Official Title: An Open-label Extension Study to Evaluate the Safety and Efficacy of Subcutaneous Injections of Pegvaliase (> 40 mg/day Dose) in Adults with Phenylketonuria

NCT Number: NCT03694353

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 30 July 2019

CLINICAL STUDY PROTOCOL

Study Title:	An Open-label Extension Study to Evaluate the Safety and Efficacy of Subcutaneous Injections of Pegvaliase (> 40 mg/day Dose) in Adults with Phenylketonuria
Protocol Number:	165-304
Active Investigational Product:	pegvaliase (formerly BMN 165)
IND Number:	IND 076269
Indication:	Phenylketonuria
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 3
Responsible Medical Monitor:	PI , RN, MS
Reference Therapy:	None
Treatment Duration:	Approximately 121 weeks
Doses of Investigational Product:	> 40 mg/day to 60 mg/day
Study Population:	Individuals with phenylketonuria (PKU) aged ≥ 18 years and ≤ 70 years who previously received pegvaliase in PAL-003 or 165-302 (> 40 mg/day dose)
Date of Original Protocol:	11 April 2018
Date of Amendment 1:	30 July 2019

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 1

Date: 30 July 2019

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 1 to the 165-304 protocol is provided below.

1. The study duration has been extended from approximately 61 weeks to 121 weeks.

Rationale: The study is ongoing and extending the duration should ensure that all subjects on the study continue to have access to pegvaliase without involuntary drug holidays.

2. Additional immunogenicity assays have been added.

Rationale: Because patients in 165-304 will receive pegvaliase doses higher than the currently approved maximum dose of 40 mg/day, more drug may be available to potentially combine with antibodies to form circulating immune complexes (CICs), which could increase the risk of immune-mediated events. Therefore, additional immunogenicity evaluations have been added; the additional evaluations will be performed on samples already identified for collection in the protocol. No additional blood draws will be required.

3. Changes were made to dosing exception language for 1 subject who had transitioned from PAL-003 to 165-304 on a higher dose.

Rationale: In a parent study for PAL-003 (the phase 2 study PAL-002), dosing with pegvaliase was weight-based, and the maximum permitted dose early in the study was up to 5.0 mg/kg/week. One subject who continued on 120 mg/day dosing in PAL-003 based on the maximum reported body weight of ~220 kg and the demonstrated efficacy of that dose, has transitioned from PAL-003 into 165-304. The protocol is amended to remove reference to previous weight-based dosing while still including a dosing exception (not to exceed 120 mg/day dose) for this subject. In addition, the amendment sets the maximum dose increase that an investigator can request at “not to exceed 60 mg/day”, with the exception of the aforementioned patient.

4. Study background information has been updated to reflect commercial approval of pegvaliase as an available treatment option for patients with PKU in the US and EU.
5. Additional minor changes have been made for purposes of consistency and clarity.

Specific changes included in this amendment, including the Synopsis, since the original protocol (dated 11 April 2018) are outlined in Section 24.

2 SYNOPSIS

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 **NAME OF FINISHED PRODUCT**: pegvaliase (formerly BMN 165) **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: An Open-label Extension Study to Evaluate the Safety and Efficacy of Subcutaneous Injections of Pegvaliase (> 40 mg/day Dose) in Adults with Phenylketonuria		
PROTOCOL NUMBER: 165-304		
STUDY SITES: Up to 29 sites in the United States		
PHASE OF DEVELOPMENT: Phase 3		
STUDY RATIONALE: Study 165-304 is an open-label extension for subjects who participated in Studies PAL-003 and 165-302 at doses > 40 mg/day. The objective is to evaluate long-term safety and efficacy in subjects treated at doses exceeding the approved pegvaliase labeled dose (the currently approved label specifies up to and including 40 mg/day dose only). Literature reports suggest the majority of adults with PKU cannot adhere to severe phenylalanine (Phe) intake restrictions. Even among adults reporting to adhere to severe Phe intake restrictions, the majority fail to maintain recommended blood Phe levels. Baseline blood Phe levels and diet from the literature and previous pegvaliase clinical studies confirm this finding among adult participants. Adults with PKU with poor metabolic control represent a patient population in great need of additional therapeutic options.		
OBJECTIVES: The primary objective of the study is: • To evaluate the long-term safety and efficacy of pegvaliase (> 40 mg/day dose) in adult patients with PKU The secondary objective of the study is: • To characterize dietary protein intake from medical food and from intact food during long-term treatment with pegvaliase (> 40 mg/day dose) in adult patients with PKU The exploratory objective of the study is: • To characterize the long-term immunogenicity profile of pegvaliase (> 40 mg/day dose) in adult patients with PKU		
STUDY DESIGN AND PLAN: This is a Phase 3 open-label extension study enrolling approximately 40 adult subjects with PKU who were previously treated with pegvaliase in Studies PAL-003 or 165-302. The study is designed to evaluate the long-term safety and efficacy of pegvaliase administered as prefilled syringe drug product at a dose of > 40 mg/day to 60 mg/day, inclusive. Dose regimens other than daily dosing at		

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> 40 mg/day to 60 mg/day (with the exception of 1 subject enrolled from the PAL-003 study who receives a pegvaliase dose not to exceed 120 mg/day) may be allowed provided the investigator consults with the medical monitor and obtains approval from the medical monitor prior to starting the alternative regimen. Subjects will continue their prior pegvaliase dose regimen on the 165-304 study, including 1 subject enrolled from the PAL-003 study who receives a pegvaliase dose not to exceed 120 mg/day. A subject who dose reduces to a dose of 40 mg/day or lower for 32 consecutive weeks will be discontinued from study drug and withdrawn from the study as they will have the option to transition to commercial drug. Dose reductions may be performed if warranted due to adverse events (AEs) or hypophenylalaninemia. Dose increases to up to 60 mg/day may be performed per investigator discretion in consultation with the sponsor's medical monitor. Dosing will continue for approximately 121 weeks. After providing informed consent, subjects undergo screening evaluations to determine study eligibility. Screening assessments must be performed within 28 days of the first 165-304 dose of pegvaliase on Day 1. Study PAL-003 or 165-302 Study Completion Visit assessments may be used for the purpose of screening, with Day 1 of 165-304 taking place the same day. Pegvaliase dosing should continue without interruption from the previous study; beginning on Day 1, subjects will receive the same dose and regimen of pegvaliase they were receiving in 165-302 or PAL-003. Subsequent revisions to dosing regimens are allowed following consultation with the medical monitor.

A subject (or a subject-designated caregiver) must have met predefined self-administration criteria in PAL-003 or 165-302 to qualify for pegvaliase self-administration, including demonstrated working knowledge of the signs and symptoms of a hypersensitivity reaction, including anaphylaxis, and what to do if a hypersensitivity reaction is suspected. Eligible subjects (or caregivers) have been trained to self-administer pegvaliase.

A competent adult will observe the subject during pegvaliase administration and for a minimum of 1 hour following pegvaliase administration upon reintroduction of pegvaliase after resolution of a Grade 3 or higher hypersensitivity adverse event (HAE), any dose interruption of ≥ 4 days, and for a dose increase to 60 mg/day; administration of pegvaliase may only be performed if this person is present. Observations should be performed for all doses administered for 1 week after reintroduction of pegvaliase or a dose increase to 60 mg/day. Information and training on how to recognize a possible reaction, the severity of the reaction, and instructions on what to do if a reaction occurs will be provided to any person designated to observe the subject during pegvaliase administration.

Following a dose interruption of ≥ 4 doses that is not due to safety, the investigator should consult with the medical monitor and obtain approval from the medical monitor prior to the subject restarting pegvaliase.

Subjects are given 2 epinephrine injectors and are instructed to carry 1 epinephrine injector with them at all times. Each subject is contacted weekly to monitor for self-administration problems and/or AEs. Premedication with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen)

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should be administered approximately 2 to 3 hours prior to pegvaliase administration for 1 week upon reintroduction of pegvaliase after resolution of a grade 3 or higher HAE, following any dose interruption of ≥ 4 days, and for a dose increases to 60 mg/day. If a non-steroidal anti-inflammatory medication (NSAID) is administered as a premedication, it should be given with food. Subjects may also be pre-medicated at any time in the study at the discretion of the investigator. Subjects are provided with a workbook to document the date and time of pegvaliase injections, the injection site, and suspected AEs.

A subject's ability to maintain a consistent diet is essential for the success of the study by ensuring that the efficacy and safety end points are attributable to study treatment rather than to changes in dietary protein intake. A dietitian under investigator supervision will manage subject diet for the entire duration of the study. Subjects are provided 3-day diaries in which all dietary protein intake (including medical food and intact food) must be recorded for 3 consecutive days immediately prior to each scheduled clinic visit for review with a dietitian. All subjects will be provided the option of tyrosine supplementation (500 mg, 3 times per day with meals) at the discretion of the investigator. Subjects are instructed not to change their dietary protein intake during the study.

Because the risks of taking pegvaliase during pregnancy and breastfeeding are unknown, subjects cannot take pegvaliase if they are trying to conceive, are pregnant, or are breastfeeding. Subjects must be willing to use 2 acceptable methods of contraception while participating in the study and until 4 weeks after the study. Male subjects who are planning to impregnate a female partner and female subjects who are trying to become pregnant during the study must be temporarily discontinued from pegvaliase for 4 weeks prior to trying to conceive. During that time, subjects must use 2 acceptable methods of contraception. Subjects who are planning to become pregnant (or impregnate a female partner) may modify their diet in consultation with the investigator and/or study dietitian. Subjects who are confirmed to be pregnant by a serum pregnancy test and are temporarily off pegvaliase are not required to perform the scheduled urine pregnancy tests. Subjects who are pregnant or are trying to conceive and have temporarily discontinued pegvaliase should not perform the scheduled pharmacokinetic (PK) assessments. Male subjects who have impregnated a female partner may re-start pegvaliase after conception following the investigator's consultation with and approval by the medical monitor. Male subjects must use a barrier method for contraception prior to restarting pegvaliase. Female subjects who remain in the study after temporary discontinuation of pegvaliase due to pregnancy may restart pegvaliase dosing after a confirmed negative urine pregnancy test result, the birth (or termination of the pregnancy) has been reported, and breastfeeding has been completed (if applicable), or after the subject is no longer actively trying to conceive. Re-starting pegvaliase dosing requires prior consultation with the investigator and approval by the medical monitor. Female subjects must return to the protocol-required contraception use, which must include 1 barrier method, immediately after the birth (or termination of the pregnancy).

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Except for subjects transitioning to commercial drug, if pegvaliase is discontinued before study completion, every effort will be made to maintain the subject in the study and continue study visits and assessments, provided the subject's health, safety, and welfare are not detrimentally affected.

In addition to BioMarin, a Data Monitoring Committee (DMC) monitors the safety of study subjects. The DMC is an independent committee that acts in an advisory capacity to BioMarin.

Response to Hypersensitivity Adverse Events

Subjects are evaluated for safety throughout the study and are trained to recognize potential HAEs (including anaphylaxis) and how to respond. Subjects are instructed to contact the investigator for any suspected HAE. After a telephone assessment, the investigator may require further evaluation at the clinic. If a hypersensitivity reaction (eg, injection-site reaction, rash, joint pain, itching) occurs, the subject may be advised to premedicate with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen) approximately 2 to 3 hours prior to subsequent pegvaliase doses. If NSAIDs are administered as a premedication, they should be given with food.

HAEs, including anaphylaxis, are expected with pegvaliase administration. In response to a suspected HAE, pegvaliase dosing may be modified or halted depending on the severity of the event and suspected pegvaliase causality. Severity for HAEs will be per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades.

Subjects who experience an injection-site skin reaction that lasts ≥14 days including reactions that could be potential vasculitis should be referred to a dermatologist for consultation and a skin biopsy.

Individual Stopping Criteria

Subjects who have an NCI-CTCAE grade ≥ 3 anaphylaxis event that is, in the judgment of the investigator and the sponsor's medical monitor, related to study drug and suspected to meet Brown's criteria for severe (grade 3) hypersensitivity may be permanently discontinued from study drug.

Dosing in Response to Hypersensitivity Adverse Events

Dosing in response to an HAE depends on the NCI-CTCAE grade and suspected relationship to study drug. Dosing instructions are as follows and are regardless of previous occurrence:

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NCI-CTCAE Grade [a]	Related to Study Drug	Action with Study Drug			Individual Stopping Criteria [d]	HRV Assessment [e]
		Maintain [b]	Reduce [c]	Interrupt [c]		
1	Yes or No	X	(X) Optional	(X) Optional		Investigator discretion
2	Yes or No	X	(X) Optional	(X) Optional		Investigator discretion
3	No	X	(X) Optional	(X) Optional		Investigator discretion
3	Yes	X	(X) Optional	(X) Optional		Yes (if within 24 hours of onset)
3 [d]	Yes				X Immediately consult with sponsor medical monitor	Yes (if within 24 hours of onset)
4 [d]	Yes or No				X Immediately consult with sponsor medical monitor	Yes (if within 24 hours of onset)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events, version 5.0; HRV, Hypersensitivity Reaction Visit; NCI, National Cancer Institute.

[a] NCI-CTCAE grade determination is performed by the investigator and may be done either via telephone or clinic visit.

[b] The investigator will instruct the subject to maintain the pegvaliase dose at the time of AE onset until improvement to grade 1 or resolution (per investigator assessment in the clinic or via telephone).

[c] The pegvaliase dose may be reduced or interrupted if necessary per investigator determination.

[d] If a subject has an NCI-CTCAE grade ≥ 3 anaphylaxis event that is related to study drug and is suspected to meet Brown's criteria for severe (grade 3) hypersensitivity in the judgment of the investigator and the sponsor's medical monitor, the subject may be permanently discontinued from study drug.

[e] If the investigator determines that the NCI-CTCAE grade ≥ 3 hypersensitivity reaction is related to administration with study drug, the subject will be asked to return to the clinic within 24 hours of event onset for a hypersensitivity reaction visit (HRV) assessment, including laboratory tests (chemistry, hematology, urinalysis, anti-pegvaliase IgE [sampling must be performed > 8 hours after event onset and before the next dose of study drug], urine albumin/creatinine ratio, urinary N-methyl histamine, CRP, C3, C4, and tryptase).

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Once an AE (other than anaphylaxis) improves to grade 1 or resolves, the pegvaliase dose may be increased, maintained, or reduced, at the discretion of the investigator. If reduced, the recommended pegvaliase dose reductions include: from 60 mg/day to 40 mg/day, from 50 mg/day to 20 mg/day, or from 40 mg/day to 20 mg/day, with reductions from intermediate doses at the discretion of the investigator. If dosing has been interrupted due to an AE (other than anaphylaxis) and the investigator determines it is safe for the subject to resume dosing, the first dose after improvement of the AE should be performed in the clinic.

Additionally, the subject should be premedicated with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen) approximately 2 to 3 hours prior to each dose of pegvaliase for 1 week upon return to dosing if the dose interruption is ≥ 4 days. If NSAIDs are administered as a premedication, they should be given with food. Also, a competent adult should observe the subject during pegvaliase administration and for a minimum of 1 hour following pegvaliase administration for 1 week upon return to dosing if the dose interruption is ≥4 days; administration of pegvaliase may only be performed if this person is present.

Response to Anaphylaxis

If the investigator suspects that the event is anaphylaxis, the subject will be assessed in the clinic and the sponsor's medical monitor should be immediately notified. Laboratory assessments for suspected anaphylaxis events should be performed prior to the next administration of pegvaliase (if applicable) and include anti-pegvaliase IgE (for optimal results, sampling must be performed > 8 hours after event onset) and tryptase (for optimal results, perform within 24 hours of event onset). If the investigator determines it is safe for the subject to resume dosing with pegvaliase following resolution of anaphylaxis, the dose level will be reduced as follows:

Scheduled Dose at Time of Anaphylaxis Onset	Dose Following Resolution of Anaphylaxis Event [a]
50 mg/day	20 mg/day
60 mg/day	40 mg/day

[a] Dose may be lowered further per investigator discretion. Dose frequency should be the same as the dose regimen at the time of anaphylaxis onset; however, dose frequency may be revised per investigator discretion and in consultation with the sponsor's medical monitor.

The first dose administered after resolution of anaphylaxis is to be administered at the clinic with equipment for emergency resuscitation (including epinephrine) within easy access. Additionally, the subject should be premedicated with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen) approximately 2 to 3 hours prior to each dose of pegvaliase for 1 week upon return to dosing regardless of the duration of dose interruption. If NSAIDs are administered as a premedication, they should be given with food. Also, a competent adult should observe the subject during pegvaliase administration and for a minimum of 1 hour following pegvaliase administration

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for 1 week upon return to dosing regardless of the duration of dose interruption; administration of pegvaliase may only be performed if this person is present.

Study Stopping Criteria for Adverse Events during Treatment with Pegvaliase

If an anaphylaxis event occurs **and** meets Brown's criteria for severe (grade 3) hypersensitivity, the DMC chair and/or committee will be informed to review and advise the sponsor on potential changes to the study conduct. Clinically severe hypersensitivity (Brown's criteria, severe [grade 3]) is defined as significant hypoxia, hypotension or neurologic compromise that is life-threatening or required treatment to prevent a life-threatening event:

- Cyanosis or $SpO_2 \leq 92\%$
- Hypotension with SBP < 90 mm Hg (adults)
- Neurologic alteration: confusion, loss of consciousness, collapse, or incontinence

NUMBER OF SUBJECTS PLANNED:

Approximately 40 subjects will be enrolled.

DIAGNOSIS AND ENTRY CRITERIA:

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

- Must be enrolled in PAL-003 or 165-302 Part 4 at the time of screening for 165-304 and most recently receiving pegvaliase at a dose > 40 mg/day
- Is at least 18 years of age and no older than 70 years of age at the time of screening
- Has identified a competent person or persons ≥ 18 years of age who can observe the subject during study drug administration and for a minimum of 1 hour following administration in situations required per protocol
  - A home healthcare nurse may perform the study drug observations.
- For females with childbearing potential, must have a negative pregnancy test at screening and be willing to have additional pregnancy tests during the study. (Females are considered not to have childbearing potential if they have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy.)
- If sexually active and not planning to become pregnant (self or partner), must be willing to use 2 acceptable methods of contraception while participating in the study and for 4 weeks after the study:
  - Acceptable methods of contraception include: (1) primary forms: hormonal (combination hormone-containing pills, patch, vaginal ring, or intrauterine device) or non-hormonal (copper-containing intrauterine device, tubal sterilization); (2) secondary forms: includes barrier forms and other forms of birth control and must include spermicide (eg, male condom; female condom is not an acceptable secondary form).

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- Males (including partners) post vasectomy for 2 years with no known pregnancies do not need to use any other forms of contraception during the study.
- Females (including partners) who have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy do not need to use any other forms of contraception during the study.

- Is 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; a legally authorized representative may provide written consent and assent may be requested
- Is willing and able to comply with all study procedures
- Is in generally good health, as evidenced by physical examination and/or clinical laboratory evaluations (hematology, chemistry, and urinalysis)

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

- Use of any investigational product (except pegvaliase) or investigational medical device within 30 days prior to screening or requirement for any investigational agent prior to completion of all scheduled study assessments
- Use of any medication (except pegvaliase) intended to treat PKU, including the use of large neutral amino acids, within 2 days prior to the administration of pegvaliase (Day 1)
- Use or planned use of any injectable drugs containing PEG (other than pegvaliase), including medroxyprogesterone injection, within 3 months prior to screening and during study participation
- A history of organ transplantation or on chronic immunosuppressive therapy
- A history of substance abuse (as defined by the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders [DSM]) in the past 12 months or current alcohol or drug abuse
- Current participation in the Kuvan® registry study (PKU Demographics, Outcomes and Safety [PKUDOS])
- Concurrent disease or condition that would interfere with study participation or safety (eg, history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurological, oncologic, or psychiatric disease)
- Any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or terminating early from the study

INVESTIGATIONAL PRODUCT, DOSE, ROUTE, AND REGIMEN:

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Pegvaliase is recombinant Anabaena variabilis phenylalanine ammonia lyase-PEG and is provided in prefilled syringes to subjects for subcutaneous self (or caregiver) administration.		
DURATION OF TREATMENT: Approximately 121 weeks		

STATISTICAL METHODS AND CRITERIA FOR EVALUATION:

Sample Size:

Subjects who were previously treated with pegvaliase (doses > 40 mg/day) in Studies PAL-003 or 165-302 may be enrolled into this study. No formal sample size calculation was conducted for this study. Approximately 40 subjects are expected to be enrolled.

Analysis Populations:

The safety population will consist of all subjects who receive at least 1 dose of pegvaliase during the study.

The efficacy population will consist of all subjects who receive at least 1 dose of pegvaliase during the study and have post-treatment blood Phe concentration measurements.

The PK population will consist of all subjects with at least 1 PK measurement.

Safety Analysis: All subjects who receive any amount of pegvaliase in this study will be included in the safety analyses. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity. A by-subject listing will be provided for those subjects who experience a serious AE (SAE), including death, or experience an AE associated with early withdrawal from the study or study drug. Hypersensitivity AEs and AEs that result in dosing interruption or dose level reduction and the percentage of subjects who report these AEs will be presented.

Other Safety Variables: Clinical laboratory data will be summarized by the type of laboratory test. Frequency and percentage of subjects who experience abnormal (ie, outside of reference range) and/or clinically significant abnormalities after pegvaliase administration will be presented for each clinical laboratory test. For each clinical laboratory test, descriptive statistics will be provided for baseline and all subsequent visits. Changes from baseline to the post-baseline visits will also be provided. Descriptive statistics for vital signs, physical examination results, electrocardiogram (ECG) test results, and immunogenicity test results will also be provided. Additionally, antibody incidences and titers will be summarized at the scheduled time point.

Efficacy Analysis: Data from all subjects who receive any amount of pegvaliase and who have any post-treatment efficacy data will be included in the efficacy analysis.

Blood Phe concentration at each scheduled time point will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Change in blood Phe

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concentration from baseline (to be defined in the Statistical Analysis Plan [SAP]) to each scheduled time point will also be summarized. The relationship between dietary Phe and protein intake (per information reported on the subject diet diary) and blood Phe concentration will also be explored. **Pharmacokinetics Analyses**: Trough concentrations of pegvaliase will be evaluated to assess steady-state trough exposure. Pegvaliase trough concentrations will be summarized descriptively by study visit.		

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACMG	American College of Medical Genetics and Genomics
ADHD-RS	Attention Deficit Hyperactivity Disorder Rating Scale
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BH4	tetrahydrobiopterin
BPV	BioMarin Pharmacovigilance
C3	complement component 3
C4	complement component 4
CFR	Code of Federal Regulations
CIC	circulating immune complex
C_{max}	maximum observed plasma concentration
CRA	Clinical Research Associate
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DSM	American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ENU2	BTBR*Pah*^{enu2} mouse model
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAE	hypersensitivity adverse event
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRV	Hypersensitivity Reaction Visit
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgE	immunoglobulin E

IgG	immunoglobulin G
IgG4	immunoglobulin G4
IgM	immunoglobulin M
IP	investigational product
IND	investigational new drug
IRB	Institutional Review Board
I/T/M	induction and gradual up-titration to maintenance dosing regimen
MedDRA	Medical Dictionary for Regulatory Activities
MNT	medical nutritional therapy
NCI	National Cancer Institute
NIAID/FAAN	National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
NIH	National Institutes of Health
NOAEL	no observable adverse effect level
NSAID	non-steroidal anti-inflammatory medication
PAH	phenylalanine hydroxylase
PAL	phenylalanine ammonia lyase
PD	pharmacodynamics
PEG	polyethylene glycol
Phe	phenylalanine
PK	pharmacokinetics
PKU	phenylketonuria
PKUDOS	PKU Demographics, Outcomes and Safety
rAvPAL-PEG	recombinant *Anabaena variabilis* phenylalanine ammonia lyase-PEG
RDA	recommended dietary allowance
RDT	Randomization Discontinuation Treatment
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SDV	source data verified
SGOT	serum glutamic oxalo-acetic transaminase
SGPT	serum glutamic pyruvate transaminase
SOI	Statement of Investigator
SpO_2	blood oxygen saturation
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	elimination half-life
T_{max}	time to maximum concentration
US	United States

Definition of Terms:

Investigational Product (IP):

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation [ICH] of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6 R2]).

The terms "IP", "study drug", and "pegvaliase" are used interchangeably in the protocol.

5 ETHICS

BioMarin Pharmaceutical Inc. (hereafter referred to as BioMarin or the sponsor) conducts its studies according to the highest ethical and scientific standards. The following sections articulate standards to which investigators will be held accountable, as well as matters of compliance to document adherence to such standards.

5.1 Institutional Review Board or Independent Ethics Committee

Investigators are expected to interact with Ethics Committees (ECs) promptly, as required, during the course of the study. This includes, but is not limited to, providing appropriate documentation to support study initiation and maintaining appropriate flow of safety and other information during the course of the study and for study close-out activities. BioMarin (or designee) will assist investigators with access to timely and accurate information and with assurance of prompt resolution of any queries.

Prior to initiating the study, the investigator will obtain written confirmation that the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) [for Canadian protocols, Research Ethics Board (REB)] 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/EC/REB will be provided to BioMarin Pharmaceutical Inc. (BioMarin) or its designee. The investigator will provide the IRB/EC/REB with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated for subjects who do not speak the local language at the clinical site. The study will not be initiated and investigational product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/EC/REB confirming unconditional approval of the protocol, the ICF, and all subject recruitment materials are obtained in writing by the investigator and copies are received at BioMarin or its designee. 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 to the IRB/EC/REB and BioMarin by the investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

It is expected that investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible subjects for study enrollment; adhering to adverse event (AE) reporting, diagnostic, or other procedures as specified in the protocol; and assuring appropriate compliance with study treatment administration and accountability.

This study will be conducted in accordance with the following:

- European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, for studies conducted within any European country
- 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(R2) (ICH E6 R2)
- The ethical principles established by the Declaration of Helsinki

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/EC 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, or his/her legally authorized representative, will provide written, informed consent before any study-related tests or evaluations are performed.

5.3 Subject Information and Informed Consent

A properly written and executed informed consent form (ICF), in compliance with ICH E6 R2 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, 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 provide the documents to BioMarin for approval prior to submission to the IRB/EC/REB approval. BioMarin and the IRB/EC/REB must approve the documents before they are implemented. A copy of the approved ICF and, if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

A subject with a legally authorized representative will provide written assent (if required), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent. The investigator will provide copies of the signed ICF to each subject (or the legally authorized representative of the subject) and will maintain the original in the record file of the subject.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

During administration of informed consent, expectations regarding participation in the study should be made clear to subjects. Subjects who are not willing and/or are not able to comply with all aspects of the study should not be encouraged to participate.

Prior to beginning the study, the investigator at each site must provide to BioMarin or designee a fully executed and signed Statement of Investigator (SOI) form. A US Food and Drug Administration (FDA) Form FDA 1572 serves as an acceptable SOI form. If Form FDA 1572 may not be used in a particular region, the investigator must provide a fully executed SOI on the form provided by the sponsor. All investigators and sub-investigators must be listed on Form FDA 1572 or its equivalent SOI. Financial Disclosure Forms must also be completed for all investigators and sub-investigators listed on Form FDA 1572 or the SOI 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. BioMarin's Pharmacovigilance Department (or designee) will be responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities as required.

In multicenter studies, a coordinating investigator will be identified who will be responsible for study overview. The coordinating investigator will read the clinical study report (CSR) and confirm that it accurately describes the conduct and results of the study, to the best of his or her knowledge. The coordinating investigator will be chosen on the basis of active participation in the study, ability to interpret data, and willingness to review and sign the report in a specified timeframe. The identity of the coordinating investigator and a list of all investigators participating in the study will be provided in the CSR.

Home healthcare may be administered by a vendor that is provided by the sponsor or a study site. Training and oversight of home healthcare personnel will be provided by the sponsor.

Pharmacokinetic tests and antibody tests will be performed by BioMarin or a contract research organization (CRO). Clinical laboratory tests will be analyzed and processed by a central laboratory, with the exception of urine pregnancy tests, which will be analyzed by a local laboratory. A central laboratory will also be used to perform analysis of blood phenylalanine (Phe) concentrations.

7 INTRODUCTION

Phenylketonuria (PKU, OMIM 261600) is a rare autosomal recessive genetic disorder that is characterized by an inability of the body to break down the amino acid, phenylalanine (Phe), and is caused by mutations in the gene encoding phenylalanine hydroxylase (PAH). The estimated prevalence of PKU is 1 in 15,000 births in the United States (NIHCDP, 2001). 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.

The pathophysiology of PKU is well understood. A substantial body of evidence confirms that elevated Phe is directly toxic to cells in the brain, where it causes inhibition of protein synthesis in humans and animals (Wall, 1990), affects the normal morphology of myelinating proteins (Dyer, 1996), and leads to arrested or delayed development of dendrites and synapses in the cerebral cortex (Huttenlocher, 2000). Neuropathology in PKU has been shown to derive from oxidative stress, impaired neurotransmitter metabolism, impaired protein synthesis and lipid metabolism, and brain energy metabolism alterations (Schuck, 2015). The neurotoxicity of elevated Phe is a direct effect of Phe itself (Kaufman, 1989); no abnormal Phe metabolites are observed in the PKU individual and normal Phe metabolites are toxic only at concentrations that are much higher than those reported in individuals with PKU.

Without highly restricted Phe intake, individuals with PKU quickly reach and sustain toxic concentrations of blood Phe. Individuals with classic PKU may have a complete absence or profound deficiency of PAH and typically show very high elevations of blood Phe ($\geq$ 1200 µmol/L). Uncontrolled blood Phe in adults is associated with executive dysfunction and significant behavioral and psychiatric problems, including depression and anxiety, and results in a negative impact on patient quality of life (Moyle, 2007; Pietz, 1997; Smith, 2000; Waisbren, 1999; Gassio, 2003). High blood Phe levels negatively affect mood and ability to sustain attention in adults with PKU (ten Hoedt, 2011). Studies have reported widespread correlations between improved cognitive performance in adults with PKU and control of blood Phe during their life span (Palermo, 2017; Romani, 2017). The prevalence of psychiatric and neurologic symptoms in adults with PKU is higher than the US National Institutes of Health estimates for disease prevalence in adults in the general population (NIMH, 2013).

The American College of Medical Genetics and Genomics (ACMG) practice guidelines for PKU recommend life-long management and maintenance of metabolic control as essential to optimal functioning of individuals with PKU, with a goal of maintaining blood Phe

concentrations ≤ 360 µmol/L (Vockley, 2014). Similar European guidelines for the management of PKU recommend treatment target Phe levels of ≤ 600 µmol/L for patients older than 12 years (van Spronsen, 2017).

Historically the only treatment option available for patients with PKU was medical nutritional therapy (MNT) with severe restriction of Phe intake, alone or as adjunct to Kuvan® (sapropterin 6R-tetrahydrobiopterin or 6R-BH4). Phe restriction with MNT involves consumption of semisynthetic medical foods that provide a source of Phe-free protein, modified low-protein foods, small amount of natural protein (to provide required amounts of Phe), and other supplements (eg, vitamins, minerals) to correct nutritional deficiencies that can result from Phe restriction. MNT with severe Phe restriction can help some patients control their blood Phe levels, although data show that even when PKU patients report adherence with MNT, many patients continue to have very high blood Phe levels of approximately 926 µmol/L (Koch, 2002), demonstrating that MNT is not an effective treatment option for many adults with PKU. For the majority of adults with PKU, chronic MNT with Phe restriction is not sustainable nor feasible as a treatment option (Walter, 2002; Burton, 2010).

BioMarin has developed pegvaliase, a genetically modified phenylalanine ammonia lyase (PAL) enzyme product of the cyanobacterium *Anabaena variabilis* that is PEGylated to decrease immunogenicity and increase half-life, as a novel treatment for PKU.

A brief review of pegvaliase (also referred to as rAvPAL-PEG or BMN 165) is provided below. A comprehensive review of pegvaliase is contained in the Investigator's Brochure supplied by BioMarin. Investigators are to review this document prior to initiating this study.

7.1 Nonclinical Studies

The nonclinical program was specifically designed to support the chronic use of pegvaliase for PKU patients 16 years of age and older. The studies completed were comprehensive and included single and repeat-dose pharmacodynamic (PD), safety pharmacology, toxicokinetic and toxicity evaluations in ENU2 mice, and normal rats and monkeys. Developmental and reproductive toxicity studies were conducted in rats and rabbits. The pharmacological activity of pegvaliase was demonstrated in a rodent model of PKU, the ENU2 mouse. ENU2 mice exhibit hyperphenylalaninemia similar to PKU patients and were utilized to help determine initial dose levels of pegvaliase for clinical trials. All nonclinical studies used the subcutaneous (SC) route of administration, and the results from these studies were used to inform the starting clinical dose of pegvaliase.

7.1.1 Pharmacology

Pharmacology was assessed in the BTBR *Pah*^{enu2} (ENU2) mouse model of PKU. The ENU2 mouse model exhibits characteristics similar to those of PKU patients, including hyperphenylalaninemia (baseline plasma Phe concentrations of 1000 to 2000 μM) and hypopigmentation. The repeat-dose studies in the BTBR*Pah*^{enu2} mouse demonstrated the pegvaliase-related pharmacological activity resulting in decreased plasma Phe levels. There were no pegvaliase-related effects on respiratory or central nervous system parameters after a single SC administration to rats or cardiovascular parameters after a single SC administration to monkeys.

7.1.2 Pharmacokinetics

The pharmacokinetics (PK) of pegvaliase in rats, rabbits, and monkeys were similar to humans with respect to a 1-compartment model with 1st order absorption and elimination. Time to maximum concentration (T_{max}) and elimination half-life ($t_{1/2}$) were 1 to 3 days, and there was evidence of accumulation in all species. AUC and maximum observed plasma concentration (C_{max}) were approximately dose proportional, with a high inter-animal variability in pegvaliase plasma levels at a given dose. Pegvaliase exposure decreased with multiple dosing, likely attributable to anti-drug antibody responses; exposures returned to levels comparable to Week 1 after Week 4 in the rat. Inter-animal variability in anti-drug antibody response and accumulation were high after repeat pegvaliase administration.

7.1.3 Toxicology

The nonclinical safety program for pegvaliase included single-dose and repeat-dose toxicity studies in rats and monkeys in order to characterize the potential toxicity and exaggerated pharmacology of pegvaliase. Developmental and reproductive toxicity studies were also conducted in rats and rabbits. The studies included toxicological endpoints as well as toxicokinetic and immunogenicity parameters. Plasma Phe levels were also assessed as a primary PD endpoint. The main pegvaliase safety-related findings identified from nonclinical studies were: (1) dose-dependent polyethylene glycol (PEG)-related findings, including vacuolation of renal tubule cells and histiocytic cells, in the repeat-dose rat toxicity studies, (2) dose-dependent, pegvaliase-related arterial inflammation in small arteries and arterioles in cynomolgus monkeys, and (3) dose-dependent reductions in body weight gain and maternal and fetal toxicity attributed to sustained reduction of Phe levels to below normal in wild-type animals. These findings were dose and time dependent, and resolved or partially resolved after a recovery period. The identified hazards from the nonclinical studies helped inform safety monitoring in clinical trials with pegvaliase.

7.1.3.1 Safety Factors for the Phase 3 Starting Dose Based on the Chronic Nonclinical NOAELs

Safety factors were derived from no observable adverse effect level (NOAEL) PK data obtained following the first SC dose in the 26-week rat and 39-week monkey studies and the first 2.5 mg (0.03 mg/kg) SC dose in the Phase 1 (PAL-001) clinical study. The predicted C_{max} and $AUC_{0\text{-}inf}$ in humans at the Phase 3 starting dose level of 2.5 mg/week in naïve patients are, respectively, 298 ng/mL (C_{max}) and 50,658 ng-hr/mL ($AUC_{0\text{-}inf}$). A challenge with the safety factor determination was the high variability in exposure following repeat dosing in both animals and humans, believed to be due to the generation of anti-drug antibodies that bind to and rapidly reduce pegvaliase exposure. This initial reduction followed by a later increase in exposure has made obtaining a robust steady-state plasma drug level challenging. A conservative method was used to estimate the safety factors using PK data following the first dose (up to 72 hours post-dose), where anti-drug antibody effect was negligible, and plasma drug levels were high.

Given the nonclinical PK data and expected Phase 3 exposure in humans based on PAL-001, safety factors calculated for peak exposure (C_{max}) are 4.4-fold and 78.6-fold higher than anticipated human exposure based on rat and monkey data, respectively. On a systemic exposure basis, safety factors calculated from $AUC_{0\text{-}72hr}$ are 1.3-fold (rat) and 18.3-fold (monkey) higher than anticipated human exposure.

7.2 Previous Clinical Studies

The pegvaliase clinical development program has included 8 clinical studies, representing the largest development program conducted to date in adults with PKU: a single-dose Phase 1 study (PAL-001); 3 multi-dose Phase 2 studies (PAL-002, PAL-004, and 165-205) that were followed by the Phase 2 long-term open-label study (PAL-003); and 3 Phase 3 studies (165-301, 165-302, and the 165-302 substudy 165-303). The Phase 2 long-term open-label study PAL-003 and Part 4 open-label extension of Phase 3 Study 165-302 are ongoing to assess long-term efficacy and safety.

Pegvaliase clinical studies included adult patients with a PKU diagnosis and blood Phe concentration > 600 µmol/L at screening and over the past 6 months. Baseline characteristics and demographics demonstrate that the studied population in pegvaliase clinical trials is representative of the general adult PKU population, including the high mean blood Phe values demonstrating significant need for effective treatment options to control blood Phe. Results from these studies have shown that pegvaliase is well tolerated and reduces blood Phe levels. Refer to the Investigator's Brochure for detailed results from previous clinical studies.

7.3 Study Rationale

Study 165-304 is an open-label extension for subjects who participated in Studies PAL-003 and 165-302 at doses > 40 mg/day. The objective is to evaluate long-term safety and efficacy in subjects treated at doses exceeding the currently approved pegvaliase label (the label specifies up to and including 40 mg/day dose only).

Literature reports suggest the majority of adults with PKU cannot adhere to severe Phe intake restrictions (Cunningham, 2012). Even among adults reporting to adhere to severe Phe intake restrictions, the majority fail to maintain recommended blood Phe levels (Modan-Moses, 2007). Baseline blood Phe levels and diet from previous pegvaliase clinical studies confirm this finding among adult participants. Adults with PKU with poor metabolic control represent a patient population in great need of additional therapeutic options.

7.4 Summary of Overall Risks and Benefits

7.4.1 Analysis of Condition

Phenylketonuria is a serious inherited metabolic disorder in which Phe accumulates to abnormally high levels in the blood and brain, resulting in significant negative effects on neurocognitive, neuropsychological, and executive function performance in adults with PKU.

Phenylketonuria is estimated to occur in 1 in 15,000 newborns in the United States. As a result of newborn screening efforts implemented in the 1960s and early 1970s, virtually all individuals with PKU or PAH deficiency under the age of 40 are diagnosed at birth and treatment is implemented soon thereafter.

Adult PKU patients often have untreated blood Phe levels > 1,200 µmol/L. Historically, there were 2 treatment options available for patients with PKU: medical nutritional therapy (MNT) with Phe restriction, and sapropterin dihydrochloride (Kuvan) as adjunct to MNT and Phe restriction. Most PKU patients require lifelong stringent Phe restriction and MNT to control blood Phe levels and to help prevent complications associated with high Phe levels in the brain.

Uncontrolled blood Phe in adulthood is associated with impairment of neuropsychiatric, neurocognitive, and executive function, a heterogeneous variety of behavioral and psychiatric problems including depression and anxiety, and negatively affects patient quality of life (Moyle, 2007; Pietz, 1997; Smith, 2000; Waisbren, 1999; Gassio, 2003). High blood Phe levels also negatively affect mood and the ability to sustain attention in adults with PKU (ten Hoedt, 2011). Several interventional studies of restricted Phe intake to control blood Phe in adult PKU patients have shown improvements on neuropsychiatric and executive function domains when subjects are at lower blood Phe levels (Bilder, 2016). These findings suggest

that neuropsychiatric and executive functioning deficits are reversible in adults with PKU. Other recently published studies have reported widespread correlations between cognitive performance in adults with PKU and control of Phe during their lifespan, suggesting that it is important to maintain low blood Phe through life in order to provide optimal neurocognitive function (Palermo, 2017; Romani, 2017).

The American College of Medical Genetics and Genomics (ACMG) practice guidelines recommend lifelong management of PKU, with a goal of maintaining blood Phe concentrations ≤ 360 µmol/L (Vockley, 2014). Similar European guidelines for the management of PKU recommend treatment target Phe levels of ≤ 600 µmol/L for patients older than 12 years of age (van Spronsen, 2017).

7.4.2 Unmet Medical Need and Current Treatment Options

There is a significant unmet need for patients with PKU because lifelong control of blood Phe levels with Phe restriction and MNT alone is unachievable for most patients, and addition of Kuvan to treatment is only effective in a sub-population of patients with less severe PKU (Blau, 2015).

Medical Nutritional Therapy (MNT)

Although strict adherence to Phe restriction and MNT can be effective in lowering blood Phe levels and preventing the severe neurological consequences of high blood Phe levels, most adult PKU patients are unable to maintain target blood Phe levels with restriction in protein intake alone, as lifelong restriction of natural protein and adherence to MNT imposes such a personal and social burden that it becomes practically impossible to sustain for the vast majority of subjects. For the majority of adults with PKU, chronic MNT with Phe restrictions is not sustainable nor feasible as a treatment option as most foods contain protein (Walter, 2002; Burton, 2010). In a study monitoring adherence to a low Phe diet, 78% of the adult PKU population were not maintaining nutritional low-Phe restrictions (Walter, 2002).

The stringent MNT with onerous Phe-restriction proscribes consumption of natural protein such as meat, fish, chicken, eggs, nuts, beans, milk, and other dairy products as well as many higher protein grains and starches, thus significantly limiting food choices. In addition, PKU patients require concomitant administration of unpalatable synthetic Phe-free amino acid supplements to ensure adequate nutritional intake of protein. The stringent MNT has been found to cause nutritional deficiencies (eg, in vitamin B12 and other B vitamins, vitamin D, folate, calcium, and iron with associated health consequences), as well as social isolation related to the important role of food in our social interactions, the time burden of planning, assessing, calculating, and recording food intake, and the very limited number of natural

foods that can be eaten (MacDonald, 2016). PKU patients also suffer the impact of significant risk factors for non-PKU morbidity related to MNT, such as obesity, bone disease and dietary deficiencies, which result from a lifetime of attempted and increasingly unachievable control of Phe intake.

In addition, chronically elevated blood Phe levels can, by compromising the neurocognitive functions needed to maintain adherence to MNT, potentially create a negative cycle of worsening disease control. Tasks such as monitoring dietary Phe intake, menu planning, avoiding prohibited foods, remembering to order MNT and low protein foods, and attending clinical appointments and routine blood testing visits may all be compromised by the effects of chronically elevated blood Phe levels.

Sapropterin Dihydrochloride (Kuvan)

Sapropterin dihydrochloride (Kuvan) is a synthetic oral formulation of BH4, which works by increasing PAH activity in PKU patients with some residual enzyme function (Blau, 2015). Kuvan is an approved pharmacological treatment for children and adults for the treatment of BH4-responsive PKU in the US. Approval of Kuvan was based on demonstrating blood Phe reduction in clinical trials and is indicated for use in conjunction with Phe-restricted intake to lower blood Phe concentrations. However, only approximately 20% to 56% of PKU patients respond to sapropterin therapy.

Pegvaliase (Palynziq®)

Pegvaliase was approved in the United States on 24 May 2018 under the name Palynziq for maintenance dosages up to 40 mg/day to reduce blood Phe concentrations in adult patients with PKU who have uncontrolled blood Phe concentrations > 600 µmol/L on existing management, addressing a substantial unmet medical need for the adult PKU patient population. On 3 May 2019, pegvaliase was also approved in the EU to reduce blood Phe in patients with PKU aged 16 years and older who have inadequate blood Phe control (defined as blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options.

7.4.3 Clinical Benefit

Treatment of PKU by replacement of the PAH enzyme is not technically feasible because of its poor stability and the requirement for sapropterin co-factor co-generation, which only occurs in hepatocytes. Therefore, a search was undertaken for a BH4 independent enzyme that would be active in plasma.

Substantial Reduction in Blood Phenylalanine

Phase 3 placebo-controlled and Phase 2 and Phase 3 long-term extension studies of pegvaliase for the treatment of adult subjects with PKU have shown evidence of blood Phe lowering effectiveness in adults with PKU with uncontrolled blood Phe > 600 µmol/L with existing treatment. Substantial and sustained blood Phe reductions were observed throughout the pegvaliase clinical program.

The first phase 3 study (165-301) characterized the safety and tolerability of the recommended low dose induction and gradual up-titration to maintenance (I/T/M) dosing regimen to a target dose of pegvaliase 20 mg or 40 mg/day of self-administered SC injections, using either a vial and syringe presentation or the proposed prefilled syringe (PFS) marketing presentation, to achieve a stable, pre-specified reduction in blood Phe of ≥ 20% from pre-treatment baseline prior entry to the Randomization Discontinuation Treatment (RDT) phase (Part 2) of pivotal study 165-302. Subjects who achieved ≥20% blood Phe reduction entered the RDT and were randomized to either continue pegvaliase treatment or start placebo for 8 weeks.

Subjects enrolled in 165-301 had a mean blood Phe level of ~1200 µmol/L at pre-treatment baseline, suggesting poor metabolic control. In the 8-week RDT portion of 165-302, pegvaliase-treated subjects maintained mean blood Phe levels at 527.2 µmol/L compared to their RDT baseline of 503.9 µmol/L. In the placebo-treated group, mean blood Phe levels increased to 1385.7 µmol/L compared to their RDT baseline of 536.0 µmol/L. Study 165-302 met its primary endpoint of change in blood Phe compared to each placebo group ($p < 0.0001$). This beneficial treatment effect represents a 62% improvement in blood Phe compared to placebo.

Among subjects in the I/T/M Population (all dose levels) who completed 1 year of treatment, 73.2% achieved ≥ 20% blood Phe reduction, 46.1% achieved blood Phe reduction to ≤ 360 µmol/L, and 34.6% achieved blood Phe reduction to ≤ 120 µmol/L within the year. A higher proportion of subjects met lower Phe reduction thresholds by 24 months of treatment: 79.5% achieved ≥ 20% blood Phe reduction, 62.0% achieved blood Phe reduction to ≤ 360 µmol/L, and 53.4% achieved blood Phe reduction to ≤ 120 µmol/L. These findings are clinically meaningful in the context of current ACMG management guidelines for the treatment of PKU recommending that serum Phe be maintained at ≤ 360 µmol/L throughout life for optimal clinical outcomes (Vockley, 2014).

These substantial and sustained reductions in blood Phe were achieved in adult PKU patients treated with pegvaliase despite a majority of patients (> 80%) not adhering to MNT at baseline and consuming significant amounts of protein from natural foods (mean intake 39 grams/day). Full Phe restriction for PKU patients typically allows minimal natural protein

intake outside of MNT, but a majority of the subjects in the pivotal study were estimated to be eating approximately 60% of the daily-recommended allowance for protein for a healthy adult as natural intact protein.

7.4.4 Risk

The safety of pegvaliase was evaluated in 6 multiple dose studies in adult PKU patients totaling 579.6 patient-years of exposure with the recommended I/T/M dosing regimen for pegvaliase, including 403.4 patient-years of exposure with the to-be-marketed PFS presentation. Thus, important identified and potential risks associated with pegvaliase use have been sufficiently characterized to inform benefit-risk decisions by adult PKU patients and their treating physicians.

The most commonly reported treatment-emergent AEs were arthralgia (72.6%), injection site reaction (64.9%), headache (51.2%), and injection site erythema (50.2%). In the I/T/M population hypersensitivity adverse events (HAEs) were very common (94%), and included arthralgia (71%), rash (38%), pruritus (31%), urticaria (30%), pyrexia (22%) and injection site rash (21%). The highest HAE severity was Grade 1 for 18.2% of subjects or Grade 2 for 62.5% subjects. Most (91.6%) HAEs did not require pegvaliase dose modification, and 97.5% of HAEs resolved. The mechanism of HAEs, including anaphylaxis, is Type III immune complex-mediated hypersensitivity, with the highest frequency of HAEs occurring during the first 6 months of pegvaliase dosing when early antibody responses – PEG IgM, PEG IgG and PAL IgM – and circulating immune complexes (CICs) are highest, and mean C3 and C4 complement levels are lowest. A reduction in the incidence and event rate of HAEs was observed after 6 months, as the anti-PEG IgG and IgM antibodies declined to baseline levels and CIC and C3/C4 levels returned towards baseline.

Type III, non-IgE-mediated anaphylaxis was the most clinically important identified risk in the pegvaliase development program. An independent allergist/immunologist assessed that 13/285 (4.6%) of the I/T/M study population experienced signs/symptoms consistent with a clinical diagnosis of anaphylaxis based on published diagnostic criteria (Sampson, 2006); 1.1% (3/285) of the anaphylaxis cases were assessed as severe based on published severity grading criteria specific to generalized hypersensitivity (Brown, 2004).

Signs and symptoms associated with anaphylaxis per sponsor's assessment against National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria were reported with higher rates in the first year (0.06 events/person-year in first 6 months and 0.08 events/person-year in the second 6 months) in the I/T/M study population. Of note, 8 (61.5%) subjects who experienced an initial anaphylaxis event continued pegvaliase treatment and 4 subjects did not have

recurrence of anaphylaxis. These observations and paucity of IgE detection support that the mechanism of anaphylaxis is Type III IC-mediated hypersensitivity rather than Type I hypersensitivity, which is associated with an immediate exaggerated response upon re-exposure to an allergen.

The incidence of severe anaphylaxis was reduced with pre-medication prior to pegvaliase injections, and all occurrences of anaphylaxis were managed successfully and resolved without sequelae.

While Type III HAEs and laboratory findings such as reduced complement levels have occurred with pegvaliase administration, there have been no reported events suggestive of pegvaliase induced ongoing immune complex-mediated end-organ damage.

7.4.5 Benefit-Risk Conclusions

Pegvaliase is a novel enzyme substitution therapy, indicated to reduce blood Phe in adult patients with PKU who have uncontrolled (> 600 µmol/L) blood Phe with existing management. A comprehensive clinical development program has demonstrated that prolonged exposure to pegvaliase is well tolerated and effective in reducing blood Phe concentration in adult patients with PKU.

A majority of adult PKU subjects completed induction and titration and continued to the maintenance phase of pegvaliase treatment with daily self-administered SC injections of pegvaliase, and experienced substantial and sustained reductions in blood Phe levels to within recommended treatment guidelines for PKU management. Significant blood Phe reductions were achieved in subjects consuming nearly the daily recommended allowance for protein as intact protein from natural foods. In addition, blood Phe reduction was associated with improvements in neurocognitive benefit as evidenced by long-term data on neurocognitive endpoints like the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD RS)-IV in open label extension.

Type III, non-IgE-mediated anaphylaxis was the most clinically important identified risk in the pegvaliase development program, occurring in 4.6% of the I/T/M study population. All occurrences of anaphylaxis were managed successfully with the safe use conditions implemented in the clinical studies.

Pegvaliase treatment at doses up to 40 mg/day demonstrated a positive benefit-risk balance in adults with PKU, with long-term treatment at doses greater than 40 mg/day up to 60 mg/day dose, inclusive, to be further evaluated in the 165-304 open-label extension study.

Pegvaliase can address an unmet medical need for adult PKU patients who have uncontrolled blood Phe despite the current treatment options of chronic stringent Phe restriction and

MNT with or without the addition of Kuvan treatment, and has the potential to have a meaningful impact on the lives of adult PKU patients.

8 STUDY OBJECTIVES

The primary objective of the study is:

- To evaluate the long-term safety and efficacy of pegvaliase (> 40 mg/day dose) in adult patients with PKU

The secondary objective of the study is:

- To characterize dietary protein intake from medical food and from intact food during long-term treatment with pegvaliase (> 40 mg/day dose) in adult patients with PKU

The exploratory objective of the study is:

- To characterize the long-term immunogenicity profile of pegvaliase (> 40 mg/day dose) in adult patients with PKU

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 3 open-label extension study enrolling approximately 40 adult subjects with PKU who were previously treated with pegvaliase in Studies PAL-003 or 165-302. The study is designed to evaluate the long-term safety and efficacy of pegvaliase administered as prefilled syringe drug product at a dose of > 40 mg/day to 60 mg/day, inclusive. Dose regimens other than daily dosing at > 40 mg/day to 60 mg/day (with the exception of 1 subject enrolled from the PAL-003 study who receives a pegvaliase dose not to exceed 120 mg/day) may be allowed provided the investigator consults with the medical monitor and obtains approval from the medical monitor prior to starting the alternative regimen. Subjects will continue their prior pegvaliase dose regimen on the 165-304 study, including 1 subject enrolled from the PAL-003 study who receives a pegvaliase dose not to exceed 120 mg/day. A subject who dose reduces to a dose of 40 mg/day or lower for 32 consecutive weeks will be discontinued from study drug and withdrawn from the study as they will have the option to transition to commercial drug. Dose reductions may be performed if warranted due to AEs or hypophenylalaninemia. Dose increases to up to 60 mg/day may be performed per investigator discretion in consultation with the sponsor's medical monitor. Dosing will continue for approximately 121 weeks.

After providing informed consent, subjects undergo screening evaluations to determine study eligibility. Screening assessments must be performed within 28 days of the first 165-304 dose of pegvaliase on Day 1. Study PAL-003 or 165-302 Study Completion Visit assessments may be used for the purpose of screening, with Day 1 of 165-304 taking place the same day. Pegvaliase dosing should continue without interruption from the previous study; beginning on Day 1, subjects will receive the same dose and regimen of pegvaliase they were receiving in 165-302 or PAL-003. Subsequent revisions to dosing regimens are allowed following consultation with the medical monitor. Subjects on temporary pegvaliase hold due to pregnancy planning in PAL-003 or 165-302 (and who received pegvaliase doses > 40 mg/day dose and up to 60 mg/day dose, inclusive) will be screened and enrolled in 165-304; however, they will not receive pegvaliase until consultation with the medical monitor (temporary hold released).

A subject (or a subject-designated caregiver) must have met predefined self-administration criteria in PAL-003 or 165-302 to qualify for pegvaliase self-administration (refer to Section 9.4.4), including demonstrated working knowledge of the signs and symptoms of a hypersensitivity reaction, including anaphylaxis, and what to do if a hypersensitivity reaction

is suspected (refer to Section 9.1.1). Eligible subjects (or caregivers) have been trained to self-administer pegvaliase.

A competent adult will observe the subject during pegvaliase administration and for a minimum of 1 hour following pegvaliase administration upon reintroduction of pegvaliase after resolution of a Grade 3 or higher HAE, any dose interruption of ≥ 4 days, and for a dose increase to 60 mg/day; administration of pegvaliase may only be performed if this person is present. Observations should be performed for all doses administered for 1 week after reintroduction of pegvaliase or a dose increase to 60 mg/day. Information and training on how to recognize a possible reaction, the severity of the reaction, and instructions on what to do if a reaction occurs will be provided to any person designated to observe the subject during pegvaliase administration.

Following a dose interruption of ≥ 4 doses that is not due to safety, the investigator should consult with the medical monitor and obtain approval from the medical monitor prior to the subject restarting pegvaliase.

Subjects are given 2 epinephrine injectors and are instructed to carry 1 epinephrine injector with them at all times. Each subject is contacted weekly to monitor for self-administration problems and/or AEs. Premedication with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen) should be administered approximately 2 to 3 hours prior to pegvaliase administration for 1 week upon reintroduction of pegvaliase after resolution of a grade 3 or higher HAE, following any dose interruption of ≥ 4 days, and for a dose increases to 60 mg/day. If a non-steroidal anti-inflammatory medication (NSAID) is administered as a premedication, it should be given with food. Subjects may also be pre-medicated at any time in the study at the discretion of the investigator. Subjects are provided with a workbook to document the date and time of pegvaliase injections, the injection site, and suspected AEs.

A subject's ability to maintain a consistent diet is essential for the success of the study by ensuring that the efficacy and safety end points are attributable to study treatment rather than to changes in dietary protein intake. A dietitian under investigator supervision will manage subject diet for the entire duration of the study. Subjects are provided 3-day diaries in which all dietary protein intake (including medical food and intact food) must be recorded for 3 consecutive days immediately prior to each scheduled clinic visit for review with a dietitian. All subjects will be provided the option of tyrosine supplementation (500 mg, 3 times per day with meals) at the discretion of the investigator. Subjects are instructed not to change their dietary protein intake during the study.

Because the risks of taking pegvaliase during pregnancy and breastfeeding are unknown, subjects cannot take pegvaliase if they are trying to conceive, are pregnant, or are

breastfeeding. Subjects must be willing to use 2 acceptable methods of contraception while participating in the study and until 4 weeks after the study. Male subjects who are planning to impregnate a female partner and female subjects who are trying to become pregnant during the study must be temporarily discontinued from pegvaliase for 4 weeks prior to trying to conceive. During that time, subjects must use 2 acceptable methods of contraception (refer to Section 9.3.1). Subjects who are planning to become pregnant (or impregnate a female partner) may modify their diet in consultation with the investigator and/or study dietitian. Subjects who are confirmed to be pregnant by a serum pregnancy test and are temporarily off pegvaliase are not required to perform the scheduled urine pregnancy tests. Subjects who are pregnant or are trying to conceive and have temporarily discontinued pegvaliase should not perform the scheduled PK assessments. Male subjects who have impregnated a female partner may re-start pegvaliase after conception following the investigator's consultation with and approval by the medical monitor. Male subjects must use a barrier method for contraception prior to restarting pegvaliase. Female subjects who remain in the study after temporary discontinuation of pegvaliase due to pregnancy may restart pegvaliase dosing after a confirmed negative urine pregnancy test result, the birth (or termination of the pregnancy) has been reported, and breastfeeding has been completed (if applicable), or after the subject is no longer actively trying to conceive. Re-starting pegvaliase dosing requires prior consultation with the investigator and approval by the medical monitor. Female subjects must return to the protocol-required contraception use, which must include 1 barrier method, immediately after the birth (or termination of the pregnancy).

Except for subjects transitioning to commercial drug, if pegvaliase is discontinued before study completion, every effort will be made to maintain the subject in the study and continue study visits and assessments, provided the subject's health, safety, and welfare are not detrimentally affected.

In addition to BioMarin, a Data Monitoring Committee (DMC) monitors the safety of study subjects. The DMC is an independent committee that acts in an advisory capacity to BioMarin.

The assessments to be performed throughout the study are presented in Table 9.1.1.

Table 9.1.1: 165-304 Schedule of Events

Event or Assessment [a]	Screening/ Day 1 [b]	Weekly Contact [c]	Week 9 (Day 57) and Every 8 Weeks Thereafter (±7 days)	Hypersensitivity Reaction Visit [d]	Early Termination/ Study Completion
Demographics	X				
Medical history	X				
12 lead ECG	X				X
Physical examination	X		X	X	X
Vital signs	X		X	X	X
Weight	X		X		X
Clinical laboratory tests [e]	X		X	X	X
C-reactive protein	X		X	X	X
Complements C3 and C4	X		X	X	X
Tryptase				X	
Urine albumin/creatinine ratio [f]	X		X	X	X
Urinalysis for N-methyl histamine				X	
Urine pregnancy test [g]	X		X		X
Diet diary [h]	X		X		X
PK (plasma pegvaliase) [i]	X [j]		X		X
Plasma Phe, tyrosine [j]	X		X		X
Immunogenicity assessments [k]	X		X	X (anti-pegvaliase IgE only)	X
Adverse events [l]	X	X	X	X	X
Concomitant medication [l]	X	X	X	X	X
Administer pegvaliase [m]	X [n]	X	X		

ECG, electrocardiogram; PK, pharmacokinetics

[a] Events or assessments are pre-dose unless otherwise specified.

[b] Screening assessments must be performed during the 28 days prior to and including Day 1. Assessments performed at the Study Completion Visit and prior visits for 165-302 or PAL-003 may be used for establishing 165-304 eligibility provided they meet this time constraint and the ICF for 165-304 is signed and dated prior to those assessments.

[c] Between scheduled clinic visits, the clinic staff will contact the subject weekly to monitor if the subject is experiencing problems with self-administration, to ask about any AEs or concomitant medications, and to answer questions.

[d] If an NCI-CTCAE grade 3 (or higher) hypersensitivity reaction is suspected, the investigator may request further evaluation between 8 and 24 hours following event onset, including urinalysis for N-methyl histamine. Subjects who experience an injection-site skin reaction that lasts ≥ 14 days including reactions that could be potential vasculitis should be referred to a dermatologist for consultation and a skin biopsy. Refer to Section 12.4 for additional details regarding this visit.

[e] It is recommended that urine samples be obtained as a first or second morning void. In the event of elevated urinary protein on a test result, a repeat urinalysis should be performed no later than the next scheduled visit. This repeat urine sample must be performed in the morning at the first or second morning void to allow for accurate test results and may be performed by a home healthcare nurse.

[f] It is recommended that urine samples be obtained as a first or second morning void. Subjects with a confirmed urine/albumin creatinine ratio of ≥ 100 mg/g should be referred to a nephrologist for consultation if results were within normal range at baseline. Subjects who had elevated results at baseline followed by a confirmed subsequent increase of ≥ 100 mg/g from baseline should also be referred to a nephrologist for consultation. For subjects previously enrolled in PAL-003, blood for baseline urine/albumin creatinine ratio listed under Screening/Day 1 will be drawn pre-dose on Day 1 of 165-304.

[g] To be performed locally (if applicable). If urine pregnancy test is positive or equivocal, perform serum pregnancy test (central laboratory). Subjects who are confirmed to be pregnant per a serum pregnancy test and are temporarily off pegvaliase are not required to perform the scheduled urine pregnancy tests. Also refer to Section 9.1.

[h] Subjects should record at home all food, beverages, special low-protein foods, and medical foods consumed during the 3 consecutive days preceding a study visit.

[i] Blood is collected for PK at the same time as draw for plasma Phe and tyrosine. For subjects previously enrolled in 165-302, blood for baseline PK listed under Screening/Day 1 will be drawn pre-dose on Day 1 of 165-304.

[j] Blood is collected for plasma Phe after fasting 2.5 to 5 hours. Subjects who are pregnant or are trying to conceive and have temporarily discontinued pegvaliase should not perform the scheduled PK assessments.

[k] Immunogenicity assays include (but are not limited to) total anti-pegvaliase, anti-rAvPAL IgG, anti-rAvPAL IgM, anti-PEG IgG, anti-PEG IgM, anti-pegvaliase IgG4, and neutralizing antibodies; additional assays include IgG-C3d and IgM-C3d circulating immune complexes (CICs); anti-pegvaliase IgE is determined when appropriate (hypersensitivity or other safety concern).

[l] Subjects must be assessed for AEs and concomitant medications whenever assessed by study personnel beginning with the first dose of pegvaliase on Day 1. After pegvaliase initiation, all AEs and SAEs will be recorded until 4 weeks after either the last administration of pegvaliase or the Study Completion Visit/Early Termination Visit, whichever occurs last. If there is a skin reaction that lasts ≥ 14 days, the Skin Reaction electronic case report form (eCRF) should be completed. Subjects who experience an injection-site skin reaction that lasts ≥ 14 days including reactions that could be potential vasculitis should be referred to a dermatologist for consultation and a skin biopsy. It is recommended that a photograph of the skin reaction be taken by the subject or the site to help assess the event; photographs may be collected by the sponsor.

[m] Subjects self-administer pegvaliase. During weekly contacts, subjects are asked about pegvaliase self-administration.

[n] Following completion of the 165-302 or PAL-003 Study Completion Visit and confirmation of eligibility for 165-304, subjects may be dosed on the same day, designated 165-304 Day 1.

9.1.1 Response to Hypersensitivity Adverse Events

Subjects are evaluated for safety throughout all parts of the study and are trained to recognize potential HAEs (including a serious anaphylaxis) and how to respond. Subjects are instructed to contact the investigator for any suspected HAE. After a telephone assessment, the investigator may require further evaluation at the clinic. If a hypersensitivity reaction (eg, injection-site reaction, rash, joint pain, itching) occurs, the subject may be advised to premedicate with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen) approximately 2 to 3 hours prior to subsequent pegvaliase doses. If NSAIDs are administered as a premedication, they should be given with food.

Hypersensitivity AEs, including anaphylaxis, are expected with pegvaliase administration. Pegvaliase dosing in response to a suspected HAE may be modified or temporarily halted depending on the severity of the event and suspected pegvaliase causality. Severity for HAEs will be per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades (refer to Section 10.1).

Subjects who experience an injection-site skin reaction that lasts ≥ 14 days including reactions that could be potential vasculitis should be referred to a dermatologist for consultation and a skin biopsy.

9.1.1.1 Individual Stopping Criteria

Subjects who have an NCI-CTCAE grade ≥ 3 anaphylaxis event that is, in the judgment of the investigator and the sponsor's medical monitor, related to study drug and suspected to meet Brown's criteria (Brown, 2004) for severe (grade 3) hypersensitivity may be permanently discontinued from study drug. The sponsor's medical monitor should be immediately notified when a subject experiences an NCI-CTCAE grade ≥ 3 anaphylaxis event that is judged by the investigator to be related to pegvaliase and/or is suspected to meet Brown's criteria (Brown, 2004) for severe (grade 3) hypersensitivity.

9.1.1.2 Dosing in Response to Hypersensitivity Adverse Events

Dosing in response to an HAE depends on the NCI-CTCAE grade and suspected relationship to pegvaliase. Dosing instructions are presented in Table 9.1.1.2.1 and are regardless of previous occurrence.

Table 9.1.1.2.1: Dosing after Hypersensitivity Adverse Event

NCI-CTCAE Grade [a]	Related to Study Drug	Action with Study Drug			Individual Stopping Criteria [d]	HRV Assessment [e]
		Maintain [b]	Reduce [c]	Interrupt [c]		
1	Yes or No	X	(X) Optional	(X) Optional		Investigator discretion
2	Yes or No	X	(X) Optional	(X) Optional		Investigator discretion
3	No	X	(X) Optional	(X) Optional		Investigator discretion
3	Yes	X	(X) Optional	(X) Optional		Yes (if within 24 hours of onset)
3 [d]	Yes				X Immediately consult with sponsor medical monitor	Yes (if within 24 hours of onset)
4 [d]	Yes or No				X Immediately consult with sponsor medical monitor	Yes (if within 24 hours of onset)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events, version 5.0; HRV, Hypersensitivity Reaction Visit; NCI, National Cancer Institute.

[a] NCI-CTCAE grade determination is performed by the investigator and may be done either via telephone or clinic visit.

[b] The investigator will instruct the subject to maintain the pegvaliase dose at the time of AE onset until improvement to grade 1 or resolution (per investigator assessment in the clinic or via telephone).

[c] The pegvaliase dose may be reduced or interrupted if necessary per investigator determination.

[d] If a subject has an NCI-CTCAE grade ≥3 anaphylaxis event that is related to study drug and is suspected to meet Brown's criteria for severe (grade 3) hypersensitivity in the judgment of the investigator and the sponsor's medical monitor, the subject may be permanently discontinued from study drug.

[e] If the investigator determines that the NCI-CTCAE grade ≥3 hypersensitivity reaction is related to administration with study drug, the subject will be asked to return to the clinic within 24 hours of event onset for a hypersensitivity reaction visit (HRV) assessment, including laboratory tests (chemistry, hematology, urinalysis, anti-pegvaliase IgE [sampling must be performed > 8 hours after event onset and before the next dose of study drug], urine albumin/creatinine ratio, urinary N-methyl histamine, CRP, C3, C4, and tryptase).

Once an AE (other than anaphylaxis) improves to grade 1 or resolves, the pegvaliase dose may be increased, maintained, or reduced, at the discretion of the investigator. If reduced, the recommended pegvaliase dose reductions include: from 60 mg/day to 40 mg/day, from 50 mg/day to 20 mg/day, or from 40 mg/day to 20 mg/day, with reductions from intermediate doses at the discretion of the investigator. If dosing has been interrupted due to an AE (other than anaphylaxis) and the investigator determines it is safe for the subject to resume dosing, the first dose after improvement of the AE should be performed in the clinic.

Additionally, the subject should be premedicated with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen) approximately 2 to 3 hours prior to each dose of pegvaliase for 1 week upon return to dosing if the dose interruption is ≥ 4 days. If NSAIDs are administered as a premedication, they should be given with food. Also, a competent adult should observe the subject during pegvaliase administration and for a minimum of 1 hour following pegvaliase administration for 1 week upon return to dosing if the dose interruption is ≥4 days; administration of pegvaliase may only be performed if this person is present.

9.1.1.3 Response to Anaphylaxis

If the investigator suspects that the event is anaphylaxis, the subject will be assessed in the clinic and the sponsor's medical monitor should be immediately notified. Refer to Section 10.1.2 for safety reporting instructions for anaphylaxis events (serious or nonserious and irrespective of severity). Laboratory assessments for suspected anaphylaxis events should be performed prior to the next administration of pegvaliase (if applicable) and include anti-pegvaliase IgE (for optimal results, sampling must be performed > 8 hours after event onset) and tryptase (for optimal results, perform within 24 hours of event onset). If the investigator determines it is safe for the subject to resume dosing with pegvaliase following resolution of anaphylaxis, the dose level will be as presented in Table 9.1.1.3.1.

Table 9.1.1.3.1: Dosing after Anaphylaxis Event

Scheduled Dose at Time of Anaphylaxis Onset	Dose Following Resolution of Anaphylaxis Event [a]
50 mg/day	20 mg/day
60 mg/day	40 mg/day

[a] Dose may be lowered further per investigator discretion. Dose frequency should be the same as the dose regimen at the time of anaphylaxis onset; however, dose frequency may be revised per investigator discretion and in consultation with the sponsor's medical monitor.

The first dose administered after resolution of anaphylaxis is to be administered at the clinic with equipment for emergency resuscitation (including epinephrine) within easy access. Additionally, the subject should be premedicated with H1 antagonist, H2 antagonist, and antipyretic (eg, acetaminophen) approximately 2 to 3 hours prior to each dose of pegvaliase for 1 week upon return to dosing regardless of the duration of dose interruption. If NSAIDs are administered as a premedication, they should be given with food. Also, a competent adult should observe the subject during pegvaliase administration and for a minimum of 1 hour following pegvaliase administration for 1 week upon return to dosing regardless of the duration of dose interruption; administration of pegvaliase may only be performed if this person is present.

9.1.2 Study Stopping Criteria for Adverse Events during Treatment with Pegvaliase

If an anaphylaxis event occurs **and** meets Brown's criteria (Brown, 2004) for severe (grade 3) hypersensitivity, the DMC chair and/or committee will be informed to review and advise the sponsor on potential changes to the study conduct. Clinically severe hypersensitivity (Brown's criteria, severe [grade 3]) is defined as significant hypoxia, hypotension or neurologic compromise that is life-threatening or required treatment to prevent a life-threatening event:

- Cyanosis or $SpO_2 \leq 92\%$
- Hypotension with SBP < 90 mm Hg (adults)
- Neurologic alteration: confusion, loss of consciousness, collapse, or incontinence

Brown's severity criteria are presented in Table 9.1.2.1.

Table 9.1.2.1: Severity Criteria (Brown, 2004)

Brown's Criteria for Hypersensitivity Reactions	Definition
Mild (1) skin and subcutaneous tissue	Generalized erythema, urticaria, periorbital edema, or angioedema
Moderate (2) features suggested respiratory, cardiovascular, or gastrointestinal involvement	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (pre-syncope), diaphoresis, chest or throat tightness, or abdominal pain
Severe (3) hypoxia or neurologic compromise	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence

SBP, systolic blood pressure; SpO_2, blood oxygen saturation.

9.2 Discussion of Study Design, Including Choice of Control Group

This is an open-label extension study with no control group. Refer to Section 7.3 for the study rationale.

9.3 Selection of Study Population

Individuals with PKU aged ≥ 18 years and ≤ 70 years who previously received pegvaliase in PAL-003 or 165-302 (> 40 mg/day dose up to 60 mg/day dose, inclusive) are candidates for participation in the study. The rationale for selection of these subjects for study participation is provided in Section 7.3. 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 inclusion criteria:

- Must be enrolled in PAL-003 or 165-302 Part 4 at the time of screening for 165-304 and most recently receiving pegvaliase at a dose > 40 mg/day
- Is at least 18 years of age and no older than 70 years of age at the time of screening
- Has identified a competent person or persons ≥ 18 years of age who can observe the subject during study drug administration and for a minimum of 1 hour following administration in situations required per protocol
    - A home healthcare nurse may perform the study drug observations.
- For females with childbearing potential, must have a negative pregnancy test at screening and be willing to have additional pregnancy tests during the study. (Females are considered not to have childbearing potential if they have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy.)
- If sexually active and not planning to become pregnant (self or partner), must be willing to use 2 acceptable methods of contraception while participating in the study and for 4 weeks after the study:
    - Acceptable methods of contraception include: (1) primary forms: hormonal (combination hormone-containing pills, patch, vaginal ring, or intrauterine device) or non-hormonal (copper-containing intrauterine device, tubal sterilization); (2) secondary forms: includes barrier forms and other forms of birth control and must include spermicide (e.g., male condom; female condom is not an acceptable secondary form).
    - Males (including partners) post vasectomy for 2 years with no known pregnancies do not need to use any other forms of contraception during the study.
    - Females (including partners) who have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy do not need to use any other forms of contraception during the study.
- Is 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; a legally authorized representative may provide written consent and assent may be requested
- Is willing and able to comply with all study procedures
- Is in generally good health, as evidenced by physical examination and/or clinical laboratory evaluations (hematology, chemistry, and urinalysis)

9.3.2 Exclusion Criteria

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

- Use of any investigational product (except pegvaliase) or investigational medical device within 30 days prior to screening or requirement for any investigational agent prior to completion of all scheduled study assessments
- Use of any medication (except pegvaliase) intended to treat PKU, including the use of large neutral amino acids, within 2 days prior to the administration of pegvaliase (Day 1)
- Use or planned use of any injectable drugs containing PEG (other than pegvaliase), including medroxyprogesterone injection, within 3 months prior to screening and during study participation
- A history of organ transplantation or on chronic immunosuppressive therapy
- A history of substance abuse (as defined by the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders [DSM]) in the past 12 months or current alcohol or drug abuse
- Current participation in the Kuvan® registry study (PKU Demographics, Outcomes and Safety [PKUDOS])
- Concurrent disease or condition that would interfere with study participation or safety (eg, history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurological, oncologic, or psychiatric disease)
- Any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or terminating early from the study

9.3.3 Removal of Subjects from Treatment or Assessment

Subjects (or their legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out (refer to Section 12.5). BioMarin must be notified of all subject withdrawals as soon as possible.

BioMarin reserves the right to discontinue the study at any time. Premature termination of the study may occur because of regulatory authority decision, a change in the opinion of the IRB/IEC/REB, clinical or safety reasons, or at the discretion of the sponsor. The sponsor

reserves the right to discontinue the development of pegvaliase at any time, or to discontinue participation by an individual investigator or site for poor enrollment or noncompliance. Any decision to terminate the study will be promptly communicated to investigators, regulatory authorities, and IRB/IEC/REB. The investigator is responsible for communicating any decision to terminate a study to hospital staff involved in the conduct of the study and the participating subjects (and their families).

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

- Subject experiences a serious or intolerable AE
- Subject develops a clinically significant laboratory abnormality
- Subject requires medication or medical procedure prohibited by the protocol
- 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

Subjects who have an NCI-CTCAE grade ≥ 3 anaphylaxis event that is, in the judgment of the investigator and the sponsor's medical monitor, related to study drug and suspected to meet Brown's criteria (Brown, 2004) for severe (grade 3) hypersensitivity may be permanently discontinued from study drug. The sponsor's medical monitor should be immediately notified when a subject experiences an NCI-CTCAE grade ≥ 3 anaphylaxis event that is possibly or probably related to pegvaliase and/or is suspected to meet Brown's criteria (Brown, 2004) for severe (grade 3) hypersensitivity.

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 should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the investigator. This information should be recorded in the study records.

The investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB/ECREB. It is the investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as HIPAA in the US, from each subject or, if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the investigator's responsibility to obtain a

written request to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.4 Subject Identification and Replacement of Subjects

Subjects will not be replaced in this study. Each subject will retain the unique subject identifier assigned in their previous study. This unique identifier will be on all case report form (CRF) pages.

9.3.5 Duration of Subject Participation

Following a screening period of up to 28 days, subjects receive pegvaliase for approximately 121 weeks or until study closure.

9.4 Treatments

9.4.1 Treatments Administered

Pegvaliase is administered SC via open-label pre-filled syringe.

9.4.2 Identity of Investigational Product

The investigational product is pegvaliase (recombinant *Anabaena variabilis* phenylalanine ammonia lyase-PEG). For subcutaneous self (or caregiver) administration, subjects are supplied with prefilled syringes in 3 sizes. Sizes are 2.5 mg (0.5 mL of 5 mg/mL protein concentration), 10 mg (0.5 mL of 20 mg/mL protein concentration), and 20 mg (1.0 mL of 20 mg/mL protein concentration).

The excipients in this drug product are tromethamine, tromethamine-hydrochloride, sodium chloride, L-phenylalanine, and water for injection.

9.4.2.1 Product Characteristics and Labeling

Drug product packaging is identified with lot and identification numbers and provided in a box labeled with the study number.

9.4.3 Storage

At the study site, all study drug must be stored at 5 ±3°C (41 ±5°F), under the conditions specified in the Investigator's Brochure, and in a secure area accessible only to the designated pharmacists and clinical site personnel. All study drug must be stored and inventoried, and the inventories must be carefully and accurately documented according to applicable state, federal, and local regulations; ICH GCP, and study procedures. Information regarding storage of study drug in subjects' homes is provided in the subject self-administration training materials in the Study Reference Manual (refer to Section 9.4.4).

9.4.4 Directions for Administration

The injection sites for administration of pegvaliase should alternate between doses. Injection sites should not be near an open wound or mole.

Subjects (or a subject-designated caregiver) must meet all of the following criteria to be eligible to self-administer the drug:

- Has no known cognitive impairments that may increase the safety risk per investigator assessment
- Has no medical history or current medications that may compromise self-administration of pegvaliase per investigator assessment
- Has completed all required self-administration training and has demonstrated self-administration competency per investigator assessment, including how to prepare pegvaliase for administration and safely perform the injection

Refer to Section 9.1.1 for study drug administration requirements regarding the presence of a competent adult and premedication requirements.

Following a dose interruption of ≥4 doses that is not due to safety, the investigator should consult with the medical monitor and obtain approval from the medical monitor prior to the subject restarting pegvaliase. Dose regimens may be revised provided the investigator consults with the sponsor's medical monitor and obtains approval from the medical monitor prior to starting an alternative dose regimen.

If a subject has an NCI-CTCAE grade 3 or higher AE during the study, the subject's suitability for self-administration of pegvaliase will be re-assessed by the investigator. In addition, the suitability for self-administration of pegvaliase will be re-assessed by the investigator if a subject experiences any issues with self-administration.

Between scheduled clinic visits, the clinic staff will contact the subject weekly to monitor if the subject is experiencing problems with self-administration, for any AEs, and to answer questions throughout the duration of the study. The subject must perform the scheduled assessments and procedures in the clinic as outlined in 9.1.1 and Section 12. All subjects were trained in previous studies. Training materials and other information specific to the study site personnel are provided in the Study Reference Manual, which includes self-administration training materials and instruction on the following:

- How to prepare and perform the injections of pegvaliase safely
- How to receive, store, and return both used and unused pegvaliase
- How to safely use and dispose of prefilled syringes used for injections of pegvaliase

- How to use a prefilled syringe every time drug is administered
- How to care for the injection site after an injection of pegvaliase
- How to document each pegvaliase injection
- How to identify an AE and how to report this to the study site
- How and when to use epinephrine
- Whom to contact at the study site in case of an emergency

Subjects will be provided with a workbook to document the date and time of pegvaliase injections, injection site, any suspected AEs, and other relevant information. Dosing in response to an AE should be determined by the investigator (refer to Section 9.1.1).

9.4.5 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

9.4.6 Selection of Doses Used in the Study

The rationale for the selected dose (> 40 mg/day dose up to ≤ 60 mg/day dose, inclusive) is provided in Section 7.3. Subjects will begin Study 165-304 on the same dose and dosing regimens they were on at the end of the previous study (165-302 or PAL-003).

9.4.6.1 Selection of Timing of Dose for Each Subject

Subjects are encouraged to administer study drug at approximately the same time each day to minimize diurnal variation in blood Phe and tyrosine.

9.4.7 Blinding

Subjects will receive open-label pegvaliase.

9.4.8 Prior and Concomitant Medication

All prescription and over-the-counter medication taken by a subject for 30 days before screening are recorded on the designated eCRF.

The investigator may prescribe additional medications during the study as long as the prescribed medication is not prohibited by the protocol (refer to Section 9.3.2). In the event of an emergency, any needed medications may be prescribed without prior approval but the medical monitor must be notified of the use of any contraindicated medication immediately thereafter. Any concomitant medication added or discontinued during the study should be recorded on the appropriate eCRF.

For instruction regarding premedication, refer to Section 9.1.

9.4.9 Treatment Compliance

The date, time, and quantity of each dose of study drug administered to each subject must be recorded by the subject in a workbook provided for the study. The site staff will collect the workbook at scheduled 8 week clinic visits and transcribe this information to the appropriate eCRF. These data will be used to assess compliance and will be reviewed by CRAs (refer to Section 11).

9.5 Investigational Product Accountability

The investigator (or designee) is responsible for maintaining accurate records (including dates and quantities) of IP received, subjects to whom IP is dispensed (subject-by-subject dose-specific accounting), IP returned, and IP lost or accidentally or deliberately destroyed. The investigator (or designee) must retain all unused or expired study drug syringes until the study monitor (on-site CRA) confirms accountability data. Used prefilled syringes are not retained; accountability is based on syringe label stickers in subject study workbook.

9.5.1 Return and Disposition of Clinical Supplies

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to BioMarin and retained in the investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to BioMarin's designated Drug Destruction Facility upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by BioMarin.

Subjects are provided instructions for returning unused study drug prefilled syringes and for proper disposal of used study drug prefilled syringes or study drug materials.

All study drug should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

Diet will be assessed for its role in blood Phe reduction relative to pegvaliase dosing.
A dietitian will be involved with reviewing, counseling, analyzing, and managing subject diet throughout the study.

A 3-day diet diary and a nutrient analysis software program (Metabolic Pro®) will be used to establish baseline Phe and protein intake levels prior to Day 1. Protein from medical foods (Phe-free amino acid fortified food sources) and protein from intact foods (any other food sources containing Phe) are collectively referred to as dietary protein.

Baseline measurements will be used as the comparator for subsequent 3-day diet diary entries. Subjects will be required to maintain dietary protein intake levels that are consistent with their baseline levels for the entire study, with a consistent diet defined as one in which the intact protein changes are < 10% from baseline and the medical food protein changes < 10% from baseline. Subjects who are planning to become pregnant (or impregnate a female partner) may modify their diet in consultation with the investigator and/or study dietitian.

The dietitian will perform additional counseling with a subject for any intact protein and/or medical food protein intake changes that are ≥ 10% from baseline.

Further corrective actions will be implemented when the intact protein and/or medical food protein is ≥±25% from baseline. After the subject demonstrates ≥ 25% change from baseline intake of intact protein and/or medical food protein, the dietitian will counsel the subject to resume their baseline diet and may perform another 3-day diet record and blood Phe concentration assessment in 2 weeks. If the subject demonstrates ≥±25% change in intake of intact protein and/or medical food protein at the next scheduled study visit (8 weeks), a discussion with the medical monitor may be required to discuss further actions related to non-adherence with consistent dietary protein intake throughout the study, at the discretion of the investigator.

The 3-day diet diary should reflect the 3 consecutive days prior to the scheduled study visit.

If dietary protein intake is determined to be inconsistent with baseline values, it is recommended that the dietitian counsel the subject on how to return to baseline values by modifying intake of intact protein and/or medical food protein. If diet changes have been implemented, a blood Phe concentration assessment and 3-day diet record should be collected 2 weeks after implementation, in addition to all regularly scheduled assessments. Any changes must also be documented on the appropriate eCRF.

- If blood Phe levels decrease to ≤ 30 µmol/L and it is determined that a subject is consuming less than their recommended dietary allowance (RDA) for intact protein (RDAs for intact protein: men 18 years of age: 52 g/day; men ≥ 19 years of age: 56 g/day; women 18 years of age: 46 g/day; women ≥ 19 years of age: 46 g/day), the dietitian may instruct the subject to increase their intact protein by 10 grams and decrease their medical food protein by 5 grams. This increased intake will now be the new reference baseline for dietary protein intake for future dietary assessments.

- If blood Phe levels decrease to ≤ 30 µmol/L and it is determined that a subject is consuming more than his or her RDA but less than 2x his or her RDA for intact protein, the dietitian may instruct the subject to increase intact protein intake by 10% and decrease medical food protein intake by 5 grams compared to his or her current dietary intake. This increased intake becomes the new reference baseline for dietary protein intake for the subject's future dietary assessments.
- If blood Phe levels decrease to ≤ 30 µmol/L and it is determined that a subject is consuming ≥2x his or her RDA for intact protein, the dietitian may instruct the subject to maintain his or her current intact protein intake and medical food protein intake. The subject will continue to use the same reference baseline for dietary protein intake for future dietary assessments.

Any dietary changes must be documented in the subject's 3-day diet diary and on the appropriate eCRF.

9.7 Efficacy and Safety Variables

9.7.1 Efficacy and Safety Measurements Assessed

The Schedule of Events (Table 9.1.1) outlines the timing of required events and assessments.

9.7.2 Primary Efficacy Variable

Blood samples for Phe concentration are taken after fasting for 2.5 to 5 hours as indicated in Table 9.1.1 and analyzed by a central laboratory.

9.7.3 Secondary Efficacy Variables

9.7.3.1 Dietary Protein Intake

A subject's diet is monitored using a 3-day diet diary. The 3-day dietary record (diet diary) is completed by subjects, brought to clinic visits for review, and maintained with the study source documents. Subjects record all food, beverages, special low-protein foods, and medical foods consumed for 3 consecutive days prior to the scheduled clinic visit. Data are analyzed by the nutritional software (Metabolic Pro®) for total kcals, protein, Phe, tyrosine, and the percentage of daily recommended intake provided for protein, Phe, tyrosine, vitamins, and minerals (refer to Section 9.6).

9.7.3.2 Pharmacokinetics and Pharmacodynamics

Blood samples for PK (plasma pegvaliase) and PD (plasma Phe) analysis are drawn according to the Schedule of Events (9.1.1). Analysis of pegvaliase plasma concentrations will be performed by BioMarin or a contract research organization.

9.7.4 Exploratory Sample Analyses

Blood and urine samples may be analyzed to evaluate biochemical, molecular, cellular and genetic/genomic aspects of PKU and to develop the assays used for these evaluations. For each portion of the blood and urine samples reserved for protocol-specified analyses, there may be multiple sample aliquots. The unused aliquots may be used during the study for assay development or other purposes stated in Section 9.7.4.

9.7.5 Safety Variables

Safety in this study will be determined from evaluations of AEs, clinical laboratory assessments, vital signs, physical examinations, electrocardiogram (ECG) results, and immunogenicity tests.

9.7.5.1 Adverse Events

The occurrence of AEs will be assessed continuously commencing with the first dose of study drug on Day 1. The determination, evaluation, and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points outlined in Section 9.1.1.

9.7.5.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are outlined in Section 9.1.1. The scheduled clinical laboratory tests are listed in Table 9.7.5.2.1. Refer to the Lab Manual for instructions on obtaining and shipping samples.

Any abnormal test results determined to be clinically significant by the investigator should be repeated (at the investigator's discretion) until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the investigator determines that the abnormal value is no longer clinically significant.

The investigator should assess all abnormal clinical results and include a comment on whether or not the result is clinically significant. Each clinically significant laboratory result should be recorded as an AE.

In the event of elevated urinary protein on a test result, a repeat urinalysis should be performed. This repeat urine sample must be performed in the morning at the first or second morning void to allow for accurate test results and may be performed by a home healthcare nurse. Subjects with a confirmed urine/albumin creatinine ratio of ≥ 100 mg/g should be referred to a nephrologist for consultation if results were within normal range at baseline. Subjects who had elevated results at baseline followed by a confirmed subsequent increase of ≥ 100 mg/g from baseline should also be referred to a nephrologist for consultation.

The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the investigator will be recorded on the AE eCRF.

Table 9.7.5.2.1: Clinical Laboratory Tests

Blood Chemistry	Hematology	Urine Tests
Albumin	Hemoglobin	Appearance
Alkaline phosphatase	Hematocrit	Color
ALT (SGPT)	White blood cell count	pH
AST (SGOT)	Red blood cell count	Specific gravity
Total bilirubin	Platelet count	Ketones
Blood urea nitrogen	Differential cell count	Protein [a]
Creatinine		Glucose
Gamma-glutamyltransferase		Bilirubin
Total protein		Nitrite
Calcium		Urobilinogen
Sodium		Hemoglobin
Potassium		Urinary albumin/creatinine ratio [b]
Glucose		Urinary microscopy
Uric acid		Urinary N-methyl histamine
Chloride	**Complement Panel**	**Other**
Creatine phosphokinase	C3	Pregnancy test, if applicable [c]
LDH	C4	Phenylalanine
Bicarbonate		Tyrosine
		CRP
		Serum tryptase level

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C_3, C_4, complement components 3, 4; CRP, C-reactive protein; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase

[a] It is recommended that urine samples are obtained as a first or second morning void. In the event of elevated urinary protein on a test result, a repeat urinalysis should be performed. This repeat urine sample must performed in the morning at the first or second morning void to allow for accurate test results and may be performed by a home healthcare nurse.

[b] It is recommended that urine samples are obtained as a first or second morning void. Subjects with a confirmed urine/albumin creatinine ratio of ≥ 100 mg/g should be referred to a nephrologist for consultation if results were within normal range at baseline. Subjects who had elevated results at baseline followed by a confirmed subsequent increase of ≥ 100 mg/g from baseline should also be referred to a nephrologist for consultation.

[c] Urine pregnancy test performed by local laboratory. If urine pregnancy test is positive or equivocal, perform serum pregnancy test by central laboratory.

9.7.5.3 Vital Signs, Physical Examinations, and Other Observations Related to Safety

9.7.5.3.1 Vital Sign Measurements

Vital signs should be measured after resting for 5 minutes and include seated systolic blood pressure and diastolic blood pressure measured in mm Hg, heart rate in beats/minute, respiration rate in breaths/minute, and temperature in °C. Weight (kg) will also be measured. Assessments will occur at the time points outlined in Section 9.1.1.

9.7.5.3.2 Physical Examination Findings

Physical examination will include assessment of general appearance, head, eyes, ears, nose, throat, and the following body systems: cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, musculoskeletal, and neurological/psychological. Other body systems may be examined, and findings should be noted on the appropriate eCRF. Clinically significant changes from screening should be recorded as AEs (refer to Section 10). Assessments will occur at the time points outlined in Section 9.1.1.

9.7.5.3.3 Electrocardiography

A standard 12-lead ECG will be recorded, while the subject is resting, at the time points outlined in Table 9.1.1.

9.7.5.3.4 Other Laboratory Assessments

Immunogenicity will be assessed with immunogenicity assays including, but not limited to, the following:

- Total anti-pegvaliase antibodies (TAb)
- Anti-rAvPAL IgG antibodies
- Anti-rAvPAL IgM antibodies
- Anti-PEG IgG antibodies
- Anti-PEG IgM antibodies
- Anti-pegvaliase IgG4 antibodies
- Neutralizing antibodies (NAb)
- Anti-pegvaliase IgE
- IgG-C3d and IgM-C3d Circulating Immune Complexes (CICs)

Samples will be collected for immunogenicity assays at the time points indicated in the Schedule of Events (Section 9.1.1).

Antibody tests will be analyzed by BioMarin and/or CROs (refer to Section 6).

9.7.5.4 Pregnancy Testing

Female subjects with childbearing potential will have a urine pregnancy test performed at the time points specified in the Schedule of Events (Section 9.1.1). Subjects who are confirmed to be pregnant by a serum pregnancy test and are temporarily off study drug are not required to perform the scheduled urine pregnancy tests.

Additional pregnancy tests will be performed at any visit when pregnancy status is in question. Serum pregnancy tests must be performed in the event of a positive or equivocal urine pregnancy test result.

Refer to Section 10.3.1.9 for details on the reporting procedures in the event of pregnancy.

10 REPORTING ADVERSE EVENTS

10.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-defined events of special interest that are deemed critical to the safety evaluation of the study drug.

10.1.1 Adverse Events

For this protocol, a reportable AE is any untoward medical occurrence (eg, sign, symptom, illness, disease, or injury) in a subject administered the study drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures, medication washout, or no-treatment run-in).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and the AE.

For this study, a medical device is defined as the prefilled syringe and all of the component parts. Adverse events assessed by the investigator as related to the device, including malfunction, injury, or medication error, will be captured as AEs.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

10.1.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence at any dose that meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

Note: Life-threatening refers to an event that places the patient at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs in-patient hospitalization.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child or fetus of a subject exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction – that, based on medical judgment, may jeopardize the patient or require intervention to prevent one of the above consequences (eg, anaphylaxis)

All AEs that do not meet any of the criteria for SAEs should be regarded as non-serious AEs.

10.1.3 Adverse Events of Special Interest (AESI)

For this protocol, anaphylaxis per NIAID/FAAN criteria for the clinical diagnosis of anaphylaxis is designated an AESI (serious or nonserious and irrespective of severity) to facilitate rapid reporting and sponsor review. All occurrences of anaphylaxis per NIAID/FAAN criteria will be reported to the sponsor within 24 hours of the site becoming aware of the event using the SAE form. Severity and serious criteria (if applicable) should be reported on the SAE form.

10.2 Methods and Timing for Capturing and Assessing Safety Parameters

10.2.1 Adverse Event Reporting Period

After informed consent is obtained and the first administration of study drug, all non-serious AEs, AESI, SAEs, and pregnancies are reported until 4 weeks following either the last administration of study drug or the early termination visit, whichever period is longer (refer to Section 12.5). The criteria for determining SAEs is provided in Section 10.1.2.

For this study, a medical device is defined as the prefilled syringe and all of the component parts. The reporting period for device-related events begins with the first dose administered and ends with the last dose administered.

10.2.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and AESI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs, SAEs, and AESI should be recorded in the subject's medical record and on the AE eCRF.

10.2.3 Assessment of Seriousness, Severity, and Causality

The investigator responsible for the care of the subject or qualified medical designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.1.2 for SAE definitions). These assessments should be made by a study clinician with the training and authority to make a diagnosis (eg, MD/DO, physician's assistant, nurse practitioner, or DDS).

10.2.3.1 Seriousness

The investigator will assess if an AE should be classified as "serious" based on the seriousness criteria enumerated in Section 10.1.2. Seriousness serves as a guide for defining regulatory reporting obligations.

10.2.3.2 Severity

Severity (as in mild, moderate, or severe headache) is not equivalent to seriousness, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The severity of each will be assessed using the defined categories in Table 10.2.3.2.1.

The investigator will determine the severity of each AE, SAE, and AESI using the NCI-CTCAE v5.0. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5.0 as stated below.

Table 10.2.3.2.1: Adverse Event Grading (Severity) Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	
2	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [a]	
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [b]	
4	Life threatening or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be reported as SAEs
5	Death related to AE	

[a] Instrumental ADL refer to the following examples: preparing meals, shopping for groceries or clothes, using the telephone, managing money.

[b] Self-care ADL refer to the following examples: bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden.

10.2.3.3 Causality

The investigator will determine the relationship of an AE to the study drug and will record it on the source documents and AE eCRF. To ensure consistency of causality assessments, investigators should apply the guidance in Table 10.2.3.3.1.

Table 10.2.3.3.1: Categories Describing Relationship of Adverse Events to Study Drug

Relationship	Description
Not Related	Exposure to the IP has not occurred OR The administration of the IP and the occurrence of the AE are not reasonably related in time OR The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts [evidence] or arguments to suggest a causal relationship to the IP.
Related	The administration of the IP and the occurrence of the AE are reasonably related in time AND The AE could be explained equally well by factors or causes other than exposure to the IP **OR** The administration of IP and the occurrence of the AE are reasonably related in time AND The AE is more likely explained by exposure to the IP than by other factors or causes.

IP, investigational product

Factors suggestive of a causal relationship could include (but are not limited to):

- Plausible temporal relationship
- Absence of alternative explanations
- Rarity of event in a given patient or disease state
- Absence of event prior to study drug exposure
- Consistency with study product pharmacology
- Known relationship to underlying mechanism of study drug action
- Similarity to adverse reactions seen with related drug products
- Abatement of AE with discontinuation of study drug, and/or recurrence of AE with reintroduction of study drug

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the investigator's assessment of causality for

individual AE reports, the sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.3 Procedures for Recording Adverse Events

10.3.1 Recording Adverse Events on an eCRF

Investigators should use precise medical terminology when recording AEs or SAEs on an eCRF. Avoid colloquialisms and abbreviations.

Record only 1 diagnosis, sign, or symptom per event field on the AE eCRF (eg, nausea and vomiting should not be recorded in the same entry, but as 2 separate entries).

In order to classify AEs and diseases, preferred terms will be assigned by the sponsor to the original terms entered on the eCRF, using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

10.3.1.1 Diagnosis versus Signs and Symptoms

Using accepted medical terminology, enter the diagnosis (if known). If not known, enter sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, then this diagnosis should be entered on the AE form, replacing the original entries where appropriate.

10.3.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF. However, medically important events that may be linked and/or separated in time should be recorded as independent events on the eCRF. For example, if severe hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

10.3.1.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such an event should be recorded only once on the eCRF unless its severity increases or decreases (in which case it should be recorded again on the AE eCRF).

A recurrent AE is one that occurs and resolves between subject evaluation time points, but then subsequently recurs. Each recurrence of the AE should be individually recorded as a separate event on the AE eCRF.

10.3.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any laboratory result abnormality fulfilling the criteria for a SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

A clinical laboratory abnormality should be documented as an AE if it is not otherwise refuted by a repeat test to confirm the abnormality and any 1 or more of the following conditions is met:

- Accompanied by clinical symptoms
- Leading to a change in study medication (eg, dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (eg, change of dose, discontinuation of study drug, more frequent follow-up assessments, further diagnostic investigation, etc.)

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication that falls outside the laboratory reference range and meets the clinical significance criteria.

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria (these will be analyzed and reported as laboratory abnormalities), those that are considered AEs of the type explicitly exempted by the protocol, or those which are a result of an AE that has already been reported.

10.3.1.5 Pre-existing Conditions

A pre-existing condition is one that is present at the start of the study. Such conditions should be recorded as medical history on the appropriate eCRF.

A pre-existing condition should be recorded as an AE or SAE during the study only if the frequency, intensity, or character of the condition worsens during the study period. It is

important to convey the concept that a pre-existing condition has changed by including applicable language in the verbatim description of the event (eg, *more frequent* headaches).

10.3.1.6 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition (refer to Section 10.3.1.5). During the study, any new clinically significant findings and/or abnormalities discovered on physical examination that meet the definition of an AE (or an SAE) must be recorded and documented as an AE or SAE on the AE eCRF.

10.3.1.7 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE except as described below. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include planned hospitalizations or prolonged hospitalizations to:

- Perform a protocol-mandated efficacy measurement
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Receive scheduled therapy (study drug or otherwise) for the study indication
- Routine hospitalization for childbirth, including planned caesarean section

10.3.1.8 Deaths

All deaths that occur during the AE reporting period (refer to Section 10.2.1), regardless of attribution, will be recorded on the AE eCRF and expeditiously reported to the sponsor as an SAE within 24 hours.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” or “Death of Unknown Cause” on the eCRF. If the death is attributed to progression of the disease or condition being studies, record “-” as the SAE term on the eCRF.

10.3.1.9 Pregnancy

Pregnancy in either a subject or the partner of a subject who has taken study drug should be reported within 24 hours of the site becoming aware of the pregnancy. The pregnancy should be reported by faxing the Pregnancy Form in the study reference materials to BioMarin Pharmacovigilance (BPV) and completing the pregnancy eCRF in the electronic data capture (EDC) system. The investigator must make every effort to follow the subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the

Pregnancy Follow-up Form in the study reference materials. The pregnancy follow-up eCRF must also be completed and reported to BPV within 24 hours. In the event of pregnancy in the partner of a study subject, the investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the sponsor considers these to be medically significant), recorded on the eCRF, and expeditiously reported to the sponsor as an SAE.

10.4 Reporting Requirements

The sponsor is responsible for identifying, preparing, and reporting all suspected unexpected serious adverse reactions (SUSARs) to the relevant competent authorities, ethics committees, and investigators in accordance with requirements identified in the clinical trials regulations.

10.4.1 Expedited Reporting Requirements

All SAEs and AESI that occur during the course of the AE Reporting Period (refer to Section 10.2.1), whether or not considered related to study drug, must be reported by entering the information in the AE eCRF and completing the SAE report form. The SAE report form must be submitted to BPV within 24 hours of the site becoming aware of the event. Each SAE must also be reported on the appropriate eCRF. Investigators should not wait to collect information that fully documents the event before notifying BPV of an SAE. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by BioMarin as soon as it becomes available.

Adverse events assessed by the investigator as related to the device (ie, prefilled syringe), including malfunction, injury, or medication error, will be captured in in the EDC system. All serious events related to the device will be reported to BPV within 24 hours using the device-related event report form.

The reporting period for SAEs begins after the first dose of study drug in the 165-304 study and continues until 4 weeks following either the last administration of study drug or study discontinuation/termination, whichever is longer.

10.4.2 IRB Reporting Requirements

Reporting of SAEs to the IRB will be done in compliance with the standard operating procedures and policies of the IRB and with applicable regulatory requirements. Adequate documentation must be obtained by BioMarin showing that the IRB was properly and promptly notified as required.

10.5 Follow-up of Subjects after Adverse Events

The investigator should follow all unresolved AEs, unless the subject is lost to follow-up, or it has been determined that the study treatment or participation was not the cause of the AE The outcome of AEs should be documented on the AE eCRF and in the subject's medical record to facilitate source data verification.

The investigator should follow all unresolved SAEs to resolution, unless the subject is lost to follow up, or it has been determined that the study treatment or participation was not the cause of the SAE. Resolution of the SAE (with dates) should be documented on the AE eCRF and the SAE report form, as well as the subject's medical record to facilitate source data verification.

For some SAEs, the sponsor may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (eg, hospital discharge summary, consultant report, or autopsy report) deemed necessary to appropriately evaluate the SAE report.

10.6 Post-Study Adverse Events

At the last scheduled visit, the investigator should instruct each subject to report, to the investigator and/or to BPV directly, any subsequent SAEs that the subject's personal physician(s) believes might be related to prior study treatment.

The investigator should notify the study sponsor of any death or SAE occurring at any time after a subject has discontinued or terminated study participation, if the investigator believes that the death or SAE may have been related to prior study treatment. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that participated in this study.

10.7 BioMarin Pharmacovigilance Contact Information

Contact information for BioMarin Pharmacovigilance is as follows:

BioMarin Pharmaceutical Inc.

Address	105 Digital Drive Novato, CA 94949
Phone:	(415) 506-6179
Fax:	(415) 532-3144
E-mail:	drugsafety@bmrn.com

The investigator is encouraged to discuss with the medical monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the medical monitor is as follows:

Name:	PI , RN, MS
Address:	105 Digital Drive Novato, CA 94949 USA
Phone:	PI
Fax:	PI
E-mail:	PI

11 APPROPRIATENESS OF MEASUREMENTS

11.1 Blood Phe Concentration

Blood Phe concentration is an appropriate measure for efficacy as several studies have shown a correlation between blood Phe levels and clinical symptoms in patients with PKU (Vockley, 2014). In addition, the National Institutes of Health (NIH) guidelines on the treatment of PKU are based on assessments of blood Phe levels (NIH, 2000). A discussion of blood Phe concentration and its relationship with PKU is provided in Section 7.

11.2 Safety and Pharmacokinetics

Safety and PK assessments in this study are recognized as reliable, accurate, and relevant.

11.3 Diet Diary

Refer to Section 9.6 and Section 9.7.3.1 for information about the 3-day diet diary.

12 STUDY PROCEDURES

12.1 Pre-Study

An ICF must be signed and dated by the subject (or legally authorized representative when appropriate), investigator (or designee), and witness before any study-related procedures are performed.

12.2 Screening Visit/Week 1, Day 1 (Days -28 to Day 1)

After subjects provide informed consent for this study, assessments and procedures must be completed within the 28 days prior to and including Day 1. Any required assessment or procedure completed for Study PAL-003 or 165-302 may be used for screening purposes provided it was performed within 28 days of Day 1 in this study and the ICF for this study was signed before the assessment in the prior study was performed. Following completion of the 165-302 or PAL-003 Study Completion Visit and confirmation of eligibility for 165-304, subjects may be dosed on the same day, designated 165-304 Day 1.

The following study activities will be performed at the Screening/Week 1, Day 1 visit:

- Demographics
- Medical history
- 12-lead ECG
- Physical examination
- Vital signs
- Weight
- Clinical laboratory tests
- C-reactive protein (CRP)
- Complements C3 and C4
- Urine albumin/creatinine ratio. For subjects previously enrolled in PAL-003, blood for baseline urine/albumin creatinine ratio listed under Screening will be drawn pre-dose on Day 1 of 165-304.
- Urine pregnancy test, if applicable. A serum pregnancy test must be performed in the event of any positive or equivocal urine pregnancy test result.
- Diet diary issued to subject for use in reporting at Week 9 visit
- PK (plasma pegvaliase). For subjects previously enrolled in 165-302, blood for baseline PK listed under Screening will be drawn pre-dose on Day 1 of 165-304.
- Plasma Phe, tyrosine

- Immunogenicity assessments
- AEs
- Concomitant medications
- Pegvaliase injection (after eligibility for 165-304 is established)

12.3 On Study Treatment and Assessments

Events and assessments should be performed pre-dose unless otherwise specified.
All scheduled assessments and procedures must be performed in the clinic or by a home healthcare nurse with the exception of administration of study drug, which may be done outside of the clinic. A home healthcare nurse may be made available to perform the following study assessments:

- Injection training and education visits
- Study drug administration
- Observation of subject for 1 hour post-dose
- Collection and/or preparation and shipment of blood and/or urine samples

Assessment of AEs and concomitant medications should be performed whenever the subject is seen by site staff or a home healthcare professional.

If there is a skin reaction that lasts ≥14 days including reactions that could be potential vasculitis, the Skin Reaction eCRF should be completed and the subject should be referred to a dermatologist for consultation and a skin biopsy. It is recommended that a photograph of the skin reaction be taken by the subject or the site to help assess the event; photographs may be collected by the sponsor. Subjects who discontinue from study drug early will be asked to continue to perform the visit assessments until study completion (refer to Section 9.3.3).

12.3.1 Week 9 (Day 57) and Every 8 Weeks Thereafter (± 7 Days)

The following study activities are performed in the study clinic:

- Physical examination
- Vital signs
- Weight
- Clinical laboratory tests. It is recommended that urine samples are obtained as a first or second morning void.
- C-reactive protein (CRP)
- Complements C3 and C4

- Urine albumin/creatinine ratio
- Urine pregnancy test, if applicable. A serum pregnancy test must be performed in the event of any positive or equivocal urine pregnancy test result.
- Diet diary review with dietitian
- PK (plasma pegvaliase)
- Plasma Phe, tyrosine
- Immunogenicity assessments
- AEs
- Concomitant medications
- Pegvaliase injection

12.3.2 Weekly Contacts (Week 2 Until Study Completion)

In the weeks when subjects do not have a scheduled clinic visit, the following study activities are performed via telephone, email or other mode of communication:

- Clinic staff asks whether there are any problems with self-administration of study drug and answers any questions.
- Assessment of AEs
- Concomitant medications

12.4 Hypersensitivity Reaction Visit

Subjects with an NCI-CTCAE grade 3 or 4 suspected hypersensitivity reaction assessed by the investigator as related to study drug should return to the clinic between 8 and 24 hours following event onset for the following HRV evaluations:

- Physical examination
- Vital signs
- Clinical laboratory tests. It is recommended that urine samples are obtained as a first or second morning void.
- C-reactive protein (CRP)
- Complements C3 and C4
- Tryptase
- Urine albumin/creatinine ratio
- Urinalysis for N-methyl histamine
- Immunogenicity assessment (anti-pegvaliase IgE only)

- Assessment of AEs
- Concomitant medications

Subjects who experience an injection-site skin reaction that lasts ≥ 14 days including reactions that could be potential vasculitis should be referred to a dermatologist for consultation and a skin biopsy.

12.5 Study Completion or Early Termination Visit

Subjects should perform the Study Completion Visit 4 weeks after the last dose of study drug or after completion of study participation, whichever occurs last.

For subjects who terminate from the study early, the Early Termination visit should occur within 4 weeks after the last study drug dose or after withdrawal from study participation, whichever occurs last. If study drug is discontinued before study completion, the investigator will ask the subject to remain in the study to continue study visits and assessments, provided the subject's health, safety, and welfare would not be detrimentally affected (refer to Section 9.3.3).

Any unresolved SAE, AE that caused a subject to withdraw from the study, or clinically significant abnormal laboratory value or vital sign measurement identified at this visit will be followed by the investigator until resolution. Every reasonable effort should be made to contact any subject who is lost to follow-up (refer to Section 9.3.3).

The following study activities will be performed in the study clinic at the Study Completion or Early Termination visit:

- 12-lead ECG
- Physical examination
- Vital signs
- Weight
- Clinical laboratory tests. It is recommended that urine samples are obtained as a first or second morning void.
- C-reactive protein (CRP)
- Complements C3 and C4
- Urine albumin/creatinine ratio
- Urine pregnancy test, if applicable. A serum pregnancy test must be performed in the event of any positive or equivocal urine pregnancy test result.
- Diet diary for review with dietitian

- PK (plasma pegvaliase)
- Plasma Phe, tyrosine
- Immunogenicity assessments
- AEs
- Concomitant medications

13 DATA QUALITY ASSURANCE

BioMarin personnel or designees will visit the study site prior to initiation of the study to review with the site personnel information about the IP, protocol and other regulatory document requirements, 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, SAE reporting, and drug accountability records.

Sites will enter study data into eCRFs in the study EDC system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications.

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 before study completion, the investigator will ask the subject to remain in the study to continue study visits and assessments, provided the subject's health, safety, and welfare are not detrimentally affected.

For AEs and concomitant medications, partially missing dates will be imputed conservatively.

14.2 Safety Analysis

14.2.1 Adverse Events

The most current version of the Medical Dictionary for Regulatory Activities terminology (MedDRA) will be used by the sponsor to assign system organ class and preferred term classification to events and diseases based on the original terms entered on the eCRF.

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity. A by-subject listing will be provided for those subjects who experience an SAE, including death, or experience an AE associated with early withdrawal from the study or study drug. Hypersensitivity AEs and AEs that result in dosing interruption or dose level reduction, and the percentage of subjects who report these AEs will be presented.

14.2.2 Other Safety Variables

Clinical laboratory data will be summarized by the type of laboratory test. Frequency and percentage of subjects who experience abnormal (ie, outside of reference range) and/or clinically significant abnormalities after study drug administration will be presented for each clinical laboratory test by study drug group. For each clinical laboratory test, descriptive statistics will be provided for baseline and all subsequent visits. Changes from baseline to the post-baseline visits will also be provided. Descriptive statistics for vital signs, physical examination results, ECG test results, and immunogenicity test results will also be provided. Additionally, antibody incidences and titers will be summarized at the scheduled time point.

14.3 Primary Efficacy Analysis

Data from all subjects who receive at least 1 dose of study drug and who have any post-treatment efficacy data will be included in the efficacy analysis.

Blood Phe concentration at each scheduled time point will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Change in blood Phe concentration from baseline (to be defined in the SAP) to each scheduled time point will also be summarized.

14.4 Secondary Efficacy Analysis

Average of 3-day dietary record at each scheduled time point will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum).
The relationship between dietary Phe and protein intake (per information reported on the subject diet diary) and blood Phe concentration will also be explored.

14.5 Pharmacokinetics Analyses

Trough concentrations of pegvaliase will be evaluated to assess steady-state trough exposure of pegvaliase administered using prefilled syringe.

14.6 Determination of Sample Size

Subjects who were previously treated with pegvaliase in Studies PAL-003 or 165-302 may be enrolled into this study. No formal sample size calculation was conducted for this study. Approximately 40 subjects are expected to be enrolled.

14.7 Analysis Populations

The safety population will consist of all subjects who receive at least 1 dose of pegvaliase during the study.

The efficacy population will consist of all subjects who receive at least 1 dose of pegvaliase during the study and have post-treatment blood Phe concentration measurements.

The PK population will consist of all subjects with at least 1 PK measurement.

14.8 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 DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) will act in an advisory capacity to BioMarin to monitor subject safety and the efficacy of pegvaliase in subjects who participate in Study 165-304. The DMC responsibilities may include the following:

- Review the study protocol, Investigator's Brochure, and plans for data monitoring
- Evaluate subject risk/benefit and other factors that could affect individual study or program outcome based on efficacy and safety data from current studies as well as external evidence such as scientific or therapeutic developments
- Assess data report quality, data monitoring timeliness, and protocol compliance; request additional information if warranted
- Protect the safety of the study participants in accordance with the stopping rules as defined in the study protocol
- Make recommendations to BioMarin concerning continuation or termination of the study or other modifications of the study based on their observations

16 COMPENSATION, INSURANCE AND INDEMNITY

There will be no charge to study 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/REB approval, BioMarin may reimburse the reasonable cost of travel for study-related visits in accordance with BioMarin's study-specific travel and reimbursement policy. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort related solely to the study subject's disease. Costs associated with such hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected outside the study.

The investigator should contact BioMarin immediately upon notification that a study subject has been injured by the study drug or by procedures performed as part of the study. Any subject who experiences a study-related injury should be instructed by the investigator to seek immediate 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, 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. If the cost of the medical treatment is not covered by health insurance or another third party that usually pays these costs, then either BioMarin or the institution may pay for reasonable and necessary medical services to treat the injuries caused by the study drug or study procedures. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing and/or regardless of fault. If this is the case, BioMarin will comply with the law.

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic case report forms will be provided for each subject. The investigator must review and electronically sign the completed eCRF casebook to verify its accuracy.

eCRFs must be completed using a validated web-based application. Study site personnel 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 value will be corrected 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 personnel making the correction 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.

BioMarin's policy is that study data on the eCRFs 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 (or their legally authorized representative) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If direct source document verification of study data by the site monitor is prohibited by institutional policy or local law, then the investigator must make available facilities and/or personnel to allow GCP-compliant source verification to occur. Examples of such methods include certified copies of records which have study data visible but sensitive information redacted, or other GCP-compliant means agreed between the investigator and the sponsor.

A CRA designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" (SDV). 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 subject's eCRF casebook can be locked, data fields must be source data verified and all queries closed. Refer to the Study Monitoring Plan for details on which fields must be source data verified. The Data Manager, or designee, will then set the status of the forms,

visits, and the entire casebook to Locked. The investigator will then electronically sign the casebook, specifying that the information on the eCRFs is accurate and complete.
Upon completion of the CSR, an electronic copy of each site's casebooks will be copied to a compact disk (CD) and sent to each site for retention with other study documents.

18 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 to the clinical files, including original medical records, of the study subjects, and, if requested, agrees to assist the monitors.
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's 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 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.

19 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, that is, 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 (eg, 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 US 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. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a BioMarin agreement. BioMarin must be notified and will assist with retention should 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.

20 USE OF INFORMATION AND PUBLICATION

BioMarin recognizes the importance of communicating medical study data and therefore encourages the publication of these data 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 investigator/institution. Consideration for authorship of all publications will be based on compliance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals ("Uniform Requirements") of the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org/about-icmje/faqs/icmje-recommendations/) and good publication practices (GPP).

21 REFERENCES

American Psychiatric Association. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. In: American Psychiatric Association, editor. Washington, DC: 2000: 85-93.

Bilder DA, Noel JK, Baker ER, et al. Systematic review and meta-analysis of neuropsychiatric symptoms and executive functioning in adults with phenylketonuria. Developmental Neuropsychology. 2016.

Blau, N, Longo, N. Alternative therapies to address the unmet medical needs of patients with phenylketonuria. Expert Opin Pharmacother 16[6], 791-800. 2015.

Brown, SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 114[2], 371-376. 2004.

Burton, BK, Bausell, H, Katz, R et al. Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria (PKU) Mol Genet Metab, doi:10.1016/j.ymgme.2010.06.015. 2010.

Cunningham, A, Bausell, H, Brown, M, Chapman, M et. al. Recommendations for the use of sapropterin in phenylketonuria. Mol Genet Metab 106[3], 269-276. 2012.

Dyer, CA, Kendler, A, Philbotte, T, et al. Evidence for central nervous system glial cell plasticity in phenylketonuria. J Neuropathol Exp Neurol 55[7], 795-814. 1996.

Gassio R, Campistol J, Vilaseca MA, et al. Do adults with phenylketonuria improve their quality of life after introduction/resumption of a phenylalanine-restricted diet? Acta Paediatr 92[12], 1474-1478. 2003.

Huttenlocher, P. The neuropathology of phenylketonuria: human and animal studies. Eur J Pediatr 159 [Suppl 2], S102-S106. 2000.

Kaufman, S. An evaluation of the possible neurotoxicity of metabolites of phenylalanine. J Pediatr 114[5], 895-900. 1989.

Koch R, Burton B, Hoganson G, et al. Phenylketonuria in adulthood: a collaborative study. J Inherit Metab Dis 25, 333-46. 2002.

MacDonald, A, Smith, TA, de Silva, S, et al. The personal burden for caregivers of children with phenylketonuria: a cross-sectional study investigating time burden and costs in the UK. Molecular Genetics and Metabolism Reports 9, 1–5. 2016.

Modan-Moses, D, Vered, I, Schwartz, G, Anikster, Y, et al. Peak bone mass in patients with phenylketonuria. J Inherit Metab Dis 30[2], 202-208. 2007.

Moyle, JJ, Fox, AM, Arthur, M, Bynevelt, M et. al. Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. Neuropsychol Rev 17[2], 91-101. 2007.

NIH. Phenylketonuria (PKU): screening and management. NIH Consensus Statement 17[3], 1-33. 2000.

NIHCDP (National Institutes of Health Consensus Development Panel). National Institutes of Health consensus development conference statement: phenylketonuria: screening and management. October 16-18, 2000. Pediatrics 108(4), 972-983. 2001.

NIMH. The Numbers Count: Mental Disorders in America. NIH 1-8. 2013.

Palermo, L, Geberhiwot, T, MacDonald, A, et al. Cognitive outcomes in early-treated adults with phenylketonuria (PKU): a comprehensive picture across domains. Neuropsychology 31[3], 255–267. 2017.

Pietz, J, Fatkenheuer, B, Burgard, P, Armbruster, M, et al. Psychiatric disorders in adult patients with early-treated phenylketonuria. Pediatrics 99[3], 345-350. 1997.

Romani, C, Palermo, L, MacDonald, A, et al. The impact of phenylalanine levels on cognitive outcomes in adults with phenylketonuria: effects across tasks and developmental stages. Neuropsychology, Vol. 31[3], 242–254. 2017.

Sampson, HA, Munoz-Furlong, A, Campbell, RL, Adkinson, NF, Jr, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 117[2], 391-397. 2006.

Schuck, PF, Malgarin, F, Cararo, JH, et al. Phenylketonuria pathophysiology: on the role of metabolic alterations. Aging and Disease 6[5], 390-99. 2015.

Smith, I, Knowles, J. Behaviour in early treated phenylketonuria: a systematic review. Eur J Pediatr 159 Suppl 2, S89-S93. 2000.

Ten Hoedt AE, de Sonneville LM, Francois B, et al. High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial. J Inherit Metab Dis 34(1), 165-171. 2011.

van Spronsen, FJ, van Wegberg, AMJ, Ahring, K, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. www.thelancet.com/diabetes-endocrinology. 2017.

Vockley, J, Andersson, HC, Antshel, KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med 16[2],188-200. 2014.

Waisbren. Handbook of Neurodevelopmental and Genetic Disorders in Children. In: Goldstein S, Reynolds CR, editors. New York: Guildford Publications, 1999: 433-458.

Wall, KM, Pardridge, WM. Decreases in brain protein synthesis elicited by moderate increases in plasma phenylalanine. Biochemical and Biophysical Research Communications 168[3], 1177-1183. 1990.

Walter, JH, White, FJ, Hall, SK, MacDonald, A, et al. How practical are recommendations for dietary control in phenylketonuria? Lancet 360[9326], 55-57. 2002.

22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572 and/or principles of ICH E6 R2 GCP, the investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, 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, or any persons used as controls, that the drugs 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/or ICH E6 R2 Sections 2.9 and 4.8 are met. As well, he or she will ensure that IRB/IEC review and approval in 21 CFR Part 56 and/or ICH E6 R2 Section 2.6 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 and/or ICH E6 R2 Section 4.11.
- 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
- Adequate and accurate records in accordance with 21 CFR 312.62 and/or ICH E6 R2 Section 4.9 are kept, and those records are available for inspection in accordance with 21 CFR 312.68 and/or ICH E6 R2 Section 4.9.7.
- The IRB/EC/REB complies with the requirements of 21 CFR Part 56, ICH Section 3.0, and other applicable regulations, and conducts 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/EC/REB. Additionally, he or she will not make any changes in the research without IRB/EC/REB 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 and/or ICH E6 R2.

23 SIGNATURE PAGE

Protocol Title: An Open-label Extension Study to Evaluate the Safety and Efficacy of Subcutaneous Injections of Pegvaliase (> 40 mg/day Dose) in Adults with Phenylketonuria

Protocol Number: 165-304 Amendment 1

Protocol Date: 30 July 2019

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 R2, as stated in the protocol, and other information supplied to me.

Investigator Signature Date

Printed name:_____

Accepted for the Sponsor:

DocuSigned by:
PI
Signer Name: PI
Signing Reason: I approve this document
Signing Time: 7/31/2019 5:56:05 PM PDT
14381DB6B0824291921CEC24324D6E1A

Medical Monitor Signature Date

Printed name:_____

24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See page 2). Text that has been added or inserted is indicated by underlined font, and deleted text is indicated by ~~strikethrough~~ font.

Section No./Title	Revision	Rationale
Synopsis (Study Rationale)	Study 165-304 is an open-label extension for subjects who participated in Studies PAL-003 and 165-302 at doses > 40 mg/day. The objective is to evaluate long-term safety and efficacy in subjects treated at doses exceeding the ~~proposed~~approved pegvaliase ~~label~~labeled dose (the currently approved label specifies up to and including 40 mg/day dose only).	4
Synopsis (Study Design and Plan)	This is a Phase 3 open-label extension study enrolling approximately 40 adult subjects with PKU who were previously treated with pegvaliase in Studies PAL-003 or 165-302. The study is designed to evaluate the long-term safety and efficacy of pegvaliase administered as prefilled syringe drug product at a dose of > 40 mg/day to 60 mg/day, inclusive. Dose regimens other than daily dosing at > 40 mg/day to 60 mg/day (~~up to 5.0 mg/week but~~with the exception of 1 subject enrolled from the PAL-003 study who receives a pegvaliase dose not to exceed 120 mg/day) may be allowed provided the investigator consults with the medical monitor and obtains approval from the medical monitor prior to starting the alternative regimen. Subjects will continue their prior pegvaliase dose regimen on the 165-304 study, including 1 subject enrolled from the PAL-003 study who receives a pegvaliase ~~weekly~~ dose ~~up~~not to ~~5.0~~exceed 120 mg/~~kg.~~day. A subject who dose reduces to a dose of 40 mg/day or lower for 32 consecutive weeks will be discontinued from study drug and withdrawn from the study as they will have the option to transition to commercial drug. Dose reductions may be performed if warranted due to adverse events (AEs) or hypophenylalaninemia. Dose increases to up to 60 mg/day may be performed per investigator discretion in consultation with the sponsor's medical monitor. Dosing will continue for approximately ~~61~~121 weeks.	1, 3
Synopsis (Duration of Treatment)	Approximately ~~61~~121 weeks	1
7/Introduction	~~Currently~~Historically the only treatment option available for patients with PKU ~~is~~was medical nutritional therapy (MNT) with severe restriction of Phe intake, alone or as adjunct to Kuvan® (sapropterin 6R-tetrahydrobiopterin or 6R-BH4).	4
7.3/Study Rationale	Study 165-304 is an open-label extension for subjects who participated in Studies PAL-003 and 165-302 at doses > 40 mg/day. The objective is to evaluate long-term safety and efficacy in subjects treated at doses exceeding the ~~proposed~~currently approved pegvaliase label (the label specifies up to and including 40 mg/day dose only).	4

Section No./Title	Revision	Rationale
7.4.1/Analysis of Condition	Adult PKU patients often have untreated blood Phe levels > 1,200 µmol/L. ~~Currently~~Historically, there ~~are~~were 2 treatment options available for patients with PKU: medical nutritional therapy (MNT) with Phe restriction, and sapropterin dihydrochloride (Kuvan) as adjunct to MNT and Phe restriction.	4
7.4.2/Unmet Medical Need and Current Treatment Options	Sapropterin dihydrochloride (Kuvan) is a synthetic oral formulation of BH4, which works by increasing PAH activity in PKU patients with some residual enzyme function (Blau, 2015). ~~Kuvan is approved for children and adults in the United States for the treatment of BH4-responsive PKU in conjunction with Phe-restricted intake, and in the European Union for BH4-responsive PKU and BH4 deficiency.~~ ~~In the pivotal clinical studies of Kuvan, only approximately 25% to 80% of pediatric and adult PKU patients reached a minimum 30% reduction in blood Phe from baseline after treatment with Kuvan at either a 10 mg/kg or 20 mg/kg dose (Kuvan package insert; Blau 2015).~~ Kuvan is an approved pharmacological treatment for children and adults for the treatment of BH4-responsive PKU in the US. Approval of Kuvan was based on demonstrating blood Phe reduction in clinical trials and is indicated for use in conjunction with Phe-restricted intake to lower blood Phe concentrations. However, only approximately 20% to 56% of PKU patients respond to sapropterin therapy. **Pegvaliase (Palynziq®)** Pegvaliase was approved in the United States on 24 May 2018 under the name Palynziq for maintenance dosages up to 40 mg/day to reduce blood Phe concentrations in adult patients with PKU who have uncontrolled blood Phe concentrations > 600 µmol/L on existing management, addressing a substantial unmet medical need for the adult PKU patient population. On 3 May 2019, pegvaliase was also approved in the EU to reduce blood Phe in patients with PKU aged 16 years and older who have inadequate blood Phe control (defined as blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options.	4
7.4.4/Risk	The safety of pegvaliase was evaluated in 6 multiple dose studies in adult PKU patients totaling ~~473.4~~579.6 patient-years of exposure with the recommended I/T/M dosing regimen for pegvaliase, including ~~298.6~~403.4 patient-years of exposure with the to-be-marketed PFS presentation. Thus, important identified and potential risks associated with pegvaliase use have been sufficiently characterized to inform benefit-risk decisions by adult PKU patients and their treating physicians.	5

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	The most commonly reported treatment-emergent AEs were arthralgia (~~70~~72.6%), injection site reaction (~~65~~64.9%), headache (~~52~~51.2%), and injection site erythema (~~43~~50.2%). In the ~~multiple dose studies of pegvaliase,~~I/T/M population hypersensitivity adverse events (HAEs) were very common (~~93.5~~94%), and included arthralgia (~~69.5~~71%), rash (~~40.2~~38%), pruritus (31~~.4~~%), urticaria (~~29.6%), serum sickness (2.1%),~~30%), pyrexia (22%) and ~~angioedema (0.4~~injection site rash (21%). The highest HAE severity was Grade 1 for ~~22.6~~18.2% of subjects or Grade 2 for ~~58.9~~62.5% subjects. Most (91.6%) HAEs did not require pegvaliase dose modification, and 97.5% of HAEs resolved.	
9.1/Overall Study Design and Plan	This is a Phase 3 open-label extension study enrolling approximately 40 adult subjects with PKU who were previously treated with pegvaliase in Studies PAL-003 or 165-302. The study is designed to evaluate the long-term safety and efficacy of pegvaliase administered as prefilled syringe drug product at a dose of > 40 mg/day to 60 mg/day, inclusive. Dose regimens other than daily dosing at > 40 mg/day to 60 mg/day (~~up to 5.0 mg/week but~~with the exception of 1 subject enrolled from the PAL-003 study who receives a pegvaliase dose not to exceed 120 mg/day) may be allowed provided the investigator consults with the medical monitor and obtains approval from the medical monitor prior to starting the alternative regimen. Subjects will continue their prior pegvaliase dose regimen on the 165-304 study, including 1 subject enrolled from the PAL-003 study who receives a pegvaliase ~~weekly~~ dose ~~up~~not to ~~5.0~~exceed 120 mg/~~kg~~day. A subject who dose reduces to a dose of 40 mg/day or lower for 32 consecutive weeks will be discontinued from study drug and withdrawn from the study as they will have the option to transition to commercial drug. Dose reductions may be performed if warranted due to AEs or hypophenylalaninemia. Dose increases to up to 60 mg/day may be performed per investigator discretion in consultation with the sponsor's medical monitor. Dosing will continue for approximately ~~61~~121 weeks.	1, 3
Table 9.1.1/SOE (footnotes)	[k] Immunogenicity assays include (but are not limited to) total anti-pegvaliase, anti-rAvPAL IgG, anti-rAvPAL IgM, anti-PEG IgG, anti-PEG IgM, anti-pegvaliase IgG4, and neutralizing antibodies; additional assays include IgG-C3d and IgM-C3d circulating immune complexes (CICs); anti-pegvaliase IgE is determined when appropriate (hypersensitivity or other safety concern).	2
Table 9.1.1.2.1/Dosing After HAE (footnotes)	[c] The pegvaliase dose may be reduced or interrupted if necessary per investigator determination~~. The investigator should consult with the sponsor's medical monitor prior to performing dose reductions during Part 2.~~..	5
9.3.5/Duration of Subject Participation	Following a screening period of up to 28 days, subjects receive pegvaliase for approximately ~~61~~121 weeks or until study closure.	1

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9.7.4/Exploratory Sample Analysis	Blood and urine samples may be analyzed to evaluate biochemical, molecular, cellular and genetic/genomic aspects of PKU and to develop the assays used for these evaluations. For each portion of the blood and urine samples reserved for protocol-specified analyses, there may be multiple sample aliquots. ~~Once samples have been successfully analyzed during the study per protocol,~~The unused ~~sample portions~~aliquots may be used during the study ~~and afterwards to evaluate the biochemical, molecular, cellular, and genetic/genomic aspects of PKU and to develop the assays used for these evaluations.~~for assay development or other purposes stated in Section 9.7.4.	5
9.7.5.3.4/Other Laboratory Assessments	Immunogenicity will be assessed ~~by determining antibody response~~ with immunogenicity assays including, but not limited to, the following: • Anti-PEG IgG antibodies • Anti-PEG IgM antibodies • Anti-pegvaliase IgG4 antibodies • IgG-C3d and IgM-C3d Circulating Immune Complexes (CICs)	2
10.2.3/Assessment of Seriousness, Severity, and Causality	The investigator responsible for the care of the subject or qualified medical designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.1.2 for SAE definitions).	5
10.3.1.7/ Hospitalization, Prolonged Hospitalization, or Surgery	Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE except as described below. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include planned hospitalizations or prolonged hospitalizations to: • Routine hospitalization for childbirth, including planned caesarean section	5
10.5/Follow-Up after AEs	The investigator should follow all unresolved AEs ~~and SAEs until the events are resolved or have stabilized.~~, unless the subject is lost to follow-up, or it has been determined that the study treatment or participation was not the cause of the AE ~~or SAE. Resolution~~ The outcome of AEs ~~and SAEs (with dates)~~ should be documented on the AE eCRF and in the subject's medical record to facilitate source data verification. The investigator should follow all unresolved SAEs to resolution, unless the subject is lost to follow up, or it has been determined that the study treatment or participation was not the cause of the SAE. Resolution of the SAE (with dates)	5

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	should be documented on the AE eCRF and the SAE report form, as well as the subject's medical record to facilitate source data verification.	