

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761079Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



IND 076269

MEETING MINUTES

BioMarin Pharmaceutical Inc.
Attention: Laurel Konkol
Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Konkol:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMN 165 (pegvaliase).

We also refer to the meeting between representatives of your firm and the FDA on December 12, 2016. The purpose of the meeting was to discuss BioMarin's plan to submit a Biologics License Application (BLA) for pegvaliase (BMN 165), indicated for patients aged 18 years and older with phenylketonuria (PKU).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Jenny Doan, BSN, MSN, PMP
Division of Gastroenterology and Inborn Errors
Products Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: December 12, 2016 from 2:00 to 3:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 076269
Product Name: BMN 165 (pegvaliase)
Indication: treatment of severe phenylketonuria
Sponsor/Applicant Name: BioMarin Pharmaceutical Inc

Meeting Chair: Laurie Muldowney, MD
Meeting Recorder: Jenny Doan, RPM

FDA ATTENDEES:

Office of New Drug/Office of Drug Evaluation III (ODEIII)

Julie Beitz, MD, Director
Amy Egan, MD, Associate Director

Division of Gastroenterology and Inborn Errors Products

Dragos Roman, MD, Associate Division Director
Laurie Muldowney, MD, Medical Team Leader
Patroula Smpokou, MD, Medical Reviewer
Kevin Bugin, MS, RAC, Chief, Project Management Staff
Jenny Doan, BSN, MSN, PMP, Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Pharmacology III

Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader
Christine Hon, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics

Yeh-Fong Chen, PhD, Biostatistics Team Leader

Office of Biotechnology Products/Division of Biotechnology Review and Research III

Amy Rosenberg, MD, Director

Office of Biotechnology Products/Division of Biotechnology Review and Research IV

Joslyn Brunelle, PhD, Quality Team Leader

Frederick Mills, PhD, Biologist
Andrea Franco, PhD, Quality Reviewer

Center for Devices and Radiological Health/Office of Device Evaluation
Janice Ferguson, Reviewer

Clinical Outcome Assessments Staff
Nikunj Patel, PharmD, Reviewer

Division of Neurology Products
Teresa Buracchio, MD, Reviewer
Nicholas Kozauer, MD, Team Leader

Office of Surveillance and Epidemiology
Jamie Wilkins Parker, Division of Risk Management Team Leader
Matt Barlow, Division of Medication Error Prevention and Analysis Primary Reviewer
Kim Swank, Division of Pharmacovigilance Reviewer
Ling Y (Eileen) Wu, Division of Pharmacovigilance Team Leader
Kira Leishear, Division of Epidemiology Reviewer

Rare Diseases Program
Larry Bauer

Sponsor Attendees:

Robert Baffi, PhD, Executive Vice President, Technical Operations
Sianna Castillo, PhD, Associate Director, Regulatory Affairs CMC
Clapton Dias, BPharm, PhD, Senior Director, Clinical Pharmacology
Henry Fuchs, MD, President, Worldwide R&D
Brad Glasscock, PharmD, Vice President, Regulatory Affairs
Cary Harding, MD, Professor, Oregon Health and Science University, Department of
Molecular and Medical Genetics, Department of Pediatrics, Division of Metabolism
(Chair of pegvaliase Clinical Steering Committee/study investigator)
Chito Hernandez, PhD, Vice President, Biometrics
Mimi Lin, Director, Pharmacovigilance
Alison McGregor, PhD, Director, Regulatory Affairs
Stuart McMillan, Executive Director, Regulatory Affairs
Markus Merilainen, MD, Medical Director, Clinical Sciences
Geoffrey Nichol, BMedSc, MB, ChB, Vice President, Clinical Sciences
James Nickas, Pharm.D, Vice President, Pharmacovigilance
Sarah Noonberg, MD, PhD, Group Vice President, Head of Global Clinical Development

Charles O'Neill, Ph.D, DABT, Vice President, Pharmacological Sciences

Becky Schweighardt, PhD, Senior Director, Immunogenicity Assessment

Camilla Simpson, MSc, Group Vice President, Head of Global Regulatory Affairs

Xinqun Yang, PhD, Director, Biostatistics

Holly Weng, MD, MHS, Executive Medical Director, Clinical Sciences

(b) (4) (consultant)

1.0 BACKGROUND

On September 14, 2016, the Sponsor (BioMarin) submitted a meeting request to discuss BioMarin's plan to submit a Biologics License Application (BLA) for pegvaliase (BMN 165), indicated for patients aged 18 years and older with phenylketonuria (PKU). The meeting was granted and scheduled to take place on December 12, 2016. The preliminary comments were sent to BioMarin on December 9, 2016. The meeting took place as scheduled.

2.0 DISCUSSION

Non-clinical Pharmacology and Toxicology

Question 1:

Does the Agency agree that the proposed non-clinical data package will provide an adequate basis for submission of a BLA for pegvaliase in the proposed adult indication?

FDA Response:

Yes, we agree that the nonclinical program (i.e. completed studies, ongoing studies, and a carcinogenicity risk assessment) will be adequate to support the BLA submission.

Meeting Discussion:

No further discussion required.

Clinical Development

Question 2:

Does the Agency agree that the proposed clinical data package:

2a. Will provide an adequate basis for submission of a BLA for pegvaliase in the proposed adult indication?

FDA Response:

We agree that the proposed clinical data package appears to provide an adequate basis for BLA submission for pegvaliase in the adult PKU population. However, please clarify the number of patients with immunogenicity data (i.e. C3, C4, immunoglobulins, CIC data, including duration of exposure) to be included at BLA submission. The appropriate indication for the studied population will be determined after BLA data review. We remind

you that IgM-CIC and IgG-CIC assay validation data and clinical data from all phase 3 patients (not only from a subset of those, as previously proposed) should be submitted with the BLA (as discussed at teleconference on 11/22/2016-refer to meeting minutes).

Meeting Discussion:

See slide 5 & 6 of Sponsor's presentation. The Sponsor provided an outline of the total number of patients with immunogenicity data to be included in the BLA and Day-120 Safety Update. FDA stated that while the proposal appeared reasonable; the outline did not provide the number of patients treated with the prefilled syringe (PFS). The Sponsor should include a justification for the appropriateness of the dataset to be included in the initial BLA submission. The immunogenicity dataset to be submitted in the BLA should include an adequate number of patients treated with the PFS, either alone or predominantly with PFS drug formulation, the intended commercial drug product, in order to provide sufficient information regarding the risk for immunogenicity and IC- related safety issues in the patient population.

2b. Is supportive of BioMarin's proposed pathway supporting full approval?

FDA Response:

No, we cannot agree at this time. Based on your summary description in the background package, it does not appear that a significant neurocognitive benefit was demonstrated, in addition to phenylalanine (Phe) reduction, during your pivotal trial to support the regular approval pathway for your product in the adult PKU population. However, if you are able to provide new data and scientific evidence in your BLA linking blood Phe reduction to clinically meaningful effect(s) on specific disease aspects in adults with PKU, then a regular approval pathway may be possible.

In addition, we remind you that, in order to be considered for the accelerated approval pathway (21CFR 601, subpart E), adequate scientific evidence should be provided in your BLA that PKU in adult patients satisfies the regulatory criterion for a serious condition, that your product would provide a meaningful advantage over available therapies (i.e. Phe-restricted diet, Kuvan), and that blood Phe reduction represents a surrogate endpoint that is reasonably likely to predict clinical benefit in adult PKU patients. In addition, we remind you that for drugs granted accelerated approval, postmarketing confirmatory trial(s) are required in order to verify and describe the clinical benefit. We refer you to "FDA Guidance for Industry: Expedited Programs for Serious Conditions– Drugs and Biologics" for further details:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

Meeting Discussion:

See slide 7-10 of Sponsor's presentation. Based on the data available FDA does not agree that the full approval pathway is appropriate at this time. As such, the Sponsor should focus on the possibility of using the accelerated approval pathway with the need for a confirmatory trial as noted in the response above. The additional post-hoc, exploratory analysis of potential correlation between Phe reduction and improvement in the ADHD-RS (inattention domain)

score was presented during the meeting, and while encouraging it was not compelling due to significant limitations (e.g. open label trial design, 1-month recall period for ADHD-RS for a scale assessing inattention in a cognitively- or psychiatrically-impaired patient population, weak correlation between Phe level and ADHD-RS inattention domain score based on the presented analysis). FDA reiterated that the Sponsor should refer to the FDA guidance discussing accelerated approval, as indicated in FDA's response above, for further details of the specific requirements that need to be met for a drug to be considered for the accelerated approval pathway.

Post-Meeting Comment:

We refer you to the meeting minutes (September 30, 2014) for concerns regarding ADHD-RS inattention scale in the PKU patient population. Additionally, ADHD-RS scale was developed to assess inattention related to ADHD; as such, you will likely need PKU patient input to inform that ADHD-RS is a fit-for-purpose, well-defined and reliable instrument to assess inattention in PKU patients.

(b) (4)

Question 4:

Does the Agency agree that the proposed drug product presentation (pre-filled syringe) is acceptable for licensure?

FDA Response:

No, we cannot agree at this time that the proposed to-be-marketed presentation (pre-filled syringe, PFS) is acceptable for licensure. A determination about the acceptability of the PFS presentation will be made after the review of the analytical and pharmacokinetic (PK) comparability between the vial-and-syringe (VS) presentation and the PFS presentation, as well as efficacy and safety data supporting the use of PFS drug product provided in your upcoming BLA submission.

We note that you switched from the VS presentation to the PFS presentation during the pegvaliase clinical development program. The VS presentation was used in the phase 1 and phase 2 studies, whereas VS and PFS presentations were both used in your phase 3 studies.

You have concluded that pegvaliase PK was not comparable between the VS presentation and the PFS presentation based on results from your study 165-302 Part 3, which showed that PK exposure was 64% - 68% higher in the PFS presentation than in the VS presentation. Despite the lack of PK comparability, you are proposing the PFS presentation as the to-be-marketed product. Therefore, you need to comprehensively evaluate the pharmacodynamics, efficacy, and safety of the PFS presentation in your clinical studies and provide adequate data to support commercialization of the PFS drug product.

We note that the PFS presentation was used mostly in Part 4 of Study 165-302, but subjects in Part 4 received various pegvaliase dosages ranging from 10 mg/day to 60 mg/kg. Therefore, in the recommended comprehensive evaluation, you need to clearly present data taking into consideration the dosage used and the duration of drug exposure at different dosages in Part 4. Provide in the BLA all analysis datasets for the immunogenicity and safety assessments when using the PFS.

To facilitate our evaluation of the clinical data related to the use of the PFS presentation, we have the following comments:

For Both Phase 3 Studies

1. We note that Table 8.7.6.1 summarizes the number of subjects exposed to pegvaliase by drug product presentation based on the cumulative exposure across phase 3 studies. In addition to the data presented in Table 8.7.6.1, we request that you summarize the number of subjects who received continuous pegvaliase exposure at the same dose category for ≥ 6 months, ≥ 1 year, and ≥ 2 years by drug product presentation (PFS, VS, and combined) across phase 3 studies as outlined in Table 1 below.

Table 1. Number of Subjects Continuously Exposed to Pegvaliase at the Same Dose Category Separated by Drug Product Presentation Across Phase 3 Studies

	Drug Product Presentation				
	20 mg/d	>20 mg/d - <40 mg/d	40 mg/d	>40 mg/d - <60 mg/d	≥ 60 mg/d
≥ 6 months					
≥ 1 year					
≥ 2 years					

For Study 165-302 Part 3 (Within-Subject PK/PD Assessment between the VS and PFS Presentations in the Dedicated PK Comparability Assessment Period)

2. Using the combined data from the 20 mg/day and the 40 mg/day dose groups, Table 8.7.2.1 compared plasma pegvaliase PK parameter values (i.e., $AUC_{0-24,ss}$ and $C_{max,ss}$) between VS and PFS in Study 165-302 Part 3. We recommend that you create a new table that compares the two PK parameters from VS and PFS separately for the 20 mg/day dose group and the 40 mg/day dose group.
3. Table 8.7.2.1 demonstrated that $AUC_{0-24,ss}$ and $C_{max,ss}$ were 64% and 68% higher in the PFS presentation than in the VS presentation, respectively, but Figure 8.7.4.3 and Table 8.7.4.2 showed a similar mean change and mean percentage change of Phe reduction from naïve baseline between the VS and the PFS presentations. Provide explanations for the discrepancy between the PK and the PD results.
4. In Figure 8.7.2.1, we note that the PK exposure (i.e., $AUC_{0-24,ss}$ and $C_{max,ss}$) range achieved with the 20 mg/day dosing regimen was similar to the exposure range achieved with the 40 mg/day dosing regimen; the observation applies to both the VS and PFS product presentations. These data seem to suggest that doses higher than 20 mg may not necessarily achieve higher exposures. Provide explanations for the similar exposure range between the 20 mg/day dose group and the 40 mg/day dose

group. In addition, provide data to support the need for the 40 mg/day dosing regimen to achieve a higher exposure and a better PD response.

5. You summarized the antibody titers in all subjects in the randomized discontinuation trial (RDT) population while on VS (165-302, Part 2, Week 8) and after switching to PFS (165-302, Part 3, Week 4) in Table 8.7.5.1. In addition to this table, we request that you summarize the antibody titers only in the 27 subjects who were included in the PK comparability assessment.

For Study 165-301 (Between-Subject PK/PD Assessment between VS and PFS Presentations during Induction, Titration, and Maintenance Periods)

6. Figure 8.7.3.1 depicts the mean \pm standard error of trough pegvaliase concentration over time by randomized dose group and by drug product presentation in Study 165-301. We note that the number of subjects declined from Week 0 to Week 36 for both dose groups and both drug product presentations. To illustrate the observed decline over time, we summarized the number of subjects at Weeks 0 and 36 in Table 2.

Table 2. The number of subjects at Weeks 0 and 36 by randomized dose group and drug product presentation

Dose Group	Drug Product Presentation	# Subjects at Week 0	# Subjects at Week 36
20 mg/d	VS	67	28
20 mg/d	PFS	57	10
40 mg/d	VS	67	22
40 mg/d	PFS	56	7

Provide explanations for: (1) the overall decline in the number of subjects from Week 0 to Week 36, (2) the smaller fraction of subjects remained at Week 36 for the PFS presentation compared to that for the VS presentation at both dose levels, and (3) the continuous increase in pegvaliase concentration over time starting from Week 12 in the 40 mg/day dose group receiving the PFS presentation, while no such concentration increase was observed in the 40 mg/day dose group receiving the VS presentation.

7. Figure 8.7.4.4 presents the mean percentage change in blood Phe level from naïve baseline over time by randomized dose and by drug product presentation in Study 165-301. The Phe level reduction in the 40 mg/day dose group receiving the PFS presentation increased from ~30% at Week 12 to ~60% at Week 20, and remained relatively stable afterwards. Of note, the mean trough pegvaliase concentration at Week 20 was approximately 9000 ng/mL (Figure 8.7.3.1). This time course of percent Phe reduction is different from the time course of pegvaliase concentration which started to rise from Week 8 and continued to increase through Week 36 (Figure 8.7.3.1). Furthermore, all these observations are inconsistent with the fitted

PK/PD curve for PFS shown in Figure 8.7.4.2, which predicts that 60% Phe reduction would be observed at pegvaliase concentration at approximately 1000 ng/mL and 100% reduction in Phe levels is achievable. Provide explanations for these discrepancies.

8. Figure 8.7.5.1 depicts PAL IgG (a) and TAb (b) titers over time in Study 165-301 by drug product presentation in all subjects. We request that you plot TAb titers, the antibody titers of the four isotypes (i.e., PAL IgG, PAL IgM, PEG IgG, and PEG IgM), and NAb titers over time by dose group and by drug product presentation in subjects whose concentration data are included in Figure 8.7.3.1. In addition, construct a new table summarizing these immunogenicity data by dose group and by product presentation over time. The number of subjects in the new figure and the new table should correspond to the number of subjects in Figure 8.7.3.1 at each time point.

For Study 165-302 Part 1 (Phe Level Assessment Period)

9. Part 1 of Study 165-302 was an open-label screening period designed to establish eligibility for participation in Part 2, and the duration of Part 1 ranged from 3 to 13 weeks. Some of the eligible subjects received PFS alone in Study 165-301 and transitioned to receiving VS in Part 1 (and Part 2). Provide temporal profiles for mean trough pegvaliase concentration, Phe reduction, and antibody titers as described above for all subjects who transitioned from PFS in Study 165-301 to VS in Study 165-302, Part 2. Summarize the number (and percentage) of subjects with stabilized trough concentration and Phe level before enrollment into Study 165-302 Part 2.

Meeting Discussion:

The Sponsor's proposed definition of "continuous pegvaliase exposure" (slide 12 of Sponsor's presentation) appears reasonable; however, FDA recommended that the Sponsor consider and explore additional thresholds of "compliance" (e.g., 80% and 90%) within each dosage category to ensure that the provided analyses are informative. The Sponsor agreed and confirmed that they will submit data on dose changes within each dosage category, as some patients were not on a fixed dose throughout the study period but have been changed to lower/higher drug dose based on tolerability and/or response.

Regulatory

Question 5:

Does the Agency have comments regarding BioMarin's proposed risk evaluation and mitigation strategy (REMS)?

FDA Response:

Your proposed risk evaluation and mitigation strategy (REMS), although described as a communication plan, actually consists of elements to assure safe use (ETASU) to address the risks of anaphylaxis and severe hypersensitivity reactions. Therefore, we encourage

you to submit a proposed REMS with ETASU with your BLA application should you believe it to be required to ensure that the benefits of your product outweigh its risks.

Refer to the following Guidance for Industry for the correct format and content for your proposal and submit accordingly: <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm184128.pdf>

In order to facilitate an efficient review of proposed REMS, all materials identified within your proposal that will be necessary to implement the REMS should be submitted.

A complete review of the REMS, in conjunction with the full clinical review of the BLA, will be necessary to determine that any submitted REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

Meeting Discussion:

No further discussion required.

Question 6:

6a. Does the Agency agree with BioMarin's proposed structure and format of the pegvaliase BLA?

FDA Response:

From a content standpoint, we have the following comments:

- **You should provide patient disposition/discontinuation information (e.g., dose, time of discontinuation, reason for discontinuation for any reason, including the specific AE for patients who discontinue due to AE) for all patients in studies 165-301 and 165-302, as well as all other feeder trials into study 165-302 (along with a disposition dataset). You should tabulate all patient discontinuations from all these studies separately by each study and also by the combined population.**
- **As previously communicated during a March 2016 industry meeting, your future BLA submission should also include a robust benefit-risk evaluation which clearly considers both the benefit expectations as well as the risk tolerance for the proposed patient population. A survey of adult PKU patients (such as from the NPKUA or other groups) assessing their willingness to accept specific risks and side effects (e.g. anaphylaxis, hypersensitivity reactions, etc.) would be helpful to justify that the potential benefits of this therapy may outweigh the risks in this patient population.**
- **We acknowledge your intent to not submit part III elements (summary level clinical site datasets) of Bioresearch Monitoring Program (BIMO) as described in your briefing package. While we encourage the submission of these datasets to facilitate the timely selection of appropriate clinical sites for FDA inspection, electronic submission of these datasets is voluntary at this time. Please see the additional information below from the Office of Scientific Investigations.**

You should additionally provide the following analyses (with datasets) in your BLA submission:

- **Time to blood Phe level $\leq 600 \mu\text{M}$, $\leq 360 \mu\text{M}$, and $\leq 120 \mu\text{M}$ for each treatment group (and placebo) in all phase 3 studies.**
- **Proportion of treated patients with $\geq 30\%$ and $\geq 50\%$ Phe reduction from pre-treatment baseline in all phase 3 studies.**
- **Percent change in blood Phe from pre-treatment baseline by genotype in all phase 3 studies.**
- **Occurrence of SAEs and AEs of special interest by genotype in all studies.**
- **Dietary Phe tolerance over time for those on 20mg, 40 mg. and 60mg/day doses in all phase 3 studies.**

From a technical standpoint, the proposed structure and format for the planned BLA is generally acceptable with the following additional comments:

- **Besides bookmarks and hyperlinks, all pdf files more than 5 pages long, should also have Table of Contents (TOC)**
- **Please provide the Reviewer's Guide in module 1.2, as a separate document from the cover letter**
- **For archival purposes, also submit a pdf file of any document submitted in word (e.g. Medication Guide). When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.**

Meeting Discussion:

See slides 14 and 15 of Sponsor's presentation. The Sponsor explained that genotype and Phe tolerance data were not collected during this drug development program. FDA discussed that genotype data may have been important for PKU diagnosis confirmation and exclusion of mild, primary BH4 deficiency in some adults with hyperphenylalaninemia (for the completed and future trial eligibility) and in terms of potential analyses relating genotype (and, thus, disease severity in some cases) with drug response or adverse event occurrence.

(b) (4)

6b. Does FDA require non-executable SAS programs for analysis datasets to be submitted with the BLA?

FDA Response:

Yes, please provide your SAS programs for major efficacy analyses, including those for the primary and secondary endpoints, as well as your SAS programs that were used to derive the analysis data from the raw data.

Meeting Discussion:

No further discussion required.

6c. Does the Agency agree with BioMarin's plan for the provision of patient profiles (which include graphic patient profile and listings) and subject narratives in the BLA?

FDA Response:

We agree with your proposal to provide patient profiles for all subjects in your phase 2 and phase 3 studies. Submit the analysis datasets used to generate these patient profiles in the BLA.

In addition to your proposed patient profile elements, the following should also be included:

- a) **The amount of dietary protein intake for each subject as well as any change(s) in that over the duration of the studies, accompanied by the reason(s) for the change and the time of change,**
- b) **Any/all intercurrent illnesses for each subject (with timing, duration, etiology, and management/treatment provided) which may have affected blood Phe concentration,**
- c) **Drug product presentation (i.e., VS or PFS), pegvaliase concentration, Phe levels, Phe/Tyr ratio, and antibody titers from each isotype. These variables should be included in the listings as well as the graphic patient profiles.**

Patient narratives, in addition to those proposed in your package, should also be provided for all AEs potentially associated with immune complex deposition (e.g. albuminuria, hematuria, creatinine increase, etc).

All patient narratives for hypersensitivity AEs (HAE) and events meeting NIAID/FAAN criteria should include the following information:

- **Premedication(s) given prior to the event**
- **Specify when the event occurred (i.e., with which infusion) and whether the event occurred during or after infusion. If the event occurred after infusion, specify the number of hours after infusion the event occurred.**
- **Detail of the event – specify affected body location/distribution, duration of the event, changes in vital signs, and concurrent symptoms**
- **Any relevant lab work (e.g., IgE antibody status, complement levels, tryptase, skin testing results, etc)**
- **Medications and medical interventions administered to treat the event**

- **Outcome of the event**
- **If the patient resumed treatment, specify how soon after the event he/she resumed treatment. Indicate whether any changes were made to premedication(s) with the restart of treatment and whether symptoms recurred.**

You should also provide summary AE tables of all hypersensitivity reactions by SMQ and PT. This should include angioedema, anaphylactic reaction, and hypersensitivity SMQs with relevant PTs.

Meeting Discussion:

See slide 16 of Sponsor's presentation. FDA noted that the proposal to submit patient narratives for AEs associated with IC deposition in the BLA seems reasonable. FDA requested additional patient narratives for grade 3 and higher AEs of arthralgia and myalgia. The Sponsor agreed.

6d. Does the Agency agree with BioMarin's plan for the Integrated Summary of Efficacy (Section 9.5.3), Integrated Summary of Safety (Section 9.5.4), and Integrated Immunogenicity Report (Section 9.5.5)?

FDA Response:

We do not agree with your plans for the clinical summary sections located in Module 2.7 to serve as the narrative portion of the ISE and the ISS. The exception described in Section IIC of "FDA Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document" is intended for rare situations, in which the Module 2 summaries would be sufficiently detailed while still concise enough to meet the suggested size limitations for Module 2. Your primary evidence of efficacy will be based on the results of 2 studies (165-301 and 165-302) and your safety data will come from 7 studies. As such, Module 5 is the appropriate CTD section for more in-depth analyses, as well as tables, figures, and datasets.

You should submit all data for efficacy and safety for the ≥ 60 mg dose group separately from the 20mg and 40 mg dose groups in your BLA submission

We agree with your plan to provide an Integrated Immunogenicity Report as an appendix to the ISS. In addition to providing the integrated analysis of immunogenicity separated by study, you should also include side-by-side tables of HAEs, anaphylaxis, and other immune-related AEs as well as immunogenicity laboratory markers (C3, C4, IgM, IgG, CIC, renal function, urine protein/creatinine ratio, hematuria) separated by drug product presentation (PFS, VS, and combined). Specifically for the integrated analyses of immunogenicity, you should especially present the pooled data from all studies with I/T/M design.

Meeting Discussion:

No further discussion required.

6e. Does the Agency agree with the approach to use two separate and complete Drug Substance sections in Module 3 to describe the manufacture of pegvaliase?

FDA Response:

Yes, we agree.

Meeting Discussion:

No further discussion required.

6f. Does the Agency agree with BioMarin's plan for scheduling a meeting post submission to orient reviewers to the data?

FDA Response:

Yes, we agree.

Meeting Discussion:

No further discussion required.

Question 7:

Does the Agency agree with the proposed content and timing of planned information to be submitted in the 120-Day safety update?

FDA Response:

The proposed content and timing of your 120-day safety update seems reasonable; however, you should be aware that, depending on the amount of additional data submitted, this submission may lead to a major amendment. We remind you that IgG4 assay validation data and clinical data for all patients in your phase 3 trials should be submitted with the 120-day safety update as well (as previously agreed upon during the teleconference on 11/22/2016).

FDA Additional Comments:

- 1. Clarify the number of patients with immunogenicity data (i.e. C3, C4, immunoglobulins, CIC data) available, including duration of exposure, at the time of BLA submission, separated by drug product presentation and also combined.**
- 2. We noted that you excluded certain subjects from the PK/PD correlation analysis in the comparability analysis between the two product presentations (e.g., subjects enrolled prior to Amendment 2 and subjects randomized to placebo in the RDT, etc.) We recommend that these subjects be included in your overall integrated PK/PD analysis or provide justification for the exclusions.**
- 3. In this meeting package, you have not provided information on the bioanalytical assay(s) used to measure pegvaliase concentrations for PK assessment, or any population PK (and/or population PK/PD analysis) plan. We remind you to refer to the meeting minutes from the Type C meetings on 11/22/16, 7/21/16, and 3/15/2016 for our recommendations regarding the PK assay and the clinical**

pharmacology related data and data analyses. We request that you also provide PK results analyzed by non-compartmental analysis and any PK/PD analysis results associated with this PK information. Submit all datasets including the original PK and PD data, PK/PD analysis datasets, and PK/PD parameter datasets for our review.

4. If you plan to include pharmacometric analyses, e.g., population PK modeling and PK-PD or exposure-response analysis, in your submission, please refer to the URL below for general expectations of submitting pharmacometric data and models.
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>
5. If you plan to use model-based simulations to support the proposed dosing regimen(s), the methodology of the simulations should be clearly articulated in the report. The datasets and codes for key simulations should be provided.
6. Regarding the population PK datasets:
 - a) Provide the unique subject identification number (e.g., USUBJID) for each subject.
 - b) Include all observations for pegvaliase concentration including concentrations that were below the limit of quantitation.
 - c) Include PK sampling time points that have missing data.
7. We note that some subjects in your clinical studies had very high plasma pegvaliase trough concentrations. We remind you to include the drug tolerance for each of the antidrug antibody assays in the Assay Validation Reports for our review.

Meeting Discussion:

No further discussion required.

Additional Post-Meeting FDA Comments:

1. *Combination products under 21 CFR Part 3 are subject to 21 CFR Part 4 “Current Good Manufacturing Practice Requirements for Combination Products” which is accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>. Additional preliminary draft guidance is available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>*
2. *For information on where to provide device constituent part information using the eCTD format please see eCTD Technical Conformance Guide: Technical Specifications Document: “Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications” <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/UCM465411.pdf>. (September 2016)*

3.0 Other Important Information

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA and Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

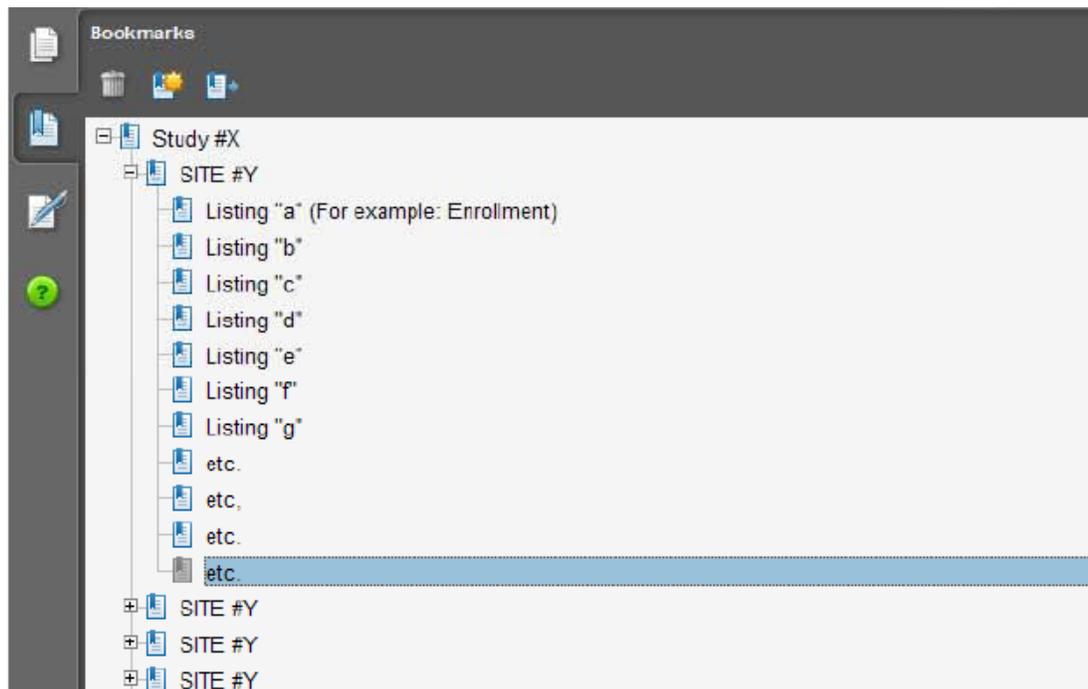
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - b. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ATTACHMENTS AND HANDOUTS



Final Presentation
Color.pdf

APPEARS THIS WAY ON ORIGINAL

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

/s/

JENNY N DOAN
12/16/2016



IND 076269

MEETING MINUTES

BioMarin Pharmaceutical Inc.
Attention: Barbara J. Winslow, Ph.D., RAC, CCRP
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Dr. Winslow:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMN165 (rAvPAL-PEG).

We also refer to the meeting between representatives of your firm and the FDA on January 29, 2013. The purpose of the meeting was to discuss the adequacy of the proposed nonclinical and clinical Phase 3 programs to support licensure of BMN165.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: January 29, 2013
Meeting Location: Building 22, Room 1419

Application Number: IND 076269
Product Name: BMN 165 (rAvPAL-PEG)
Indication: To reduce blood phenylalanine (Phe) levels in adult
Phenylketonuria (PKU) patients (b) (4)
(b) (4)

Sponsor/Applicant Name: BioMarin

Meeting Chair: Andrew Mulberg, M.D.
Meeting Recorder: Elizabeth Ford, R.N.

FDA ATTENDEES

Office of New Drugs

John Jenkins, Director

Office of Drug Evaluation III

Julie Beitz, M.D., Director

Victoria Kusiak, M.D., Deputy Director

Division of Gastroenterology and Inborn Error Products (DGIEP)

Andrew Mulberg, M.D., Deputy Director

Melanie Blank, M.D., Acting Clinical Team Leader

Wen-Yi Gao, M.D., Clinical Reviewer

David Joseph, Ph.D., Nonclinical Team Leader

Fang Cai, Ph.D., Nonclinical Reviewer

Elizabeth A.S. Ford, R.N., Senior Regulatory Health Project Manager

Office of Translational Sciences

Office of Clinical Pharmacology/Division of Clinical Pharmacology 3

Yow-Ming Wang, Ph.D., Biologics Team Leader

Christine Hon, Ph.D., Clinical Pharmacology Reviewer

Office of Translational Sciences
Office of Clinical Pharmacology/Division of Pharmacometrics
Nitin Mehrotra, Acting Team Leader
Jingyu Yu, Reviewer

Office of Biotechnology Products
Division of Therapeutic Proteins
Emanuela Lacana, Ph.D., Associate Chief, Laboratory of Chemistry
Joslyn Brunelle, Ph.D., Product Quality Reviewer, Laboratory of Chemistry
Daniela Verthelyi, M.D., Ph.D., Chief, Laboratory of Immunology
Jin Hai Wang, M.D., Medical Officer, Laboratory of Immunology

Office of Biostatistics/Division of Biometrics III
Behrang Vali, Biostatistics Reviewer

Office of New Drugs/Immediate Office
Anne Pariser, M.D., Associate Director, Rare Diseases Program
Larry Bauer, R.N., M.A., Regulatory Health Project Manager
Erica Radden, M.D., Medical Officer, Pediatric and Maternal Health Staff
Matthew Bacho, Senior Regulatory Health Project Manager

Center for Devices and Radiological Health
Office of Device Evaluation
Division of Anesthesiology, General Hospital, Dental and Infection Control Devices
General Hospital Devices Branch
Gail Gantt, Nurse Consultant

Center for Devices and Radiological Health
Office of Device Evaluation
QuynhNhu Nguyen, Biomedical Engineer, Combination Products Human Factors Specialist

SPONSOR ATTENDEES

Lisa Bell, Ph.D., Vice President, Regulatory Affairs
Henry Fuchs, MD, Chief Medical Officer
Zhonghua Karen Gu, Ph.D., Senior Biostatistician
Boyd Hansen, Ph.D., Senior Director, BioMetrics
Miko Maruoka, Sr. Manager, Regulatory Affairs
Terry Milby, Sr. Director, Regulatory Affairs
Charles O'Neill, Ph.D., DABT, Vice President, Pharmacological Sciences
Saba Sile, MD, Medical Director, Clinical Sciences
Barbara Winslow, Ph.D., Associate Director, Regulatory Affairs
Frank Sasinowski, J.D., Director, Hyman, Phelps & McNamara, P.C.
Robert Baffi, Ph.D., Executive Vice President, Technical Operations
Sandra Shpilberg (Executive Director, Program Management & Product Development)
Wolfgang Dummer, M.D., Ph.D. (Vice President, Clinical Sciences)

1.0 BACKGROUND

On October 12, 2012, BioMarin Pharmaceutical Inc. (BioMarin) requested a type B meeting to discuss BMN 165 (rAvPAL-PEG), an enzyme substitution therapy developed for reduction of blood Phe levels in individuals (b) (4) who have hyperphenylalaninemia due to PKU. BioMarin seeks agreement with the Agency on the adequacy of the proposed nonclinical and clinical Phase 3 programs to support licensure of BMN165 for treatment of adults with PKU.

2.0 DISCUSSION

2.1 Clinical Questions

Question 1: Does the Agency agree that the Phase 3 program is adequate to demonstrate efficacy and safety of BMN 165 in individuals (b) (4) with hyperphenylalaninemia due to PKU?

FDA Response to Question 1:

The proposed Phase 3 program is not adequate for both the efficacy assessment and safety monitoring. Please see the specific reasons listed under questions 1a and 1b.

Question 1a: The proposed pivotal randomized, double-blind, placebo-controlled, 3-arm, discontinuation study (BMN 165-302) including patient population, selected doses, study duration, inclusion/exclusion criteria, primary and secondary endpoints, and statistical analysis plan is adequate to demonstrate efficacy of BMN 165.

FDA Response to Question 1a:

The proposed design for study BMN 165-302 has several deficiencies and therefore, as currently proposed, is not adequate to demonstrate efficacy of BMN165. The deficiencies are as follows:

- 1) **Patient population:** The patient population (b) (4) that you have proposed is acceptable. When an acceptable safety profile has been established in this population, you may begin (b) (4)
(b) (4)
- 2) **Dose:** We are concerned about your selection of dosing. The PK/PD model that you used to determine your dosing selection is problematic as delineated in the answer to Question 5.
- 3) **Study design:** We highly recommend that you conduct Study 301 as a randomized placebo-controlled study and use study 302 as a confirmatory study. You may also consider using clinical endpoints in study 301 to demonstrate superiority over placebo. Additionally, a randomized withdrawal period in study 301 could confirm

the demonstration of efficacy. Altering the design of 301 to a placebo-controlled trial will eliminate the concern that improved dietary control could be accounting for improvement in phenylalanine levels.

- 4) **Phenylalanine Responder:** You will need to provide scientific justification for choosing 600 $\mu\text{mol/L}$ as your criterion for a responder. Refer to the following article for an approach to responding to this request:
<http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=623>
- 5) **Endpoint:** Change in serum Phe may not reflect a clinically meaningful difference. For this reason, you will need to define a responder (using an absolute serum phenylalanine goal or a percent decrease in serum phenylalanine) and provide a scientific (data-based) justification for that definition. You will also need to define a “failure” for the randomized portion of the trial, and provide a data-based justification for that definition. The clinical relevance of change in serum Phe levels has not been established in adults. For this reason, your primary endpoints should be clinical endpoints, such as performance on neurological or psychological testing or a patient reported outcome measure. Alternatively, we would consider approving your application under 21 CFR 601.41 Subpart E (Accelerated Approval of Biological Products for Serious or Life-threatening Illnesses) which states, “Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Confirmatory studies would usually be studies already underway.”
- 6) **Phase 4 commitment:** Studies to satisfy phase 4 commitments must be adequate and well-controlled. Clinically meaningful endpoints will need to be met. We recommend that you consult DGIEP, the Division of Neurology, Division of Psychiatry, as well as the Study Endpoints and Label Development (SEALD) team as you develop your strategy. You may also refer to the Patient-Reported Outcomes Measures guidance,
<http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>
We recommend that you provide the Division with detailed information on your rationale for choosing the proposed clinical testing endpoints for your clinical trials. Once received, we will consult the appropriate divisions within FDA.
- 7) **Statistical Analysis:** In your information package, it is unclear if efficacy is the primary efficacy endpoint in your phase 3 trials. We recommend that you make efficacy your primary objectives and endpoints for both trials. Ordered secondary endpoints are advisable and can include clinical endpoints, biomarkers and safety endpoints.

With respect to the multiplicity adjustment procedure in study 302, please confirm that if only one dose is shown to be significantly different than placebo (utilizing Hochberg’s method) in the analysis of the primary endpoint, that only a Type I

Error probability of 0.025 will be consequently applied to the subsequent step-down procedure which corresponds to secondary endpoint testing. Also as an extra sensitivity analysis in handling missing data for both the primary and secondary endpoint analyses, please include a no-change-from-baseline single imputation strategy.

- 8) **Immunogenicity assessment:** In study BMN 165-302, you propose that immunogenicity assessments will be done at baseline pre-dose, weeks 8, 16, and 20, quarterly during Part 2, study completion, and 4 weeks after study completion. This sampling schema is acceptable. However, the assessment of immunogenicity has been mentioned briefly in the population PK/PD modeling only. We highly recommend that you include an assessment of the impact of immunogenicity on PK and PD as well as clinical safety and efficacy. The assessment typically can be done by a comparison of PK/PD data in subjects who are antibody positive to subjects who are antibody negative. Given that your product may induce antibody in all subjects, we recommend that you explore the relationship between antibody titer and the PK, PD, safety, and efficacy data. In addition to the methods mentioned above, we suggest that you explore the feasibility of incorporating antibody titers as a covariate in the population PK/PD model. You should submit the validated immunogenicity assays to the Agency for review prior to testing pivotal trial samples.

Additional Discussion:

BioMarin agreed to provide additional information and rationale regarding target Phe levels in adults. In addition, will provide additional information regarding neurocognitive measures as pertains to this patient population.

Regarding study 302: (see attached slides)

BioMarin agreed to provide a package to the Division including detailed rationale for the selection of the neurocognitive measures used in the clinical trial to enable the team to obtain multidisciplinary feedback within the Agency.

FDA provided feedback regarding the proposed safety database (see slide deck), recommending 1 year of exposure for at least 50% of patients on the proposed marketed dose (in this disease process for this proposed product).

FDA will have further internal discussions regarding the development program proposed, and provide feedback to BioMarin.

Post Meeting Comments:

We confirm our advice as outlined above, and would like to clarify our proposal:

You may consider further evidence to inform the development program (responder definition [FDA response to 1a]), i.e. a study examining the change in phe that correlates with preliminary evidence of neurocognitive changes/deterioration in patients who are withdrawn from BMN 165.

FDA strongly recommends BioMarin meet with the Agency to discuss the data that is the foundation of the responder definition prior to embarking on clinical trials. This is of extreme importance due to the rarity of the disease, unmet need and limited opportunity for study.

Question 1b: The proposed open-label randomized study in treatment-naïve PKU subjects (BMN 165-301), including the dose and schedule rationale, patient population, study duration, inclusion/exclusion criteria, and primary and secondary endpoints, is adequate to support safety of BMN 165.

FDA Response to Question 1b:

1) We are concerned by certain safety signals that were observed in your nonclinical studies and your phase 1 and phase 2 trials, specifically:

- **Dose-dependent vacuolar degeneration of renal tubule and vacuolation in histiocytic cells in the liver, spleen, lymph node and adrenal cortex in rats was noted.**
- **Dose-dependent arterial inflammation, associated with immunohistochemical staining of IgG, IgM and C3 complement split products, was observed in monkeys.**
- **Serum anti-PAL IgG, anti-PAL IgM, and neutralizing antibodies were detected after repeat administration in rats and monkeys.**
- **Signs and symptoms of allergic reactions/serum sickness in your clinical trials.**
- **Anaphylaxis was observed after injection of Depo-Provera.**

You will need to devise a schema for regular monitoring of renal, liver, immunological and adrenal dysfunction in your clinical trials. You will also need to monitor for the development of post-injection reactions that should be recorded by the type of reaction (i.e., urticaria, wheezing, wheezing and uricaria, pulmonary edema, etc.). You will need to conduct analyses on any suspected allergic responses (regardless of antibody titer) by time after injection. For this reason, patients should be instructed to keep a strict adverse event diary. Frequent phone calls to patients between visits should be made to encourage patients to record the time, type and severity of AEs. Patients should also record the time of their injections.

The phase 3 protocols state that subjects will be provided with training and instruction on how to identify an AE and SAE, what to do in response to an event and whom to contact if an AE is suspected. The protocol does not state how patients will be instructed in the case of a suspected anaphylactic reaction and whether they will have access to inhalers, or epipens. Patients will need to be instructed on how to manage serious and severe anaphylactic reactions including when to call 911 and this needs to be explicitly stated in the protocol. The patients should be able to demonstrate a working knowledge of how to manage the different levels of severity of an allergic reaction before they are allowed to self-inject at home. Furthermore, there should be periodic reassessments. You will need to revise your protocols accordingly.

Female patients may be sensitized to Depo-Provera for life. It appears prudent to advise patients that they could suffer serious allergic and potentially life-threatening reactions to

Depo-provera even after many years since their last injection of BMN165. There should be wording to this effect in the informed consent.

You will need to provide your informed consent form and investigator brochures for our review.

Additionally, you will need to monitor the patients for tyrosine depletion and provide provision for tyrosine supplementation in your protocol. Because tyrosine is derived from phenylalanine, patients with PKU can be deficient in tyrosine. Tyrosine is involved in the production of neurotransmitter and stress hormones, and its deficiency may lead to confounding mood changes and neurocognitive disorders (which could further confound efficacy assessments by neuro- and psychological testing).

2) Provide Individual Stopping Criteria for the proposed clinical trial. We propose the following stopping criterion:

- **For individual subject: In the event of a single subject CTCAE Grade 3 (severe AE) or higher adverse event, regardless of whether it is attributed to BMN165 unless it is caused by an accident that could not reasonably be attributable to the drug.**

You should also propose study stopping criteria.

3) Immunogenicity assessment: In study BMN 165-301, immunogenicity assessment was proposed to be done at days 1 and 25, weeks 8, 12, 16, 20 and 24, study completion, and 4 weeks after study completion. Because BMN 165 will be given on day 1 and all subjects will develop antibody over time, we recommend that you perform additional testing at baseline pre-dose and an early time point at day 14 (i.e., week 2) to evaluate the development of antibody. We also recommend that you assess the impact of immunogenicity on PK and PD as well as clinical safety and efficacy (see response to Question 1a).

Question 2: Does the Agency agree with the selected secondary endpoints in Study BMN 165-302? Does the Agency agree that the plan to assess these endpoints in the clinical program is adequate to evaluate change in mood and neurocognitive signs and symptoms in patients with PKU, and sufficient to support a label claim if the results meet prespecified analysis endpoints?

FDA Response to Question 2: See the response to question 1a.

Question 3: Does the Agency agree with the selected secondary endpoints in Study BMN 165-02? Does the Agency agree that the plan to assess these endpoints in the clinical program is adequate to evaluate change in mood and neurocognitive signs and symptoms in patients with PKU, and sufficient to support a label claim if the results meet prespecified analysis endpoints?

FDA Response to Question 3: See response to question 1a.

Question 4: Does the Agency agree with the proposed plan to demonstrate the safety, efficacy and utility of at-home use of BMN 165 via a pre-filled syringe for product licensure?

FDA Response to Question 4:

You will need to provide the following information for FDA review before we can determine whether the prefilled syringe and final finished combination product is safe and effective: detailed information on the prefilled syringe; e.g., design of syringe, needle, sharps protector and steps for the final manufacture of the prefilled syringe. You will also need to indicate whether the syringe is specifically designed for this product and submit any design requirements provided by BioMarin. If BioMarin intends to rely on a syringe, needle or sharps protection master file or cleared 510(k), please provide that information. For additional information we recommend that you consider the following guidance document that includes information for syringes being submitted under an NDA/BLA.

- Scientific and Technical Considerations for Pen, Jet, and Related Injectors Intended for Use With Drugs and Biological Products;
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

On page 34, Section 4 Clinical data Information, subsection 4.1.5, you discussed Phase 2 studies where subjects self-inject using a vial/syringe after being adequately trained by clinic staff. The proposed Phase 3 study also includes self/caregiver-administration after training. See section 2.3. for Additional FDA Comments: Human Factors

Question 5: Does the Agency agree that the overall proposed clinical safety database, the pediatric plan and the PK modeling and simulation plan are adequate to support product licensure?

FDA Response to Question 5:

We do not agree that the overall proposed clinical safety database are adequate to support product licensure. See FDA responses to Questions 1b.

The pediatric plan (b) (4) appears to be acceptable.

In general, your PK modeling and simulation plan is acceptable. However, we have the following concerns and recommendations:

- The single dose PK does not appear to be dose proportional according to the data from PAL-001. Revise the PK model if the PK is not dose proportional.
- As your current PK/PD model was fitted to the PK and PD data simultaneously, we recommend that you confirm time-varying characteristics (single dose vs. maintenance stage) of BMN 165 PK parameters by modeling PK independently of the PD data. The antidrug antibody titer may be tested as a covariate in population PK model as time-varying characteristics may be attributed to immunogenicity.

- **A sequential approach should be adopted to refine your current PK/PD model with your Phase 1 and Phase 2 data. Whether your PK/PD modeling and simulation plan is adequate to support dose selection will depend on the results of the recommended sequential modeling of PK and PD data.**
- **We recommend that you construct a final population PK model by including all available PK data from Phases 1, 2, and 3 studies in order to update your current estimates of PK parameters. Whether your PK modeling and simulation plan is adequate to support product licensure will be a review issue.**
- **We noted that you have elected to exclude data collected in the titration phase from PK/PD modeling because PK data from this time period were below the limit of quantification. Clarify if the current limitation with respect to PK data from the titration phase is related to the sampling schedule and can be resolved with an optimized PK sample collection schedule in future studies. If yes, we recommend that you implement an improved PK sampling schedule in future studies and develop a PK/PD model that can capture the time course of Phe and drug concentration throughout all three phases of the study, i.e., induction, titration, and maintenance phase.**
- **We encourage you update your current PK/PD mode with PK/PD data collected from Phase 3 study. This updated PK/PD model, together with your proposed exposure-response analysis, may be used to support the dose selection.**

Pediatric and Maternal Health Staff (PMHS) Comments:

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 made the pediatric study requirements under the Pediatric Research Equity Act (PREA) permanent; however, PREA does not apply as your product received Orphan Designation. (b) (4)

(b) (4)

2.2. Nonclinical Questions

Question 6: Does the Agency agree that the proposed nonclinical program is sufficient to initiate the proposed Phase 3 clinical studies and is adequate to support product licensure?

FDA Response to Question 6:

The proposed nonclinical program appears to be adequate to support your Phase 3 clinical trial. However, full reports of the fertility/embryo-fetal development study in rats and the embryo-fetal development study in rabbits should be submitted for review and evaluation prior to initiation of the Phase 3 clinical study. It appears that the maintenance doses (20 and 40 mg/day) in your proposed Phase 3 studies will produce AUCs that were associated with PEG accumulation in rats (adrenal cortex, kidneys, liver, spleen, testes, lymph nodes) and arterial inflammation in monkeys, with evidence of immune complex deposition. The potential adverse effects of PEG accumulation in tissues are not well understood.

Additional information will be needed to allow for hazard assessment of PEG accumulation, which may occur during chronic administration of BMN-165 (see below). Your Phase 3 studies should include clinical monitoring to address the concerns from PEG accumulation in rats (e.g., kidney function) and arterial inflammation in monkeys.

To support a BLA submission, your nonclinical data package should also include a carcinogenicity assessment of BMN 165, in accordance with the addendum to ICH guidance S6. The nonclinical studies you have submitted do not provide information on the major site(s) of pharmacodynamic activity (i.e. enzymatic transformation of phenylalanine), or the tissue distribution of BMN 165. Provide studies to address these issues in your BLA submission. In addition, you need to provide information to address the concern about PEG accumulation in rat tissues. This information should include the time course for establishment of steady-state tissue levels and evaluation of the impact on organ or tissue function where PEG accumulation is observed. To provide such information, it appears that you will need to conduct a long-term toxicity study in rats of at least 12 months duration, with at least one interim sacrifice to confirm that study-state PEG accumulation in tissues has occurred. All microscopic changes, in addition to PEG accumulation, and effects on organ function should be recorded. You may propose alternative study designs for addressing the concern about PEG accumulation, provided that the study(ies) can produce the needed information.

2.3. Additional FDA Comments: Human Factors

It appears that your proposed product, prefilled syringe, will be used to support home administration of BMN165. Section 4 Clinical data Information, subsection 4.1.5 indicates that there will be user training. Also, Section 8 indicates that Human Factors will be

discussed at a future March 20, 2013 meeting. However, your submission does not indicate how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of the highest priority task pertinent to their device. This information will provide data to assess the safety and effectiveness of your device in the hands of representative users. Please provide a comprehensive use-related risks and a justification for why an HF/usability validation study is not necessary for the proposed product. In order to have a meaningful discussion at the March 20, 2013 meeting, please ensure that you provide the requested information as part of that meeting package. In addition, in that meeting package we recommend including information to address the FDA Response to Question 4.

For a HF/usability validation protocol, please note the following comments (a-g):

a. Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials. In addition, to establish the scope and facilitate understanding of the testing you perform, please provide a graphical depiction of the user interface for your device. Please also explain the overall interaction between users and the UI and refer to it as necessary when discussing task priority, specific test results or residual risk.

A key component of human factors/usability validation testing is that users who are representative of actual users be used for the testing. Based on your analysis of your intended users and the use of your device, you should determine the extent and type of training needed and indicated for users prior to using your device. After the training need is established and the training materials prepared, you should train the user participants for your human factors/usability validation testing in the same manner that actual users will be trained. You should provide at least some lag time between training and the testing. When you design your human factors/usability validation protocol, please include this analysis and ensure that representative (i.e., realistic) training is given to all test participants. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

In assessing the clarity of instructions for use and training as part of the validation study, the Agency expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

b. User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to

adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide a use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

In addition, for human factors/usability validation testing, the Agency needs to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related failures that could have an undesirable clinical impact. Please provide a rationale for the completeness of the user tasks you include in your Human Factors/Usability validation testing.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

You should include as many representative users in your human factors/usability validation as your analysis indicates are necessary to achieve a reasonable validation. Please note that the Agency's expectations for the number of study participants to be used in Human Factors/Usability Validation are a minimum 15 per user group. Please plan to submit results of a study that includes minimum of 15 participants per group of distinct users consistent with your indicated population of users, and also describe sufficient demographic information to indicate how these participants are representative of the intended population of users. If users fall into distinct groups that are expected to interact differently with the device (different user tasks) or carry different risk profiles (e.g. level of disabilities/impairments) then the testing should include representative samples from each of these groups, divided roughly evenly but where the total could be no less than 25.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study

participants should not be your own employees, or those that have been exposed to the products prior to the testing.

For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

e. Realism of simulated use

The testing environment and realism of the simulated use was not described in sufficient detail to determine if it is reasonable for a validation study of device use, however a “focus group” approach is not likely to represent actual use conditions. Please determine the conditions under which the testing will be undertaken and include realistic and challenging scenarios of use that, in aggregate, include all critical user tasks which you have identified.

f. Data Collection and Analysis

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants’ adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Your data analysis should be prioritized based on identified risk and task priority (from highest to lowest) to determine the magnitude and significance of the use errors, failures and difficulties that occurred during the testing.

g. Report

The Agency expects to review a report of the human factors/usability evaluation and validation testing. The report should begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

We strongly recommend that you submit your draft protocol in advance for us to review in order to ensure that your methods and the resulting data will be acceptable. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

3.0 PREA PEDIATRIC STUDY PLAN

Since PREA does not apply to an orphan product, your plan to submit the PSP within 180 days of the EOP2 meeting is fine. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Comments from Statistics regarding Data Standards:

Please provide the following for each adequate and well-controlled study, per 21 CFR 314.126, which you plan to include in your eventual BLA submission:

1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively. Define.PDF is also an acceptable format for the data definition file.
2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>). We recommend that the data definition file comply with the latest CDISC/Define.XML standard, however Define.PDF is also acceptable.
3. A well commented and organized software program written for each analysis dataset and efficacy table created.

5.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

6.0 ACTION ITEMS

None.

7.0 ATTACHMENTS AND HANDOUTS

BioMarin slides entitled "IND 076269_BioMarin SLIDES_29Jan2013.pdf"

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

/s/

ELIZABETH A FORD
02/22/2013