CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Substudy to Evaluate Executive Function in Adults with Phenylketonuria Who Are Participating in the Phase 3 Study, 165-302
Protocol Number:	165-303
Active Investigational Product:	BMN 165 (pegvaliase)
IND Number:	IND 076269
Indication:	Phenylketonuria
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 3
Responsible Medical Monitor:	[redacted]
Study Drug:	None
Reference Therapy:	None
Study Population:	Individuals with PKU aged $\geq$ 18 years to $\leq$ 70 years who are concurrently administered study drug (BMN 165 or placebo) in Study 165-302
Date of Original Protocol:	April 24, 2015

2 SYNOPSIS

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 **NAME OF FINISHED PRODUCT**: BMN 165, pegvaliase **NAME OF ACTIVE INGREDIENT**: Recombinant *Anabaena variabilis* phenylalanine ammonia lyase (rAvPAL)	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

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

PROTOCOL NUMBER: 165-303

STUDY SITES: Approximately 40 selected sites who are also participating in Study 165-302

PHASE OF DEVELOPMENT: Phase 3

STUDY RATIONALE:

Study 165-302 is an ongoing, placebo-controlled, randomized, discontinuation study of BMN 165 (pegvaliase), with a planned enrollment of a large number of adults with PKU. This study, 165-303, offers an opportunity to assess additional neurocognitive function domains and BMN 165 in a significant number of adults with PKU by leveraging patients who are already participating in Study 165-302. Study 165-303 is Phase 3 substudy enrolling approximately 100 adults (18 to $\leq$ 70 years old) with PKU who are concurrently administered study drug (BMN 165 and/or placebo) in Part 2 of the Phase 3 study, 165-302. No additional study drug is administered during this study. Subjects who enroll into this study perform assessments at selected time points to assess executive function. In addition, subjects will complete a seven-item questionnaire that asks about their current-state perceptions of attention, energy level, tiredness, confusion, sadness, anger, and tension.

The systematic literature review and meta-analysis was performed in individuals with PKU aged $\geq$ 16 years old to explore blood Phe levels and neurocognitive deficiencies in the adult PKU population. The review identified 14 studies that compared executive function assessments for adults with PKU whose blood Phe levels were controlled from an early age versus adults without PKU (matched for age and gender). Of these 14 studies, 12 showed a significant difference between the two groups of adults for the executive function domains of attention, cognitive flexibility, and inhibitory control. Furthermore, the review identified 10 studies that assessed the effects of blood Phe levels on executive function in adults with PKU. Of these 10 studies, 8 reported that better scores were associated with lower blood Phe levels for working memory, attention, cognitive flexibility, and inhibitory control. In this study, the executive function domains of attention, working memory, cognitive flexibility, and inhibitory control will be further investigated using the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd).

CANTAB cognitive assessments tool is a computerized and validated set of tasks designed for neuropsychological research. The CANTAB has shown sensitivity to the pharmacological effects for a

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number of diseases, such as Attention Deficit Hyperactivity Disorder (ADHD), Alzheimer's disease, Parkinson's disease, and major depressive disorder. The CANTAB was chosen for this study because of its demonstrated sensitivity in detecting cognitive impairments in PKU, as well as its sensitivity to detecting changes in dopamine function. In patients with PKU, significant impairments on tests of fronto-striatal function, including sustained attention (i.e. rapid visual information processing [RVP]), working memory (ie, spatial working memory [SWM]), and response inhibition (i.e. stop signal task [SST]), were observed in subjects with plasma Phe levels > 0.72 µmol/L. Importantly, RVP, SWM), and SST tests have also been shown to be sensitive to pharmacological modulation of the dopaminergic system, suggesting that these tasks are suitable for assessing the pharmacological effects of BMN 165.

The effect of BMN 165 on inattention and mood is being assessed in adults with PKU using the investigator-rated Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) and the subject- and observer-rated Profile of Mood States (POMS) assessment tools in Study 165-302. Interpretation of change in inattention and mood as measured by the ADHD-RS and POMS in Study 165-302 will be explored further using a subject global assessment. The subject global assessment is a paper-based, seven-item questionnaire that will be administered to subjects as part of this study; subjects will be asked to rate their current-state perceptions of attention, energy level, tiredness, confusion, sadness, anger, and tension on 5-point scales.

OBJECTIVES:

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 CANTAB tasks.

The exploratory objective of this study is to evaluate patient self perception in adult subjects with PKU who are participating in Study 165-302 for use as anchors in the interpretation of change over time in measures of inattention and mood.

STUDY DESIGN AND PLAN:

This is a Phase 3 substudy enrolling approximately 100 subjects, aged ≥ 18 to ≤ 70 years old, with PKU who are concurrently treated with BMN 165 or placebo in Part 2 and BMN 165 in Part 4 of Study 165-302. No study drug is administered as part of this study. For this study, subjects will be asked to perform computer-based assessments (CANTAB) that assess executive function (specifically, attention, working memory, cognitive flexibility) and to answer questions about their current state of self perception (subject global assessment comprised of seven questions).

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

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Study 165-302. Screening assessments may be completed within 14 days before Day 1 or on Day 1 of this study. If screening assessments are performed on Day 1, they must be performed before any other Day 1 assessments.

Executive function will be assessed using a selected set of three tasks from the CANTAB tool (Rapid Visual Processing [RVP], Spatial Working Memory [SWM], and Stop Signal Task [SST]). Each subject's self perception of their current state will be measured using a subject global assessment questionnaire that contains seven questions about current state perception of attention, energy level, tiredness, confusion, sadness, anger and tension. The subject global assessment and CANTAB tasks will be administered at the site at five time points during this study and must coincide with the time points in Part 2 and Part 4 of Study 165-302: upon entry into Part 2 (Day 1 of Week 1), upon completion of Part 2 (Week 8) and at the Week 9, Week 25, and Week 49 visits of Part 4. The 165-302 study assessments (ADHD-RS and POMS) must be performed first, followed by the subject global assessment and then the CANTAB. The first study drug administration given in Part 2 of Study 165-302 should be given last, after the CANTAB. 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.

NUMBER OF SUBJECTS PLANNED: Approximately 100 subjects at selected sites are planned for enrollment into this study.

DIAGNOSIS AND ENTRY CRITERIA:

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 assessment.
- Are willing and able to comply with all study procedures.

Individuals who meet the following exclusion criterion 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

INVESTIGATIONAL PRODUCT, PLACEBO, DOSE, ROUTE AND REGIMEN:

No investigational product is administered as part of this study.

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DURATION OF STUDY:
No study drug is administered as part of this study. After the 14-day screening period, subjects will be asked to complete assessments and procedures for this study for 63 weeks.

STATISTICAL METHODS AND CRITERIA FOR EVALUATION:

Determination of Sample Size:

[redacted]

Analysis Populations:

The intent-to-treat (ITT) population will consist of all subjects who are enrolled into the study with at least one executive function assessment.

Primary Efficacy Endpoints:

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

- RVP mean latency
  - RVP mean latency is the mean response latency during assessment sequence blocks where the subject responded correctly (milliseconds).
- SWM between errors
  - SWM between errors measures 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 delay
  - SST stop signal delay is 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 these variables collected in Part 2, Week 8.

Secondary Efficacy Endpoints:

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

- RVP A prime
  - RVP A prime represents the signal detection measure of sensitivity to the target,

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regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, measure of how good the subject is at detecting target sequences.

- SWM strategy
  - For assessed problems with six boxes or more, SWM strategy is the number of distinct boxes used by the subject to begin a new search for a token (within the same problem).
- SST proportion of successful stops
  - SST proportion of successful stops measures the proportion of completed stop trials that were successful stops.

Each secondary efficacy endpoint will be analyzed similar to the primary efficacy endpoints at Part 2, Week 8.

Exploratory Efficacy Endpoints:

Exploratory endpoints are as follows:

Primary Efficacy Analysis:

No multiplicity adjustment will be performed for multiple primary efficacy endpoints. Each primary efficacy endpoint will be compared between High Active Group (Study 165-302) and the pooled Placebo Groups (Study 165-302) and between the Low Active Group (Study 165-302) and the pooled Placebo Groups (Study 165-302) using Analysis of Covariance Model (ANCOVA) with treatment and baseline assessment as factors. For this study, baseline is defined as the assessment collected during the Part 2, Day 1 of Week 1 visit (predose) of Study 165-302.

The primary efficacy endpoints will also be summarized descriptively over time in Part 4 at Week 9,

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Week 25, and Week 49.

Secondary Efficacy Analysis:

Each secondary efficacy endpoint will be analyzed similar to the primary efficacy endpoints.

Exploratory Efficacy Analysis:

Descriptive statistics for the exploratory efficacy endpoints will be provided for scheduled visits. More details regarding the exploratory efficacy analysis will be provided in the Statistical Analysis Plan (SAP).

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADHD	attention deficit hyperactivity disorder
ADHD-RS	Attention Deficit Hyperactivity Disorder Rating Scale (investigator-rated with adult prompts)
AE	adverse event
BH4	tetrahydrobiopterin
CANTAB	Cambridge Neuropyschological Test Automated Battery
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	case report form
CRO	contract research organization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GO RT	GO reaction time
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent to treat
PAH	phenylalanine hydroxylase
PAL	phenylalanine ammonia lyase
PEG	polyethylene glycol
Phe	phenylalanine
PKU	phenylketonuria
POMS	Profile of Mood States
rAvPAL-PEG	recombinant *Anabaena variabilis* phenylalanine ammonia lyase-PEG
RVP	Rapid Visual Processing
SAP	Statistical Analysis Plan
SD	standard deviation
SSP	Spatial Span
SST	Stop Signal Task
SWM	Spatial Working Memory
US	United States

5 ETHICS

5.1 Institutional Review Board or Independent Ethics Committee

Prior to initiating the study, the investigator will obtain written confirmation that the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/IEC will be provided to the sponsor (BioMarin Pharmaceutical Inc. or BioMarin) or its designee. The investigator will provide the IRB/IEC with all appropriate material, including the protocol; the Investigator's Brochure (IB); the Informed Consent Form (ICF) inclusive of compensation procedures; and any other written information provided to subjects, including all ICFs translated to a language other than the native language of the clinical site. The study will not be initiated and supplies will not be shipped to the site until appropriate documents from the IRB obtained in writing by the investigator and copies are received at BioMarin (or designee) confirming unconditional approval of the protocol, the ICF, and all subject recruitment materials. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the study are made available to the IRB/IEC and to BioMarin by the investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

This study will be conducted in accordance with the following:

- US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable
- ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (ICH E6)
- The ethical principles established by the Declaration of Helsinki

The study will be conducted under a protocol reviewed and approved by an IRB/IEC and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks. The rights and welfare of the subjects will be respected, and the investigators conducting the study do not find the hazards to outweigh the potential benefits.

Each subject will provide written and informed consent before any study-related tests or evaluations are performed.

5.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), United States (US) Code of Federal Regulations (CFR) 21 CFR §50 and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The investigator will prepare the ICF and will provide the documents to BioMarin for approval prior to submission to the IRB/IEC. BioMarin and the IRB/IEC/ must approve the documents before they are implemented. A copy of the approved ICF and a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site (if applicable) must also be received by BioMarin (or designee) before any study-related tests or evaluations are performed.

The investigator will provide copies of the signed ICF to each subject and will maintain the original ICF in the subject's file.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, each investigator must provide to BioMarin (or designee) a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of subjects in this study.

The study will be administered and monitored by employees or representatives of BioMarin. Clinical research associates (CRAs; or trained designees) will monitor each site on a periodic basis and perform verification of source documentation for each subject, as well as other required review processes.

A vendor specializing in executive function (attention, working memory, cognitive flexibility) testing provides study staff training for the CANTAB administration. The vendor may also collect data for analysis.

7 INTRODUCTION

Phenylketonuria (PKU) is an inherited, autosomal, recessive disease characterized by a deficiency in the liver enzyme, phenylalanine hydroxylase (PAH). PAH catalyzes the conversion of the essential amino acid phenylalanine (Phe) to tyrosine, and this enzymatic activity is facilitated by tetrahydrobiopterin (BH4). PAH deficiency results in abnormally elevated concentrations of Phe, which is toxic to the brain (Kaufman, 1989, J Pediatr.). High Phe levels during infancy and early childhood cause profound cognitive and developmental defects, and poorly controlled blood Phe levels in older children and adolescents are associated with learning disabilities, attention deficit hyperactivity disorder, and behavioral problems (Moyle, 2007, Neuropsychol.Rev.), (Moyle, 2007, J Clin.Exp.Neuropsychol.), (Pietz, 1997, Pediatrics), (Smith, 2000, Eur.J Pediatr.), (Waisbren, 1999, Guildford Publications), (Waisbren, 2007, Mol.Genet.Metab), (Stemerdink, 2000, J.Inherit.Metab Dis.). With newborn screening followed by a Phe-restricted diet, the most severe manifestation of the disease—mental retardation—is prevented. But the PKU or Phe-restricted diet is difficult to maintain and is not without sequelae. The diet requires significant restriction of high-protein food, which leaves patients with nutritional deficits that must be remedied with a Phe-free, amino acid supplements that are difficult to eat. Uncontrolled blood Phe levels in adulthood are associated with executive dysfunction, depression, and a variety of behavioral and psychiatric problems, (Moyle, 2007, Neuropsychol.Rev.), (Pietz, 1997, Pediatrics), (Smith, 2000, Eur.J Pediatr.), (Waisbren, 1999, Guildford Publications).

BioMarin Pharmaceutical Inc. is developing BMN 165 (pegvaliase; recombinant *Anabaena variabilis* phenylalanine ammonia lyase-PEG [rAvPAL-PEG]) as an enzyme substitution therapy to reduce blood Phe concentrations in patients with PKU. BMN 165 is a genetically modified cyanobacterium phenylalanine ammonia lyase enzyme (homologue of human phenylalanine hydroxylase [PAH]), expressed in *E. coli* and PEGylated after production to decrease immunogenicity. The BMN 165 clinical program evaluates the effect of BMN 165 on blood Phe levels and will characterize the relationship of blood Phe to other important clinical outcomes. Two Phase 3 studies of BMN 165, 165-301 (A Phase 3, Open-Label, Randomized, Multi-Center Study to Assess the Safety and Tolerability of an Induction, Titration, and Maintenance Dose Regimen of BMN 165 Self Administered by Adults With Phenylketonuria Not Previously Treated with BMN 165) and 165-302 (A Four-Part, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Four-Arm, Discontinuation Study to Evaluate the Efficacy and Safety of Subcutaneous Injections of BMN 165 Self Administered by Adults with Phenylketonuria), are underway to assess the effect of BMN 165 on blood Phe levels, inattentiveness, hyperactivity/impulsivity, and mood (anger, anxiety, confusion,

depression, tiredness, and vigor)in adults with PKU. Additional evaluation of BMN 165 on other neurocognitive domains in adults with PKU will be performed with this Phase 3 substudy.

7.1 Study Rationale

Study 165-302 is an ongoing, placebo-controlled, randomized, discontinuation study of BMN 165 (pegvaliase), with a planned enrollment of a large number of adults with PKU. This study, 165-303, offers an opportunity to assess additional neurocognitive function domains and BMN 165 in a significant number of adults with PKU by leveraging patients who are already participating in Study 165-302. Study 165-303 is Phase 3 substudy enrolling approximately 100 adults (18 to $\leq$ 70 years old) with PKU who are concurrently administered study drug (BMN 165 and/or placebo) in Part 2 of the Phase 3 study, 165-302 (refer to Section 9.1 for additional details regarding the study design). No additional study drug is administered during this study. Subjects who enroll into this study perform assessments at selected time points to assess executive function. In addition, subjects will complete a seven-item questionnaire that asks about their current-state perceptions of attention, energy level, tiredness, confusion, sadness, anger, and tension

The systematic literature review and meta-analysis was performed in individuals with PKU aged $\geq$ 16 years old to explore blood Phe levels and neurocognitive deficiencies in the adult PKU population (Bilder, 2014, Poster). The review identified 14 studies that compared executive function assessments for adults with PKU whose blood Phe levels were controlled from an early age versus adults without PKU (matched for age and gender). Of these 14 studies, 12 showed a significant difference between the two groups of adults for the executive function domains of attention, cognitive flexibility, and inhibitory control. Furthermore, the review identified 10 studies that assessed the effects of blood Phe levels on executive function in adults with PKU. Of these 10 studies, 8 reported that better scores were associated with lower blood Phe levels for working memory, attention, cognitive flexibility, and inhibitory control. In this study, the executive function domains of attention, working memory, cognitive flexibility, and inhibitory control will be further investigated using the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd).

CANTAB cognitive assessments tool is a computerized and validated set of tasks designed for neuropsychological research. The CANTAB has shown sensitivity to the pharmacological effects for a number of diseases, such as Attention Deficit Hyperactivity Disorder (ADHD), Alzheimer's disease, Parkinson's disease, and major depressive disorder. The CANTAB was

chosen for this study because of its demonstrated sensitivity in detecting cognitive impairments in PKU, as well as its sensitivity to detecting changes in dopamine function. In patients with PKU, significant impairments on tests of fronto-striatal function, including sustained attention (ie, rapid visual information processing [RVP]), working memory (i.e. spatial working memory [SWM]), and response inhibition (i.e. stop signal task [SST]), were observed in subjects with plasma Phe levels > 0.72 µmol/L (Bik-Multanowski, 2010, Mol Gen Metab). Importantly, RVP (Turner, 2005, Psychopharma), SWM (Harmer, 2001, Psychopharma), and SST tests (Aron, 2003, Biol Psych) have also been shown to be sensitive to pharmacological modulation of the dopaminergic system, suggesting that these tasks are suitable for assessing the pharmacological effects of BMN 165.

The effect of BMN 165 on inattention and mood is being assessed in adults with PKU using the investigator-rated Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) and the subject- and observer-rated Profile of Mood States (POMS) assessment tools in Study 165-302. Interpretation of change in inattention and mood as measured by the ADHD-RS and POMS in Study 165-302 will be explored further using a subject global assessment. The subject global assessment is a paper-based, seven-item questionnaire that will be administered to subjects as part of this study; subjects will be asked to rate their current-state perceptions of attention, energy level, tiredness, confusion, sadness, anger, and tension on 5-point scales.

8 STUDY OBJECTIVES

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 CANTAB tasks.

The exploratory objective of this study is to evaluate patient self perception in adult subjects with PKU who are participating in Study 165-302 for use as anchors in the interpretation of change over time in measures of inattention and mood.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 3 substudy enrolling approximately 100 subjects, aged ≥ 18 to ≤ 70 years old, with PKU who are concurrently treated with BMN 165 or placebo in Part 2 and BMN 165 in Part 4 of Study 165-302. No study drug is administered as part of this study. For this study, subjects will be asked to perform computer-based assessments (CANTAB) that assess executive function (specifically, attention, working memory, cognitive flexibility) and to answer questions about their current state of self perception (subject global assessment comprised of seven questions).

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 may be completed within 14 days before Day 1 or on Day 1 of this study. If screening assessments are performed on Day 1, they must be performed before any other Day 1 assessments.

Executive function will be assessed using a selected set of three tasks from the CANTAB tool (Rapid Visual Processing [RVP], Spatial Working Memory [SWM], and Stop Signal Task [SST]). Each subject's self perception of their current state will be measured using a subject global assessment questionnaire that contains seven questions about current state perception of attention, energy level, tiredness, confusion, sadness, anger and tension.

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. Assessments for evaluation of executive function will be performed as presented in Table 9.1.1.

Table 9.1.1: Schedule of Events

Event or Assessment[a]	Screening[b] Day -14 to Day 1	Part 2: Week 1 of Day 1 of Study 165-302[c] (Baseline) ± 1 day	Part 2: Week 8 of Study 165-302 − 5 days of Day 56	Part 4: Week 9 of Study 165-302 ± 3 days	Part 4: Week 25 of Study 165-302 ± 7 days	Part 4: Week 49 of Study 165-302[d] ± 7 days	Early Termination[e]
Informed consent	X						
Demographics (date of birth)	X						
CANTAB practice session		X					
Subject global assessment questionnaire[f]		X	X	X	X	X	X
CANTAB		X	X	X	X	X	X

ADHD-RS, Attention Deficit Hyperactivity Disorder Rating Scale (investigator-rated with adult prompts); CANTAB, Cambridge Neuropsychological Test Automated Battery; POMS, Profile of Mood States.

All scheduled visits are in the study clinic. Assessments for this study must be performed at the same scheduled clinic visit performed for Study 165-302. Adverse event reporting and data collection must be performed in Study 165-302. For all visits after the Baseline Visit, assessment should be performed in the following order: ADHD/POMS of Study 165-302, subject global assessment, CANTAB, and study drug administration in Study 165-302.

[a]No study procedures or assessments are to be performed before informed consent is obtained. After written informed consent, screening assessments must be within 14 days before Day 1 of this study.

[b] Screening assessments may be completed within 14 days before Day 1 or on Day 1 of this study. If screening assessments are performed on Day 1, they must be performed before any other Day 1 assessments.

[c]Assessments to establish baseline must be performed in the following order: CANTAB practice session, ADHD and POMS of Study 165-302, subject global assessment, CANTAB (Part 2, Day 1 of Week 1), and study drug administration in Study 165-302.

[d]This is the last scheduled visit for this study.

[e]The visit should be performed within 8 weeks after the last scheduled visit.

[f]Must be performed before administration of the CANTAB in this study.

9.2 Discussion of Study Design, Including Choice of Control Group

A discussion of the chosen study design is provided in Section 7.1.

9.3 Selection of Study Population

Subjects at least 18 to ≤70 years old with PKU who are concurrently participating in Study 165-302 have been selected for this study. Additional details regarding subjects who may or may not be eligible for participation are provided in Section 9.1. Rationale for selection of these subjects for study participation is provided in Section 7.1. Additional criteria for study participation are presented in Section 9.3.1 and Section 9.3.2.

9.3.1 Inclusion Criteria

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 assessment.
- Are willing and able to comply with all study procedures.

9.3.2 Exclusion Criteria

Individuals who meet the following exclusion criterion 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

9.3.3 Removal of Subjects from Treatment or Assessment

Subjects may withdraw their consent to participate in this study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. Subject participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. Procedures listed for the Early Termination visit should be performed (refer to Section 12.3.1.3 and Section 12.3.2.4).

BioMarin must be notified of all subject withdrawals as soon as possible. BioMarin also reserves the right to discontinue the study at any time for either clinical or administrative

reasons and to discontinue participation by an individual investigator or site for poor enrollment or noncompliance.

Reasons for which the investigator or BioMarin may withdraw a subject from the study include, but are not limited to, the following:

- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone, a certified letter will be sent to the subject requesting contact with the investigator. This information should be recorded in the study records.

Before enrollment in the study, the investigator (or designee) must explain to each subject that the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB/IEC. It is the responsibility of the investigator (or designee) to obtain written permission to use protected health information per country-specific regulations, such as HIPAA in the United States, from each subject.
If permission to use protected health information is withdrawn, it is the responsibility of the investigator to obtain a written request to ensure that no further data will be collected from the subject. The subject will then be terminated from the study.

If study drug is discontinued in Study 165-302 before study completion, the investigator will ask the subject to remain in this study (165-303) to continue study visits and assessments, provided the subject's health, safety, and welfare are not detrimentally affected.

9.3.4 Subject Identification and Replacement of Subjects

Subjects are not replaced in this study. Each subject is assigned a unique subject identifier, which is on all case report form (CRF) pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier is used.

9.3.5 Duration of Subject Participation

Following a screening period of up to 14 days, subjects will be assessed for 63 weeks as part of this study.

9.4 Treatments

9.4.1 Treatments Administered

No study drug is administered in this study. After the screening period, subjects will be asked to complete assessments and procedures for this study for 63 weeks.

9.4.2 Return and Disposition of Clinical Supplies

All study-related materials should be stored, inventoried, reconciled, and returned according to applicable state and federal regulations and study procedures.

9.5 Efficacy Variables

The CANTAB battery of tasks 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. For this study, three computerized CANTAB tasks, the RVP, SWM, and SST, have been selected for evaluation. These CANTAB tasks were reviewed for relevance and feasibility by a panel of neuropsychologists working with PKU patients. The panel reviewed the systematic literature review and meta-analysis and provided input from their clinical and research experience. Each CANTAB task is administered using a standardized touch-screen tablet computer, provided by Cambridge Cognition Ltd. 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 task 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 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 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 subject global assessment is a paper-based, seven-item questionnaire that will be administered to subjects as part of this study; subjects will be asked to rate their current-state perceptions 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).

The Schedule of Events tables in Section 9.1 outline the timing of required events and assessments.

9.5.1 Primary Efficacy Variable

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

- RVP mean latency
    - RVP mean latency is the mean response latency during assessment sequence blocks where the subject responded correctly (milliseconds).
- SWM between errors
    - SWM between errors measures 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 delay
    - SST stop signal delay is 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 these variables collected in Part 2, Week 8.

9.5.2 Secondary Efficacy Variables

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

- RVP A prime
    - RVP A prime represents 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). In essence, measure of how good the subject is at detecting target sequences.
- SWM strategy
    - For assessed problems with six boxes or more, SWM strategy is the number of distinct boxes used by the subject to begin a new search for a token (within the same problem).
- SST proportion of successful stops
    - SST proportion of successful stops measures the proportion of completed stop trials that were successful stops.

Each secondary efficacy endpoint will be analyzed similar to the primary efficacy endpoints at Part 2, Week 8.

9.5.3 Exploratory Efficacy Variables

Exploratory endpoints are as follows:

9.5.4 Safety Variables

In this study, safety will be determined from evaluation of AEs in Study 165-302.

10 REPORTING ADVERSE EVENTS

Subjects participating in this study will also be concurrently participating in Study 165-302. AEs relative to any study drug or study procedure performed as part of Study 165-302 or this study should be reported for Study 165-302.

11 APPROPRIATENESS OF MEASUREMENTS

11.1 CANTAB and Subject Global Assessment

A discussion of executive function and its relationship with PKU is provided in Section 7.1. A description of the CANTAB tools and subject global assessment questionnaire administered in this study are also provided in Section 9.5.

12 STUDY PROCEDURES

Assessment of AEs and concomitant medications should be performed as part of Study 165-302. Subjects who discontinue from study drug early in Study 165-302 will be asked to continue to perform the visit assessments of this study until study completion (refer to Section 9.3.3).

12.1 Prestudy

An ICF must be signed and dated by the subject (or legal guardian if appropriate), investigator (or designee), and witness before any study-related procedures are performed.

12.2 Screening Visit (Days -14 to Day 1)

Once written informed consent has been obtained, subject demographic information (date of birth) should be recorded at the Screening Visit. Screening assessments may be completed within 14 days before Day 1 or on Day 1 of this study. If screening assessments are performed on Day 1, they must be performed before any other Day 1 assessments.

12.3 Study Visits

All assessments should be performed at approximately the same time of day for each visit (refer to Section 12.3.1 [Part 2] and Section 12.3.2 [Part 4]).

12.3.1 Part 2

The subject global assessment and CANTAB should be administered in the clinic at the same time as the visits performed for Part 2 of Study 165-302.

12.3.1.1 Part 2: Week 1 of Day 1 of Study 165-302 (Baseline [± 1 day])

Assessments should be performed in the following order:

- CANTAB practice session,
- ADHD and POMS of Study 165-302,
- Subject global assessment,
- CANTAB, and
- Study drug administration in Study 165-302

12.3.1.2 Part 2: Week 8 of Study 165-302 (− 5 days of Day 56)

Assessments should be performed in the following order:

- ADHD and POMS of Study 165-302,
- Subject global assessment,
- CANTAB, and
- Study drug administration in Study 165-302

12.3.1.3 Early Termination

The Early Termination Visit should be performed within 8 weeks of the last scheduled visit. Assessments should be performed in the following order if a subject terminates from the study early during Part 2:

- ADHD and POMS of Study 165-302,
- Subject global assessment,
- CANTAB

12.3.2 Part 4

The subject global assessment and CANTAB should be administered in the clinic at the same time as the visits performed for Part 4 of Study 165-302.

12.3.2.1 Part 4: Week 9 of Study 165-302 (± 3 days)

Assessments should be performed in the following order:

- ADHD and POMS of Study 165-302,
- Subject global assessment,
- CANTAB, and
- Study drug administration in Study 165-302

12.3.2.2 Part 4: Week 25 of Study 165-302 (± 7 days)

Assessments should be performed in the following order:

- ADHD and POMS of Study 165-302,
- Subject global assessment,
- CANTAB, and
- Study drug administration in Study 165-302

12.3.2.3 Part 4: Week 49 of Study 165-302 (± 7 days)

This is the last scheduled visit for this study. Assessments should be performed in the following order:

- ADHD and POMS of Study 165-302,
- Subject global assessment,
- CANTAB, and
- Study drug administration in Study 165-302

12.3.2.4 Early Termination

The Early Termination Visit should be performed within 8 weeks of the last scheduled visit. Assessments should be performed in the following order if a subject terminates from the study early during Part 4:

- ADHD and POMS of Study 165-302,
- Subject global assessment,
- CANTAB

13 DATA QUALITY ASSURANCE

BioMarin personnel (or designees) may visit the study site prior to initiation of the study to review with the site personnel information about the protocol and other regulatory document requirements; applicable randomization procedures; source document requirements; CRFs; monitoring requirements; and procedures for reporting AEs, including SAEs.

At visits during and after the study, a CRA will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of data on CRFs from source documents, adherence to protocol, and randomization (if applicable).

The designated clinical data management group will enter or transfer CRF data into a study database if applicable.

Data quality control and analysis will be performed by BioMarin (or a designee) based on a predefined analysis plan.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The Statistical Analysis Plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS version 9.2.

14.1 Procedures for Accounting for Missing, Unused and Spurious Data

Because the completeness of the data affects the integrity and accuracy of the final study analysis, every effort will be made to ensure complete, accurate and timely data collection and, therefore, avoid missing data. If study drug is discontinued in Study 165-302 before completion of 165-302, the investigator will ask the subject to remain in this study (165-303) to continue the visits and assessments of this study, provided the subject's health, safety, and welfare are not detrimentally affected.

Missing data will be imputed for the primary and secondary endpoints. Additional details regarding missing data will be provided in the SAP.

14.2 Analysis Populations

The intent-to-treat (ITT) population will consist of all subjects who are enrolled into the study with at least one executive function assessment.

14.3 Primary Efficacy Analysis

No multiplicity adjustment will be performed for multiple primary efficacy endpoints. Each primary efficacy endpoint will be compared between High Active Group (Study 165-302) and the pooled Placebo Groups (Study 165-302) and between the Low Active Group (Study 165-302) and the pooled Placebo Groups (Study 165-302) using Analysis of Covariance Model (ANCOVA) with treatment and baseline assessment as factors. For this study, baseline is defined as the assessment collected during the Part 2, Day 1 visit (predose) of Study 165-302.

The primary efficacy endpoints will also be summarized descriptively over time in Part 4 at Week 9, Week 25, and Week 49.

14.4 Secondary Efficacy Analysis

Each secondary efficacy endpoint will be analyzed similar to the primary efficacy endpoints.

14.5 Exploratory Efficacy Analysis

Descriptive statistics for the exploratory efficacy endpoints will be provided for scheduled visits. More details regarding the exploratory efficacy analysis will be provided in the Statistical Analysis Plan (SAP).

14.6 Determination of Sample Size

[redacted]

14.7 Changes in the Conduct of the Study or Planned Analyses

Only BioMarin may modify the protocol. Any change in study conduct considered necessary by the investigator will be made only after consultation with BioMarin who will then issue a formal protocol amendment to implement the change. The only exception is when an investigator considers that subject safety is compromised without immediate action. In these circumstances, immediate approval by the chair of the IRB must be sought and the investigator should inform BioMarin and the full IRB/IEC within 2 working days after the safety issue occurs.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by BioMarin and the IRB/IEC, and all active subjects must again provide informed consent.

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.

15 COMPENSATION, INSURANCE AND INDEMNITY

There will be no charge to subjects to be in this study. BioMarin will pay all costs of tests, procedures, and treatments that are part of this study. In addition, after IRB/IEC approval, BioMarin may reimburse the cost of travel for study-related visits. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort that are not part of this study whether or not related to the subject's disease. Costs associated with hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The investigator should contact BioMarin immediately upon notification that a study subject has been injured by the procedures performed as part of the study. Any subject who experiences a study-related injury should be instructed by the investigator to seek medical treatment at a pre-specified medical institution if possible or at the closest medical treatment facility if necessary. The subject should be given the name of a person to contact to seek further information about treatment and assistance with treatment for study-related injuries. The treating physician should bill the subject's health insurance company or other third party payer for the cost of this medical treatment, unless the executed Clinical Trial Agreement between BioMarin and the institution of the investigator specifies otherwise. If the subject has followed the investigator instructions, BioMarin may pay for reasonable and necessary medical services to treat the injuries caused by the study procedures. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, BioMarin will comply with the law.

16 CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic CRFs will be provided for each subject. The investigator must review and electronically sign the completed CRF casebook to verify its accuracy.

CRFs must be completed using a web-based application that has been developed for the study and has been validated. Study site personnel (or designee) will be trained on the application and will enter the clinical data from source documentation. Unless explicitly allowed in the CRF instructions, blank data fields are not acceptable.

In the event of an entry error or if new information becomes available, the site personnel will correct the value by deselecting the erroneous response and then selecting or entering the factual response. In compliance with 21 CFR Part 11, the system will require the site personnel to enter a reason for changing the value. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction, and the identity of the operator.

Study data on the CRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The investigator must therefore agree to allow direct access to all source data. Subjects must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

A CRA designated by BioMarin will compare the CRFs with the original source documents at the study site and will evaluate them for completeness and accuracy before designating them as "Source Data Verified." If an error is discovered at any time or a clarification is needed, the CRA (or designee) will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Before a CRF casebook can be locked, data fields must be source data verified and queries closed. The investigator will then electronically sign the casebook, specifying that the information on the CRFs is accurate and complete. The Data Manager (or designee) will then set the status of the forms, visits, and the entire casebook to Locked. Upon completion of the clinical study report, an electronic copy of each site's casebooks will be copied to a compact disk and will be sent to each site for retention with other study documents.

17 STUDY MONITORING AND AUDITING

Qualified individuals designated by BioMarin will monitor all aspects of the study according to GCP and standard operating procedures for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical supplies; dispensing and storage areas; and the clinical files, including original medical records, of the study subjects. The investigator also agrees to assist the monitors if requested. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by BioMarin (or its designees).

Members of BioMarin GCP Compliance Department (or designees) may conduct an audit of a clinical site at any time before, during, or after completion of the study. The investigator will be informed if an audit is to take place and will be advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an audit of the study. If informed of such an inspection, the investigator should notify BioMarin immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

18 RETENTION OF RECORDS

The investigator must retain all study records required by BioMarin and by the applicable regulations in a secure and safe facility. The investigator must consult a BioMarin representative before disposal of any study records and must notify BioMarin of any change in the location, disposition, or custody of the study files. The investigator /institution must take measures to prevent accidental or premature destruction of essential documents, i.e., documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the U.S. or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator /institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice but not less than 15 years. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by a BioMarin agreement. BioMarin must be notified and will assist with retention should an investigator /institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of BioMarin to inform the investigator /institution as to when these documents no longer need to be retained.

19 USE OF INFORMATION AND PUBLICATION

BioMarin recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between BioMarin and the institution of the investigator.

20 REFERENCES

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21 INVESTIGATOR RESPONSIBILITIES

21.1 Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572, the investigator will ensure the following:

- He or she will conduct the study in accordance with the relevant and current protocol and will only make changes in a protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects that the data obtained are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IRB review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments.
- He or she will ensure that adequate and accurate records are in accordance with 21 CFR 312.62 and will make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC complies with the requirements of 21 CFR Part 56, and other applicable regulations and will conduct initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

22 SIGNATURE PAGE

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

Protocol Number: 165-303

I have read the forgoing protocol and agree to conduct this study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines, including ICH E6, as stated in the protocol, and other information supplied to me.

Investigator Signature Date

Printed Name:_____

Accepted for the Sponsor: