination with data in this study when necessary for efficacy analysis.

4.1 Analysis Populations

The intent-to-treat (ITT) population will consist of all subjects who are randomized to Part 2 of Study 165-302 and are enrolled in Study 165-303.

4.2 Treatment Group Presentation

When analyzing data collected while subjects are in Part 2 of Study 165-302, the following treatment groups will be used for presentation:

- Pooled active group
- Pooled placebo group

When analyzing data collected while subjects are in Part 4 of Study 165-302, all subjects will be combined and an overall summary will be provided.

4.3 Pooling of Data from Sites with Small Enrollment

Due to the small sample size, the analyses will not be adjusted by site or pooled sites.

4.4 Study Day Derivation

Study days in Part 2 of Study 165-302 will be obtained by subtracting the initial study drug start date (Day 1, Week 1 of Part 2 during Study 165-302) from a visit date plus 1 if the visit date occurs after the corresponding initial study drug start date. Otherwise, the study day for will be the visit date minus the initial study drug start date. Study days in Part 4 of Study 165-302 will be calculate similarly based on the first study drug start date in Part 4.

4.5 Visit Window for Analysis

All efficacy data will be summarized by study week of assessment. An assessment for a subject will be classified according to the study day of the assessment where it falls within a window. The windows are designated for each scheduled week of visit and centered on 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 for numerical variable, the average of the two assessments will be used for analyses. For categorical variable, the worse of the 2 equidistant measurements, which indicating less treatment effect, will be used.

Table 4.5.1 lists the weeks assigned for the analyses of the assessments collected in this study and the corresponding range of treatment days (window) during which a visit may have occurred.

Table 4.5.1: Visit Time Windows

Study Part	Derived Visit	Target Day[a]	Window[b]
Part 2	Baseline	Day 1	Day 1
	Week 8	Day 56	Day 43 to Day 56
Study Part	**Derived Visit**	**Target Day[c]**	**Window[b]**
Part 4	Week 9	Day 57	Day 1 to Day 113
	Week 25	Day 169	Day 114 to Day 253
	Week 49	Day 337	Day 254 and above

[a] Target days are relative to the first dosing day of Study 165-302, Part 2.

[b] Visit day is calculated by (visit date – first dosing day of corresponding study part + 1).

[c] Target days are relative to the first dosing day of Study 165-302, Part 4.

4.6 Multiplicity Adjustment

No multiplicity adjustment will be produced for this study.

4.7 Handling of Dropouts and Missing Data

Subjects who discontinued prematurely will not be replaced and missing data not imputed.

5 SUBJECT DISPOSITION

The number of subjects entering the study, completed Week 8 Part 2 of Study 165-302, the number of subjects who completed the study, and the number of subjects in the ITT analysis population will be summarized for all enrolled subjects. For subjects who prematurely discontinued the study, the primary reason for discontinuation will be summarized. A subject listing of completion and early termination will also be provided.

6 PROTOCOL 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.

Subjects with protocol deviations will be provided in a listing. Subjects with inclusion or exclusion deviations will also be provided in a separate listing.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic information will be summarized for the ITT population. The demographics including age, age group, gender, race, ethnicity, will be summarized using descriptive statistics.

Throughout this document, age groups are defined based on the age at screening as follows:

- 18 to <66 years of age
- >=66 years of age

Subject characteristics at Study 165-302 Part 2 baseline will be summarized for the ITT population. Baseline subject characteristics will include height, weight, BMI, blood Phe concentration, [redacted]

8 EFFICACY EVALUATIONS

All efficacy analyses will be based on the ITT population.

8.1 Efficacy Variables

Three selected CANTAB tasks, the RVP, SWM, and SST, are included for efficacy analysis. They are computer-based tasks that are designed for GCP-compliant studies, and each electronic data capture build meets FDA regulations for computerized systems used in clinical trials and 21 CFR Part 11. These CANTAB tasks were reviewed for relevance and feasibility by a panel of neuropsychologists working with PKU patients. The selected CANTAB tasks are considered to have the sensitivity for detecting changes in the neurocognitive functional domains (Bilder, 2014, Poster) relevant for adults with PKU: sustained attention, inhibitory control, and working memory:

- The RVP measures sustained attention. In this task, a series of random digits continuously appears in the middle of the screen. Subjects are asked to recognize a specific sequence of digits and are asked to press a button on the screen whenever this specific sequence of digits appears within this series of continuous digits.
- The SWM task measures visuospatial working memory. During this task, a number of boxes appears on a screen. The objective of the task is to find a token under a box and to place this token in a designated area. There is only one token under one box during each round and the location of the token rotates in each round to a different box, other than a box within which the token was found in previous rounds. The subject is therefore asked to remember which boxes previously contained tokens so as to better the chances and speed of finding tokens under boxes which did not previously contain tokens.
- The SST task measures inhibitory control and cognitive flexibility. The SST is a 2-part task. During part 1, an arrow appears on the screen and subjects are asked to press an arrow button on the screen corresponding with the direction of the arrow displayed. During part 2 of the task, subjects follow the same instructions as in part 1; however, they are asked to withhold their response (do not press an arrow button) if they hear an auditory signal (beep) when the arrow is displayed.

The subject global assessment is also an efficacy variable of this study.

8.2 Primary Efficacy Endpoint

The primary efficacy variables (as assessed by the CANTAB) are as follows:

- RVP mean response latency - defined as the mean response latency during assessment sequence blocks where the subject responded correctly (milliseconds).

- SWM between errors 4-8 boxes – defined as the total number of times the subject revisits a box in which a token has previously been found in the same problem (calculated for assessed problems only).
- SST stop signal reaction time – defined as the length of time between the go stimulus and the stop stimulus at which the subject is able to successfully inhibit their response on 50% of trials.

The primary efficacy endpoints are change from baseline in these variables at Part 2 Week 8.

8.2.1 Primary Analysis Method

Descriptive summaries will be presented for the primary efficacy endpoints.

8.2.2 Secondary Analysis Method

Descriptive summaries will also be present for data collected in Part 4 for the primary efficacy variables at each scheduled visit.

8.3 Secondary Efficacy Analysis Endpoint

The secondary efficacy variables (as assessed by the CANTAB) are as follows:

- RVP A prime (A') – defined as the signal detection measure of sensitivity to the target, regardless of response tendency (the expected range is 0.00 to 1.00; bad to good).
- SWM strategy 6-8 boxes – defined as the number of distinct boxes used by the subject to begin a new search for a token (within the same problem). Calculated for assessed problems with six boxes or more.
- SST proportion of successful stops – defined as the proportion of completed stop trials that were successful stops.

The secondary efficacy endpoints are the change from Baseline in these variables at Part 2 Week 8.

8.3.1 Primary Analysis Method

Descriptive summaries will be presented for the primary efficacy endpoints.

8.3.2 Secondary Analysis Method

Descriptive summaries will also be present for data collected in Part 4 for the primary efficacy variables at each scheduled visit.

8.4 Exploratory Efficacy Endpoint

8.4.1 Stop Signal Task

SST (as assessed by the CANTAB) related endpoints will be summarized based on the following assessments:

[redacted]

Descriptive summaries will be presented for each variable at each visit. Change from baseline will be presented as well. These results will also be listed.

8.4.2 Subject Global Assessment

The subject global assessment questionnaire contains 7 items involving assessments of attention, energy level, tiredness, confusion, sadness, anger, and tension. Each item will be converted to a numerical 5-point scale (0-4 for all items except for attention and energy level in which the scale will be 1-5). The higher score represents a higher severity. The sum of all items will represent the total score of the subject global assessments.

Descriptive summaries will be presented for each item and total score at each visit. Change from baseline will be presented as well. A subject listing of these items will be provided.

9 SAFETY EVALUATIONS

Safety will not be assessed for this study.