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.

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Study name: 165-304

Overview

Purpose (Check only 1):

- ☐ Final draft SAP
- ☐ Revision(s) to the final draft SAP
- ☑ Final SAP
- ☐ Amendment(s) to the final SAP
- ☐ The TOC of TLGs defined by the SAP
- ☐ TLG mockups and specifications defined by a SAP
- ☐ Revision(s) to the TLG mockups and specifications document after its approval, determined by the Biostatistican to require SART approval
- ☐ Request(s) for major changes to mockups and specifications after review of TLG outputs produced for the Dry Run
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Comments

Approval

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Statistical Analysis Plan

Study 165-304

07 May 2021

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
BMI	body mass index
C3	complement component 3
C4	complement component 4
CRP	C-reactive protein
CRF	Case Report Form
CSR CTCAE	clinical study report Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
HAE	hypersensitivity adverse event
HI	hyperactivity/impulsivity
IA	inattention
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
ITT	intent-to-treat
IWRS LOCF	Interactive Web Response System last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
Nab	neutralizing antibody
NIAID/FAAN	National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
NCA	non-compartmental analysis
NSAID	non-steroidal anti-inflammatory drug
PAL	phenylalanine
PD	pharmacodynamics
PEG	polyethylene glycol
Phe	phenylalanine

Abbreviation	Definition
PK	pharmacokinetics
PKU	phenylketonuria
PT	preferred term
rAvPAL-PEG	recombinant *Anabaena variabilis* phenylalanine ammonia lyase-PEG
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SMQ	Standardized MedDRA Queries
TEAE	treatment-emergent adverse event
$t_{1/2}$	elimination half-life
TMD	total mood disturbance
V/F	apparent volume of distribution
Tab	total antibody
WHO Drug	World Health Organization Drug Dictionary

2 INTRODUCTION

Study 165-304 is an open-label extension study to evaluate long-term safety and efficacy of subcutaneous injections of pegvaliase (> 40 mg/day Dose) in adults with phenylketonuria. The purpose of this Statistical Analysis Plan (SAP) is to provide a comprehensive description of methods of the data analyses outlined in the protocol (30 July 2019).

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.

2.1 Objectives of Study

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

2.2 Study Design

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).

2.3 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. Additional criteria for study participation are presented in Protocol 165-304 Section 9.3.1 and Section 9.3.2.

2.4 Study Dosage and Administration

Subject will begin the study on the same dose and dosing regimens they were on at the completion of the previous study. Subjects will receive pegvaliase SC via pre-filled syringe at a dose of >40 mg/day to 60 mg/day, inclusive. Dose reductions may be performed if warranted due to AE or hypophenylalaninemia. Dose increases to up to 60 mg/day may be performed per investigator discretion in consultation with the sponsor's medical monitor

2.5 Sample Size Determination

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.

2.6 Blinding and Randomization Methods

2.6.1 Blinding Method

Subjects will receive open-label pegvaliase.

2.6.2 Randomization Method

This is an open-label study.

2.7 Interim Analysis

Not applicable.

3 GENERAL ANALYSIS CONSIDERATION

Descriptive summaries of continuous variables will include the mean, standard deviation (SD), median, minimum, maximum, and, where appropriate, 95% confidence interval for the mean. Descriptive summaries of categorical variables will include n, frequency, and percentage.

Baseline data and relevant dosing data from parent studies will be integrated together with data in Study 165-304 for long term safety and efficacy analyses, when appropriate.

Additional analyses will be conducted as appropriate to evaluate the impact of the COVID19 pandemic on the study conduct and results, especially for the treatment effect as estimated in the trial.

3.1 Analysis Populations

3.1.1 Efficacy

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

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

3.1.2 Safety

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

3.2 Treatment Group Presentation

The following treatment groups will be considered in summary tables:

- Daily dose at each Phe/safety assessment (<20mg, 20 to < 40 mg, 40 to <60 mg, ≥60 mg and Any Dose)

3.3 Pooling of Data from Sites with Small Enrollment

Since the enrollment for each site is expected to be small, the analyses will not be adjusted by site or pooled sites.

3.4 Study Day Derivation

Study days will be derived as follows:

- The drug start date in study 304 will be assigned as Study Day 1
- For visit occurs on or after drug start date, Study day = visit date – day 1 date + 1

- For visit occurs before drug start date, Study day = visit date – day 1 date. There is no Study Day 0

3.4.1 Baseline Definition

The parent study baseline (naïve baseline) for all safety and efficacy endpoint is defined as the last non-missing measurement prior to the initiation of pegvaliase in the parent study.

The 304 study baseline for all safety and efficacy endpoint (when applicable) is defined as the last non-missing measurement collected prior to first pegvaliase dose in study 304.

3.5 Visit Window for Analysis

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

Table 3.5.1 lists the scheduled weeks of the assessments collected in this study and the corresponding range of treatment days (window) during which a visit may have occurred.

Table 3.5.1: Visit Time Windows for the Treatment Period

Derived Visit	Target Day[a]	Window[b]
Screening/Day 1	Day -1	Day -28 to 1
Week 9	Day 57	Day 2 to Day 84
Week XX (XX>9, every 8 weeks)	Day (XX-1)*7+1	Day (XX-5)*7 + 1 to Day (XX+3)*7

[a] Target days are relative to the first dosing day of study drug.

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

3.6 Handling of Dropouts and Missing Data

Subjects who discontinued prematurely will not be replaced. To investigate the robustness of the primary analysis, last observation carried forward (LOCF) imputation approach will be used as sensitivity analysis.

4 SUBJECT DISPOSITION

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

5 DISCONTINUATION AND COMPLETION

For subjects who prematurely discontinued study, the primary reason for discontinuation will be summarized by treatment group. A similar summary will be provided for subjects who discontinue study drug. A subject listing of completion and early termination from study will also be provided.

6 PROTOCOL DEVIATIONS

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

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

All protocol deviations collected in 165-304 will be summarized. Subjects with protocol deviations will be provided in a listing. Subjects with inclusion or exclusion criteria deviations will also be provided in a separate listing.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic information will be summarized for the efficacy analysis population as well as the safety population. Demographics, including age, age group, sex, race, and ethnicity, will be summarized by descriptive statistics.

Subject characteristics at study 165-304 baseline as well as parent study baseline (naïve baseline) will be summarized for the efficacy analysis population and safety population. Baseline subject characteristics will include height, weight, BMI, blood Phe concentration, intake of protein and dietary Phe, three-day average dietary intake, percent of subjects on restricted diet, and antibody status.

8 MEDICAL HISTORY

Each subject's chronic diseases, disorders, and surgeries in the past will be collected as general medical history. General medical history will be summarized by system organ class (SOC) and Preferred Term (PT) by descending order of frequency for all subjects enrolled in 165-304. A by-subject listing of each subject's medical history collected at the Screening Visit will also be provided.

9 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

Prior and concomitant medications will be summarized for all subjects entering 165-304. For analysis purposes, the following definitions will be used to determine prior and concomitant medications:

- Prior medications: any medications taken within 30 days prior to screening and prior to the date of initial study drug administration in 165-304.
- Concomitant medications: any medications initially taken on or after the date of initial study drug administration.
- Prior and concomitant medications: any medications taken both prior to the date of initial study drug administration and on or after the date of initial study drug administration will be reported both as prior and concomitant medications. Therefore, any medications taken prior to the first dose date where the stop date is reported as "continuing" or missing will be considered both as prior and concomitant medications.

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

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

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

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

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) dictionary (September 2014). Prior and concomitant medication use will be separately summarized by Anatomical Therapeutic Chemical (ATC) medication class (Level 4) and preferred name (ie, generic medication name). A subject reporting the same medication more than once will be counted once when calculating the number and

percentage of subjects who received that medication. A subject listing of each subject's prior and concomitant medications will be provided.

10 STUDY DRUG USAGE

Study drug usage rate will be calculated based on the drug exposure records captured in eCRFs and dispensed drug amount captured in the Interactive web response system (IWRS).

The overall study drug usage rate will be derived from the total amount of study drug intake divided by the total dispensed study drug amount over the study period and multiplied by 100%.

11 EXTENT OF EXPOSURE TO STUDY DRUG

Total number of days on drug, total amount of study drug (mg) and mean daily dose (mg) will be presented using summary statistics such as n, mean, SD, median, minimum, and maximum for the following variables:

- Average of daily doses (mg) received
- Total Doses (mg) received
- Total duration of treatment

Any dose interruption longer than 28 days will be excluded from the total exposure duration calculation.

The extent of exposure will be summarized using observed data collected on the exposure CRF only.

A by-subject listing of each subject's extent of exposure and compliance will be provided.

12 EFFICACY EVALUATIONS

Unless specified otherwise, efficacy analyses will be based on the efficacy population.

12.1 Primary Efficacy Variables

The primary efficacy variable is phe concentration, the following will be summarized:

- Observed values, change and percent change from parent study baseline in blood Phe concentration at each visit
- Percent of subjects with blood Phe <= 120 µmol/L at each visit during study
- Percent of subjects with blood Phe <= 360 µmol/L at each visit during study
- Percent of subjects with blood Phe <= 600 µmol/L at each visit during study

The efficacy variable will be summarized by 8-week cycle for blood Phe. Plots for mean blood Phe concentration, change from baseline and percentage change from baseline in blood Phe concentration will be generated for both observed values and values after LOCF imputation. A subject listing of blood Phe concentration will be provided.

12.2 Secondary Efficacy Variables

The parameters of interest for dietary intake include:

- Protein intake from medical food
- Protein intake from intact food
- Total protein intake
- Total calorie intake
- Total tyrosine intake
- Total phenylalanine intake

The observed values, change and percent change from naïve baseline at parent studies for all parameters at each visit will be summarized for the efficacy population. The values collected on the three-day diet diary will be averaged for each parameter at each visit before being summarized. In addition, similar analysis will be performed for percentage of daily recommended intake provided for protein, Phe, tyrosine, vitamins and minerals. A subject listing will also be provided.

12.3 Pharmacokinetics

Table summary and subject listing of plasma pegvaliase concentration by study visit will be provided.

13 SAFETY EVALUATIONS

Safety will be assessed by examining the incidence, exposure adjusted event rate, severity grade, and relationship to study drug of all treatment-emergent adverse events (TEAEs) reported during the study period. In addition, clinical laboratory results, vital signs, pregnancy test, physical exam and ECG values will be assessed.

13.1 Adverse Events

AEs will be coded in accordance with the MedDRA (version 23.0). Only treatment-emergent adverse events (TEAEs) occurring and reported during the study period will be included in the adverse event summaries. A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of the study drug administration until 30 days after last dose of the study. If the onset date of an AE is missing, the AE will be considered treatment-emergent.

13.1.1 All Adverse Events

The incidence and frequency of all treatment-emergent AEs will be summarized by system organ class (SOC), preferred term (PT), relationship to study drug and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grades. For those AEs that occurred more than once during the study, the maximum severity will be used to summarize the AEs by severity.

If the onset date or end date of an adverse event is partial, the same imputation rules described in Section 9 will be applied.

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

- All AEs by SOC and PT
- All AEs by SOC, PT and severity
- AEs assessed by investigators as related to study drug by SOC and PT
- AEs assessed by investigators as related to study drug by SOC, PT and severity
- Serious AEs (SAEs) by SOC and PT
- All AEs by PT in descending frequency order
- All AEs by SOC and PT with exposure adjusted event rate
- Neuropsychiatric AEs by SOC, PT and severity
- AEs assessed by investigators as related to PFS/Device malfunction
- AEs leading to withdrawal from study by SOC and PT

- AEs leading to study drug discontinuation by SOC and PT

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

- AE profile summary table, including:
  - Duration of the events during 165-304
  - Recurrence of the events (summary for number of events per subject)
  - Actions related to study drug
  - Outcomes of the events
- Pre-medication usage
- Common treatment
- Incidence rate over time

The AEs of special interest include:

- Anaphylaxis per NIAID/FAAN criteria
- Acute systemic hypersensitivity reaction
- Anaphylaxis per FDA criteria

The sponsor defined AEs of Clinical clinical significance include:

- Hypersensitivity Reaction
- Angioedema
- Serum sickness
- Severe injection site reaction
- Hypophenylalanemia (see low blood Phe levels below)
- Generalized skin reaction with ≥ 14 day duration
- Injection site skin reaction with ≥ 14 day duration
- Persistent arthralgia (> 6 months duration)

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

In addition to standard AE listings, by-subject listings of injection site reaction AEs, HAEs, and psychiatric AEs under each identification strategies will be provided. Study drug dose

level at onset date of each of the AE, and immunogenicity test results will be presented on the listings. AEs will be sorted by onset date, preferred term, and end date.

13.1.2 Low Blood Phe (Blood Phe < 30 µmol/L) Analysis

Safety from subjects who experienced two consecutive low blood Phe (< 30 µmol/L) measurements will be summarized.

13.1.3 Other Adverse Event Analysis

All lab adverse events (defined as AEs with SOC equal to "Investigational Product") that are NCI CTCAE grade ≥3 will be summarized.

13.2 Clinical Laboratory Tests

Standard descriptive statistics will be presented for clinical laboratory tests, including hematology, chemistry and urinalysis, at each scheduled visit and for change in laboratory values from baseline. The proportion of subjects who experienced at least one laboratory test result outside the normal ranges will be presented for each measurement as appropriate. Shift table from baseline to most extreme post-baseline value based on normal range and based on CTC grading (where available) will also be generated for each parameter as appropriate. A subject listing of laboratory test results for hematology, chemistry, urinalysis, and other laboratory tests will be provided separately. Values with CTC grade as 3 or above will be flagged in the listings.

A listing of laboratory test results for subjects with alanine transaminase (ALT) or alanine aminotransferase (AST) ≥ 3xULN and total bilirubin ≥ 2xULN will also be provided.

13.3 Vital Signs

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

Summary statistics including n, mean, SD, median, minimum, and maximum will be provided for these parameters at each visit. A subject listing will also be provided.

13.4 12-lead Electrocardiogram

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

13.5 Physical Examination

Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic/psychological systems. Other body systems may be examined. A subject listing for clinically significant findings at each visit will be provided.

13.6 Immunogenicity Tests

Immunogenicity will be performed using validated immunogenicity assays. Blood samples for routine immunogenicity testing will be collected every 8 weeks or at an Early Termination visit. Routine immunogenicity testing will include assays for total anti-pegvaliase antibodies (TAb), anti-rAvPAL IgG, anti-rAvPAL IgM, anti-PEG IgG, anti-PEG IgM, neutralizing antibodies (NAb), anti-pegvaliase IgG4, and circulating immune complexes (IgG CIC and IgM CIC). In the event of a Hypersensitivity Reaction visit (HRV), sampling and testing will be performed for anti-pegvaliase IgE, as well as other potentially-related clinical laboratory tests, including CRP, complement C3 and C4, and tryptase.

For immunogenicity analysis, an incidence table and titer summary statistics including mean, median, standard deviation, and minimum/maximum titer values at each study visit will be provided for each antibody analyte. Plots of mean titer and percent positivity over time will also be generated. A listing of anti-pegvaliase IgE test results will be provided by subject.

Anti-drug antibody impact on safety will be evaluated. Plots and tables will be generated to explore the potential impact of anti-drug antibodies on HAE frequency and severity. A listing will be provided for each subject who has Hypersensitivity Reaction Visit, with the most proximal antibody test result listed for each analyte, and when available, CRP, complement C3 and C4, and tryptase at the time of the event.

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

13.7 Pregnancy Test

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

14 APPENDICES

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

MedDRA version: most current version at program termination

1: Anaphylaxis AEs per NIAID/FAAN criteria

Anaphylaxis per NIAID/FAAN is defined using the NIAID/FAAN clinical diagnostic criteria through review on the potential anaphylaxis per NIAID/FAAN cases, which are identified using Broad algorithmic anaphylactic reaction SMQ:

Algorithm = A or (B and C) or (D and (B or C))

Name of Search	Category	Preferred Term
Broad Algorithmic Anaphylactic Reaction SMQ	A	Anaphylactic reaction
	A	Anaphylactic shock
	A	Anaphylactic transfusion reaction
	A	Anaphylactoid reaction
	A	Anaphylactoid shock
	A	Circulatory collapse
	A	First use syndrome
	A	Kounis syndrome
	A	Shock
	A	Type I hypersensitivity
	B	Acute respiratory failure
	B	Asthma
	B	Bronchial oedema
	B	Bronchospasm
	B	Cardio-respiratory distress
	B	Chest discomfort
	B	Choking
	B	Choking sensation
	B	Circumoral oedema
	B	Cough
	B	Cyanosis
	B	Dyspnoea
	B	Hyperventilation
	B	Laryngeal dyspnoea

Name of Search	Category	Preferred Term
	B	Laryngeal oedema
	B	Laryngospasm
	B	Laryngotracheal oedema
	B	Mouth swelling
	B	Nasal obstruction
	B	Oedema mouth
	B	Oropharyngeal spasm
	B	Oropharyngeal swelling
	B	Respiratory arrest
	B	Respiratory distress
	B	Respiratory failure
	B	Reversible airways obstruction
	B	Sensation of foreign body
	B	Sneezing
	B	Stridor
	B	Swollen tongue
	B	Tachypnoea
	B	Throat tightness
	B	Tongue oedema
	B	Tracheal obstruction
	B	Tracheal oedema
	B	Upper airway obstruction
	B	Wheezing
	C	Allergic oedema
	C	Angioedema
	C	Erythema
	C	Eye oedema
	C	Eye pruritus
	C	Eye swelling
	C	Eyelid oedema
	C	Face oedema
	C	Flushing
	C	Generalised erythema
	C	Injection site urticaria
	C	Lip oedema
	C	Lip swelling

Name of Search	Category	Preferred Term
	C	Ocular hyperaemia
	C	Oedema
	C	Periorbital oedema
	C	Pruritus
	C	Pruritus allergic
	C	Pruritus generalised
	C	Rash
	C	Rash erythematous
	C	Rash generalised
	C	Rash pruritic
	C	Skin swelling
	C	Swelling
	C	Swelling face
	C	Urticaria
	C	Urticaria papular
	D	Blood pressure decreased
	D	Blood pressure diastolic decreased
	D	Blood pressure systolic decreased
	D	Cardiac arrest
	D	Cardio-respiratory arrest
	D	Cardiovascular insufficiency
	D	Diastolic hypotension
	D	Hypotension

2: Acute systemic hypersensitivity reaction

An anaphylaxis episode which meets the NIAID/FAAN criteria and is positively adjudicated by an independent expert allergist/immunologist as anaphylaxis according to the NIAID/FAAN criteria and based on clinical judgment of the significance of symptoms, is referred to as an acute systemic hypersensitivity reaction.

3: Anaphylaxis per FDA criteria

Anaphylaxis events defined according to the DPARP methodology are referred to as "anaphylaxis per FDA criteria". The FDA's assessment methodology includes individual case safety reports with any of the following characteristics:

- Clinical manifestations consistent with NIAID/FAAN Criterion 1 (skin involvement + respiratory or cardiovascular compromise); and
- Verbatim reports of anaphylaxis or anaphylactic reaction, even if NIAID/FAAN criteria were not met; and
- Cases involving subject injection of epinephrine alone, even if subject did not experience signs/symptoms necessary to meet NIAID/FAAN criteria.

Anaphylaxis episodes meeting these FDA criteria are the primary focus of the safety assessment.

4: Hypersensitivity AEs

Hypersensitivity AEs will be identified in two ways:

Broad Algorithmic anaphylactic reaction Standardized MedDRA Queries (SMQ):

Algorithm = A or (B and C) or (D and (B or C))

Modified Hypersensitivity SMQ to include below additional preferred terms

Name of Search	Preferred Term
Additional preferred terms for Modified Hypersensitivity SMQ	Arthralgia Arthritis Eye inflammation Eye irritation Eye pain Joint stiffness Joint swelling Pyrexia Vision blurred Polyarthritis

5: Hypersensitivity Reaction

Hypersensitivity reactions are defined as the modified hypersensitivity SMQ (narrow SMQ) or an anaphylaxis event as described in Appendix 1 – Listing 1 and adjudicated by BioMarin's Pharmacovigilance group.

The following terms should be added to the Modified Hypersensitivity (Narrow SMQ) search criteria:

- Dyspnoea
- Pruritus

- Arthritis
- Arthralgia

The following terms should be excluded from the Modified Hypersensitivity (Narrow SMQ) search criteria:

- injection site rash
- injection site urticaria

6: Angioedema per sponsor criteria

A 2-step process to identify angioedema per sponsor criteria, the following assessment was performed on the entire AE dataset:

- Step 1: all reported ADRs suggestive of angioedema using the Angioedema MedDRA HLT search, which includes the following 21 PTs: angioedema, circumoral oedema, eyelid oedema, face oedema, Gleich's syndrome, hereditary angioedema, idiopathic angioedema, intestinal angioedema, laryngeal oedema, laryngotracheal oedema, lip oedema, lip swelling, mouth swelling, oculorespiratory syndrome, oedema mouth, oropharyngeal swelling, periorbital oedema, pharyngeal oedema, swelling face, swollen tongue, and tongue oedema.
- Step 2: BioMarin then clinically assessed the retrieved data identified from Step 1 to assign concurrent events into episodes and to exclude:
    - False positive ADR reports that have clear confounders which impact assessment, eg, onset of event(s) ≥ 30 days after last dose or events/episodes with a very clear alternative etiology, such as throat swelling secondary to intubation). Cases were not excluded where the events have a long duration which may be atypical for angioedema, or where events occurred concurrent with other conditions which may have contributed to their development (eg, eye swelling reported during episode(s) of seasonal allergy).
- Episodes which occurred as part of an acute systemic hypersensitivity reaction and, therefore, will already be included in the incidence for acute systemic hypersensitivity reactions (to avoid duplication).

In the sponsor's opinion, the methodology described above is more likely to be reflective of the true incidence of angioedema manifestations.

7: Serum Sickness

Serum sickness-like reaction will be defined by including all preferred term of serum sickness, serum sickness-like reactions and Type III immune complex mediated reactions.

8: Severe Injection-site reaction

Severe injection site reaction will be identified as any injection site reaction report that is reported as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or above in severity and meeting MedDRA high level term (HLT) for Injection site reaction, or is reported as a Serious Adverse Reaction, irrespective of severity.

9: Hypophenylalanemia

Hypophenylalaninemia is defined as a blood phenylalanine (Phe) level ≤ 30 µmol/L for a minimum of 2 consecutive values, with the start of the event defined as the first blood Phe assessment day with < 30 µmol/L and the end of the event defined as the day prior to the first blood Phe assessment ≥ 30 umol/L

10: Injection site skin reaction with ≥ 14 day duration

Injection site skin reaction with ≥ 14 day duration will be identified by preferred term search using the list below. To be included as injection site skin reaction, the duration of the event needs to be ≥ 14 days (Multiple AE records with same preferred term and ≤ 1 day difference between the start date and end date are considered as same event).

Name of Search	Preferred Term
Injection site skin reaction	Injection site anaesthesia
	Injection site extravasation
	Injection site phlebitis
	Injection site movement impairment
	Injection site lymphadenopathy
	Injection site atrophy
	Injection site cyst
	Injection site erosion
	Injection site fibrosis
	Injection site granuloma
	Injection site induration
	Injection site mass
	Injection site necrosis
	Injection site oedema
	Injection site ulcer

Name of Search	Preferred Term
	Injection site hypersensitivity
	Injection site irritation
	Injection site discomfort
	Injection site dysaesthesia
	Injection site hyperaesthesia
	Injection site hypoaesthesia
	Injection site swelling
	Injection site calcification
	Injection site pustule
	Injection site nodule
	Injection site scar
	Injection site bruising
	Injection site haematoma
	Injection site haemorrhage
	Injection site hypertrophy
	Injection site pain
	Injection site paraesthesia
	Injection site pruritus
	Injection site urticaria
	Injection site papule
	Injection site macule
	Injection site vasculitis
	Injection site plaque
	Injection site discolouration
	Injection site injury
	Injection site abscess
	Injection site abscess sterile
	Injection site dermatitis
	Injection site erythema
	Injection site infection
	Injection site inflammation
	Injection site rash
	Injection site reaction
	Injection site thrombosis
	Injection site vesicles
	Injection site ischaemia
	Injection site cellulitis

Name of Search	Preferred Term
	Injection site discharge Injection site scab Injection site eczema Injection site recall reaction Injection site exfoliation

11: Generalized skin reaction with ≥ 14 day duration

Generalized skin reaction with ≥ 14 day duration will be identified in following ways:

- Preferred term search using below listing, or
- Broad vasculitis SMQ

To be included as generalized skin reaction, the duration of the event needs to be ≥ 14 days (Multiple AE records with same preferred term and ≤ 1 day difference between the start date and end date are considered as same event).

Name of Search	Preferred Term
Generalized Skin Reaction	Acute febrile neutrophilic dermatosis Benign neoplasm of skin Blood blister Dry skin Eczema Eczema nummular Erythema infectiosum Furuncle Gangrene Henoch-Schonlein purpura Hypertrophic scar Neoplasm skin Dermatitis Dermatitis allergic Purpura fulminans Dermatitis exfoliative Dermatitis exfoliative generalised Skin disorder Drug eruption Skin dystrophy Xanthoma Acute generalised exanthematous pustulosis Dry gangrene Itching scar Cheilitis granulomatosa

Name of Search	Preferred Term
	Granuloma
	Granuloma skin
	Keratolysis exfoliativa acquired
	Hypersensitivity vasculitis
	Septal panniculitis
	Erythema elevatum diutinum
	Acute cutaneous lupus erythematosus
	Rash rubelliform
	Eczema vesicular
	Hand dermatitis
	Pigmentation disorder
	Excessive granulation tissue
	Atypical fibroxanthoma
	Eruptive pseudoangiomatosis
	Capillaritis
	Cutaneovisceral angiomatosis with thrombocytopenia
	Coma blister
	Infected dermal cyst
	Skin wound
	Eosinophilic panniculitis
	Atypical lymphocytic lobular panniculitis
	Panniculitis
	Papule
	Purpura
	Chronic papillomatous dermatitis
	Xanthogranuloma
	Cheilosis
	Epidermolysis bullosa
	Granuloma annulare
	Haemorrhage subcutaneous
	Haemorrhage subepidermal
	Lipoatrophy
	Psoriatic arthropathy
	Rash papulosquamous
	Scar
	Seborrhoea
	Seborrhoeic dermatitis
	Skin irritation
	Stevens-Johnson syndrome
	Weber-Christian disease
	Rheumatoid nodule
	Thrombocytopenic purpura
	Thrombotic thrombocytopenic purpura

Name of Search	Preferred Term
	Excoriation
	Epidermolysis
	Vascular purpura
	Necrobiosis lipoidica diabeticorum
	Epidermal necrosis
	Lipohypertrophy
	Drug reaction with eosinophilia and systemic symptoms
	Cutaneous calcification
	Skin induration
	Palpable purpura
	Medical device site laceration
	Blister
	Blister infected
	Carbuncle
	Cellulitis
	Cellulitis enterococcal
	Cellulitis gangrenous
	Cellulitis staphylococcal
	Cellulitis streptococcal
	Cheilitis
	CREST syndrome
	Erythema nodosum
	Eyelid oedema
	Face oedema
	Idiopathic urticaria
	Infected skin ulcer
	Jaundice
	Laryngeal oedema
	Laryngotracheal oedema
	Lichenification
	Lip oedema
	Lip swelling
	Livedo reticularis
	Lupus vulgaris
	Morphoea
	Mucocutaneous ulceration
	Neurodermatitis
	Nodular vasculitis
	Oedema mouth
	Oropharyngeal swelling
	Osler's nodes
	Pemphigoid
	Pemphigus

Name of Search	Preferred Term
	Periorbital oedema
	Pharyngeal oedema
	Pruritus
	Psoriasis
	Skin mass
	Pustular psoriasis
	Pyoderma
	Red man syndrome
	Scleroderma
	Skin atrophy
	Skin hyperpigmentation
	Palisaded neutrophilic granulomatous dermatitis
	Skin hypopigmentation
	Skin hypoplasia
	Skin infection
	Subcutaneous abscess
	Subcutaneous haematoma
	Swelling face
	Swollen tongue
	Systemic lupus erythematosus
	Systemic lupus erythematosus rash
	Systemic sclerosis
	Tongue oedema
	Toxic epidermal necrolysis
	Urticaria
	Urticaria papular
	Skin maceration
	Lip blister
	Skin ulcer haemorrhage
	Lupus-like syndrome
	Skin tightness
	Sclerodactylia
	Granulomatous dermatitis
	Circumoral oedema
	Urticaria chronic
	Pruritus generalised
	Scleroedema
	Cutaneous lupus erythematosus
	Mucocutaneous rash
	Subacute cutaneous lupus erythematosus
	Chronic cutaneous lupus erythematosus
	Toxic skin eruption
	Dermatitis psoriasiform

Name of Search	Preferred Term
	Skin toxicity
	Erythema migrans
	Pruritus allergic
	Skin haemorrhage
	Overlap syndrome
	Haemorrhagic vasculitis
	Idiopathic angioedema
	Blister rupture
	Mouth swelling
	Autoimmune dermatitis
	Angioedema
	Cutaneous vasculitis
	Dermatitis atopic
	Dermatitis infected
	Ecchymosis
	Erythema
	Erythema induratum
	Erythema multiforme
	Macule
	Palmar erythema
	Panniculitis lobular
	Petechiae
	Rash
	Rash erythematous
	Rash follicular
	Rash generalised
	Rash macular
	Rash maculo-papular
	Rash morbilliform
	Rash papular
	Rash pruritic
	Rash pustular
	Rash vesicular
	Skin erosion
	Skin exfoliation
	Skin hypertrophy
	Skin lesion
	Skin necrosis
	Skin reaction
	Skin ulcer
	Vasculitic rash
	Rash maculovesicular
	Skin fibrosis

Name of Search	Preferred Term
	Skin swelling Skin oedema Haemorrhagic urticaria Recall phenomenon Vascular skin disorder Necrotising panniculitis Exfoliative rash Perivascular dermatitis Angiodermatitis Skin plaque Chronic pigmented purpura Dermatitis bullous Interstitial granulolmatous dermatitis Skin hyperplasia Vasculitic ulcer

12: Persistent arthralgia (> 6 months)

Arthralgia will be identified as the preferred terms of arthralgia, pain in extremity, back pain, musculoskeletal pain, and neck pain. To be included in the results, the duration of the event should be > 6 months (Multiple AE records with same reported term and ≤ 1 day difference between the start date and end date are considered as same event).