

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761079Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24**

Date: May 22, 2018

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Subject: Active Risk Identification and Assessment (ARIA) Sufficiency Memo
for Pregnancy Safety Concerns

Drug Name: Palynziq (pegvaliase)

Application Type/Number: BLA 761079

Applicant/sponsor: Biomarin Pharmaceutical, Inc.

OSE RCM #: 2017 - 1327

A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Palynziq (pegvaliase) is an enzyme substitution therapy indicated to reduce blood phenylalanine (Phe) concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations > 600 $\mu\text{mol/L}$ on existing management. Palynziq substitutes for the deficient PAH enzyme in patients with PKU by providing an alternate pathway for Phe breakdown via the enzymatic conversion of Phe to trans-cinnamic acid (t-CA) and ammonia, both excreted in the urine. Palynziq is administered daily as a subcutaneous injection through a single-dose prefilled syringe. The proposed dosing follows an induction, titration, and maintenance (I/T/M) dosage regimen by which the dose is slowly increased over a period of a few weeks. The Applicant proposes that a patient should stay at 20 mg daily for 24 weeks and the dose may be increased to 40 mg daily based on individual patient response (Phe concentration) and tolerability. If a patient does not achieve at least a 20% reduction in blood Phe concentration from their pre-treatment baseline after an additional 16 weeks of treatment with 40mg daily, then the product should be discontinued.

1.2. Describe the Safety Concern

Elevated maternal blood Phe concentration during early pregnancy is teratogenic and may result in Phe embryopathy. The embryopathic effects of elevated Phe levels during pregnancy in maternal PKU include growth retardation, microcephaly, psychomotor retardation, and congenital heart defects.¹ Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in PKU-affected women demonstrated that uncontrolled phenylalanine concentrations above 600 micromol/L are associated with an increased risk for miscarriage, major birth defects (including microcephaly, major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ. To reduce the risk of hyperphenylalaninemia-induced teratogenic effects, target blood phenylalanine concentrations of 120 to 360 micromol/L should be maintained for 3 months before conception and throughout pregnancy.²

There is limited data on the developmental effects of Palynziq use in pregnant woman. Based on the 120-day safety update report and cumulative pregnancy data, 10 female subjects became pregnant during treatment, with information on timing of exposure missing.¹ In summary, the 10 pregnancies included 3 therapeutic/induced abortions, 1 missed abortion, 1 stillbirth, 1 normal delivery, 1 delivery of an infant with transient systolic murmur which resolved without intervention, and 3 ongoing at the time of the Safety Update data cutoff. As described above, it is known that pregnant patients with PKU are at increased developmental risk with elevated Phe levels, so causality can be difficult to establish with limited subject details and lab data. In addition,

¹ Biologic License Application (BLA) Multi-Disciplinary Review and Evaluation. BLA 761079 Palynziq (pegvaliase-pqpz). Accessed May 16, 2018. DARRTS Reference ID: Pending.

² Palynziq product label. Revised May 2018. DARRTS Reference ID: Pending.

9 female partners of male study subjects (partner pregnancies) became pregnant during treatment.¹ Two male subjects have female partners who were pregnant twice, for a total of 11 partner pregnancies. In the 11 partner pregnancies, 6 pregnancies had a reported normal outcome. The remaining 5 partner pregnancies included 1 delivery of an infant with neonatal respiratory distress who was discharged after receiving 2 days of respiratory support, 1 delivery with no additional data, 2 with unknown outcomes of the delivery, and 1 ongoing at the time of the Safety Update data cutoff.

Embryofetal malformations (of the skeleton, kidneys, lungs, and eyes) and embryofetal toxicity (increased resorptions, reduced fetal weight) were observed in the offspring of pregnant rabbits (without PKU) treated with Palynziq in the nonclinical program at a dosage which was 7.5 times higher than the maximum recommended daily dose; these adverse fetal effects in the rabbit study were associated with strong signs of maternal toxicity, including marked reductions in weight gain and food consumption, and death.¹ A reproduction study in rats (without PKU) demonstrated an increase in skeletal variations, but with no malformations observed. The effects occurred at 4.2 times the maximum recommended daily dose. In a pre-/post-natal development study in rats (without PKU), Palynziq produced decreases in survival of offspring when administered daily at 19.4 times the maximum recommended daily dose. The effects on rat embryo-fetal and post-natal development were associated with maternal toxicity. The significance of these findings for humans remains unknown.

It is discussed in the label that Palynziq may cause fetal harm with supporting animal and human data, although the data is limited and insufficient to determine a drug-associated risk of adverse developmental outcomes.² Further evaluation in the post-marketing setting is necessary for appropriate education of patients and prescribers when considering the use of Palynziq during pregnancy. A post-approval pregnancy monitoring program has been proposed to further evaluate safety risks associated with Palynziq treatment in pregnant women with PKU and their offspring. In addition, the product label includes the following language: *“There is a pregnancy surveillance program for Palynziq. If Palynziq is administered during pregnancy, or if a patient becomes pregnant while receiving Palynziq or within one month following the last dose of Palynziq, healthcare providers should report Palynziq exposure by calling 1 866 906 6100.”*

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

- No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify:** A Pregnancy Monitoring Program is being considered to further evaluate a nonspecific safety concern associated with Palynziq treatment in pregnant women with PKU and their offspring.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes and Covariates: ARIA is not sufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Covariates: ARIA is not sufficient to capture maternal blood phenylalanine concentrations during pregnancy making it impossible to examine the associations between Palynziq treatment, blood Phe levels and adverse outcomes in the pregnant women and their offspring.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy



outcomes.

Other parameters were not formally discussed given that the mother-infant linkage is not currently available in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

The following language (still in draft form) has been proposed for PMRs related to pregnancy outcomes:

A prospective, observational study to assess the risks of pregnancy complications and adverse effects on the developing fetus and newborn (including, but not limited to, fetal malformations and pre-natal and post-natal growth restriction) from Palynziq treatment during pregnancy. The study will collect and analyze data on blood phenylalanine concentrations during pregnancy in treated pregnant women with PKU and examine associations between Palynziq treatment, blood phenylalanine concentrations, and adverse outcomes in the pregnant women and their offspring (fetus/newborn). The study duration will be at a minimum of 10 years. An interim report will be submitted every two years during the conduct of the study.

The finalized PMR language will be issued upon approval.

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/s/

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Version: 2018-01-24**

Date: May 22, 2018

Reviewer: Michelle R. Iannacone, PhD, MPH
Division of Epidemiology I

Team Leader: Patricia L. Bright, PhD, MSPH
Division of Epidemiology I

Deputy Division Director: Sukhminder Sandhu, PhD, MS MPH
Division of Epidemiology I

Subject: Active Risk Identification and Assessment (ARIA) Sufficiency Memo:
Immune-mediated adverse reactions associated with Palynziq
treatment in PKU patients

Drug Name: Palynziq (pegvaliase)

Application Type/Number: BLA 761079

Applicant/sponsor: Biomarin Pharmaceutical, Inc.

OSE RCM #: 2017-1327

EXECUTIVE SUMMARY (place "X" in appropriate boxes)

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Palynziq (pegvaliase) is an enzyme substitution therapy indicated to reduce blood phenylalanine (Phe) concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations > 600 µmol/L on existing management. Palynziq substitutes for the deficient PAH enzyme in patients with PKU by providing an alternate pathway for Phe breakdown via the enzymatic conversion of Phe to trans-cinnamic acid (t-CA) and ammonia, both excreted in the urine. Palynziq is administered daily as a subcutaneous injection through a single-dose prefilled syringe. The proposed dosing follows an induction, titration, and maintenance (I/T/M) dosage regimen by which the dose is slowly increased over a period of a few weeks. The Applicant proposes that a patient should stay at 20 mg daily for 24 weeks and the dose may be increased to 40 mg daily based on individual patient response (Phe concentration) and tolerability. If a patient does not achieve at least a 20% reduction in blood Phe concentration from their pre-treatment baseline after an additional 16 weeks of treatment with 40mg daily, then the product should be discontinued¹.

1.2. Describe the Safety Concern

The primary safety signal identified with Palynziq is the high immunogenicity manifesting with various rates and severities of hypersensitivity events, including anaphylaxis. The safety review¹

¹ Biologic License Application (BLA) Multi-Disciplinary Review and Evaluation. BLA 761079 Palynziq (pegvaliase-pqpz). Accessed May 16, 2018. DARRTS Reference ID: Pending.

focused on describing and analyzing the immunogenicity profile and related safety events in the exposed patient population.

The primary safety concern from the phase 2 and phase 3 clinical trials is the long-term risks of immune-mediated adverse reactions (including but not limited to hypersensitivity reactions, anaphylaxis, injection-site reactions, generalized skin reactions, and arthralgia)¹.

The overall incidence of anaphylaxis in the phase 2 and 3 trials of Palynziq (pegvaliase) was 9% (among all doses used) in the induction, titration, and maintenance (I/T/M) population and decreased with longer duration of exposure. This corresponds to 26 out of 285 subjects who had 37 anaphylactic reactions. The exposure-adjusted rate of anaphylaxis was 0.15 event rate/person-year in the induction/titration phase which decreased to 0.04 event rate/person-year in the maintenance phase. In the clinical trials, anaphylaxis generally occurred within 1 hour after injection (84%; 28/37 episodes); however, delayed reactions have occurred (up to 48 hours). Most episodes of anaphylaxis occurred within the first year of dosing (78%; 29/37 episodes), but cases have occurred at any time, even more than two years from initiation of treatment. Eighteen out of the 26 (69%) patients who experienced anaphylaxis were rechallenged with Palynziq and 5 patients had recurrence of anaphylaxis¹.

The anaphylaxis rate noted with Palynziq treatment appears to be comparable to that of other biologic products approved for IEM (e.g. enzyme replacement therapies for lysosomal storage disease). However, the mechanism of anaphylaxis appears to be mediated by immune complex/complement activation, but the specifics are unknown, as there was no predictive antibody or titer level. The mechanism is most consistent with a non-IgE Type III immune complex-mediated reaction¹.

The product will be labeled with a boxed warning stating “Anaphylaxis has been reported after administration of Palynziq, and may occur at any time during treatment [REDACTED] (b) (4) (5.1).”

In the clinical trials, injection site reactions occurred as early as the first dose and at any time during treatment. Injection site reactions were more frequent during the induction/titration phase (1.9 episodes/patient-year) and decreased over time (0.4 episodes/patient-year in the Maintenance Phase). The mean duration of injection site reaction was 8 days, and 92% of injection site reactions had a duration of less than 14 days. Injection site reactions persisted up to 970 days (0.7% of injection site reactions persisted at least 180 days), and 99% of injection site reactions resolved by the time of the data cut-off².

In clinical trials, 125 out of 285 (44%) patients treated with Palynziq experienced generalized skin reactions (not limited to the injection site) lasting more than 14 days. Generalized skin reactions were more frequent during the Induction/Titration Phase (0.7 episodes/patient-year), and decreased over time (0.3 episodes/patient-year in the Maintenance Phase).

The product will be labeled to include injection site reactions and generalized skin reactions in the Adverse Reactions section (6.1)².

² Palynziq product label. Revised May 2018. DARRTS Reference ID: Pending.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The Division of Gastroenterology and Inborn Error Products (DGIEP), with concurrence by OSE, requires a post-market observational study to assess the known serious risk for immune-mediated adverse reactions from Palynziq. DGIEP specifically requires information about immunologic factors (i.e., anti-drug antibodies and neutralizing antibodies against Palynziq) associated with anaphylaxis. DGIEP requires detailed information from post-market settings to inform appropriate clinical strategies for mitigating the risk for anaphylaxis from Palynziq to supplement existing labeling efforts (i.e., boxed warning).

1.5. Effect Size of Interest or Estimated Sample Size Desired

A sample size of 750 subjects has been proposed by the Sponsor for the postmarket study. However, the Agency has not finalized the negotiation for sample size at the time of the Memo. If an agreement on the sample is not reached prior to approval, the Agency will negotiate the final sample size during the review of the postmarket protocol.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Palynziq is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management. The patient population will include adult patients from the indicated population.

2.2 Is ARIA sufficient to assess the intended population?

No. Although adults with PKU could be identified using ARIA by limiting the age range for analysis to 18 years and older and identifying patients in that population with an ICD-10 code of E70.0 (classical phenylketonuria), ARIA could not identify those with uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management. Non-standard laboratory tests are not routinely captured by ARIA tools in Sentinel.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is incident use of Palynziq.

3.2 Comparator Exposure(s)

Not applicable. The study population is Palynziq exposed patients. There is no comparator drug available³. Because Palynziq is self-administered daily (following a weekly initiation phase) this also makes self-controlled designs challenging.

Is ARIA sufficient to identify the exposure of interest?

Initial dosage of Palynziq is 2.5 mg once per week for 4 weeks. Titration of dosage is administered in a step-wise manner over at least 5 weeks based on tolerability to achieve a dosage of 20 mg subcutaneously once daily. Consideration will be given to increasing the dosage to a maximum of 40 mg subcutaneously once daily in patients who have been on 20 mg once daily continuously for at least 24 weeks who have not achieved a 20% reduction in blood phenylalanine concentration from baseline or a blood phenylalanine concentration ≤ 600 micromol/L.

ARIA is sufficient to capture patients with pharmacy benefits who receive at least one dispensing of Palynziq. ARIA is also sufficient to capture procedure codes in outpatient, physician-supervised administration of subcutaneous injections, such as Palynziq, which may occur with the first few injections. However, if data are needed on the self-administered dose during titration, such dose levels could only be approximated from the available data. Therefore, ARIA may be sufficient to identify the exposure, but would not be fully sufficient to identify anaphylaxis risk factors including dose and titration information, although these might be estimated from the available data.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest include immune-mediated adverse reactions, including hypersensitivity reactions. The main hypersensitivity reactions of interest include anaphylaxis, injection-site reactions, and generalized skin reactions.

4.2 Is ARIA sufficient to assess the outcome of interest?

No. Depending on the safety application, diagnostic codes in outpatient administration claims may or may not capture with acceptable accuracy the outcome of anaphylaxis⁴ or hypersensitivity reactions other than anaphylaxis⁵. However, there is the potential for low sensitivity in detecting hypersensitivity reactions, anaphylaxis, injection-site reactions, generalized skin reactions, and arthralgia related to Palynziq exposure.

³ Although Kuvan is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH₄-) responsive PKU, Palynziq appears to benefit different patients with PKU than Kuvan based on different mechanism of action.

⁴ Pharmacoepidemiol Drug Saf. 2013 Sep 5; 22(11):1205-13. doi: 10.1002/pds.3505. Validation of Anaphylaxis in the Food and Drug Administration's Mini-Sentinel. Walsh KE, Cutrona SL, Foy S, Baker MA, Forrow S, Shoaibi A, Pawloski PA, Conroy M, Fine AM, Nigrovic LE, Selvam N, Selvan MS, Cooper WO, Andrade S.

⁵ Pharmacoepidemiol Drug Saf. 2012 Jan; 21(S1), 248-55. doi: 10.1002/pds.2333. A Systematic Review of Validated Methods for Identifying Hypersensitivity Reactions other than Anaphylaxis (Fever, Rash, and Lymphadenopathy), Using Administrative and Claims Data. Schneider G, Kachroo S, Jones N, Crean S, Rotella P, Avetisyan R, Reynolds MW.

Patients using Palynziq will have, and be educated on, the use of injectable epinephrine. It is unknown what proportion of hypersensitivity reactions, anaphylaxis, injection-site reactions, generalized skin reactions, and arthralgia will be captured by insurance claims across the Sentinel data partners. If the patient does not receive medical treatment for these events or if the diagnosis is not captured in the billing codes, the sensitivity for detecting the events of interest could be low. A study evaluating anaphylactic reactions associated with intravenous iron products in claims data from the U.S. fee-for-service Medicare program suggests a low sensitivity for detecting anaphylaxis (8%-35%)⁶. Identifying injection-site reactions, generalized skin reactions, and arthralgia may correspond to an even lower sensitivity than anaphylaxis if these events do not cause the patient to report to a medical facility for treatment.

Conversely, angioedema appears to have a more robust algorithm in claims data based on a study⁷ using an ICD-9-CM code of 995.1 (recorded in any position during an outpatient, inpatient, or emergency department encounter). That algorithm was validated with a positive predictive value (PPV) from 90% to 95% in claims data. However, the clinical trial data did not identify a signal for angioedema in isolation of other hypersensitivity events and the clinical team concluded that assessing angioedema distinct from other hypersensitivity events would not be sufficient to assess the known serious risk for immune-mediated adverse reactions from Palynziq. Furthermore, capturing the information necessary to determine risk factors associated with hypersensitivity reactions requires longitudinal, prospective data collection.

5 COVARIATES

5.1 Covariates of Interest

Several covariates, including diet, anti-drug and neutralizing antibody titers against Palynziq, immunologic and inflammatory responses on major organ function, frequency pharmacologic intervention use, and laboratory abnormalities were deemed highly desirable by OND to help clarify clinical factors and develop mitigation strategies. Collection of this data on factors that may help reduce the incidence of adverse events and increase the safe use of Palynziq could possibly be used to inform the product label.

5.2 Is ARIA sufficient to assess the covariates of interest?

No. Answers to the safety concern requires that patients track their diet and requires results from non-standard laboratory tests conducted on blood collected prospectively per a schedule fixed by a protocol.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

⁶ Comparative Risk of Anaphylactic Reactions Associated With Intravenous Iron Products. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, MaCurdy TE, Houstoun M, Ryan Q, Wong S, Mott K, Sheu TC, Limb S, Worrall C, Kelman JA, Reichman ME. JAMA. 2015 Nov 17; 314(19):2062-8. doi: 0.1001/jama.2015.15572.

⁷ Arch Intern Med. 2012 Nov 12; 172(20):1582-9. doi: 10.1001/2013.jamainternmed.34. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Toh S1, Reichman ME, Houstoun M, Ross Southworth M, Ding X, Hernandez AF, Levenson M, Li L, McCloskey C, Shoaibi A, Wu E, Zornberg G, Hennessy S

The study design would be a longitudinal, prospective study for up to 10 years of follow-up.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA is sufficient with respect to design / analytic tools available to assess the question of interest.

7 NEXT STEPS

As a result of the Signal Assessment Meeting deliberations and documented in this ARIA memo, ARIA was deemed insufficient to study hypersensitivity events and the potential associated risk factors among PKU patients using Palynziq treatment. The next step is to communicate expectations for the PMR with OND. OSE suggests the following language (the finalized language for the observational PMR will be issued upon approval):

Prospective, longitudinal, observational study to assess long-term risks of severe immune-mediated adverse reactions in adult patients with phenylketonuria (PKU) treated with Palynziq. Each patient will be treated with Palynziq over a minimum of 10 years. Evaluate the incidence rates of immune-mediated adverse reactions (including, but not limited to, hypersensitivity reactions, anaphylaxis, generalized skin reactions, and arthralgia), and collect information, including a full description of clinical features of the adverse reactions, to investigate associations and temporal relationships between the incidence and severity of all immune-mediated adverse reactions and other potential associated risk factors. Evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers), their effects on major organ function (e.g., kidney function), and immune-mediated effects on blood phenylalanine therapeutic response. Collect and analyze additional information, including, but not limited to, PAH genotype, dietary practices, and prior medical history. Specify concise case definitions, validation methods, and procedures for all study outcomes. An interim report will be submitted every two years during the conduct of the study.

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 5/8/18

To: BLA 761079 File

Amy S.

Rosenberg -S

Digitally signed by Amy S. Rosenberg -S
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Date: 2018.05.10 14:14:21 -04'00'

From: Amy S. Rosenberg MD, DBRR3, OBP

Through: Daniela Verthelyi, Ph.D., M.D., Chief, Laboratory of
Immunology, DBRR3, OBP Daniela I.

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Date: 2018.05.10 14:16:35 -04'00'

Re: Consult regarding Immunogenicity and toxicology issues for Pegvaliase
Biologics License Application (BLA 761079)

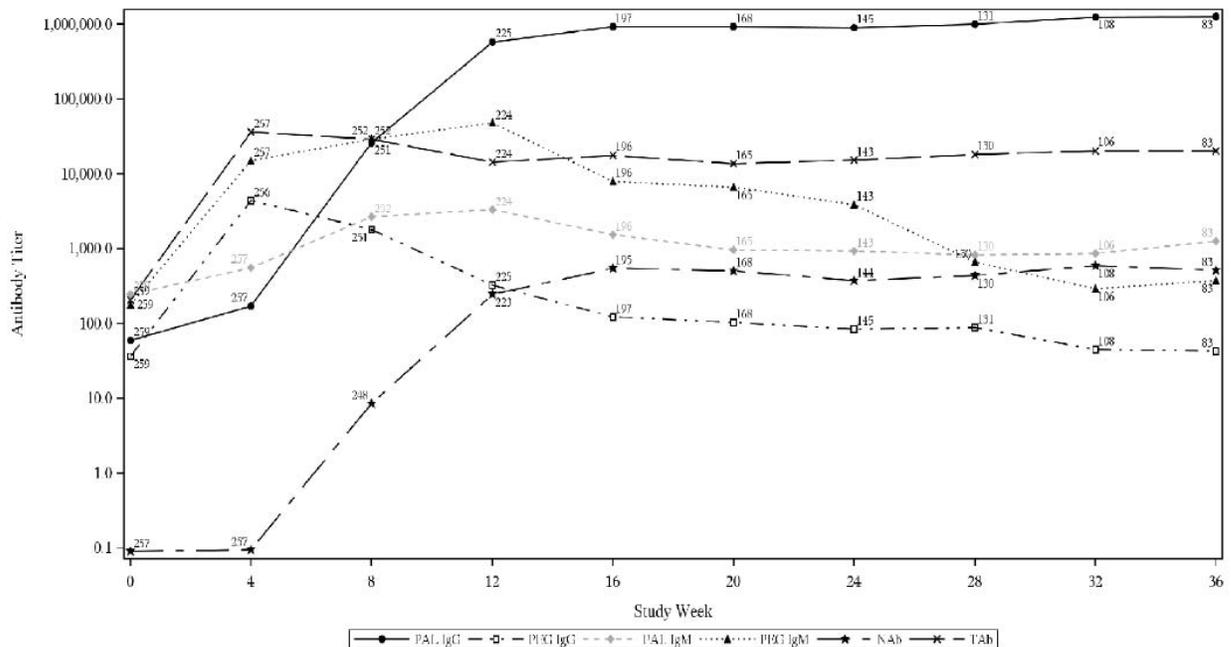
I am writing this memorandum to 1) express my opinion that the approval for this product, in the face of an unrelenting, high titer immune mediated antibody response, and with evidence of Type III immune complex formation that likely induces clinical manifestations of skin and joint disease, as well as a significant occurrence of Type I immediate hypersensitivity responses, in the setting of a disease that is not considered life-threatening, should be fully vetted before an Advisory Committee composed of external experts as well as before a full Center Director Briefing and 2) to address the questions that were initially posed to the Immunogenicity Review Committee pertaining to this BLA, including the toxicological issues regarding CIC and administration of high doses of PEG daily, as PEG is non-biodegradable and its fate in such patients over an extended period of time is not clear.

To my knowledge, approval of this product with its associated immunogenicity profile and issues is unprecedented. Firstly, 100% of patients mount high titer and sustained antibody responses, of which the titer is $>1:1 \times 10^6$, again, an unprecedented level for a chronically administered drug. Importantly, the neutralizing antibody titer incidence continues to rise

over the 36 week time frame of measure to encompass nearly 80% of patients. (Fig 12.2.1.1.1 and Fig 14.6.3.2 below). Moreover, among patients remaining in study, the levels of total and neutralizing (Tab and NAB) remain stably high. As can be seen, none of these patients tolerizes over time, not surprisingly, given that this is a foreign bacterial enzyme and some patients enter the trial with preexisting immunity due to the presence of bacteria in the gut.



Immunogenicity:
 Mean antibody titers over time
 Phase 3 Population duration first 36 weeks of treatment
 source: Figure 14.3.6.3.2, 165-301 CSR

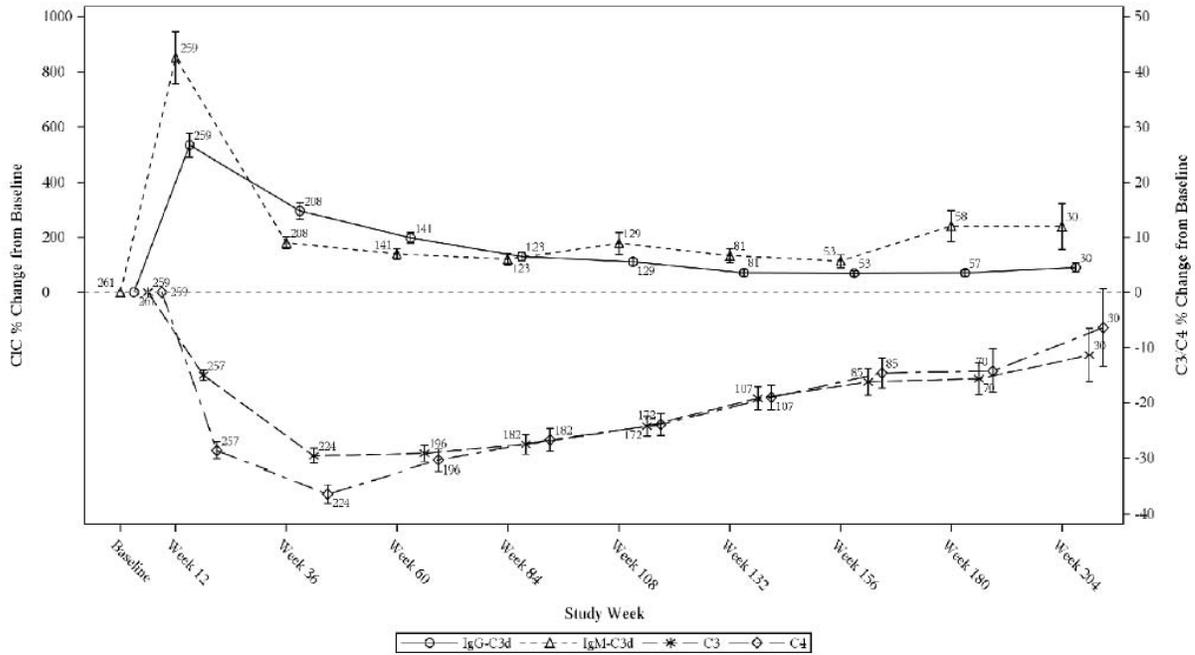


The presence of such high and sustained ADA to the enzyme (the anti-PEG response diminishes significantly but does not full disappear over the 36 week time frame) causes formation of circulating immune complexes (CIC) and lowered levels of complement components C3 and C4. As shown below, CIC levels rise and C3/C4 levels fall over the initial 36 weeks and then fall and rise, respectively, to approach, but never reach, baseline levels over the

ensuing 168 weeks. However, and crucial is the “dropout” factor. The reason for extensive dropouts over the course of the study has not been sufficiently clarified.



Immunogenicity:
 % change in IgG CIC Level and C3/C4 from baseline over time
 Phase 3 Population with parent study 165-301



Thus, as regards % change in CIC Level and C3/C4 from baseline over time in the phase 3 population (parent study 165-301), 261 patients winnows down to 30 at study’s end (week 204). It may well be that the patients who enjoy extended treatment are the ones for whom C3/C4 and CIC normalize over time, but this is a very distinct minority of patients and whether such patient responses can be predicted is not evident, at least from data thus far submitted. However, even for such long term treated patients, CIC remain above baseline while the C3/C4 levels approach, but do not recover to baseline levels suggesting the possibility of ongoing tissue deposition.

The drop-out rate is sizeable even in the shorter term studies. For example over a 36 week time frame, 257 patients at the onset winnow down to 83 by week 36. In the longer term, over 396 weeks (phase 3), 260 patients at onset winnows down to 1 patient at study's end. This likely indicates lack of tolerability of this treatment and should be a major caveat regarding approval. Critically, there is a grave concern for the clinical effects of such CIC, a contention bolstered by the finding that there is a very substantial proportion of patients with clinical symptomatology likely related to CIC.

AE by Dose on or Prior to AE Onset (I/T/M Population)



Number of Subjects with Event (%) Number of Events (event rate per person-year)	Dose on or Prior to Time of Onset					
	Placebo ^a (n=28)	> 0 and < 20 mg/day (n=285)	≥ 20 and < 40 mg/day (n=257)	≥ 40 and < 60 mg/day (n=223)	≥ 60 mg/day (n=86)	Any Dose Level (N=285)
Deaths	0	1 (0.4%)	0	0	0	1 (0.4%)
AEs of special interest/significance						
HAEs	4 (14.3%) 6 (1.37)	226 (79.3%) 1307 (12.59)	154 (59.9%) 904 (8.25)	164 (73.5%) 1155 (5.53)	32 (37.2%) 146 (3.14)	266 (93.3%) 3518 (7.43)
Anaphylaxis per NIAID/FAAN criteria	0 0	10 (3.5%) 10 (0.10)	13 (5.1%) 15 (0.14)	17 (7.6%) 23 (0.11)	1 (1.2%) 2 (0.04)	33 (11.6%) 50 (0.11)
Anaphylaxis assessed by external expert	0 0	3 (1.1%) 3 (0.03)	5 (1.9%) 5 (0.05)	8 (3.6%) 11 (0.05)	1 (1.2%) 2 (0.04)	13 (4.6%) 21 (0.04)
Injection-site reactions	7 (25.0%) 10 (2.29)	243 (85.3%) 2073 (19.96)	126 (49.0%) 1253 (11.43)	141 (63.2%) 1033 (4.94)	30 (34.9%) 121 (2.60)	263 (92.3%) 4490 (9.49)
Injection-site skin reactions lasting ≥ 14 days	1 (3.6%) 1 (0.23)	54 (18.9%) 125 (1.20)	30 (11.7%) 94 (0.86)	61 (27.4%) 101 (0.48)	13 (15.1%) 18 (0.39)	119 (41.8%) 339 (0.72)
Generalized skin reactions lasting ≥ 14 days	0 0	33 (11.6%) 46 (0.44)	38 (14.8%) 53 (0.48)	56 (25.1%) 86 (0.41)	10 (11.6%) 16 (0.34)	110 (38.6%) 201 (0.42)
Arthralgia	3 (10.7%) 3 (0.69)	155 (54.4%) 534 (5.14)	95 (37.0%) 347 (3.17)	85 (38.1%) 277 (1.33)	11 (12.8%) 23 (0.50)	203 (71.2%) 1184 (2.50)

Sponsor's Table 2.7.4.3.1.2: Overview of Adverse Events by Dose on or Prior to Adverse Event Onset (I/T/M Population), Summary of Clinical Safety, pages 23-24.

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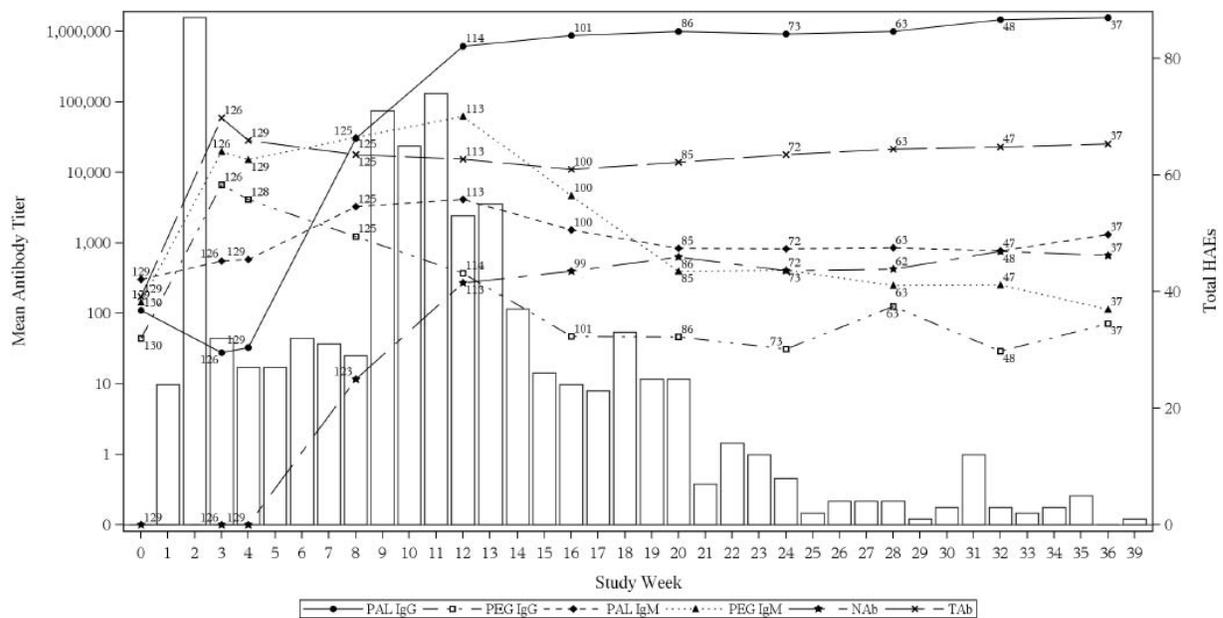
For example, per above Table, 42% of patients experienced injection site reactions lasting over 14 days, 39% experienced generalized skin reactions lasting over 14 days, and stunningly, 71% of patients experienced arthralgia of uncertain etiology but potentially due to CIC. Although renal toxicity has not yet been detected, it should be noted that changes in BUN/Cr and measures of protein in the urine) are not sensitive measures of organ damage, and once abnormal, indicate the presence of significant and possibly irreversible damage to the kidney.

Hypersensitivity (Type 1) Adverse Events.

93% of treated patients had hypersensitivity adverse events of which 12% experienced anaphylaxis per the NIAID definition



Immunogenicity: Frequency of HAEs and antibody titers over time Study 165-301, 40 mg/day group



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The mechanism of such anaphylaxis responses was investigated and found not to be IgE mediated. Although it is stated that

- The frequency of HAEs decreased over time in long term treatment as the incidence of these antibodies decreased, and C3/C4 and CIC levels returned towards baseline

it must be remembered that the dropout of patients plays a highly significant role in this decrease thus enriching for patients not likely to develop HAEs

after the initial time frame: in the figure above, 130 patients assessed at baseline winnows down to 37 at study's end (39 weeks).

Efficacy Concerns

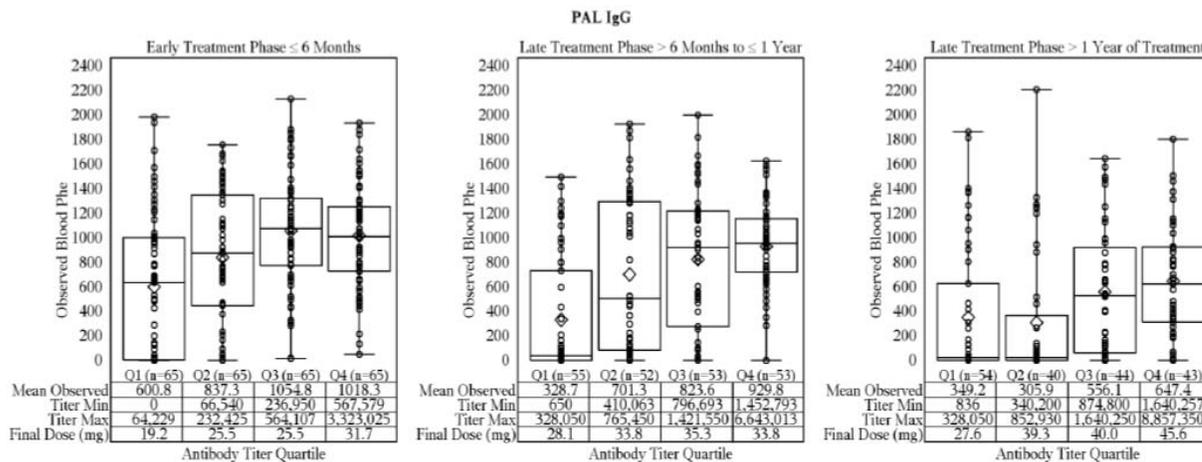
As regards efficacy, lowering of phenylalanine (Phe) levels, this is also dependent on the level of the antibody response.

ADA increased the clearance of pegvaliase, leading to lower mean pegvaliase trough concentrations and lower mean blood Phe reduction. Per the below figure, there is substantial variation in measured blood Phe levels among patients in all antibody quartile levels, with some patients in all quartiles experiencing persistent high Phe levels, but it is clear that those with the highest levels of total and IgG PAL antibodies have less mean Phe reduction than those in other quartiles. However, what is not clear from the data is the impact of ADA on individual patient responses, eg, Phe levels prior to onset of treatment, Phe levels prior to induction of ADA, profile of the antibody response (titer, duration, NAB etc) , and effect of such ADA responses on blood Phe. In this regard, description of the risk-benefit analysis may vary considerably on an individual basis. The risk-benefit profile is critical to determining responses to the questions posed to the IRC. Finally, the level of Phe reduction associated with a beneficial effect on disease manifestations has not been clearly defined. In the absence of such information, assessment of risk in the context of potential benefit is not possible.



Immunogenicity:

Observed blood Phe concentration ($\mu\text{mol/L}$) and PAL IgG antibody titer by treatment phase
Study 165-301



The review team sought the input of the Immunogenicity Review Committee regarding specific questions. These are included in my review of this BLA as being highly pertinent questions and my responses are included in the context of the immunogenicity concerns of the BLA.

PMR/PMC studies to assess the long-term effect of pegvaliase immunogenicity in patients with PKU:

Question: How should the potential CIC (and PEG) deposition in major organs be clinically assessed and monitored in a PMR (biomarkers, frequency of monitoring, duration of monitoring)?

Answer: it is not possible to routinely biopsy major target organs for assessment of CIC and PEG deposition. Would accumulation in skin, an easily accessible organ, serve as a surrogate for end organ accumulation? Skin appears to be a possible target site for CIC, given the long lasting skin reactions described in patients in this trial. Moreover, it has been used to assess substrate accumulation in lieu of renal biopsies in Fabry patients (ref below). However, given

that there are numerous FcR expressing cells in peripheral blood (B cells, macrophages), this tissue could be a potential source of cells to assess for content of both CIC as well as PEG.

Animal model data may or may not be helpful. Blood Phe level is the biomarker of efficacy and the risk/benefit for individual patients per above is not clear: ie what level of Phe reduction is worth the risk of end organ damage either due to CIC or to PEG accumulation over a prolonged time frame? Again, the dropout of patients from the studies is highly significant and indicates that those experiencing severe AEs may drop out over the course of a year or less. Thus a “survival of the fittest” from the perspective of the antibody response to Pegvaliase refers to those whose ADA response is relatively weaker.

[Bénichou B¹, Goyal S, Sung C, Norfleet AM, O'Brien FMol Genet Metab.](#) 2009 Jan;96(1):4-12. doi: 10.1016/j.ymgme.2008.10.004. Epub 2008 Nov 20. **A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease.**

Question: Since both CIC (and PEG) may theoretically deposit in major organs over time, how would one discern effects from one vs the other?

Answer: There may be different deposition sites for CIC vs PEG but again, the ethics and practicality of biopsy of major target organs in patients is not clear. The question of sampling PBL, skin or another easily accessible tissue serving as a surrogate for other vital organs remains.

Question: Would an immune tolerance induction regimen be a viable option to investigate in the post-marketing setting? If yes, what trial design would be most appropriate?

Answer: Since this is not a life threatening indication, and the need for treatment not immediate, more specific and less immune suppressive tolerance induction regimens would be reasonable to investigate, though a major caveat is that many patients are previously primed to the phenylalanine lyase via exposure to the enzyme from gut bacteria putting a higher bar on tolerance induction. Thus, it is reasonable to

consider the following less immune suppressive, more specific tolerance induction regimens:

- 1) Oral tolerance. May take weeks for effective course of therapy. Again, may be a problem due to preexisting immunity. *Front Immunol.* 2017 Nov 24;8:1604. doi: Innovative Approaches for Immune Tolerance to Factor VIII in the Treatment of Hemophilia A. Sherman A1, Biswas M1, Herzog RW1.
- 2) Rapamycin nanoparticles administered at the onset of therapy. This approach is being investigated in the context of administration of other “foreign” enzymes such as urate oxidase and a-glucosidase in CRIM negative Pompe Disease (*Front Immunol.* 2018 Feb 20;9:230. doi: 10.3389/fimmu.2018.00230. eCollection 2018.)
- 3) Other nanoparticle approaches in which the drug itself is encapsulated ([Harnessing Nanoparticles for Immune Modulation: \(Trends in Immunology 36, 419-427; July 2016\).](#))
- 4) Finally, assessment of the risk to benefit ratio for this product may allow for a short prophylactic immune suppressive course of tolerance induction per the CRIM negative Pompe Disease patients. This regimen, consisting of rituximab, methotrexate and IVIG given at the onset of therapy, is associated with minimal AEs even in as fragile a population as the infantile Pompe patients (*JCI Insight.* 2017 Aug 17;2(16). pii: 94328. doi: 10.1172/jci.insight.94328.
- 5) Other protocols per the Immune Tolerance Network’s portfolio of potential therapeutics to treat autoimmunity and prevent/treat transplant rejection. <https://www.immunetolerance.org/>

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/s/

BENJAMIN P VALI

05/10/2018

Signing on behalf of Amy S. Rosenberg and Daniela I. Verthelyi

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 2, 2018

To: Benjamin Vali, MS, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for PALYNZIQ (pegvaliase-pqz) injection, for subcutaneous use

BLA: 761079

In response to Division of Gastroenterology and Inborn Errors Products' (DGIEP) consult request dated August 27, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for PALYNZIQ (pegvaliase-pqz) injection, for subcutaneous use.

PI and Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI, Medication Guide, and IFU received by electronic mail from DGIEP on April 16, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on May 1, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling provided by DGIEP, and was available in SharePoint on March 26, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
05/02/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 30, 2018

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, Pharm.D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): Palynziq (pegvaliase-pqpz)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761079

Applicant: BioMarin Pharmaceutical Inc.

1 INTRODUCTION

On June 30, 2017, BioMarin Pharmaceutical Inc. submitted for the Agency's review an Original Biologics License Application (BLA) 761079 for Palynziq (pegvaliase-pqpz) injection. The proposed indication is to reduce blood phenylalanine levels in adult patients with phenylketonuria (PKU) who have uncontrolled blood Phe levels > 600 $\mu\text{mol/L}$ on existing management.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on August 27, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Palynziq (pegvaliase-pqpz) injection.

DMPP conferred with the Division of Medication Error Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on March 1, 2018.

The Risk Evaluation and Mitigation Strategy (REMS) was reviewed by the Division of Risk Management (DRISK) on April 16, 2018.

2 MATERIAL REVIEWED

- Draft Palynziq (pegvaliase-pqpz) injection MG and IFU received on March 22, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 16, 2018.
- Draft Palynziq (pegvaliase-pqpz) injection Prescribing Information (PI) received on June 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 16, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
04/30/2018

ADEWALE A ADELEYE
05/01/2018

MARCIA B WILLIAMS
05/01/2018

LASHAWN M GRIFFITHS
05/01/2018

Consult Question Responses

Consult from CDER/ DGIEP on BLA for Palynziq

- 1. As there appear to be inconsistencies in AE coding for anaphylaxis events using different terms such as “anaphylaxis,” “anaphylactic reaction,” “anaphylactoid,” and “severe hypersensitivity,” we would appreciate input on the appropriate criteria to use to categorize events as anaphylaxis (symptoms, diagnostic criteria, timing from drug administration).**

CBER Response to Question 1:

The definition of anaphylaxis varies based on its intended application. Traditionally, this term has referred to clinical manifestations of a systemic, immediate hypersensitivity reaction caused by IgE-mediated immunologic release of mediators from mast cells and basophils. However, more recently, a change in terminology was proposed such that anaphylaxis refers to a severe, life-threatening, generalized, or systemic hypersensitivity reaction (regardless of mechanism--immunologic, non-immunologic, or idiopathic). In 2005, the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) sponsored a symposium in which well-defined criteria for diagnosis of anaphylaxis were established. Use of these criteria for categorization of events as anaphylaxis is reasonable since these criteria were based on broad consensus among experts from multiple specialties and from multiple medical organizations and government bodies with representatives from North America, Europe, and Australia [Sampson HA et al. Second Symposium on the Definition and Management of Anaphylaxis. *J Allergy Clin Immunol* 2006; 117:391-397]. In addition, results of a few studies evaluating these criteria suggest their utility in the diagnosis of anaphylaxis. In one emergency department study, these criteria were analyzed retrospectively and were found to have 96% sensitivity, 82% specificity, 67% positive predictive value, and 96% negative predictive value [Campbell RL et al. Evaluation of National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol* 2012;129:748-52]. In another emergency department study, prospective and retrospective analysis of the data led to similar rates for these criteria [Loprinzi Brauer et al. Prospective Validation of the NIAID/FAAN Criteria for Emergency Department Diagnosis of Anaphylaxis. *J Allergy Clin Immunol Pract* 2016;4:1220-6]. Of note, these criteria do not distinguish between the immunologic mechanisms of anaphylaxis (IgE-mediated, other antibody-mediated, complement-mediated, non-immune, or other).

Should you seek to develop a set of terms to use to query the safety database, it should be noted that a search with narrow or broad scope terms could lead to different results emphasizing either specificity or sensitivity. The current approach in our division is to evaluate the case narratives for suspected, probable and definite cases of anaphylaxis. To this end, we have asked sponsors to provide case narratives for these cases as well as for any case where a subject was treated with epinephrine. We have not, to date, developed a set of MedDRA terms or “search strategy” in order to evaluate the safety data base another way. It is our understanding that algorithmic searches, such as the algorithmic Anaphylactic Reaction SMQ utilized by the sponsor, are generally used in large databases to increase specificity, although irrelevant cases may still be retrieved. The algorithmic Anaphylactic Reaction SMQ pairs clinical signs and symptoms with

MedDRA terms (version 18.0) in order to identify cases of anaphylaxis. Although standardized MedDRA query analyses may have limitations, it may be reasonable to use this method to broadly capture suspected cases of anaphylaxis, and if possible, evaluate case narratives for these subjects through the lens of NIAID/FAAN criteria to better understand whether this diagnosis was accurate [Lin-Chau Chang et al. PLoS One. 2017; 12(6):e0178104]. In this regard, the approach that was taken for the Phase 3 trial, of adjudicating events initially characterized as anaphylaxis according to the NIAID/FAAN criteria, appears reasonable. For future studies, adjudication by a panel of experts would be preferable as this strategy may reduce bias.

Onset of symptoms of anaphylaxis occurs within minutes to several hours from time of drug administration [Sampson HA et al. Second Symposium on the Definition and Management of Anaphylaxis. J Allergy Clin Immunol 2006; 117: 391-397; Lieberman et al. Anaphylaxis: a practice parameter update 2015. Ann Allergy Asthma Immunol 2015; 115:341-384]. We note that a definition for anaphylaxis events appears to have been pre-specified and prospectively applied in the Phase 3 study [Study 165-301, Clinical Study Report (CSR)]. According to the CSR, anaphylaxis events were defined according to the NIAID/FAAN criteria which indicate that symptoms should have occurred within minutes to several hours of drug administration. Although the definition of anaphylaxis was pre-specified, it appears that this information may not have been consistently captured in the safety database since events identified as anaphylaxis by the site physician were conservatively included, even if the event may have had a longer time to onset than hours (i.e., greater than 1 day from the time of the most recent injection) (see Question 4). In this regard, a query of the safety database according to MedDRA Preferred Terms may not identify cases that occurred within the appropriate time frame. The approach taken by the sponsor of utilizing an independent expert to adjudicate anaphylaxis events according to the NIAID/FAAN criteria appears reasonable because it would have accurately categorized cases of anaphylaxis according to time of onset.

2. We would appreciate input on the most appropriate categorization of AE terms that together create syndromes, such as serum sickness and serum sickness-like reactions.

CBER Response to Question 2:

The diagnosis of serum sickness involves a careful clinical evaluation, including history and targeted physical exam, and is based on the presence of a combination of symptoms and signs (including but not limited to pruritic rash, fever, malaise, polyarthralgias and myalgias disproportionate to the degree of swelling), all occurring following exposure to a potential offending agent. Laboratory abnormalities (including but not limited to neutropenia and elevation of acute-phase reactants and creatinine) should be consistent with the diagnosis. As the differential diagnosis for serum sickness includes a number of other conditions (e.g., viral illness with exanthems, hypersensitivity vasculitis, acute rheumatic fever, acute meningococcal or gonococcal infection, systemic juvenile arthritis), exclusion of these possibilities is an important part of the clinical evaluation. For this reason, we believe that subjects with signs and symptoms suspicious for serum sickness should ideally be prospectively identified during the clinical trial and these subjects should undergo a medical evaluation by the clinical investigator in order to determine whether a case of serum sickness occurred.

Review of the data on laboratory parameter evaluation presented in the Summary of Clinical Safety reveals elevation of IgG and IgM antibody titers, absence of IgE antibody titers, decrease in complement levels, and normal tryptase levels. Based on symptoms reported in the synopsis of the Clinical Study Report and laboratory abnormalities described, it is likely that the mechanism of symptoms occurring in this population is due to IgG-mediated immune complex deposition (Type III Hypersensitivity) as you have suggested in Question 6 below.

Reviewing case narratives for suspected and possible serum sickness cases in order to see which cases progressed to anaphylaxis may be a useful approach to understanding these data better.

3. The sponsor used both the CTCAE grading system and the Brown's severe criteria for categorization of anaphylaxis events based on degree of severity. We would like input on which severity categorization scheme for anaphylaxis events is most clinically appropriate and meaningful (Brown's severe criteria vs. CTCAE severity grading system).

CBER Response to Question 3:

We consider anaphylaxis events to be serious adverse events (SAEs) as defined in the CFR (21CFR312.32). For this reason, in our view, grading anaphylaxis events that were carefully defined (for example, according to NIAID/FAAN criteria) would not be necessary. Along these lines, while the CTCAE and Brown grading systems may be useful in grading allergic reactions, they do not apply to the grading of anaphylaxis alone. In the CTCAE grading system, Grades 1 and 2 refer to allergic reactions that do not meet criteria for anaphylaxis. Similarly, in Brown's grading system, "mild" refers to allergic reactions that do not meet criteria for anaphylaxis.

4. The sponsor reports an anaphylaxis rate of 11.6% in study 165301.

The sponsor's categorization scheme for anaphylaxis events included all reported AEs that could be manifestations of anaphylaxis which were identified using:

- a. the broad algorithmic Anaphylactic Reaction SMQ**
- b. a modified Hypersensitivity SMQ**
- c. reports of anaphylaxis or anaphylactoid reactions by site physicians**
- d. events where epinephrine was administered**
- e. symptoms meeting any of the 3 NIAID/FAAN criteria**
- f. In addition, events identified as anaphylaxis by the site physician were conservatively included, even if the event may have had a longer time to onset than hours (i.e., greater than 1 day from the time of the most recent injection).**

An independent allergy expert also adjudicated all anaphylaxis events and conservatively considered all 3 NIAID/FAAN criteria during the adjudication. This independent expert reported an anaphylaxis rate of 4.6% (13 subjects with 21 episodes).

We would appreciate input on the most appropriate methods of categorization of events as anaphylaxis.

CBER Response to Question 4:

As mentioned in our response to question 1, we consider the NIAID/FAAN criteria to be an appropriate way to categorize events as anaphylaxis.

We have the following comments regarding the additional methods used to categorize anaphylaxis events:

- a) Although the algorithmic Anaphylactic Reaction SMQ is generally consistent with NIAID/FAAN criteria, the algorithmic Anaphylactic Reaction SMQ may have limitations and verification of cases (e.g., by reviewing case narratives) would be important.
- b) Based on the general information provided by the sponsor in CSR for Study 165-301 on the modified Hypersensitivity SMQ (modified by Preferred Terms (PT) added: arthralgia, arthritis, eye inflammation, eye irritation, eye pain, joint stiffness, joint swelling, pyrexia, vision blurred, and polyarthritis), the modifications more adequately characterize symptoms seen with Type III Hypersensitivity (serum sickness) itself, rather than anaphylaxis. While the Hypersensitivity SMQ itself (without the modifications made in this case) is sensitive enough to identify anaphylactic events, it may not be specific enough to adequately capture anaphylaxis (i.e., it may additionally capture non-anaphylactic events).
- c) Use of the MedDRA PT “anaphylaxis” or “anaphylactoid reaction” by site physicians should adequately characterize events as anaphylaxis due to any cause (immunologic, non-immunologic, or idiopathic) provided the diagnosis was made based on an established case definition of anaphylaxis (e.g., NIAID/FAAN) that was pre-specified in the protocol and prospectively applied. [While the PT ‘anaphylactoid reaction’ refers to a non-immunologic mechanism by which anaphylaxis occurs, use of the term has been replaced by ‘non-immunologic anaphylaxis.’ Regardless of the mechanism, the clinical definition of anaphylaxis is the same.]
- d) In certain instances, it may not be appropriate to categorize cases as anaphylaxis when epinephrine was self-administered by the subject based on subjective reasons. For this reason, training to ensure that patients/subjects understand when (and how) to use epinephrine is an important component of protocol design. Review of these cases to better understand the reasons for self-administration, if this information is available, would additionally be a useful way to understand whether these cases represent ‘true’ anaphylaxis or not. Alternatively, it may be useful to report rates of self-administered epinephrine since these represent a ‘real world’ scenario that may be useful for patients and health care providers to know.
- f) Characterization of events that “may have had a longer time to onset than hours (i.e., greater than 1 day from the time of the most recent injection)” as anaphylaxis may not accurately detect cases of anaphylaxis since symptoms occurring in a time frame greater than several hours from administration of the product are not likely to be due to anaphylaxis. In addition, since the drug product is being administered every 24 hours, it is unclear as to what is meant by ‘events occurring greater than 1 day from the time of the most recent injection’.

5. To help mitigate the anaphylaxis risk, safety mitigation strategies were added as part of a protocol amendment (amendment #2) to the phase 3 trials, including: the use of premedications, the presence of a “competent adult” during and for at least 60 minutes

after each drug administration for at least the first 6 months of treatment, and education of both the subjects and the “competent adult” on the signs and symptoms of anaphylaxis.

- a. We would like input on prior experience of your division with 1. drugs with high anaphylaxis risk and 2. strategies used to mitigate this risk.

CBER Response to Question 5a:

Our division has licensed 4 sublingual allergen immunotherapy (SLIT) products (Odactra®, Oralair® Ragwitek® and Grastek®) which are indicated for the treatment of allergic rhinitis with or without conjunctivitis. These products are allergen extracts which are self-administered either as a dissolvable tablet or as an aqueous /liquid extract under the tongue. Since the patients who are prescribed these products have known allergies to the allergens contained in these extracts, these products are expected to induce both local and systemic allergic (adverse) reactions. Although anaphylaxis with SLIT products is estimated to be low, careful risk mitigation strategies to address this risk were reflected in product labeling and included the following:

:

- a. A black box warning describes the risk of anaphylaxis and severe laryngopharyngeal edema.
- b. Health care providers advised to observe patients for 30 minutes following the initial dose, prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use and instruct patients to seek immediate medical care upon its use.
- c. The SLIT products are contraindicated in persons with a history of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy
- d. The SLIT products include a warning and precautions section which recommends that patients be informed of the signs and symptoms of severe allergic reactions and should seek immediate medical care and discontinue therapy should any of these occur. This section additionally indicates that the product may not be suitable for patients with medical conditions that reduce their ability to survive an allergic reaction or patients who may be unresponsive to epinephrine, such as those taking beta blockers.

In our review of products or protocols associated with a high risk of anaphylaxis, risk mitigation strategies implemented in protocol design have included the following:

- a. monitoring subjects by the clinical investigator in a medical setting after administration of study drug from 30 minute to 2 hours (or longer, depending on period of risk)
- b. provision that clinical staff are qualified in management of anaphylaxis
- c. incorporation of “study stopping rules” that details specific safety events that would prompt a study pause

- d. use of an independent Data Safety Monitoring Board to review safety events
- e. requirement to prescribe epinephrine to all study subjects and train them in the use of epinephrine
- f. exclusion of subjects who have medical conditions that would limit their ability to survive a systemic allergic reaction.

For subcutaneous immunotherapy products, which are routinely administered in a monitored medical setting, medications used to treat anaphylaxis, including epinephrine, are present. Patients are observed for 30 minutes after administration for symptoms and signs of anaphylaxis. They are given instructions to present to an emergency room should they self-administer epinephrine after leaving the outpatient monitored medical setting. [Cox et al (The Joint Council of Allergy, Asthma, and Immunology). Allergen Immunotherapy: A practice parameter third update. J Allergy Clin Immunol. 2011;127(1):S1-S55]

- b. We would also appreciate input on the current thinking about the use of premedications (H1/H2 antagonists, NSAIDs, others) to decrease the risk of anaphylaxis.**

CBER Response to Question 5b:

Pre-medication (with H1/H2 antagonists, NSAIDs) does not decrease the risk for anaphylaxis; however, pre-medication may be used to reduce specific symptoms (e.g., nasal or ocular itching, rhinorrhea, nasal congestion, etc.) that may arise with allergen immunotherapy. Certain symptoms associated with serum sickness, such as pruritus that may occur with rash, can be pre-treated with antihistamines. While there are no pre-medications to prevent development of symptoms associated with serum sickness, serum sickness can be treated with steroids and discontinuation of the offending agent.

- c. We would appreciate input on any prior use of a “trained observer” to mitigate anaphylaxis risk in programs in your Division where there is a high anaphylaxis risk associated with the product.**

CBER Response to Question 5c:

Our understanding is that the strategy to mitigate risk of anaphylaxis that has been used for the completed Phase 3 trials included presence of a “competent adult” during and for at least 60 minutes after each drug administration for at least the first 6 months of treatment education of both the subjects and the “competent adult” on the signs and symptoms of anaphylaxis.

We have not previously instituted the presence of a trained observer in this manner. In the case of IgE-mediated anaphylaxis, which may occur with biweekly or monthly administration of Xolair (omalizumab), patients are monitored in a medical setting for a few hours for signs/symptoms of anaphylaxis after administration of the dose for the first three doses. While they continue to receive subsequent doses via injection by

healthcare personnel, they are then only observed for 30 minutes in a monitored medical setting with each subsequent dose.

Such monitoring would apply to mitigation of the risk of anaphylaxis via Type I Hypersensitivity reactions (e.g., IgE-mediated anaphylaxis), but would not necessarily apply to Type III Hypersensitivity reactions (e.g., serum sickness).

We note that in order to qualify for self-administration of Pegvaliase, subjects (or subject-designated caregivers) were required to meet predefined criteria, including a demonstrated working knowledge of the signs and symptoms of a hypersensitivity reaction, including anaphylaxis, and what to do if such an adverse reaction occurred. Subjects were trained on self-administration and were not allowed to self-administer until they demonstrated self-administration competency in the clinic. Since these requirements are already in place and these patients are adults, the presence of a trained observer may not be necessary.

6. Based on the presumption that HAEs and anaphylaxis are caused by a type III, immune complex-mediated hypersensitivity reaction, we would appreciate input on considerations on long-term safety monitoring in patients in order to detect and mitigate (if possible) immune complex-mediated chronic complications (potentially as part of a PMR).

CBER Response to Question 6:

The product classes reviewed in our division (allergen immunotherapy products and vaccines) generally have not been associated with Type III hypersensitivity reactions.

General considerations from a clinical perspective for long-term safety monitoring with respect to serum sickness reactions may include periodic monitoring of the following laboratory studies for approximately 1 year after initiation of treatment (since Type III Hypersensitivity reactions may occur months after initiation of treatment): C1q binding assay to look for evidence of circulating immune complexes, CBC with differential to look for neutropenia and thrombocytopenia, ESR and CRP to look for elevation in these levels, urinalysis with examination of sediment to look for proteinuria and hematuria without cellular casts, and serum chemistry to look for elevation in creatinine.

Further understanding of the anaphylaxis cases seen in this population may be gained by genotyping subjects since it is presumably more likely that those with a complete deletion of the gene (resulting in complete lack of the phenylalanine hydroxylase) would be more likely to develop high titer IgM/ IgG antibodies to the phenylalanine hydroxylase.

Anubha
Tripathi -S

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Anubha Tripathi, M.D.

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/s/

BENJAMIN P VALI

03/09/2018

Signing on behalf of Anubha Tripathi and Roshan Ramanathan

LABEL AND LABELING & HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 1, 2018
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	BLA 761079
Product Name and Strength:	Palyntiq (pegvaliase-pqpz) Injection 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL
Product Type:	Drug-Device combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biomarin Pharmaceuticals, Inc.
FDA Received Date:	June 30, 2017 & February 23, 2018
OSE RCM #:	2017-1328 & 2017-1354
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director of Human Factors:	Quynh NhuNguyen, MS

1 REASON FOR REVIEW

This review is in response to DGIEP’s request for DMEPA to review the Human Factors results and proposed carton labeling, container labels, instructions for use (IFU), and prescribing information (PI) submitted on June 30, 2017. The proposed labels and labeling and Human Factor results were submitted under BLA 761079 for their new molecular entity application.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other – Preliminary Labeling Comments	F
Revised Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide a summary of the study design, errors observed with critical and essential tasks, and our analysis of the HF validation study results. We sent out an Information Request for samples of the intend-to-market product on December 20, 2017.

3.1 SUMMARY OF STUDY DESIGN

The objective of this study was to assess the intended user populations (PKU patients and their caregivers) of the Palynziq prefilled syringes and validate that Palynziq, including associated Instructions for Use (IFU) and packaging, can be correctly, safely and effectively used by the intended user populations (people with PKU and their caregivers) without patterns of (preventable) use errors that would result in harm to the user or person being injected.

A total of 45 individuals participated in this study. The sample included patients (n=15) who were diagnosed with phenylketonuria (PKU) and caregivers (n=30). All PKU patients (n=15) and half of the caregivers (n=15) were assigned to a trained condition, while the other half of the caregivers (n=15) did not receive training. Training involved participants performing a supervised injection using the 2.5 mg strength, which took place two days prior to the study session. This training is reflective of real-world use as it will be required of patients to perform the first injection under supervision of a health care professional. During the simulated use

portion of the study, participants were asked to perform an unaided injection using the 2.5 mg strength, followed by post-interaction questions, knowledge probes and IFU comprehension questions along with an IFU review. Then, participants were asked to perform a second unaided injection using either a 10 mg, 20 mg, or 40 mg dose.

3.2 RESULTS AND ANALYSIS

Overall, of the 45 participants, there were 6 failures. Additionally, 7 participants had the following difficulties:

- Difficulty removing the needle cap (n=5)
- Difficulty with Activation of Needle Safety Guard (n=2)

We note these difficulties are common difficulties found with pre-filled syringe (PFS) devices. We evaluated the subjective feedback from the participants which indicated that they experienced some difficulty with removing the needle cap as it was their first time working with a PFS. One of the participants that reported difficulty with the activation of the needle safety guard expressed difficulty understanding the concept as the participant felt the word 'retract' would have fit better than 'cover' in the IFU. We find the current terminology, 'cover,' acceptable from a medication error perspective as it correctly describes the function of the needle safety guard. In addition, it is noted that the participant successfully performed the task. Furthermore, we evaluated intend-to-market product samples. When working with the provided samples, it was noted there was no issue with the needle cap or needle safety guard, and we found no difference in difficulty when compared to other PFS products..

Tables 2 and 3 below summarize and focuses on the results of the failures observed with the critical tasks that were evaluated in the HF validation study along with the Applicant's root causes analysis for each failure. We note the Applicant proposed a mitigation strategy of adding a statement to the IFU, stating more pressure may be needed for the 10 mg and 20 mg configurations. This mitigation strategy is related to an error with one participant not administering the full dose with the 20 mg configuration.

Table 2: Unaided Injection #1 (2.5 mg dose/strength) – Failures

Tasks	Use Error	Root Cause Analysis	Additional Analysis and General Recommendations from DMEPA
Clean Injection Site	1 Participant (PKU Patient: P4) did not clean injection site	Sponsor/HF consultant stated participant focused on other aspects of the injection and knew to clean, but skipped this step. Participant stated “I missed the step 10 block.”	Our review of the IFU indicated that this step is clearly labeled; therefore, DMEPA has no further recommendations at this time.
Pinch Skin	1 Participant (PKU Patient: P7) did not pinch skin prior to injection	Participant stated was focused on cleaning the site, and that the injection pad seemed pooched already.	We discussed with the medical officer (MO) about this error as it may lead to the product being injected via the intramuscular route, which could result in a local hypersensitivity reaction. However, it does not present any serious safety concerns. Our review of the IFU indicated that this step is clearly labeled; therefore, DMEPA has no further recommendations at this time

Table 3: Unaided Injection #2 (randomized 10 mg, 20 mg, or 40 mg dose) – Failures

Task	Use Error	Root Cause Analysis	Additional Analysis and General Recommendations from DMEPA
Pinch Skin (n=2)	2 Participants (PKU Patient: P3; Untrained Caregiver: P42) did not pinch skin prior to injection	P3 [PKU patient]: “I was awkwardly doing the wrong hand and felt awkward when I did it. You are right though I forgot.	We Discussed with the MO, and this error may lead to the product being injected via the intramuscular route. This may lead to a local hypersensitivity reaction but does not present any serious safety concerns. Our review of the IFU indicated that this step is

		P42 [Untrained Caregiver]: “I’m not sure why. I just forgot [to pinch].”	clearly labeled; therefore, DMEPA has no further recommendations at this time
Administer Full Dose (n=1)	1 Participant (Untrained Caregiver: P44) did not press the plunger down fully and therefore did not deliver the full dose.	P44 did not push the plunger all the way down to deliver the full 20 mg dose. When the moderator inspected the syringe, could not identify if the full dose had been administered based on a visual inspection. The moderator then pushed down on the plunger rod over a pad to see how much drug remained inside the syringe. A small amount (roughly 5-10%) remained. Per the sponsor/consultant, this error was partially attributed the increased viscosity with the 20 mg strength (which was not told to the untrained participants). When the	We discussed with the MO and this error does not present any serious safety concerns, as the patients are titrating and dose reducing based on tolerability. The Applicant has proposed the mitigation strategy of adding the statement “More pressure may be needed to inject all the medicine for the 10 mg and 20 mg strengths” under Step 15 of the IFU. We agree with this mitigation strategy; however, we recommend also bolding this statement to increase prominence. Please see our recommendation 4a in section 4.1 below. Given that the modifications are intended to call out the user’s attention about ensuring that they are applying adequate pressure as they inject the dose due to viscosity of the product, we do not require additional HF validation testing.

		<p>participant was asked why this error occurred, the participant responded “Maybe I didn’t push all the way.”</p>	
<p>Activate Needle Safety Guard (n=1)</p>	<p>1 Participant (Untrained Caregiver: P44) did not press the plunger down fully when administering dose, did not deliver the full dose, and therefore did not activate the needle safety guard.</p>	<p>P44 did not administer the full dose (see above failure). P44 then removed the needle from the site, realized the needle guard hadn’t been activated, and immediately disposed the syringe into the sharps container.</p>	<p>This error is related to the participant not administering the full dose; therefore, the participant did not press the plunger down fully. This can also be attributed to the higher viscosity with the 20 mg configuration compared to the lower strengths.</p> <p>Per the report, the participant was aware the needle safety guard had not been activated when the needle was removed from the injection site, and immediately disposed of the syringe into the sharps container.</p> <p>We recommend adding a statement to the IFU clarifying that the activation of the needle safety guard is dependent on pushing the plunger all the way down. Please see our recommendation 4b in section 4.1 below.</p> <p>Given that this statement is intended to provide additional clarity surrounding the activation function of the needle safety guard, we do not require additional HF validation testing.</p>

4 LABELS AND LABELING ASSESSMENT

Biomarin submitted the proposed labels and labeling on June 30, 2017 under BLA 761079. The proposed labels and labeling submitted include: carton labeling, lidstock labels, container labels, prescribing information (PI), and Instructions for Use (IFU). We performed a risk assessment of the submitted labels and labeling for areas of vulnerability that may lead to medication errors. We note areas of the proposed labels and labeling that can be revised to improve clarity and understanding of important information. We note the refrigeration statement on the carton labeling can be revised to emphasize this important information. Additionally, we note the “date removed” statement on the lidstock labels can be revised to improve clarity of this important information.

We sent our preliminary labeling recommendations on February 9, 2018 (See Appendix F). The Applicant submitted the revised carton labeling and container labels, implementing our recommendations, on February 23, 2018 (see Appendix G). The revised labels and labeling are acceptable from a medication error perspective and we have no further recommendations at this time.

4.1 RECOMMENDATIONS FOR BIOMARIN

We recommend the following be implemented prior to approval of this BLA:

1. Instructions For Use

- a. We recommend bolding the statement “More pressure may be needed to inject all the medicine for the 10 mg and 20 mg strengths” found under Step 15 to emphasize this important information.
- b. We recommend adding a statement to the IFU under the appropriate step clarifying that the activation of the needle safety guard is dependent upon the plunger being pushed all the way down.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Palynziq received on June 30, 2017 from Biomarin.

Table 2. Relevant Product Information for Palynziq			
Initial Approval Date	N/A		
Active Ingredient	Pegvaliase		
Indication	indicated to reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels > 600 µmol/L on existing management		
Route of Administration	Subcutaneous		
Dosage Form	Injection		
Strength	2.5 mg/0.5 mL, 10 mg/0.5 mL, 20 mg/mL		
Dose and Frequency	Dosage*	Minimum Administration Duration Prior to Next Dosage Increase	
	2.5 mg once weekly	4 weeks [†]	
	2.5 mg twice weekly	1 week [†]	
	10 mg once weekly	1 week [†]	
	10 mg twice weekly	1 week [†]	
	10 mg four times a week	1 week [†]	
	10 mg daily	1 week [†]	
	20 mg daily	24 weeks	
	40 mg daily	Maximum recommended dosage	
	(b) (4)		
How Supplied		Pegvaliase 2.5 mg/0.5 mL	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 1, 2017, we searched DMEPA's previous reviews using the terms, pegvaliase. Our search identified four previous relevant reviews^{abcd}, and we confirmed that our previous recommendations were implemented.

^a Barlow, M. Human Factors Protocol Review for BMN-165 IND 76269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 03. RCM No.: 2015-1692.

^b Barlow, M. Label and Labeling Review for BMN-165 IND 76269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 016. RCM No.: 2015-1692.

^c Barlow, M. Human Factors Protocol Review MEMO for BMN-165 IND 76269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 APR 20. RCM No.: 2015-1692.

^d Barlow, M. Human Factors Protocol Review MEMO for BMN-165 IND 76269. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUL 12. RCM No.: 2015-1692.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design & Results



Summative HF
Validation.pdf

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F.—PRELIMINARY LABELING COMMENTS SENT ON FEBRUARY 9, 2018



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equestLabelingCom

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Palynziq labels and labeling submitted by Biomarin.

- Container label received on February 23, 2018
- Carton labeling received on February 23, 2018
- Lidstock labeling received on February 23, 2018
- Instructions for Use received on June 30, 2017
- Prescribing Information (Image not shown) received on June 30, 2017

G.2 Label and Labeling Images

Container Labels



3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page.

^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MATTHEW J BARLOW
03/02/2018

SARAH K VEE
03/02/2018

QUYNHNHU T NGUYEN
03/04/2018

- DPMH review of KUVAN (sapropterin dihydrochloride), NDA 22181 and NDA 205065, Carrie Ceresa, Pharm D, MPH, November 21, 2013. DARRTS reference ID 3410696¹

Consult Question: “DGIEP requests assistance from DPMH in the evaluation of Section 8 of the PI, specifically whether the sponsor correctly presented this section to be consistent with the Pregnancy and Lactation Labeling Rule (PLLR).”

INTRODUCTION

The Division of Gastroenterology and Inborn Errors Products consulted the Division of Pediatric and Maternal Health (DPMH) on August 27, 2017, requesting input regarding the applicant’s labeling proposal, specifically the proposed Pregnancy and Lactation (PLLR) language (subsections 8.1/8.2).

REGULATORY HISTORY

On June 30, 2017, BioMarin Pharmaceutical Inc., submitted a new 351(a) Biologics License Application (BLA) for Palynziq (pegvaliase). Palynziq is a phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia and trans-cinnamic acid. Palynziq substitutes for the deficient phenylalanine hydroxylase (PAH) enzyme activity and reduces blood phenylalanine levels. Palynziq was designated an Orphan Drug on March 8, 1995 and granted Fast Track designation on November 22, 2011.

BACKGROUND

Drug Characteristics²

- Palynziq (pegvaliase) is a phenylalanine ammonia lyase enzyme that substitutes for the deficient PAH enzyme activity and reduces blood phenylalanine levels.
- The molecular weight is 1,000 kilodaltons.
- Pegvaliase is cleared by immune-mediated mechanisms; (b) (4)
(b) (4) the mean elimination half-life for is 47.3 hours and 60.2 hours for the 20mg and 40 mg dose respectively, with individual values ranging from 14 to 132 hours.
- (b) (4)
- Serious adverse events include hypersensitivity reactions, including anaphylaxis. (There is a proposed boxed warning for labeling regarding the risk of anaphylaxis.)

Phenylketonuria and Pregnancy

- Phenylketonuria (PKU) has an incidence in the United States of approximately 1 in 10,000 to 15,000.³

¹ KUVAN (sapropterin dihydrochloride) NDA 22181 and 205065 was part of the materials reviewed, but was not relied upon for the purposes of the recommendations.

² Palynziq (pegvaliase) Proposed Package Insert

³ Marcason, W. Is There a Standard Meal Plan for Phenylketonuria (PKU)? Journal of the Academy of Nutrition and Dietetics, 2013;118 (8), 1124.

- Elevated blood levels of phenylalanine lead to the signs and symptoms of PKU, including delayed development, seizures, behavioral problems, psychiatric disorder, and intellectual disability.^{4,5,6}
- Untreated maternal PKU has increased risk of congenital heart disease, intrauterine growth retardation, dysmorphic facial features and microcephaly.^{3,4,5}
- The Maternal Phenylketonuria Collaborative Study was conducted to evaluate the effects of PKU and dietary control during pregnancy. Of 468 pregnancies followed, 331 resulted in live births. Abortion (both elective and spontaneous) occurred in 28% of pregnancies (13% spontaneous and 15% elective termination). Pregnancies with phenylalanine levels above 600 micromol/L were associated with an increase in congenital anomalies, such as facial defects, growth and neurological abnormalities, and congenital heart defects.⁷ The authors concluded that strict dietary control of phenylalanine levels during pregnancy is essential for reducing teratogenic potential effects.
- The American College of Obstetricians and Gynecologists (ACOG) recommends that phenylalanine levels less than 6mg/dL be achieved for at least three months before conception and maintained at 2-6 mg/dL during pregnancy. Dietary restriction is the main therapy, but ACOG states, “despite limited data, in women who are responsive to coenzyme tetrahydrobiopterin (BH4), sapropterin supplementation may be appropriate as an adjunct to dietary therapy.”⁸

REVIEW PREGNANCY

Nonclinical Experience

In animal reproduction studies with (non-PKU) pregnant rats, administration of pegvaliase at doses that were 1.4-times the human AUC at the maximum recommended daily dose during organogenesis resulted in skeletal variations (incomplete ossification and skeletal abnormalities).

In animal reproduction studies with (non-PKU) pregnant rabbits, administration of pegvaliase during organogenesis at 36-times the human AUC at the maximum daily dose, resulted in increased abortions, fetal malformations (including cleft palate, reduced or absent kidneys, corneal opacity, limb and facial abnormalities) and embryo/fetal lethality. These findings occurred in the presence of maternal toxicity (decreased body weights, decreased ovarian weights, and decreased food consumption) and were associated with decreased maternal blood phenylalanine (below normal levels) in non-PKU animals.

⁴ Koch, R. Maternal phenylketonuria and tetrahydrobiopterin. *Pediatrics*. 2008;122(6):1367-8.

⁵ Rouse B, et al. Maternal phenylketonuria syndrome: congenital heart defects, microcephaly, and developmental outcomes. *J Pediatr*. 2000;136(1):57-61.

⁶ Rouse B, Azen C. Effect of high maternal blood phenylalanine on offspring congenital anomalies and developmental outcome at ages 4 and 6 years: the importance of strict dietary control preconception and throughout pregnancy. *J Pediatr*. 2004;144(2):235-9.

⁷ Rouse B, et al. Maternal Phenylketonuria Collaborative Study (MPKUCS) offspring: facial anomalies, malformations, and early neurological sequelae. *Am J Med Genetic*. 1997;69:89-95.

⁸ The American College of Obstetricians and Gynecologists, Management of women with phenylketonuria. Committee opinion #636. June 2015, reaffirmed 2017.

For detailed information, the reader is referred to the full Pharmacology/Toxicology review by Fang Cai, Ph.D., and David Joseph, Ph.D.

Reviewer Comment:

Data from reproductive studies in both the rats and rabbits suggest the potential for adverse fetal outcomes with administration of pegvaliase. Although data from reproductive studies in rabbits suggest embryofetal toxicity and increased risk for birth defects, these effects were seen only in rabbits and were associated with significantly reduced phenylalanine levels and maternal toxicity. The DGIEP Pharmacology/Toxicology Team noted that it is unclear if the fetal malformations that were seen in rabbits were due to the drug or due to phenylalanine depletion.

Applicant's Review of Literature

The applicant did not provide a review of the literature.

DPMH Review of Literature:

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex⁹ using the search terms, “pegvaliase and pregnancy,” “pegvaliase and pregnant women,” “pegvaliase and pregnancy and birth defects,” “pegvaliase and fetal malformations,” “pegvaliase and stillbirth,” and “pegvaliase and miscarriage.”

No information about pegvaliase is listed in Micromedex or Reprotox. A search of the literature did not yield any references.

Review of Pharmacovigilance Database^{10,11}

The applicant reported on ten female subjects and eleven female partners of male subjects who became pregnant during clinical trials with pegvaliase. The outcomes of the female subjects who had been exposed to pegvaliase are described below:

- A 26-year-old woman discontinued treatment with pegvaliase (40mg daily x34 doses) five weeks after her last menstrual period (LMP). She maintained a phenylalanine level within recommended limits during pregnancy. At 36 weeks and 6 days' gestation, she experienced leakage of vaginal fluid-and lack of fetal movement. A stillbirth infant was delivered. The investigator noted that the stillbirth was not related to treatment with pegvaliase and was due to probable (by pathology) placental abruption. There was no information about any observed fetal malformations.
- A 20-year-old woman received three doses of pegvaliase (2.5mg per week) following her LMP. A pregnancy was discovered, and she discontinued pegvaliase. An ultrasound performed around 11 weeks after her LMP revealed no fetal heartbeat and a missed abortion. There was no information about any fetal malformations. The subject was found to have elevated blood phenylalanine levels. The investigator noted that the missed abortion might have been related to the study drug or due to the subject's elevated phenylalanine levels.
- A woman (age not reported) was exposed to two doses of pegvaliase after her LMP, and stopped after pregnancy was discovered. She delivered a term infant with a grade 1

⁹ (b) (4) information, <http://www.micromedexsolutions.com/>. Accessed 12/6/2017

¹⁰ BioMarin Pharmaceutical, Inc. Integrated Summary of Safety. June 16, 2017

¹¹ BioMarin Pharmaceutical, Inc. 120-day Safety Report Part 1, October 19, 2017.

systolic murmur that resolved on day 2 of life and neonate pustular melanosis (assessed by the investigator as non-serious).

- A woman (age not reported) received 46 doses of 10 mg/day and delivered a “healthy” infant at 39 weeks’ gestation.
- There were three induced abortions
 - An 18-year-old female had pegvaliase exposure prior to and during the first month following conception. The pregnancy was described as unwanted and the subject opted to undergo a therapeutic abortion. No information about fetal malformations was presented.
 - A 25-year-old woman terminated a pregnancy 34 days after her LMP while on treatment with pegvaliase. The woman had been receiving pegvaliase 1mg/kg 3x/week. There was no information about why the woman decided to terminate the pregnancy.
 - There was one additional induced abortion; details were not located about the age of the woman or the gestational age at which the procedure was performed.
- Three pregnancies were still on going at the time of the report, further details were not provided.

Of the eleven female partners of male subjects, there were:

- Six pregnancies with reported normal outcomes,
- One ongoing pregnancy,
- One pregnancy report noted that a neonate was delivered (but no details were provided)
- One pregnancy was lost to follow-up
- One case where the partner did not provide information about her pregnancy
- One pregnancy with respiratory distress in the neonate. In the case of the infant with respiratory distress, the following details were provided, the male subject was treated with pegvaliase prior to conception, and continued to receive pegvaliase during the female partner’s pregnancy. The subject’s partner gave birth to an infant (4.09 kg) at 40 weeks of gestation (APGAR 4/7 at 1 and 5 minutes). Delivery complications included low-grade maternal fever, nuchal cord, meconium-stained amniotic fluid, and fetal tachycardia during the last 30 minutes of the second stage of labor. The neonatal course was complicated by respiratory distress. The infant was admitted to the NICU and required respiratory and nutritional support. The infant recovered and was discharged two days after birth.

Palynziq Registry

The applicant is planning to establish a drug registry to collect data on pegvaliase in the post-marketing setting to evaluate long-term safety and effectiveness. The registry will also include data that are collected in women who become pregnant while taking Palynziq.

Summary

Limited available data with pegvaliase use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Women with PKU are at risk for increased adverse pregnancy outcomes if blood phenylalanine levels are above 6 mg/dL. In animal reproduction studies in rabbits (without PKU), pegvaliase, at doses that were 36-times the human

AUC, resulted in embryo-fetal toxicity. It is unclear how the findings in animal reproduction studies relate to humans. The mechanism of these adverse outcomes is not clear, but it is possible that the adverse findings in rabbits are related to low phenylalanine levels induced by treatment with pegvaliase. Therefore, based on the animal data, DPMH and DGEIP recommend that females of reproductive potential should be advised of the potential risk to a fetus.

In addition, DPMH recommends adding two Clinical Considerations subheadings to subsection 8.1 of Palynziq labeling, including a “Disease-associated maternal and/or embryo/fetal risk”, subheading to describe adverse maternal and fetal effects associated with untreated PKU, as well as a “Dose adjustments during pregnancy and the postpartum period” subheading to describe the need for close phenylalanine monitoring and for dose adjustments of Palynziq based on phenylalanine levels. DPMH also recommends a Data section, to describe the Maternal Phenylketonuria Collaborative Study (described above under Phenylketonuria and Pregnancy).

LACTATION

Nonclinical Experience

The applicant reports that data in rats show excretion of pegvaliase in milk at doses of >2mg/kg/day (maternal exposures 4.4 times the maximum recommended human dose (MRHD) of 40 mg/day, based on C_{trough}). Systemic exposure was not detected in the pups. In a pre-/postnatal development study in rats, pegvaliase produced decreases in pup weight and survival when administered at 6.5 times the maximum recommended daily dose.

For detailed information, the reader is referred to the full Pharmacology/Toxicology review by Fang Cai, Ph.D., and David Joseph, Ph.D.

Reviewer Comment:

It is unclear whether the adverse effects on the rat pups are due to direct effects of pegvaliase or low phenylalanine levels. Pegvaliase was not detected in the nursing pups. Pegvaliase is inactivated at a pH of 3,¹² so it is unlikely to be absorbed in an active form by the newborn.

Applicant’s Review of Literature

The applicant did not provide a review of the literature.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother’s Milk*¹³, the Drugs and Lactation Database (LactMed),¹⁴ Micromedex,⁹ and of the published literature in PubMed and Embase using the search terms “pegvaliase and lactation” and “pegvaliase and breastfeeding.” Pegvaliase is not referenced in *Medications in Mother’s Milk, Drugs in Pregnancy and Lactation*,¹⁵ Micromedex, or the LactMed database.

¹² Email communication, Tara Altepeter PhD 1/23/2018

¹³ Hale, Thomas and Rowe, Hilary E. (2017). *Medications and Mother’s Milk*. New York, NY. Springer Publishing.

¹⁴ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

A search of the literature did not yield any references.

Review of Pharmacovigilance Database

No cases related to lactation were reported.

Summary

There are no data on the presence of pegvaliase in human milk. Data from pre- and postnatal developmental studies demonstrate that pegvaliase is present in rat milk. Systemic absorption was not detected in rat pups; however, there was decreased survival, pup weight and delayed sexual maturation of offspring during lactation. The cause of the decrease in pup weight and survival during lactation is unclear. Due to species-specific differences in lactation physiology, the clinical relevance of these data is not clear. However, given the severity of the effects of pegvaliase on nursing pups, DPMH recommends that phenylalanine levels be monitored in a breastfeeding woman.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Pegvaliase produced impaired fertility in female rats at 20 mg/kg/day subcutaneously (6.5-times the human steady-state exposure at the maximum recommended daily dose), as indicated by decreases in corpora lutea, implantations, and litter size. These effects were associated with toxicity (decreased body weight, ovarian weight, and food consumption). No effects on mating or fertility were observed in female rats at 8 mg/kg/day given subcutaneously (1.4-times the human steady-state exposure at the maximum recommended daily dose) or in male rats at 20 mg/kg/day given subcutaneously.

For detailed information, the reader the reader is referred to the full Pharmacology/Toxicology review by Fang Cai, Ph.D., and David Joseph, Ph.D.

Applicant's Review of Literature

The applicant did not provide a review of the literature related to the effects of pegvaliase on human fertility.

DPMH Review of Literature

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "pegvaliase and fertility," "pegvaliase and contraception," "pegvaliase and oral contraceptives," and "pegvaliase and infertility."

No references were found related to either fertility or hormonal contraception and pegvaliase.

Review of Pharmacovigilance Database

No cases related to infertility were reported.

¹⁵ Briggs, G. G., Freeman, R. K., & Yaffe, S. J. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Tenth edition. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.

Summary

Data from animal studies indicate an effect on female fertility at doses 6.5-times the human maximum recommended daily dose. However, these findings occurred in the presence of significant maternal toxicity. In addition, there were no effects on mating or fertility in either males or females at 1.4 -times the human dose. No data in humans were reported. Data on female fertility will be presented in Section 13. Subsection 8.3 will not be included in Palynziq labeling.

CONCLUSIONS

The Pregnancy and Lactation subsections of Palynziq labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of labeling was formatted in the PLLR format to include: “Risk Summary,” “Clinical Considerations,” and “Data” subheadings.
- **Lactation, Section 8.2**
 - The “Lactation” subsection of labeling was formatted in the PLLR format to include: the “Risk Summary” and “Clinical Considerations,” subheadings.
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of labeling was updated to correspond with changes made to subsections 8.1 and 8.2 of labeling.

RECOMMENDATIONS

- 1.) DPMH recommends that the applicant implement a Pregnancy Surveillance Program to monitor outcomes of women and infants who are exposed to Palynziq during pregnancy and has suggested language for this program to be included in subsections 8.1. DPMH recommends that the following language is included in a post-marketing requirement (PMR):



- 2.) DPMH revised sections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

Pregnancy: May cause fetal harm (8.1).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in studies from animals without PKU, Palynziq may cause fetal harm when administered to a pregnant woman. Limited available data with pegvaliase-pqpz use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. There are risks to the fetus associated with poorly controlled phenylalanine levels including increased risk for miscarriage, major birth defects (including microcephaly, major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ; therefore, phenylalanine levels should be monitored during pregnancy (*see Clinical Considerations and Data*).

A reproduction study with pegvaliase in rabbits demonstrated a high incidence of malformations throughout the skeletal system, and in kidneys, lungs, and eyes. Embryo-fetal toxicity (increased resorptions and reduced fetal weight) was also observed. These effects occurred at 7.5 times the maximum recommended daily dose, and were associated with strong signs of maternal toxicity, including marked reductions in weight gain and food consumption, and death. A reproduction study in rats demonstrated an increase in skeletal variations, with no malformations observed. The effects in rats occurred at (b) (4) times the maximum recommended daily dose. In a pre-/postnatal development study in rats, pegvaliase produced decreases in survival of offspring during lactation, pup weight, and litter size, and delayed sexual maturation of offspring when administered daily at (b) (4) times the maximum recommended daily dose. The effects on rat embryo-fetal and post-natal development were associated with maternal toxicity. Advise pregnant women of the potential risk to a fetus.

There is a pregnancy pharmacovigilance program for Palynziq. If Palynziq is administered during pregnancy or if a patient becomes pregnant while receiving Palynziq or within one month following the last dose of Palynziq, healthcare providers should report Palynziq exposure by calling 1-800-983-4587.

The estimated background risk of major birth defects and miscarriage (b) (4) (b) (4). All pregnancies have a background risk of major birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Uncontrolled blood phenylalanine concentrations before and during pregnancy are associated with increased risk of adverse pregnancy outcomes. To reduce the risk of

hyperphenylalaninemia-induced (b) (4) effects, (b) (4) blood phenylalanine concentrations 120 to 360 micromol/L during pregnancy and 3 months before conception [see *Dosage and Administration* (2.2)].

Dose adjustments during pregnancy and the postpartum period

Phenylalanine levels below 30 micromol/L may be associated with adverse fetal outcomes. Monitor blood phenylalanine levels during pregnancy and adjust the dosage of Palynziq or modify dietary protein and phenylalanine intake to avoid blood phenylalanine concentrations below 30 micromol/L [see *Dosage and Administration* (2.1 and 2.2)].

Data

Human Data

Uncontrolled Maternal PKU: Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in PKU-affected women demonstrated that uncontrolled phenylalanine concentrations above 600 micromol/L are associated with an increased risk for miscarriage, major birth defects (including microcephaly, major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ.

Limited data from case reports of Palynziq use in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes.

Animal Data

All developmental toxicity studies were conducted in (b) (4) animals (rats and rabbits), in which pegvaliase treatment produced a dose-dependent reduction in maternal plasma phenylalanine concentrations. At doses which produced maternal toxicity and/or effects on embryo-fetal development, the maternal plasma phenylalanine concentrations were markedly reduced compared to the control group. The contribution of maternal phenylalanine depletion to the incidence of embryo-fetal developmental effects was not evaluated.

Subcutaneous administration of 5 mg/kg/day pegvaliase (7.5 times the maximum recommended daily dose based on mg/kg) in pregnant rabbits during the period of organogenesis produced embryo-lethality (increased resorptions), marked reduction in fetal weight, and malformations. The malformations included multiple external abnormalities of the head, body and limbs, multiple soft tissue malformations (reduced size or absence of kidneys, diaphragm hernia, corneal opacity, discoloration, or reduced size of eyes, and reduced size of lungs) and multiple skeletal malformations of the craniofacial bones, vertebrae, sternbrae, ribs, pelvis, limbs, and digits. An increase in variations and delayed ossification was also observed in all skeletal regions. The adverse developmental effects were associated with maternal toxicity, as indicated by marked impairment of weight gain and food consumption. Deaths associated with weight loss and abortion occurred in 8% of rabbits treated with 5 mg/kg/day pegvaliase.

Subcutaneous administration of 2 mg/kg/day pegvaliase (3 times the maximum recommended daily dose based on mg/kg) in pregnant rabbits had no adverse effects on embryo-fetal development. Systemic exposure to pegvaliase was detected in fetuses from rabbits treated with 2 or 5 mg/kg/day.

Pegvaliase increased fetal alterations when administered daily in rats at doses of 8 mg/kg subcutaneously and higher ((b) (4) times the human steady-state AUC at the maximum recommended daily dose) during a 28-day pre-mating period, mating, and through the period of organogenesis. The fetal alterations were limited to variations such as cervical ribs, bifid central of lumbar and thoracic vertebrae, and incomplete ossification of squamosal bones, frontal bones, lumbar vertebra arch, and ribs. Daily administration of 20 mg/kg subcutaneously ((b) (4) times the human steady-state AUC at the recommended maximum daily dose) produced reductions in litter sizes and fetal weights, which was associated with maternal toxicity (decreased body weight, ovarian weight, and food consumption). The decrease in litter sizes at 20 mg/kg subcutaneously was secondary to reductions in corpora lutea and implantations. Systemic exposure to pegvaliase was detected in fetuses from rats treated with 20 mg/kg ((b) (4) times the human steady-state AUC at the recommended maximum daily dose). Subcutaneous administration of 2 mg/kg/day pegvaliase (less than ((b) (4) the human steady state AUC at the maximum recommended daily dose) in pregnant rats had no adverse effects on embryo-fetal development.

Pegvaliase decreased ((b) (4) pup weight, and litter size, survival of offspring during lactation, and delayed sexual maturation of offspring when administered daily in rats at 20 mg/kg subcutaneous ((b) (4) times the human steady-state exposure at the recommended maximum daily dose), with dosing starting before mating and continuing through lactation. The effects in offspring were associated with maternal toxicity. No effects in offspring were observed at 8 mg/kg/day subcutaneous ((b) (4) times the human steady-state exposure at the recommended maximum daily dose). This study lacked a complete evaluation of neurobehavioral development in offspring; however, no effects of pegvaliase were noted in tests for learning and memory.

8.2 Lactation

Risk Summary

There are no data on the presence of pegvaliase in human milk, the effects on the breastfed infant, or the effects on milk production. A pre and post-natal study in rats showed that pegvaliase is present in rat milk, and that administration of pegvaliase during lactation decreased pup weight and survival. However, systemic absorption of pegvaliase was not detected in the rat pups [see *Use in Specific Populations (8.1)*]. Palynziq may cause low phenylalanine levels in human milk (see *Clinical Considerations*). The developmental and health benefits of breastfeeding should be considered along with the clinical need for Palynziq and any potential adverse effect on the breastfed infant from Palynziq or from the underlying maternal condition.

Clinical Considerations

Monitor phenylalanine levels in a breastfeeding woman.

17 PATIENT COUNSELING INFORMATION

Pregnancy

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy. [see *Use in Specific Populations (8.1)*]

- Advise women who are exposed to Palynziq during pregnancy or who become pregnant within one month following the last dose of Palynziq that there is a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to BioMarin [*see Use in Specific Populations (8.1)*].

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/s/

CATHERINE A ROCA
02/28/2018

MIRIAM C DINATALE
02/28/2018

LYNNE P YAO
03/02/2018

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY
PRODUCTS (DPARP) MEDICAL OFFICER CONSULTATION

Date: February 28, 2018
To: Irena Lavine MD, Medical Officer
Patroula Smpokou MD, Medical Officer Team Leader
Division of Gastroenterology and Inborn Errors Products (DGIEP)
From: Stacy Chin, MD, Medical Reviewer, DPARP
Through: Lydia Gilber-McClain, MD, Deputy Director, DPARP
Subject: Assessment of anaphylaxis in the pegvaliase clinical development program

General Information

BLA#: 761-079
Sponsor: BioMarin Pharmaceutical, Inc.
Drug Product: PALYNZIQ (pegvaliase)
Request From: Benjamin Vali, Regulatory Project Manager, DGIEP
Date of Request: 10/12/17
Date Received: 10/12/17
Materials: CSRs, narratives, and ADSL/ADAE datasets for Study 165-301,
Reviewed: Study 165-302, and ISS

Introduction

This Division of Pulmonary, Allergy, and Rheumatology (DPARP) medical officer review outlines the safety concerns of hypersensitivity reactions, specifically anaphylaxis, observed with pegvaliase (BLA 761079) under development for marketing in the United States as an enzyme replacement therapy for adults with phenylketonuria (PKU) who have uncontrolled blood phenylalanine levels on existing management. The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested this consult to help identify and adjudicate reported cases of anaphylaxis, resolve the inconsistencies in coding for anaphylaxis events, and provide input on the proposed risk mitigation strategies and considerations for long-term safety monitoring.

Background

PKU is a rare, autosomal recessive genetic disorder caused by mutations in the gene encoding phenylalanine hydroxylase (PAH), resulting in the inability to break down the amino acid, phenylalanine (Phe). Left untreated, accumulation of Phe in the blood and brain can lead to neurologic problems (seizures, tremors), irreversible brain damage or intellectual disability, and behavioral/social/emotional problems. Currently, the only FDA-approved treatment for PKU is sapropterin dihydrochloride (Kuvan), which is a synthetic form of tetrahydrobiopterin (BH4), a cofactor for PAH enzymatic activity; however, Kuvan is only indicated in a subset of PKU

patients who are BH4-responsive. Therefore, PKU patients are primarily managed by limiting Phe intake through a restrictive, low protein diet.

Pegvaliase is a pegylated, recombinant phenylalanine ammonia lyase protein derived from the cyanobacterium *Anabaena variabilis* that catalyzes Phe to trans-cinnamic acid and ammonia, which are subsequently excreted in the urine or metabolized, respectively.

The pegvaliase clinical program consisted of one single ascending dose study (PAL-001), several multiple ascending dose/dose-ranging studies (PAL-002, PAL-003, PAL004, 165-205), and two primary efficacy and safety studies (165-301 and 165-302). Of note, pegvaliase treatment was unblinded except for an 8-week portion (Part 2) of study 165-302. Because immunogenicity and hypersensitivity reactions were being observed during the conduct of study 165-301, the sponsor instituted a 2nd protocol amendment on August 18, 2014 (study start date May 21, 2013) which added criteria for identifying anaphylaxis events and implemented several requirements to mitigate the risks of hypersensitivity reactions during pegvaliase self-administration: mandatory premedication with H1 and H2 antagonists and NSAIDs 2-3 hours prior to each dose of study drug until completion of dose titration; presence of a competent adult observer for 1 hour following study drug administration for the first 16 weeks of the study; and issuance of and training on epinephrine autoinjectors for anaphylactic reactions. While the sponsor intended to enhance the safety of the clinical protocol by instituting the above changes, the use of premedication complicates the review of potential hypersensitivity and anaphylaxis cases since skin symptoms may have been masked. Recognizing that this safety signal must be addressed to ensure the safe use of their product, the sponsor proposed a REMs program which mirrors the changes implemented in protocol amendment #2.

Anaphylaxis – definition/case identification

Although anaphylaxis has always been regarded as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, there has been no universal agreement on the clinical definition of anaphylaxis or the criteria for diagnosis. Because the lack of specific diagnostic criteria hampered research, created confusion among health care providers, and led to inconsistent diagnosis and treatment of patients, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened meetings in 2004 and 2005 to address this need. The symposia involved over 18 physician, patient advocate, regulatory, and scientific organizations including the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; the Centers for Disease Control and Prevention; the Food Allergy Initiative; the US Food and Drug Administration; the European Academy of Allergy and Clinical Immunology; the Australasian Society of Clinical Immunology and Allergy. The symposia defined anaphylaxis as a clinical syndrome characterized by acute onset of illness with

involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems.¹ It is worth noting that the NIAID/FAAN diagnostic criteria do not grade the severity of anaphylaxis nor specify the underlying mechanism of action (e.g., IgE, non-IgE). The sponsor, however, has utilized Brown's criteria to grade the severity of anaphylaxis events in their program.² Brown's criteria is neither an accepted method of assessing anaphylaxis in the allergy community nor, in our opinion, a clinically useful means for identifying cases. For example, grade 1 "mild" anaphylaxis according to Brown's criteria is not true anaphylaxis as it only involves skin or mucosal symptoms. The sponsor has chosen to focus on cases meeting grade 3 "severe" criteria (cyanosis, hypoxia, hypotension, loss of consciousness, incontinence, confusion). While one cannot argue with the severity of grade 3 events, this method minimizes the clinical importance of other anaphylactic reactions. By virtue of multi-organ, multi-system involvement and the unpredictable nature of anaphylaxis, all anaphylactic reactions are considered severe and potentially life-threatening, and therefore, the remainder of this consult will discuss cases regardless of Brown's severity.

The three recommended NIAID/FAAN diagnostic criteria for anaphylaxis are as follows:
Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

- 1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
 - a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
- 2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c) Reduced BP or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
 - d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- 3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

¹ Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NJ, Bock SA, Branum A, 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.* 2006; 117:391-7

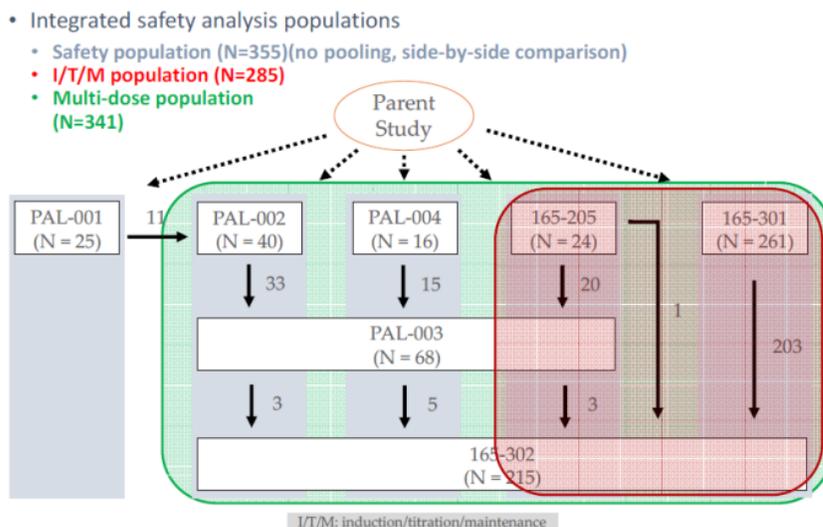
² Simon GA Brown. *J Allergy Clin Immunol.* 2004; 114(2):371-6

- b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Since their inception, DPARP has used the NIAID/FAAN criteria to review all adverse reaction case reports to identify cases consistent with anaphylaxis. DPARP has usually taken a conservative approach in the determination of anaphylaxis by limiting the identification to cases fulfilling criterion 1 above in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. One could conceivably justify using both criteria 1 and 2 to identify cases of anaphylaxis based on the knowledge that the required pre-medication could have masked skin symptoms and that study drug was administered outside of a supervised healthcare setting; while including cases that met either criteria may be more sensitive, it risks including hypersensitivity cases which did not have clear cut multiorgan system involvement.

Method for identifying cases

To identify cases of anaphylaxis, DPARP reviewed the anaphylaxis, hypersensitivity, and angioedema case narratives in the ISS (comprised of parent studies PAL001, PAL002, PAL004, 165-205, and 165-301) and the CSRs from studies 301 and 302. In addition, we performed an analysis of the ADSL and ADAE datasets in MAED using both the narrow and algorithmic SMQs for anaphylaxis and analyzed the ISS ADSL and ADAE datasets in JMP using the variables for anaphylactic reaction SMQ, anaphylaxis per NIAID/FAAN criteria custom query, and anaphylaxis adjudicated independently custom query. For the purposes of labeling, the I/T/M population is the patient population of interest; therefore, this review will focus on presenting data from the I/T/M population (shown in the figure below).



Interpreting clinical symptoms provided in case narratives through the lens of NIAID/FAAN criteria carries an inherent degree of subjectivity. For example, the presence of throat tightening could be interpreted as a mucosal symptom indicative of edema or, alternatively, as a respiratory symptom. We attempted to create consistency in our approach by classifying reported symptoms in the following manner:

- Skin or mucosal symptoms included: rash; pruritus; erythema; flushing; urticaria/hives; angioedema/swelling of the face, tongue, lips, throat, or larynx; throat tightness; difficulty swallowing
- Respiratory symptoms included: wheeze, bronchospasm, shortness of breath, chest tightness, difficulty breathing, cyanosis, hypoxia, chest discomfort; (cough alone not included)
- Symptoms of cardiovascular compromise included: collapse; pre-syncope; decreased blood pressure; hypotension; SBP \leq 90 mmHg (lightheadedness or dizziness alone not included)

With regard to timing (i.e. onset of symptoms after allergen exposure), anaphylaxis caused by IgE mechanisms is typically characterized by immediate onset of symptoms, usually within minutes to 1-2 hours depending on the route of exposure; however, delayed onset has been described. Given that the underlying pathophysiology in this case is not entirely clear, cases with symptoms meeting anaphylaxis criterion were included if the time interval between pegvaliase administration and symptom onset was 48 hours or less.

We used the most conservative method for identifying anaphylaxis cases by applying only NIAID/FAAN criterion #1. In addition, we included any cases for which the investigator reported the adverse reaction as either “anaphylaxis” or “anaphylactoid reaction” or which were treated with epinephrine, unless there was a clear alternative etiology for the reaction (for example, known food allergen or other drug culprit). Using this method, we identified 37 cases of anaphylaxis in 26 subjects (9.1% of the I/T/M population).³ The overall number of anaphylaxis cases identified by DPARP is less than the 50 events of anaphylaxis in 33 subjects (11.6% of the I/T/M population) identified during the sponsor’s internal assessment, but more than the 21 events in 13 I/T/M subjects (4.6% of the I/T/M population) adjudicated by the sponsor’s external allergist/immunologist. One additional case of anaphylaxis occurred in Subject (b) (6) six days following pegvaliase (2.5 mg) administration. Given the time interval between exposure and symptom onset, this event was not included in DPARP’s overall frequency; however, the reaction was considered an SAE and the subject was withdrawn from the treatment following the event.

³ Three additional events in two patients were identified when less restrictive criteria (NIAID/FAAN criteria 1 and 2) were used. Upon review, these cases presented with vague symptoms such as dizziness/lightheadedness or abdominal symptoms of unclear persistence. Given the number of cases identified by criterion 1 alone, including these additional cases meeting criterion 2 only is not necessary to characterize the anaphylaxis signal.

Table 1. Summary of anaphylaxis findings in the I/T/M population

	DPARP adjudication	Sponsor’s internal assessment	Sponsor’s external adjudication
Number of subjects, n (%)	26 (9.1%)	33 (11.6)	13 (4.6)
Number of events	37	50	21

Our review identified fewer cases than the sponsor’s internal assessment, but more cases than the sponsor’s external adjudication. The discrepancy in frequency and number of events has several possible explanations. The most apparent appears to be our conservative approach in defining anaphylaxis using NIAID/FAAN criterion 1 only compared to the sponsor’s use of all 3 criteria to capture all potential cases. Additionally, in reaching their overall number, the sponsor appears to have accepted reports of adverse reactions that were broader in nature and included terms such as “hypersensitivity” or “allergic reaction” as reports of anaphylaxis. Adjudication of cases was not pre-specified in the SAP; however, the external allergist/immunology provided a brief memo outlining her methodology for anaphylaxis case identification. She applied Sampson’s (NIAID/FAAN) criteria noting that criterion #1 makes anaphylaxis highly likely and that all adjudicated cases met criterion 1. It appears, however, that she made a judgment call in determining the “significance” of the described dermatologic and respiratory symptoms, and did not consider all events that met criterion #1 (i.e., presence of both dermatologic and respiratory/cardiovascular symptoms) to be anaphylaxis. Examples include cases in which shortness of breath, chest tightness, or cough in the presence of mucocutaneous symptoms were not considered “significant” due to the absence of reported wheeze or objective signs of hypoxia or hypotension. She also appears to have excluded cases that were coded as anaphylaxis by the investigator, but lacked sufficient details to meet NIAID/FAAN criteria. Because most events occurred outside of a supervised healthcare setting and consequently, vital signs were not available or recorded until after epinephrine or antihistamine treatment had been received, we believe this approach is too narrow and inconsistent with our prior application of the NIAID/FAAN criteria. Of note, the sponsor regards the externally adjudicated cases, specifically the ones meeting Brown’s grade 3-4 severity criteria, to be the most relevant, and therefore this is the incidence rate reflected in the proposed labeling and these cases serve as the justification for their proposed REMS program. Nonetheless, there is clearly a risk of anaphylactic reactions with pegvaliase treatment, regardless of numbers or adjudication method employed.

Table 1 provided at the end of this consult includes details for each anaphylactic reaction we have identified in the I/T/M population.

Potential mechanism of action

While the term “anaphylaxis” is often associated with IgE-mediated events and “anaphylactoid” with IgE-independent events, the two reactions are usually clinically indistinguishable; thus,

many allergy organizations have discarded this nomenclature in favor of immunologic vs nonimmunologic anaphylaxis. It should be noted that drugs may cause anaphylaxis due to both immunologic (e.g., IgE-mediated) and nonimmunologic-mediated etiologies. An example is vancomycin, which may produce both IgE-mediated and non-specific mast cell degranulation and anaphylaxis. Whether IgE-mediated or not, the underlying mechanism does not alter the clinical diagnosis of anaphylaxis and the risk for serious injury or even death.

The sponsor did not conduct a systematic investigation of the underlying pathophysiology of hypersensitivity reactions, but the available evidence suggests an immunologic, non-IgE mechanism. For the cases of anaphylaxis DPARP identified, most of the reactions occurred following months of exposure to pegvaliase. Furthermore, most patients had a negative re-challenge and were able to resume pegvaliase treatment without recurrence of anaphylaxis. And, while symptom onset for most reactions occurred shortly following pegvaliase administration, a handful of events exhibited delayed onset of several hours or more. These features are not typical of IgE-mediated (i.e., Type I Gell and Coombs) drug reactions which occur within the first couple of exposures and recur upon each re-exposure. None of the patients who experienced an anaphylactic reaction had detectable IgE levels to the drug (anti-PAL) or to the pegylated portion (anti-PEG) of the drug. Although not definitive, several factors suggest these may instead be Type III Gell and Coombs reactions mediated by immune complexes and complement activation: the onset after prolonged drug administration, low complement C3 and C4 levels with elevated CRP following several of the reactions, and occurrence of arthralgias and serum sickness-like reactions in the trials. In this type of reaction, antigen-antibody immune complexes bind to Fc-IgG receptors of inflammatory cells and/or activate complement. Activation of the complement system by immune complexes results in generation of active by-products (anaphylatoxins C3a, C4a, C5a) which can cause mast cell and basophil degranulation, mediator release and generation, and anaphylaxis. In addition, complement products may directly induce vascular permeability and contract smooth muscle. Although complement-mediated anaphylaxis has been described in the literature, these types of reactions are less well-understood than those mediated by IgE. Other symptoms associated with Type III reactions, such as nephritis or vasculitis, were not reported in the trials. Besides treating acute anaphylaxis episodes, Type III reactions typically resolve when the causative agent is removed from the system; the potential long-term implications of prolonged pegvaliase exposure and immune complex formation are unknown.

While tryptase is relatively specific for mast cells and is oftentimes elevated following an anaphylactic reaction, normal levels do not exclude the diagnosis of anaphylaxis. Tryptase levels were consistently normal in the cases identified in this review; however, laboratory tests were not collected in a uniform manner and the timing of tryptase testing is essential to capture elevations. Optimally, tryptase measurements should be obtained within 15 minutes to 3 hours of symptom onset.

Limitations

Most events occurred outside of a healthcare setting and were unwitnessed by investigators, study staff, or other healthcare providers. Some events coded as hypersensitivity reactions had too few details to assess whether anaphylaxis may have occurred; however, this was likely balanced out by the inclusion of all cases that were coded as anaphylaxis/anaphylactoid or that were treated with epinephrine. Thus, our review of case narratives was occasionally limited due to lack of sufficient detail and/or objective vital signs during the reaction. The use of premedication also complicates the review of potential hypersensitivity and anaphylaxis cases since skin symptoms may have been masked.

Summary

Though the number of cases identified by the sponsor and our review differ, the overall conclusion remains the same whether the frequency is 5% or 9%. Regardless of the underlying pathophysiology, anaphylaxis undoubtedly occurs with pegvaliase treatment. While the mechanism has not been fully elucidated, the reactions appear to be mediated by immune complex/complement activation. The decision to approve or not approve pegvaliase is a risk versus benefit decision to be made by DGIEP taking into account the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data. Should pegvaliase be approved, it may be important for labeling to convey both the frequency and features of anaphylactic reactions observed since most prescribers and patients associate the term anaphylaxis with typical IgE-mediated reactions. Regarding the proposed REMS, it is difficult to determine the impact of each individual intervention, since all three (premedication, trained observer, and epinephrine autoinjector) were introduced simultaneously. However, given the clear anaphylaxis signal and the potential daily home administration, educating patients and prescribers to recognize and treat anaphylaxis with an epinephrine autoinjector is a sound strategy for mitigating this potential risk, though one does not necessarily need a REMS to recommend that health care providers prescribe epinephrine autoinjectors for patients to have readily available. We generally do not recommend routine premedication with antihistamines for all patients since this can mask early skin symptoms and delay appropriate treatment. Premedication also seems an unnecessary burden with potential side effects for those who never experience an allergic reaction. As for the proposal (b) (4), this appears to be based on the number of Brown's grade 3 severity events which occurred during vs. after the first 6 months. However, as stated above, we consider all anaphylactic reactions to be severe and potentially life-threatening, and it is unclear if the decrease in number of "severe" events cited by the sponsor was due to the interventions or related to adverse drop outs earlier in the study with selective retention of responders over time.

Table 1. DPARP Adjudicated Anaphylaxis Cases

Unique Subject ID Number	Study ¹	Study day	Dose #	Pegvaliase dose ² (mg)	Premed	Time to symptom onset ³	Symptoms	SAE	Any treatment given ⁵	Epi given	Rechallenge	Anaphylactic/anaphylactoid reaction per investigator	NIAID/FAAN criterion 1	Labs ⁶
(b) (6)	302	207	237	40	✓	48 hours	Dyspnea, wheeze, angioedema (face, tongue, throat), pruritus	✓	✓	✓	Negative		✓	Tryptase nl IgE neg
	205	1	1	2.5		same day	Dyspnea, rash, urticaria				Negative		✓	IgE neg
	PAL-003	210	306	53.6		2 hours	Cough, wheeze, SOB, throat tightness, skin “whelps” at injection site	✓	✓	✓	Negative		✓	IgE neg
	205	59	20	15	✓	6 minutes	Dyspnea, flushing, hypotension, back pain, dizziness, headache		✓		Negative		✓	Tryptase high IgE neg
	205	158	86	75	✓	2 minutes	Dyspnea, flushing, pruritus, oral hypoesthesia, nausea, chills, diaphoresis		✓		Negative		✓	IgE neg
	205	254	133	56.25	✓	immediate	Labored breathing, wheeze, throat numbness, flushing, pruritus, nausea, shivering		✓		Negative		✓	Tryptase nl IgE neg
	205	407	237	75	✓	2 minutes	SOB, pruritus, angioedema, dyspnea, wheeze, difficulty swallowing, peripheral cyanosis, vision went black, sense of urinary/bowel loss	✓	✓	✓	ND	✓	✓	Tryptase nl CRP high C3/C4 low IgE neg
	301	59	12	10		shortly	SOB, dizziness, nausea/vomiting	✓	✓	✓	Negative			
	301	166	53	10	✓	2 minutes	Dyspnea, face/lip tingling, pallor, shakiness, nausea, chest tightness, vomiting	✓	✓	✓	ND	✓		
	301	78	36	40	✓	shortly	Chest tightness, lip swelling, flushing, cyanosis, vomiting, diarrhea	✓	✓	✓	Negative ⁴	✓	✓	Tryptase nl C3/C4 low IgE neg
	302	216 [†]	180	40		immediate	SOB, generalized pruritus, erythema, urticaria, throat/facial swelling, burning in ears, finger tingling	✓	✓	✓	Negative		✓	IgE neg
	301	57	14	10	✓	1 minute	Flushing, wheeze	✓			Negative	✓	✓	IgE neg
	301	70	27	20	✓	2 minutes	Flushing, wheeze	✓	✓		Negative	✓	✓	IgE neg
	302	6	181	20		30 minutes	Difficulty breathing, angioedema, warmth/tingling, vomiting,				Negative	✓	✓	IgE neg
	302	46	216	20		5 minutes	Pallor, diaphoresis, hot				Negative	✓		IgE neg
	302	126	285	40	✓	2 minutes	Difficulty breathing, facial flushing/warmth, body aches				Positive (dyspnea, flushing)	✓		IgE neg
	302	127	286	40	✓	2 minutes	Difficulty breathing, facial flushing/warmth, body aches				Negative	✓	✓	IgE neg
	302	134	292	40	✓	1 minute	Difficulty breathing, flushing, tachycardia, achy arms/legs				Negative	✓	✓	Tryptase nl C3/C4 low
	301	85	43	20	✓	same day	Maculopapular rash, chest tightness, urticaria		✓		Negative		✓	Tryptase nl IgE neg
	302	1	1	40	✓	<10 minutes	SOB, throat tightness, lightheadedness	✓	✓	✓	Negative		✓	Tryptase nl C3/C4 low
302	582	683	20	✓	21 hours	Pruritic, erythematous, maculopapular rash, urticaria, facial angioedema, chest tightness, cough, bronchospasm	✓	✓	✓	Positive (rash)		✓	IgE neg	

Unique Subject ID Number	Study ¹	Study day	Dose #	Pegvaliase dose ² (mg)	Premed	Time to symptom onset ³	Symptoms	SAE	Any treatment given ⁵	Epi given	Rechallenge	Anaphylactic/anaphylactoid reaction per investigator	NIAID/FAAN criterion 1	Labs ⁶
(b) (6)														
	302	21	230	20		1 minute	Facial angioedema, flushing, arm paresthesia, SOB, nasal congestion, ocular hyperemia, vomiting	✓	✓	✓	Positive (paresthesia, flushing) ⁴		✓	
	302	70	268	20		10 minutes	Urticaria, erythema, pruritus, cough, vomiting, chest tightness, dyspnea, difficulty swallowing		✓	✓	Negative	✓	✓	
	301	129	84	40		12 minutes	Urticaria, hand swelling, "sensations", chest tightness, SOB	✓	✓		ND	✓	✓	
	301	76	34	40		5 minutes	Pruritus and tingling in hands, lightheadedness, dizziness, erythema, urticaria, tongue/lip angioedema, hypoxia (88%)	✓	✓	✓	ND	✓	✓	Tryptase nl IgE neg
	302	834 [†]	785	40	✓	immediate	Urticaria, "allergic reaction"		✓	✓	Negative			
	301	92	49	30	unclear	1 minute	Chest tightness, SOB, lightheadedness/pre-syncope, collapse	✓	✓	✓	ND	✓		IgE neg
	301	91	40	20	✓	immediate	Dizziness, lightheadedness, flushing, throat/tongue swelling	✓	✓	✓	Negative	✓		IgE neg
	302	97	115	40	✓	immediate	Difficulty breathing, facial flushing, globus sensation in throat, dizziness, red sclera, nausea, legs felt swollen and tingly, nasal congestion	✓	✓		Negative	✓	✓	IgE neg
	302	101	119	40	✓	immediate	Difficulty breathing, felt hot, globus sensation in throat, nausea/vomiting, dizziness, sense of doom, flushing/erythema	✓	✓		Negative	✓	✓	Tryptase hi-nl C3/C4 low U-NMH nl IgE neg
	302	538*	457	40	✓	12 minutes	Pruritic rash, difficulty swallowing (later nausea, vomiting, dizziness, decreased BP with IV insertion, possibly vasovagal)	✓	✓	✓	Negative	✓		IgE neg
	301	69	25	20	✓	26 hours	Generalized rash, cough, dysphonia, dizziness, neck/face swelling, hyperventilation	✓	✓	✓	ND	✓		
	302	215	323	40	✓	4 minutes	Tachycardia, SOB, facial erythema, GI cramping, hand erythema, vomiting		✓		ND	✓	✓	Tryptase nl CRP high C3/C4 low IgE neg
	301	57	14	10	✓	immediate	Pruritus, chest discomfort, dizziness, lightheadedness, throat tightness				Negative		✓	
	301	63	21	20	✓	immediate	Warmth, chest tightness, SOB, syncope (60-90 sec), flushing, hypotension (BP 90/60 mmHg after epi)	✓	✓	✓	ND	✓	✓	Tryptase nl IgE neg
	301	129	80	40		immediate	SOB, flushing, palpitations, back pain, leg weakness, diaphoresis		✓	✓	Negative		✓	
	302	108	149	40	✓	5 minutes	Wheeze, flushing, lip swelling, hot/sweaty, felt faint, N/V, chest pain, globus sensation in throat, loose stools, shivering	✓	✓		Negative	✓	✓	Tryptase nl CRP high C3/C4 low

Shaded rows indicate cases adjudicated as anaphylaxis by the sponsor's external expert

¹ Study in which the reaction occurred

² Dose of pegvaliase administered prior to the reaction

³ Time interval between pegvaliase dose and symptom onset

⁴ Treatment subsequently discontinued

⁵ Treatments could include antihistamines, corticosteroids, inhaled bronchodilators, epinephrine, and/or IV fluids

Unique Subject ID Number	Study ¹	Study day	Dose #	Pegvaliase dose ² (mg)	Premed	Time to symptom onset ³	Symptoms	SAE	Any treatment given ⁵	Epi given	Rechallenge	Anaphylactic/anaphylactoid reaction per investigator	NIAID/FAAN criterion 1	Labs ⁶
⁶ Timing of lab measurements following reactions was variable * Case from 120-day safety update † Discrepancy in study day between narrative and dataset (table reflects study day from case narrative) Premed=protocol specified pre-medication administered prior to pegvaliase administration ND=Not done; treatment discontinued nl=normal U-NMH=24 hour urine n-methylhistamine														

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY J CHIN
02/28/2018

LYDIA I GILBERT MCCLAIN
03/01/2018
I concur

Date: February 28, 2018
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Benjamin Vali, Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Subject: Renal safety of pegvaliase (BLA 761079)

Background

Pegvaliase is recombinant phenylalanine ammonia lyase (PAL), a phenylalanine-metabolizing enzyme derived from the bacterium *Anabaena variabilis*, expressed in *E.coli*, and PEGylated (b) (4). On June 30, 2017, the Division of Gastroenterology and Inborn Errors Products (DGIEP) received a BLA for pegvaliase for the indication “to reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels > 600 µmol/L on existing management.”

Phenylketonuria (PKU) is an autosomal recessive disease that most commonly results from deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH) responsible for converting the amino acid phenylalanine to tyrosine. PAH deficiency leads to accumulation of phenylalanine and its metabolites and results in intellectual disability. Through neonatal screening programs, PKU can be detected during an asymptomatic phase, and dietary restriction of phenylalanine can mitigate the neurological consequences. Some patients with mild to moderate disease also respond to tetrahydrobiopterin (BH4), a cofactor for PAH, or the FDA-approved synthetic form of BH4, sapropterin.

In the clinical development program, pegvaliase was found to be highly immunogenic with most subjects experiencing hypersensitivity reactions including anaphylaxis, developing anti-PAL antibodies and IgG and IgM circulating immune complexes, and having reduced C3 and C4 levels. Because pegvaliase is highly PEGylated, there also is the potential for PEG deposition in the renal tubules. As a result, DGIEP is concerned that deposition of immune complexes and/or PEG in the kidney could have long-term adverse renal effects. They have consulted the Division of Cardiovascular and Renal Products (DCRP) to opine on the level of concern for adverse renal effects based on the available data and whether other analyses could be done to identify potential cases in the development program. They also anticipate requiring a post-marketing study to further characterize the safety profile of pegvaliase and have requested input on a renal monitoring strategy.

Materials Reviewed

1. Clinical Study Reports (CSRs) for Trials 165-301 and 165-302
2. Integrated Summary of Safety (ISS)
3. Integrated Subject Narratives
4. Narrative for Subject (b) (6) in the 120-day Safety Update
5. Draft prescribing information

Preclinical Findings

Rats and monkeys developed anti-PAL IgG and IgM and neutralizing antibodies. In monkeys, there was dose-dependent inflammation of small arteries and arterioles, including in the kidney, that resolved over the 13-week recovery period. There were no associated organ-related toxicities such as changes in renal function or urinalysis parameters. Histology of the vessel wall showed IgG and IgM with some increase in C3.

Rats and monkeys also developed dose-dependent, PEG-related vacuolation and hypertrophy of renal tubule cells that persisted for the 12-week recovery period. The vacuolation was not associated with organ-related toxicities such as changes in renal function or urinalysis. The applicant notes that acute exposure to high doses of PEG can result in renal toxicity, but that the PEG exposure associated with the maximum allowable dose in the phase 3 studies is less than 1/80th the reported toxic doses and is similar to the exposure in other widely used medications.

Overview of Clinical Development Program

In support of the indication, the applicant conducted two phase 3 studies (165-301 and 165-302). Additional safety data are provided by a single-dose phase 2 study (PAL-001), three multi-dose phase 2 studies (PAL-002, PAL-004, and 165-205), and an ongoing open-label extension study (PAL-003).

Study 165-301 was a phase 3, open-label study in which 261 adults with PKU were randomized 1:1 to 20 mg/day or 40 mg/day of subcutaneous pegvaliase for up to 36 weeks. Weeks 1-4 were the induction period where subjects received 2.5 mg/week. Weeks 5-34 were the titration period where subjects were titrated on an individualized basis to the randomized daily target dose. The titration period was followed by a maintenance period of at least 3 weeks during which subjects were to maintain the target dose until they reached a minimum of 26 or a maximum of 36 weeks in the study. Subjects were excluded for a creatinine >1.5 times the upper limit of normal. Renal function, urinalysis, urine albumin to creatinine ratio (UACR), C-reactive protein, erythrocyte sedimentation rate, C3 and C4 were assessed at screening or induction then every 4 weeks. The protocol did not specify any renal events as adverse events of special interest.

Study 165-302 was a four-part, phase 3 study that enrolled 215 adults with PKU who were previously treated with pegvaliase in studies PAL-003, 165-205, or 165-301.

- Part 1: 152 subjects from study 165-301 continued their randomized treatment. In addition, 12 subjects from a phase 2 study were randomized to 20 or 40 mg/day. Subjects who achieved and maintained the target dose and achieved a $\geq 20\%$ reduction in phenylalanine from baseline continued to Parts 2 and 3. Otherwise they transitioned to Part 4.
- Part 2: 95 subjects from Part 1 who achieved and maintained a dose of 20 or 40 mg/day and a $\geq 20\%$ reduction in phenylalanine from baseline were randomized 2:1 to continue pegvaliase or change to placebo.
- Part 3: 89 subjects from Part 2 entered a 6-week, open-label period to compare PK and PD of two formulations of pegvaliase.
- Part 4: 202 subjects have enrolled in an ongoing, open-label extension. All subjects are titrated as tolerated to 40 mg/day pegvaliase or as high as 60 mg/day at the investigator's discretion.

Subjects in Study 165-302 were excluded for a creatinine >1.5 times the upper limit of normal. Renal function, urinalysis and microscopy, UACR, C-reactive protein, erythrocyte sedimentation rate, C3 and C4 were assessed at screening then at Weeks 1, 4, and 8. The protocol did not specify any renal events as adverse events of special interest.

Renal Findings

Exposure and Disposition

In total, 341 patients with PKU have received more than one dose of pegvaliase for a mean (standard deviation) exposure of 24 (19) months. Overall, 115 (33.7%) subjects prematurely discontinued treatment, most commonly because of an adverse event (47 [14%]), withdrawal by subject (35 [10%]), and physician decision (12 [3.5%]). The AEs most commonly leading to discontinuation or dose interruption were arthralgia (40 [12%]), urticaria (12 [4%]), and rash (10 [3%]).

Baseline Characteristics

The median age of study subjects was 27 years (16 to 56 years). The mean baseline serum creatinine was 0.8 mg/dL.

Renal Adverse Events

Increased Creatinine

Three (0.9%) subjects had a NCI CTCAE Grade 1 increased (“serum creatinine >1.5 – 1.5x baseline; >ULN to 1.5x ULN”; see appendix) AE of blood creatinine. Subject (b) (6) had a serum creatinine of 1.1 mg/dL at screening and a maximum serum creatinine of 1.2 mg/dL during the study. Subject (b) (6) had a baseline serum creatinine of 0.9 mg/dL and a maximum serum creatinine of 1.0 mg/dL during the study. Subject (b) (6) had a baseline serum creatinine of 1.0 mg/dL and a creatinine that varied between 0.8 mg/dL and 1.0 mg/dL during the study. All subjects continued study drug.

Proteinuria

A total of 24 (7%) subjects experienced 43 AEs related to proteinuria. None were SAEs. Only one subject discontinued study drug because of proteinuria:

Subject (b) (6) was a 19 year-old female with no history of kidney disease and a baseline UACR of 16 mg/g. During treatment, she had intermittent mildly elevated UACR values to a maximum of 175 mg/g on Day 148 (Table 1, Table 2). Around that time, she also reported an AE of urticaria. C3 and C4 were below baseline. No other events suggesting immune complex disease were reported. Study drug was withdrawn on December 19, 2013, and her UACR one day after cessation of pegvaliase was 19 mg/g. Her serum creatinine remained at her baseline. External nephrology consultants opined that the case was unlikely to be immune complex glomerulonephritis.

Table 1: Renal laboratory results for subject (b) (6) - Study 165-301

	UACR (mg/mg)	Urine Protein (Negative)	Serum Creatinine (0.2-1.2 mg/dL)	Urine RBCs (0-8 RBC/hpf)
Screening (13 Jun 2013)	0.016	Trace	0.6	Unknown
Week 8 (14 Aug 2013)	0.011	Negative	0.6	Unknown
Week 12 (13 Sep 2013)	0.042	Trace	0.6	Unknown
Unscheduled (19 Sep 2013)	0.007	Negative	ND	Unknown
Unscheduled (26 Sep 2013)	0.009	Trace	ND	Unknown
Study Completion (4 Nov 2013)	0.047	Negative	0.6	Unknown

Table 2: Renal laboratory results for subject (b) (6) - Study 165-302

	UACR (mg/mg)	Urine Protein (Negative)	Serum Creatinine (0.2-1.2 mg/dL)	Urine RBCs (0-8 RBC/hpf)
Part 1 Unscheduled (22 Nov 2013)	0.175	+1	ND	Unknown
Part 1 Week 3 (29 Nov 2013)	0.016	Negative	ND	Unknown
Part 1 Week 4 (9 Dec 2013)	0.022	Negative	ND	Unknown
Part 1 Unscheduled (16 Dec 2013)	0.085	Trace	ND	Unknown
Part 1 Unscheduled (20 Dec 2013)	0.019	Negative	0.6	Unknown
ETV (2 Jan 2014)	0.019	Trace	0.7	Unknown

Two subjects had concurrent AEs of proteinuria/albuminuria and hematuria:

Subject (b) (6) was a 34-year-old female with a history of vasculitis who experienced a Grade 1 AE of hematuria (“asymptomatic; clinical or diagnostic observations only; intervention not indicated”; see appendix) starting on Day 382 while on pegvaliase 40 mg/day. On Day 410, the subject experienced a Grade 1 AE of UACR increased (“1+ proteinuria; urinary protein <1g/24 hours”); see appendix with a UACR of 40 mg/g. There was no change in serum creatinine. The subject continued study drug, and the proteinuria resolved. The subject had intermittent hematuria on urinalysis during the study including at times when the UACR was in the normal range.

Subject (b) (6) was a 19-year-old male with no relevant past medical history and a baseline UACR of 11 mg/g who experienced a Grade 1 AE of proteinuria on Day 792 while on pegvaliase 60 mg/day. He had three urinalyses that were trace positive for protein but never had an elevated UACR. The subject subsequently was reported to have an AE of hematuria without RBCs on urinalysis. There was no change in serum creatinine. The subject continued study drug, and both events resolved.

Other Subject Narratives

The applicant provided narratives including tables of renal laboratory parameters for 33 subjects identified as having abnormal renal laboratory values (n=31) and/or AEs “of elevated creatinine or suggestive of potential renal impairment” (n=33). On review, no subject had a change in serum creatinine during the study that would suggest a clinically meaningful change in renal function. Many of the subjects flagged for abnormalities in urine parameters had trace to 1+ proteinuria on urinalysis in the absence of an increase in UACR or hematuria in the absence of proteinuria. Some subjects had a UACR that was intermittently only slightly above the cutoff for albuminuria of 30 mg/g; no subject showed a trend for worsening proteinuria during the study.

On February 9, 2018, DGIEP requested our assessment of the following narrative included in the 120-day safety update:

Subject (b) (6) was a 30-year-old male with a history of hematuria and proteinuria discovered incidentally on a routine physical examination in 2007. At the time, the subject was evaluated by a nephrologist who recommended renal biopsy, which the patient declined. Before pegvaliase dosing, the subject’s UACR was 726 mg/g, he had 10 RBCs/hpf on UA, and his serum creatinine was 1.1 mg/dL. He started study drug in (b) (6). In (b) (6) he started losartan for hypertension. He continued study drug until (b) (6) when he discontinued study drug for fertility planning. At that time, his UACR was 181 mg/g, and his serum creatinine was 1.3 mg/dL. In (b) (6) the subject saw a nephrologist to reevaluate his proteinuria and renal function. In (b) (6) he had normal serum C3 and C4 levels and a negative SPEP, UPEP, ANA, and ANCA. Urine microscopy did not show casts. In (b) (6), the subject underwent renal biopsy which is described in the narrative as follows:

“On light microscopy, it was noted that more than 50% of glomeruli showed mild mesangial hypercellularity. No glomeruli with segmental sclerosis, endocapillary hypercellularity, crescents, or necrosis were seen. There was minimal tubular atrophy and interstitial fibrosis involving less than 5% of the cortex sampled, and no significant interstitial inflammatory infiltrates were noted. Arterioles showed mild hyalinosis, and there was evidence of mild arteriosclerosis.

On immunofluorescent staining, there was 3+ granular global mesangial staining for IgA, with 1+ IgG, 1+ IgM, 3+ C3, trace kappa, and 3+ lambda. The glomeruli were negative for C1q, albumin,

and fibrinogen. A few intratubular casts were positive for IgA and stained equally with kappa and lambda.

On electron microscopy, four glomeruli were seen, none of which were globally sclerotic. There was some evidence of mild global mesangial hypercellularity. Abundant mesangial electron-dense immune complex-type deposits were seen. Glomerular peripheral capillaries were patent. Glomerular basement membranes were normal in thickness, texture, and contour. No immune deposits involving the peritubular capillary walls or endothelial tubuloreticular inclusions were seen. Podocytes displayed mild foot process effacement.”

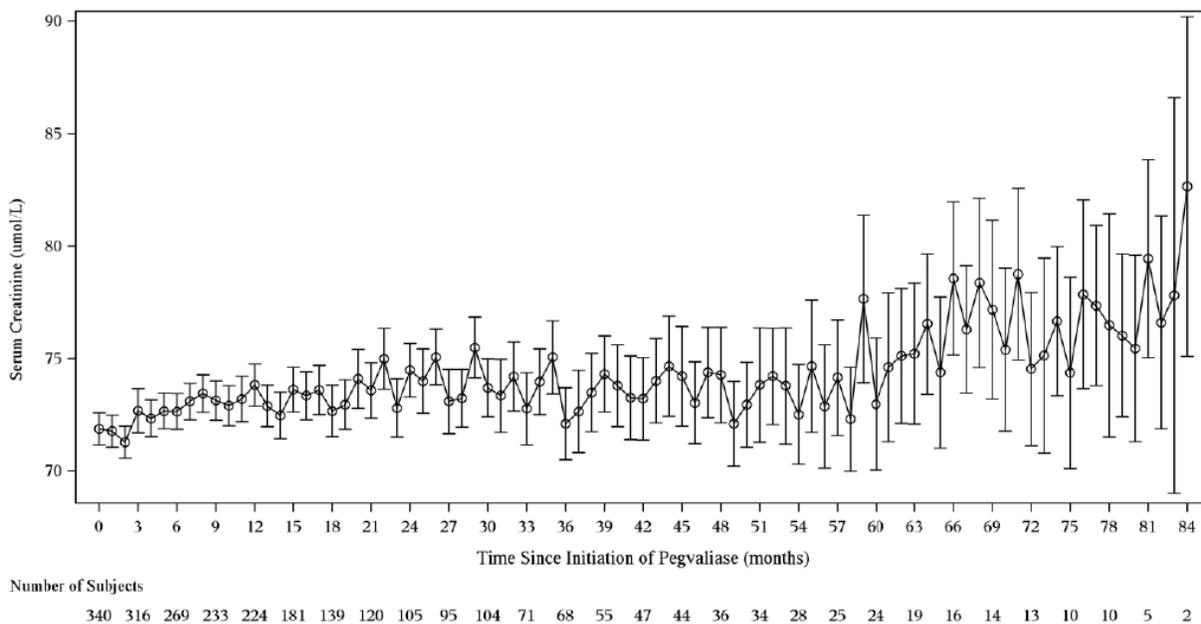
The nephrologist diagnosed the patient with IgA nephropathy. The subject's clinical case was further “discussed with a panel of academic nephrologists with experience in treating glomerular disease. They agreed with the diagnosis of IgA nephropathy and that this single diagnosis fully explains the subject's clinical findings and disease course. Their assessment was based on a history of long-standing hematuria and proteinuria predating the subject's participating in the pegvaliase program, the clinical and laboratory findings, and results of renal biopsy including electron microscopy findings demonstrating disease limited to the mesangial region. The experts agreed that none of the subject's history or clinical findings were consistent with pegvaliase involvement.”

Reviewer's comment: We agree that the subject's clinical course and biopsy findings are consistent with IgA nephropathy, and, given his history of proteinuria and hematuria since 2007, the diagnosis likely predated study drug administration.

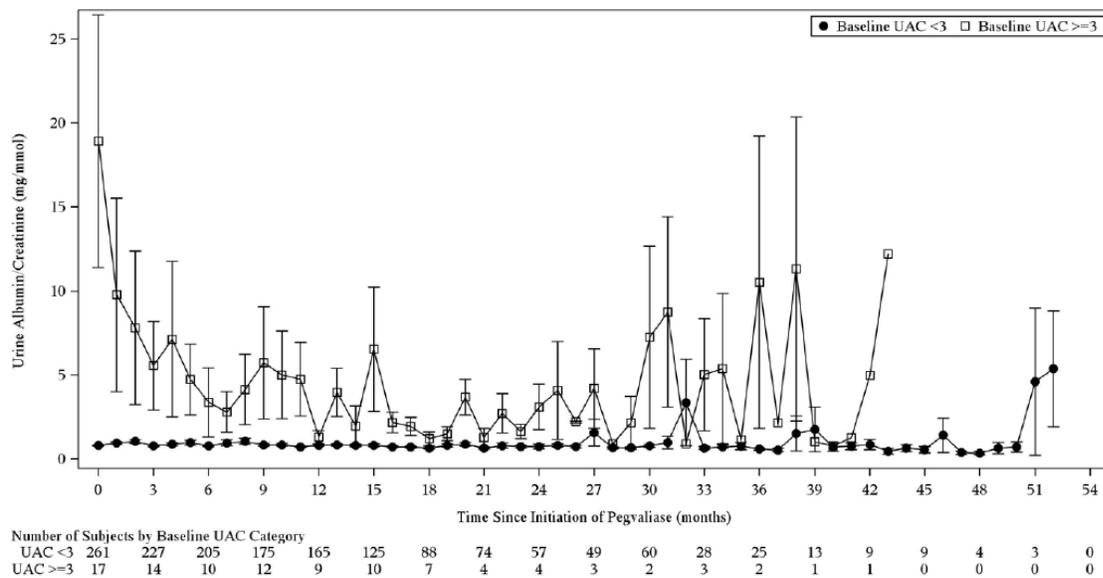
Changes in Laboratory Parameters

Mean serum creatinine and UACR over time is shown in Figures 1 and 2. The figures are difficult to interpret because very few patients are available at later time points; however, the data do not suggest an obvious safety signal.

Figure 1: Mean (SE) Serum Creatinine over Time (I/T/M Population)



Source: Applicant, Integrated Summary of Safety, Figure 2.7.4.7.1.4

Figure 2: Mean (SE) Urine Albumin/Creatinine Ratio Over Time (I/T/M population¹)

Source: Applicant, Integrated Summary of Safety, Figure 3.2.3.1.

¹Based on the Induction/Titration/Maintenance (I/T/M) population defined as all subjects dosed as per proposed for the label (n=285).

Consult Questions

1. Pegvaliase is a highly immunogenic drug with 93% of subjects having hypersensitivity. All subjects developed anti-PAL antibodies. IgG circulating immune complex (CIC) and IgM CIC were elevated and complement C3 and C4 were diminished in the majority of the subjects. We are concerned about immune complex deposition in the kidney and possible long-term kidney dysfunction. Also, pegvaliase is highly PEGylated and we are concerned about PEG deposition in renal tubules. Which biomarker(s) do you recommend for monitoring of early signs of renal toxicity as we design a postmarketing requirement (PMR)? What frequency of monitoring and trends/thresholds would be alarming as a general guideline?
2. There are 11 subjects (3.9%) (N=285, induction/titration/maintenance safety population) with UACR ≥ 3 mg/mmol on 3 or more consecutive measurements. There are 15 (4.4%) subjects in the multi-dose (MD, N=341) safety population (all subjects except for the phase 1 study) with this laboratory finding. There is only 1 (0.4%) subject in the I/T/M population and 2 subjects (0.6%) in the MD population with UACR ≥ 3 mg/mmol and hematuria (> 3 RBC/hpf or $> \text{ULN}$) on 3 or more consecutive measurements. Do you agree with a threshold of UACR ≥ 3 mg/mmol and also 3 or more consecutive measurements to identify potential renal toxicity? Although the majority of these laboratory elevations were present at baseline, were transient, or were noted in subjects with underlying risk factors for renal impairment (hypertension, diabetes, obesity), as proposed by the sponsor, do you think that these lab abnormalities could be due to early signs of immune complex glomerulonephritis or PEG deposition in the kidneys? What other laboratory analyses specific to renal function do you recommend?

DCRP Response: Your consult questions touch upon two major issues: whether there is evidence for renal toxicity based on the available data and how to design a post-marketing study to detect potential cases of renal toxicity.

We reviewed all the narratives for subjects flagged by the applicant as having abnormal renal laboratory values and/or AEs “of elevated creatinine or suggestive of potential renal impairment.” The narratives included tables of relevant renal laboratory parameters. Based on this review, we do not believe additional analyses of the renal function data are necessary. No subject exhibited a marked change in renal function or developed progressive or persistent proteinuria, and none of the narratives suggest an immune complex-mediated glomerulonephritis. One subject identified in the 120-day safety update was diagnosed with IgA nephropathy, but the diagnosis most likely pre-dated pegvaliase exposure given the subjects history of proteinuria and hematuria.

Some subjects had intermittent, small increases in UACR that may simply reflect normal laboratory variation or non-renal factors (e.g., vigorous exercise). Only one event resulted in discontinuation of study drug, and the subject’s UACR was normal the following day. Given the high frequency of anti-drug antibodies and circulating immune complexes, we cannot exclude the possibility that some of the findings on urinalysis relate to serum sickness, which can cause mild, transient proteinuria or hematuria and sometimes reversible elevations in serum creatinine. However, even if this were the case, other symptoms of serum sickness (e.g., fever, arthralgias, rash) would be expected to lead to discontinuation of the offending agent and resolution of the serum sickness, thereby limiting the potential for clinically significant renal toxicity.

Although PEG vacuoles were seen in the kidney in preclinical studies of pegvaliase, it does not appear that there were adverse renal findings on pathology or changes in clinical parameters in the animals to suggest nephrotoxicity. It is our understanding that similar vacuoles have been seen in preclinical and clinical studies of other PEGylated proteins without a clinical signal for acute or chronic nephrotoxicity to date. There is no signal for acute or chronic nephrotoxicity with pegvaliase based on the available clinical data. Although there is a theoretical risk of renal toxicity related to PEG accumulation, we do not have significant concerns at this time based on the collective experience with PEGylated proteins to date.

Although there is no signal for clinically significant renal toxicity with pegvaliase, we note that the clinical database with pegvaliase is relatively small and the mean exposure is 24 months. In addition, the population may not be at high risk for renal toxicity, should toxicity exist (i.e., subjects were relatively young with preserved renal function). It is possible that cases of immune complex-mediated glomerulonephritis will be seen in the post-marketing setting, but we believe this could be monitored through enhanced pharmacovigilance. If a post-marketing study will be required for other purposes and there is interest in using this study to further explore renal safety, we are happy to provide input on how to do so.

Appendix:**Table 3: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 Specifications**

Adverse Event	Grade				
	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	
Proteinuria	1+ proteinuria; urinary protein <1g/24 hrs	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs	urinary protein ≥3.5 g/24 hrs;	-	-
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death

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/s/

KIMBERLY A SMITH
02/28/2018

ALIZA M THOMPSON
02/28/2018

NORMAN L STOCKBRIDGE
02/28/2018

OFFICE OF DEVICE EVALUATIONDIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM****Device Constituent Review: CDER BLA761079 - CDRH ICC1700595**

Date	February 8, 2018
To	Oumou Barry
Requesting Division	OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
From	Rong Guo CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	John McMichael CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for BLA761079
Combination product	Palynziq Syringe
Recommendation	Approval

Digital Signature Concurrence Table

Reviewer	Rong Guo -S 2018.02.08 11:23:51 -05'00'
Team Lead	John C. Mcmichael -S 2018.02.08 11:31:55 -05'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.02.12 08:40:06 -05'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01322
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=1532
ICC tracking # (Lead)	ICC1700595
Submission Number	BLA761079
Sponsor	Biomarin Pharmaceutical Inc
Drug	Palynziq, Pegvaliase, BMN 165
Indications for Use	Indicated to reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels > 600 micromol/L on existing management
Device Constituent	Pre-filled syringe
Route of Administration	subcutaneous

Table 2. Important Dates	
Information Requests Sent	n/a
Review Checkpoints	Meeting / Due Date
Filing meeting	August 7, 2017
Progress meeting	November 6, 2017
Wrap up meeting	
Action Goal Date	May 28, 2018
Primary Review / Lead Device Review	

2. PURPOSE/BACKGROUND

2.1. Scope

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding BLA761079, Palynziq in pre-filled syringe. The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of Palynziq. This review did not cover manufacturing of the syringe nor human factors review.

This review covers the essential performance elements of the device under review:

- Dose accuracy
- Functional Performance
- Biocompatibility of non-primary closure components
- Sterility of the syringe

2.2. Background

Pegvaliase is a genetically modified phenylalanine ammonia lyase (rAvPAL) enzyme product derived from the cyanobacterium *Anabaena variabilis*. It is PEGylated [REDACTED] ^{(b) (4)}. Pegvaliase converts Phe to ammonia and transcinamic acid that are metabolized by the liver and excreted in the urine, respectively. It substitutes for the deficient PAH enzyme activity and reduces blood Phe levels in the body.

Pegvaliase DP is delivered to patients subcutaneously using a prefilled syringe (PFS) assembled with a needle safety device (NSD). Injections are given daily at home by the patient or their caregiver, or alternatively by a healthcare professional in a clinical environment.

Dosage (from Draft Prescribing Information in Module 1.14, submitted on October 4, 2017):

- Obtain a blood phenylalanine concentration before initiating treatment.
- The recommended starting dosage is 2.5 mg subcutaneously once per week for 4 weeks.
- Escalate the dosage in a step-wise manner based on tolerability to reach a target maintenance dosage of 20 mg subcutaneously once daily. See full prescribing information for titration regimen.
- If a minimum of 20% blood phenylalanine reduction is not achieved after 24 weeks, the dosage may be increased to 40 mg subcutaneously once daily.
- To maintain blood phenylalanine control, the dosage of Palynziq may be reduced and/or a modification of dietary phenylalanine intake may be required.
- Discontinue Palynziq if a minimum of a 20% reduction in blood phenylalanine concentration has not been achieved by (b) (4).

3. ADMINISTRATIVE
3.1. Documents Reviewed

Cross-Referenced 510(k) # or DMF		Letter of Authorization Included in NDA / BLA	
		YES	NO
(b) (4)	Syringe barrel	Yes	
	Plunger stopper	Yes	
	Plunger stopper	Yes	
	Plunger rod	Yes	
	Needle safety device	Yes	
(b) (4)		Yes	
		Yes	

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Palinziq drug-device combination product contains the following items assembled as one unit:

- Pegvaliase DP
- 1 mL glass syringe ((b) (4) Glass)
- Plunger: plunger rod (b) (4) threaded into the plunger stopper (b) (4)
- Pre-staked 26G needle (b) (4)
- Needle safety device (b) (4)
- Needle shield (b) (4)

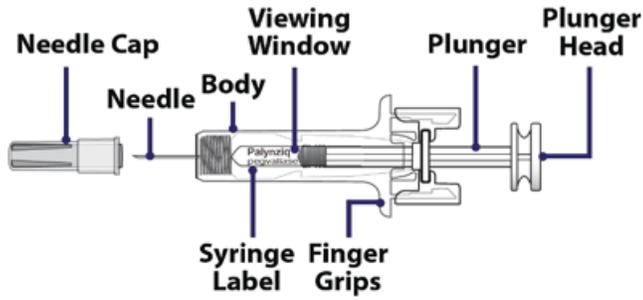


Table 3.2.P.7.1.1: Prefilled Syringe Components

Component Category	Component	Sub-Component Description	Materials of Construction	Manufacturer (b) (4)
Primary Container Components (Drug Product Contacting)	1 mL Glass Syringe (26G TW ½" 3 Bevels) and Rigid Needle Shield (RNS)	Glass Barrel ⁽¹⁾	[Redacted]	[Redacted]
		Needle ⁽²⁾		
		Rigid Needle Shield ⁽³⁾		
	Plunger Stopper	n/a		
Secondary Device Components (No Drug Product Contact)	Plunger Rod	n/a		
	Needle Safety Device	n/a		

(b) (4)

The syringe components (glass barrel, needle, (b) (4) and rigid needle shield) are assembled by the supplier, (b) (4) and delivered ready-to-fill (b) (4).

Palynziq will be supplied in three single-dose presentations:

- 2.5 mg dose (0.5 mL of 5 mg/mL pegvaliase)
- 10 mg dose (0.5 mL of 20 mg/mL pegvaliase)
- 20 mg dose (1.0 mL of 20 mg/mL pegvaliase)

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

The Sponsor states that the design input requirements are approached from a systems perspective since the syringe with staked needle, NSD, plunger-stopper, plunger rod, and rigid needle shield (RNS) are all off the shelf, non-custom materials. Detailed design input requirements are provided by the Sponsor and located at 3.2.P.7, titled DIR-165-001 Design Input Requirement, and UR-165-001 User Requirements Specification.

The design complies with the following regulations and guidances:

Document	Title
21 CFR 211.94	Drug Product Containers and Closures
21 CFR 610.60	Container Label
21 CFR 610.61	Package Label
21 CFR 820	Quality System Regulation
ISO 10993	Biological Evaluation of Medical Devices
ISO 11040-4	Prefilled syringes — Part 4: Glass barrels for Injectables
ISO 11608:2012 Part 1	Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems
ISO 13485	Quality Management System for Medical Devices

Document	Title
FDA Draft Guidance	Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, January 2015
FDA Draft Guidance	Draft Guidance for Industry and FDA Staff: Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4
FDA Guidance	Guidance for Industry and FDA Staff: Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Documentation (1999)
FDA Guidance	Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors for Use with Drugs and Biological Products (2013)
FDA Guidance	Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features (2005)
USP<1>	General Chapters, General Tests and Assays, General Requirements for Tests and Assays, Injections
DDP-165-001	Design and Development Plan BMN 165, Rev. 3
QAU-01-018	Quality Risk Management, Rev. 05
QAU-02-205	Design Controls Process, Rev. 02
UR-165-001	User Requirements BMN 165, Rev. 3

5.2. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present			Submission Location
	Yes	No	N/A	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	x			3.2.P.7 and 3.2.P.5
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x			3.2.P.7 and 3.2.P.2
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x			3.2. P.7
Validation Data			x	
<ul style="list-style-type: none"> • Human factors • Clinical data 	x			
Traceability Documentation		x		

Pegvaliase DP in (b) (4) glass vial with (b) (4) stopper was used in early clinical studies. During Phase 3 clinical studies, the container closure was changed from vial to the glass prefilled syringe with staked needle, which is the commercial presentation. Report TR-00682 located in Module 3.2.P.2 showed that the DP quality attributes for the two DP presentations (vial/stopper and PFS) are comparable based upon lot release, long term stability data, container-closure compatibility testing and additional characterization. This is deferred to CMC reviewer. All design verification and validation of the combination product are done with the to-be-marketed commercial presentation.

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Discipline Specific Design Verification / Validation*						
	Consult Needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		x			x	
Biocompatibility		x			x	
Sterility		x			x	
Software / Cybersecurity			x			
Electrical Safety / EMC			x			
Human Factors			x			

6.2. Design Verification Review

Essential Performance Requirement	Specification	Verification Test Results	
		PASS	FAIL
Break Force	(b) (4)	x	
Glide Force		x	
Fill Volume		x	
Expelled Volume		x	
Tip Cap Removal		x	
Sharps Injury Protection		x	
Biocompatibility per ISO 10993	Cytotoxicity	x	
	Irritation	x	
	Sensitization	x	
Stability and Simulated shipping/transportation Data adequately verifies device will meet essential performance requirements at expiry		x	
Sterility		x	

Dose Accuracy

Dose accuracy study is provided in Module 3.2.P.7, titled ISO 11608 testing report. The specific ISO 11608-1 dose accuracy tests performed in this study were: 1) Cool, standard, warm atmosphere testing, 2) Vibration testing, and 3) Freefall testing. Both 0.5 mL and 1 mL were tested.

Table 3.2.P.7.2.1.6.1: Summary of ISO 11608-1 Test Results

Test	Test Article (Lot Number)	Requirement	Sample Size	Result	Test Report
Dose Accuracy Cool Atmosphere Testing 5°C	2.5 mg PFS (004K13C)	Deliverable Volume ≥ 0.5 mL	20	Pass	ISO 11608-1 Testing Report
	20 mg PFS (003D14)	Deliverable Volume ≥ 1.0 mL	20	Pass	
Dose Accuracy Standard Atmosphere Testing 23°C/ 50%RH	2.5 mg PFS (004K13C)	Deliverable Volume ≥ 0.5 mL	20	Pass	
	20 mg PFS (003D14)	Deliverable Volume ≥ 1.0 mL	20	Pass	
Dose Accuracy Warm Atmosphere Testing 40°C/ 50%RH	2.5 mg PFS (004K13C)	Deliverable Volume ≥ 0.5 mL	20	Pass	
	20 mg PFS (003D14)	Deliverable Volume ≥ 1.0 mL	20	Pass	
Vibration Testing	2.5 mg PFS (004K13C)	Deliverable Volume ≥ 0.5 mL	20	Pass	
	20 mg PFS (003D14)	Deliverable Volume ≥ 1.0 mL	20	Pass	

Reviewer Comment: Per ISO 11608-1, for fixed-dose devices, the deviation can be up to 5% if the fixed dose is above 0.2 mL. Both volume 0.5 mL and 1 mL passed the acceptance criteria of ISO 11608-1 for cool, standard, and warm atmosphere testing as well as vibration Testing. Dose accuracy testing after freefall failed. The Sponsor states that the product labelling team has been notified of this risk and has updated the instructions for use (IFU) to advise the patient not to use the device if it has been dropped. The mitigation to this risk is appropriate for glass syringes. The provided dose accuracy verification is acceptable.

Break Loose Force and Gliding Force

Report TR-00326 Selection of PFS Components located in Module 3.2.P.7 includes studies conducted to minimize the force needed to inject pegvaliase PEG drug product formulations from a prefilled syringe (PFS) container closure system. Effect of needle length and internal diameter, viscosity, stopper type and geometry, PFS (b) (4) process, and temperature on glide force were studied. Glide force increases with increasing needle length, increasing viscosity, decreasing radius, decreasing temperature. No significant change in glide force was observed in PFS (b) (4) (b) (4).

Glide force result from pegvaliase PEG (Lot # P16172-12002, 20mg/1mL, (b) (4)) filled in an (b) (4) PFS (b) (4) :

Table 6.5.2: The viscosity and glide force of rAvPAL PEG at different temperatures

(b) (4)



The specification for injection force is (b) (4) and glide force is (b) (4)

Reviewer Comment: The provided specifications for injection force and glide force are appropriate. The essential performance testing of injection force and glide force is acceptable.

Sharps Injury Protection

The BioMarin BMN 165 prefilled syringe has a sharps injury prevention feature: The needle safety device (NSD) fully covers the needle after injection of the full dose and release of the plunger. Reliability of the sharps injury prevention mechanism was studied in CSR-165-011 Sharps Injury Prevention Study Report located under 3.2.P.7, per FDA Guidance Medical Devices with Sharps Injury Prevention Features (dated August 9, 2005).

Table 3.2.P.7.2.1.8.1.1: Sharps Injury Prevention Test Results

Test Method	Requirement	Test Article (Lot Number)	Sample Size (accept/reject criteria)	Result
Twenty (20) participants each perform thirty (30) unaided injections	NSD fully activated and locked out	20 mg PFS (ENG15047A)	600 (1/2)	Pass

Reviewer Comment: Simulated clinical use testing were provided and complies with the sharps injury prevention Guidance. The sharps injury protection is appropriate and acceptable.

Biocompatibility

Biocompatibility of the user contacts of the combination product is covered in this review. Assessment of the fluid path (the syringe barrel, the plunger stopper and the needle) is the scope of the CMC discipline and is not covered in this review memo as those are part of the container closure system.

The components that the user contacts consist of the following:

- 1) Needle Safety Device
- 2) (b) (4) Rigid Needle Shield (outer plastic shield)
- 3) Plunger Rods

(b) (4)

Per FDA Guidance Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process", for "Nature of Body Contact", the components listed above contact intact skin only and therefore fall under the classification "Surface Device, Intact Skin" with prolonged contact duration (>24h to 30d) determined by cumulative exposure over user's lifetime according to the following calculation: (30 seconds/injection x 2 injections/day (typical case: 40mg) x 365 days/year x 50 years) / (86,400 seconds/day) = 13 days. Cytotoxicity, sensitization and irritation testing are required.

All biocompatibility information is provided in report DVSR-165-001 Biocompatibility Report under 3.2.P.7. MEM elution test per 10993-5 In-Vitro Cytotoxicity, sensitization Guinea pig maximization per 10993-10 Tests for Irritation and Delayed-type Hypersensitivity, and intracutaneous toxicity per 10993-10 were performed at (b) (4). These tests were executed on water-filled syringes that were assembled from the same components and undergo the same sterilization, filling and assembly procedures as commercial products. All testing passed the acceptance criteria (b) (4) has also provided a written statement that biocompatibility studies have been performed for the needle safety device and plunger rods in compliance with ISO 10993-1:2009 standard for Skin Surface, Limited Contact Duration.

Reviewer Comment: The provided biocompatibility testing is appropriate and acceptable for the intended use of the user contacting of the combination product.

Sterility

The primary container components are delivered pre-sterilized and are subsequently processed (b) (4). Sterilization of the ready-to-fill syringes is conducted by the component manufacturer (b) (4) (b) (4) in accordance with ISO 11135-1:2007. Reference is made in Module 1, Section 1.4.2 to LoA (b) (4) DMF (b) (4) for information on the sterilization process and validation.



Sterilization of the plunger stoppers is conducted by the component manufacturer (b) (4). Reference is made in Module 1, Section 1.4.2 to LoA (b) (4) DMF (b) (4) and LoA (b) (4) DMF (b) (4) (b) (4) for details on the sterilization validation.

Reviewer Comment: Packaging and sterilization of (b) (4) rubber plunger stoppers (b) (4) was reviewed for NDAs 208223 and 204824 and found adequate. See review memo uploaded by David Bateman on 10/16/2015, by Erika Pfeiler on 03/18/2013, to DMF (b) (4) in DARRTS. (b) (4) was reviewed for BLA 761037 and found adequate. See review memo uploaded by Lakshmi Rani Narasimhan on 08/30/2016 to DMF (b) (4) in DARRTS.

Stability and Shelf Life

The performance stability study demonstrates that the pegvaliase DP combination product maintains its functional performance over a simulated shelf-life of 24 months per ASTM F1980. The incubation time (b) (4) simulates 23 months at 2-8 °C, plus 1 month at ambient temperature.

Table 3.2.P.7.2.1.5.1: Functional Stability Test Results

Test	Test Method	Test Article (Lot Number)	Requirement	Sample Size (accept/reject criteria)	Test Result		
					Incubation Time at 25 °C (months)		
					0	3	6.75
Container Closure Integrity	Vacuum Decay	2.5 mg PFS (ENG15045A)	No leaks	119 (0/1)	Pass	Pass	Pass
		20 mg PFS (ENG15047A)	No leaks	119 (0/1)	Pass	Pass	Pass
Rigid Needle Shield Removal Force	Tensile Test	2.5 mg PFS (ENG15045A)	Force = (b) (4)	29 (0/1)	Pass	Pass	Pass
		20 mg PFS (ENG15047A)	Force = (b) (4)	29 (0/1)	Pass	Pass	Pass
Injection Force ⁽¹⁾	Compression Test	2.5 mg PFS (ENG15045A)	Max Glide Force (b) (4)	119 (3/4) ⁽²⁾	Pass	Pass	Pass
		20 mg PFS (ENG15047A)	Max Glide Force (b) (4)	119 (3/4) ⁽²⁾	Pass	Pass	Pass
Activation of NSD	Compression Test	2.5 mg PFS (ENG15045A)	The NSD activates upon completion of injection	119 (0/1)	Pass	Pass	Pass
		20 mg PFS (ENG15047A)	The NSD activates upon completion of injection	119 (0/1)	Pass	Pass	Pass
NSD Override Force ⁽³⁾	Compression Test	2.5 mg PFS (ENG15045A)	Force (b) (4)	119 (0/1)	Pass	Pass	Pass
		20 mg PFS (ENG15047A)	Force (b) (4)	119 (0/1)	Pass	Pass	Pass
Injectable Volume	USP <1>	2.5 mg PFS (ENG15045A)	0.5mL (b) (4)	5 (0/1)	Pass	Pass	Pass
		10 mg PFS (ENG15046A)	0.5mL (b) (4)	5 (0/1)	Pass	Pass	Pass
		20 mg PFS (ENG15047A)	1.0mL (b) (4)	5 (0/1)	Pass	Pass	Pass

(b) (4)

Reviewer Comment: Device functionality is not changed after 6.75 month accelerated aging, including the essential performance requirement, such as activation force, glide force and injectable volume. The aging stability data supports the 24 months shelf life for the combination product.

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		

7.2. Summary of Risk Analysis

Risk analysis for the pegvaliase DP combination product is provided by the Sponsor under 3.2.P.7 titled RMR-165-001 Risk Management Report. The Risk Management Plan (RMP-165-001) included requirements to perform a Hazard Analysis, application FMEA (aFMEA), design FMEA (dFMEA), and process FMEA (pFMEA). Based on a comprehensive assessment of risks and systematic implementation of mitigations/controls, the overall residual risks to patient safety and product quality associated with the BMN 165 Prefilled Syringe with NSD are acceptable. No further mitigations are required at this time. The remaining residual risks from the aFMEA, dFMEA, and pFMEAs were examined and a risk-benefit analysis was included in the report. The remaining residual risks do not outweigh the clinical benefit of the BMN 165 therapy.

ICC1700595
BLA761079
Biomarin, Palinziq

Reviewer Comment: *The pegvaliase DP pre-filled syringe device risks have been managed to the point where it is appropriate for moving forward into commercial supply. The sponsor has identified that the remaining residual risks do not outweigh the clinical benefit of the BMN 165 therapy after mitigation steps from the device point of view.*

8. LABELING

(b) (4)



9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

Table 3.2.P.5.1.1: Analytical Specifications for Pegvaliase Drug Product (Unassembled Syringe)

Attribute	Test Parameter	Method	Acceptance Criteria		
			2.5 mg	10 mg	20 mg
Safety	Bacterial Endotoxin	Kinetic, Chromogenic LAL USP<85>, Ph. Eur. 2.6.14		(b) (4) EU/mL	
	Sterility	(b) (4) USP<71>, Ph. Eur. 2.6.1		No growth	
Identity	Dot Blot	Immunoblot	Positive identity by color development		
Strength	Protein Concentration	(b) (4)	(b) (4)		
Quality	Appearance	Visual Assessment	Colorless to pale yellow, clear to slightly opalescent		
	Particulate Analysis	USP<788>, Ph. Eur. 2.9.19	(b) (4) particles / syringe	(b) (4) μm	
			(b) (4) particles / syringe	(b) (4) μm	
	Injectable Volume	USP<1>, Ph. Eur. 2.9.17	(b) (4)		
Extent of PEGylation	(b) (4)	Release: (b) (4) mol PEG/mol rAvPAL	End of Shelf-life: (b) (4) mol PEG/mol rAvPAL		

Table 3.2.P.5.1.2: Analytical Specifications for Pegvaliase Drug Product (Assembled Syringe)

Attribute	Test Parameter	Method	Acceptance Criteria		
			2.5 mg	10 mg	20 mg
Safety	Rigid Needle Shield Removal Force	Material Testing	(b) (4)	measurement speed of	(b) (4)
	Needle Safety Device Override	Material Testing	(b) (4)	measurement speed of	(b) (4)
Quality	Appearance	Visual Assessment	Prefilled Syringe is free from defects		
	Injectability	Material Testing	Max glide force: (b) (4) Average glide force (b) (4)		

USP: United States Pharmacopeia; Ph. Eur.: European Pharmacopeia.

Reviewer Comment: *The lot release specifications include the device essential performance requirement. The proposed lot release for the drug product is appropriate and acceptable from device point of view.*

10. INTERACTIVE REVIEW

No device related information request was conveyed.

11. RECOMMENDATION

CDRH recommends approval based on review of the device constituent of the combination product. Review of this information found that there are sufficient verification activities for the safety and functionality of the device constituent part of the combination product to recommend approval.

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/s/

RONG GUO
02/12/2018

Clinical Inspection Summary

Date	February 9, 2018
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Irena Lavine, M.D., Medical Officer, DGIEP
BLA #	761079
Applicant	Biomarin Pharmaceutical, Inc.
Drug	Pegvaliase
NME (Yes/No)	Yes
Therapeutic Classification	Therapeutic Inborn Errors
Proposed Indication	To reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels > 600 micro mol/L on existing management
Consultation Request Date	August 29, 2017
Summary Goal Date	February 21, 2018
Action Goal Date	May 25, 2018
PDUFA Date	May 28, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this BLA consisted of inspections of three clinical investigator (CI) sites and the sponsor BioMarin Pharmaceutical, Inc. The data generated by these sites and the sponsor is acceptable in support of the application.

Two of the clinical sites and the sponsor have the classification or preliminary classification of No Action Indicated (NAI). One of the clinical sites had the preliminary classification of Voluntary Action Indicated (VAI). No significant regulatory findings or data integrity issues were noted. A pregnancy and spontaneous abortion occurred in Subject (b) (6). This occurred in July 2017, after the cut-off for the safety reporting period so it was not contained in the latest report. This was discussed with the medical officer on February 7, 2018.

II. BACKGROUND

The sponsor submitted this BLA for a replacement enzyme (pegvaliase-BMN 165) for the indication of reduction of blood phenylalanine levels in adult patients with Phenylketonuria (PKU) who have uncontrolled blood phenylalanine (Phe) levels > 600 µmol/L on existing

management. Phenylketonuria (PKU; OMIM 261600) is a rare autosomal recessive disorder characterized by a deficiency in the phenylalanine hydroxylase (PAH; EC 1.14.16.1) enzyme necessary for the conversion of the amino acid Phe to tyrosine (Tyr).

Biologic: Pegvaliase aka BMN 165

Study– Protocol number and title for all studies that were inspected

1. Protocol No. 165-301, entitled “A Phase 3, Open-Label, Randomized, Multi-Center Study to Assess the Safety and Tolerability of an Induction, Titration, and Maintenance Dose Regimen of BMN 165 Self-Administered by Adults with Phenylketonuria Not Previously Treated with BMN 165”

Number of subjects: 261 subjects

Number of sites: 31 sites

Number of countries where subjects were enrolled: U.S. only

Dates that study was conducted: May 2013 to November 2015

Efficacy endpoint: Change from baseline to end of the study in Blood phenylalanine

2. Protocol No. 165-302, entitled “A Four-Part, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Four-Arm, Discontinuation Study to Evaluate the Efficacy and Safety of Subcutaneous Injections of BMN 165 Self-Administered by Adults with Phenylketonuria”

Number of subjects: 215 subjects given test article, 95 subjects randomized

Number of sites: 29 sites

Number of countries where subjects were enrolled: U.S. only

Dates that study was conducted: July 2013 to September 2016

Efficacy endpoint: Change from baseline to end of the study in Blood phenylalanine

III. RESULTS (by site):

Name and type of inspected entity/Address	Site #/Protocol # / # of Subjects	Inspection Dates	Classification
CI: Harvey Levy, M.D. Boston Children's Hospital 1 Autumn Street, 526 Boston, MA 02115	Site 0123/ Study 165-301 30 subjects Study 165-302 21 subjects	October 19 to 27, 2017	NAI
CI: Janet Thomas, M.D. Children's Hospital Colorado 13123 East 16th Avenue, B198 Aurora, CO 80045	Site 0164/ Study 165-301 13 subjects Study 165-302 18 subjects	October 30 to November 27, 2017	*VAI
CI: Steven Amato, M.D. University of Kentucky Medical Center 740 South Limestone Street Kentucky Clinic J420 Lexington, KY 40536	Site 1090 Study 165-301 17 subjects Study 165-302 15 subjects	December 14, 2017 to January 12, 2018	*NAI
Sponsor: BioMarin Pharmaceutical, Inc. 105 Digital Drive, Novato, CA 94949	Study 165-301 Study 165-302	December 4 to 7, 2017	*NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Harvey Levy, M.D.
Boston Children's Hospital, 1 Autumn Street, Boston, MA 02115

At this site, 30 subjects were enrolled for Protocol 165-301, 29 subjects were randomized and completed the study. For Protocol 165-302, there were 21 subjects enrolled, 20 of them continuing from Protocol 165-301. There was also a transfer from Site 152, not included in the chart above. A total of 31 of the records from the two trials were reviewed, focusing on protocol adherence, specifically

appropriateness of the eligibility for each of the parts of Protocols 165-301 and 165-302 and reporting of adverse events related to allergy. As noted in the study report, there was a large number of adverse events (AEs) reported. Review of study conduct noted that the clinical investigator was very involved in the study. In detailed review of the charts, only two instances of unreported AEs were noted. Dietary source documents were compared to the line listings and no discrepancies were noted. No significant deviations or discrepancies were noted, and no Form 483 was issued.

The studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. Janet Thomas, M.D.
Children's Hospital Colorado, Aurora, CO 80045

Note: Observations below for this clinical investigator (CI) inspection are based on review of the Form FDA 483, the CI response of December 14, 2017, and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

At this site, for Protocol 165-301, a total of 15 subjects were screened at the site, 13 subjects enrolled in the study and 12 subjects completed the study. For Protocol 165-302, a total of 18 subjects were screened and enrolled in the study and 11 subjects are continuing in the study. Seven subject records were reviewed for each of the studies.

A Form FDA 483 was issued for the following violations:

1. An investigation was not conducted in accordance with the signed statement of the investigator. Specifically:
 - a. The following items were not documented for eligibility for enrollment:
 - i. No documentation whether Subject (b) (6) continued on her anti-anxiety medications on enrollment from Study 301 to Study 302 (eligibility required stable doses of medication).
 - ii. Subject (b) (6) was not maintained on a stable medical food protein regime at the time of randomization into Study 301 as required by Section 9.6 of the protocol.
 - iii. It was not documented that Subject (b) (6) was willing to use contraception during the study.
 - b. Protein and Phe diets were not printed out. Thus, the dietary history could not be verified because the site failed to always print the analyses from Food Processor and /or Metabolic Pro software.
 - c. Self-administration of test article for Subject (b) (6) was not adequately documented.

Reviewer comment: The CI responded with a corrective action plan including having the CI clarify protocol requirements when they are not clear to her and having CI and study coordinator work more closely in checking the data entry in the case report

forms. The violations cited above are sporadic, not systemic, and do not impact data quality. Although not mentioned on the Form FDA 483, but discussed in the EIR, contraceptive use discussion was not documented for Subject (b) (6). This subject became pregnant. According to the EIR, "the subject was noted to have a positive urine test during the visit completed on (b) (6) (Study 165-302; Part 4, Week 137). The subject was notified to withhold study drug the same day. The site was notified on July 25, 2017 that a sonogram confirmed the fetus had no pulse. On August 28, 2017, the subject notified the site of the miscarriage and D&C procedure performed (b) (6). The event was reported to the IRB as a Serious Adverse Event". The medical reviewer was notified of this event which had occurred after the data of the Safety Update which was from Sept 24, 2016 to May 6, 2017.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. This observation contains a listing of 13 unreported adverse events, 7 of which would be considered allergic reactions. Other events include stomach and back pain, nausea and vomiting, and two instances of sore throat.

Reviewer comment: The unreported adverse events are not serious and most of these occurred early in the trial. The CI responded to this by promising a corrective action plan with increased training and communication amongst study staff.

3. The informed consent document lacked a description of the reasonably foreseeable risks or discomforts to the subject. Specifically, the IRB approved consent (approved 12/03/2013) for Subject (b) (6) signed on 12/16/2013, and her legally authorized representative on 12/16/2013 reflecting changes for Protocol 165-301 Amendment 1 (dated 10/18/2013) failed to include any statement regarding risks for the tyrosine supplements (500 mg) required to be administered to all subjects 3 times per day. The modified consent approved by the IRB on 6/6/2014 also did not contain this information. The modified consent was signed by the subject on 6/16/2014 and her legally authorized representatives on 06/16/2014 and 6/22/2014.

Reviewer comment: The CI acknowledged that this omission was because the site used a locally generated assent form instead of the sponsor's form.

The CI responded adequately to the violations cited on the Form FDA 483. The studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

4. Steven Amato, M.D.
University of Kentucky Medical Center, Lexington, KY 40536

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final (EIR).

At this site, for Protocol 165-301, a total of 19 subjects were screened at the site, 17 subjects enrolled in the study and 15 subjects completed the study. For Protocol 165-302, a total of 15 subjects were screened and enrolled in the study and 13 subjects are continuing in the study. All subject records were reviewed. The data in the line listings was compared with the source documents. There were isolated instances of failure to report concomitant medications (ACTH, “Kroger allergy capsules”, Benadryl) and some transcription errors in the diet summaries. No significant deviations or discrepancies were noted and no Form 483 was issued.

The studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

5. BioMarin Pharmaceutical, Inc.
105 Digital Drive, Novato, CA 94949

Note: Observations below for this sponsor inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocols 165-301 and 165-302 including selection and oversight of contract research organizations (CROs), monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites above, and handling of adverse events and other sponsor/monitor related activities. Review of the sponsor documents did not note any significant deficiencies. The sponsor had issues with the original monitoring contractor so they switched to another CRO for monitoring. No issues were noted with the new CRO.

The studies appear to have been conducted adequately and the data generated by this sponsor may be used in support of the respective indication.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
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/s/

SUSAN LEIBENHAUT
02/09/2018

SUSAN D THOMPSON
02/09/2018

KASSA AYALEW
02/09/2018

DATE: 2/6/2018

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: BLA 761079

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

The conduct dates of the previously inspected study overlap with the current studies, and because OSIS inspected the site two months ago, an inspection is not needed at this time. OSIS requests the review division consider the impact of the prior inspectional findings on the current data for the following:

1. The assay's accuracy and precision based on the use of appropriate QC samples.
2. Parallelism if surrogate matrices were used for QC samples and calibration standards.
3. Cross-reactivity between the calibration and internal standards.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/s/

SHILA S NKAH
02/06/2018