# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214938Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 111299

**MEETING MINUTES**

BioMarin Pharmaceutical Inc.
Attention: Takara Leonard
Manager, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Leonard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMN 111 (vosoritide) for injection.

We also refer to the meeting between representatives of your firm and the FDA on March 4, 2020. The purpose of the meeting was to discuss the content and structure of the proposed NDA planned for submission in Q3 2020.

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 301-796-5383.

Sincerely,

*{See appended electronic signature page}*

Linda Galgay, RN, MSN
Senior Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for
Cardiology, Hematology, Endocrinology, and
Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | March 4, 2020, 1:00 PM – 2:00 PM ET |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room: 1417<br>Silver Spring, Maryland 20903 |
| **Application Number:** | IND 111299 |
| **Product Name:** | BMN 111 (vosoritide) for injection |
| **Indication:** | Treatment of achondroplasia (ACH) in patients (b)(4) whose epiphyses are not closed. |
| **Sponsor:** | BioMarin Pharmaceutical Inc. |
| **Meeting Chair:** | Lisa B. Yanoff, MD |
| **Meeting Recorder:** | Linda Galgay, RN MSN |

**FDA ATTENDEES**

| | |
|---|---|
| Peter Stein, MD | Director, Office of New Drugs |
| Mary Thanh Hai, MD | Deputy Director, Office of Cardiology, Hematology, Endocrinology and Nephrology |
| Lisa B. Yanoff | Acting Division Director |
| Marina Zemskova, MD | Clinical Team Leader |
| Geanina Roman-Popoveniuc, MD | Clinical Reviewer |
| Federica Basso, PhD | Pharmacology/Toxicology Supervisor |
| Daniel Minck, PhD | Pharmacology/Toxicology Reviewer |
| Feng Li, PhD | Division of Biometrics II, Team Leader |
| Jennifer Clark, PhD | Mathematical Statistician |
| Jaya Vaidyanathan, PhD | Clinical Pharmacology Team Leader |
| Sury Sista, PhD | Clinical Pharmacology Reviewer |
| Julie Van der Waag, MPH | Chief, Regulatory Project Management Staff |
| Linda Galgay, RN, MSN | Senior Regulatory Project Manager |
| Donna Snyder, MD, MBE | Senior Pediatric Ethicist, Team Lead |
| Maryam Mokhtarzadeh, MD | Combination Products reviewer |

## BIOMARIN ATTENDEES

BioMarin Pharmaceutical Inc.

| | |
|---|---|
| Robert Baffi | President, Global Manufacturing and Technical Operations |
| Edward Berg | Vice President, Deputy General Counsel |
| Joyce Chou | Executive Director, Formulation, Quality |
| Jonathan Day | Executive Medical Director, Clinical Science |
| Kate Delaney | Senior Director, Patient Engagement and Outcomes Research |
| Elena Fisheleva | Senior Medical Director, Clinical Science |
| Hank Fuchs | President, Worldwide Research and Development |
| Brad Glasscock | Group Vice President, Head of Global Regulatory Affairs |
| Alice Huntsman-Labed | Senior Director, Biostatistician |
| Adora Ndu | Vice President, Regulatory Affairs |
| Geoffrey Nichol | Senior Vice President, Head of Global Clinical Development |
| Yulan Qi | Director, Clinical Pharmacology |
| Tammy Rose | Executive Director, Regulatory Affairs |
| Ana Zaccaro | Director, Regulatory Affairs |

External Consultants

(b) (4)

ACH Community Representatives

(b) (6)

## 1.0 BACKGROUND

Achondroplasia is an inherited, autosomal dominant, short-stature skeletal dysplasia caused by a gain of function mutation in the fibroblast growth factor-3 (FGFR3), a negative regulator of endochondral bone formation. Achondroplasia (ACH) is the most common form of dwarfism.[1] The most obvious clinical features of ACH are short stature and disproportional growth, manifested as long narrow trunks and shortened extremities, especially in the proximal segments (e.g., humerus). Achondroplasia patients also characteristically suffer from macrocephaly and hypoplasia of the mid-face.

Achondroplasia patients are at risk for multiple complications because of their abnormal bone growth. The most severe physical complications are usually neurologic in nature and often result from abnormalities, i.e., decreased size/diameter of the cranio-cervical junction and spinal canal. Patients are at risk for internal hydrocephalus, intracranial hypertension, cervico-medullary cord compression, foramen magnum stenosis and spinal stenosis among others. Cervico-medullary cord compression can result in hypotonia, respiratory insufficiency, central sleep apnea, and, rarely, quadriplegia. The combination of impairments in body structure and function can present significant challenges in performance of activities of daily living. Major areas of participation that are affected for ACH children are mobility, self-care, education, and performance at school. Furthermore, these challenges along with their altered body schema can result in psychosocial stress for patients and their families.

Sudden death has also been linked to these complications and is reported in approximately 5-10% of ACH children.[2] Less severe, but more common complications can include: otitis media, conductive hearing loss, speech delay, developmental motor delays, dental abnormalities, obstructive sleep apnea and cor pulmonale.

BMN 111 (vosoritide) antagonizes the FGFR3 cellular signal pathway potentially allowing for improvement in abnormal bone growth. The sponsor proposes to establish that BMN 111 improves growth velocity in patients with ACH.

IND 111299 was submitted on November 29, 2011. The May 11, 2018, Joint Meeting of the Pediatric Advisory Committee (PAC) and the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) was held to identify the appropriate elements of the clinical development program for BMN 111 for the treatment of children with ACH.

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[1] Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet 2007; 370:162-72.
[2] Ireland PJ et al. Optimal management of complications associated with achondroplasia. App Clin Genet 2014; 7:117-125

The purpose of this Type B pre-NDA meeting was to discuss the outcomes of pivotal Study 111-301, and the nonclinical and clinical data package to support the submission and review of the BMN 111 NDA planned for submission in Q3 2020. The sponsor also sought to discuss the content and structure of the proposed NDA.
Objectives of the meeting were to discuss the following:

- the BMN 111 nonclinical and clinical data package to support the submission and review of an NDA
- the proposed electronic common technical document (eCTD) structure and the format of the NDA
- the proposed content and clinical cut-off date of the 120-Day Safety Update Report

FDA sent Preliminary Comments to BioMarin on March 2, 2020.

## 2.0 DISCUSSION at the meeting and BioMarin's post-meeting comments submitted on March 20, 2020

**Question 1:** Does the Agency agree that the nonclinical package, as discussed in the Type C meeting on 26 January 2017, is sufficient to support the submission and review of the NDA?

**FDA Response to Question 1:**
**The pharmacology, pharmacokinetic, and toxicology studies that have been conducted appear appropriate to support the submission of the NDA. The adequacy of the studies will be a review issue.**

***Discussion regarding Question 1:*** *There was no discussion regarding Question 1.*

**Question 2:** Does the Agency agree that the studies contained in the nonclinical package do not meet the requirement for inclusion of datasets in the defined CDISC Standard for the Exchange of Nonclinical Data (SEND) in the NDA?

**FDA Response to Question 2:**
**We agree that SEND datasets are not required for the nonclinical studies listed in the meeting package as they were initiated prior to the SEND requirement dates. For the studies submitted to the NDA after the implementation of the Technical Rejection Criteria for Study Data, the studies submitted within the eCTD modules 4.2.3.1 (Single Dose Toxicity) and 4.2.3.2 (Repeat Dose Toxicity) for this project will need to include a simplified ts.xpt. Simplified ts.xpt files will not be needed for the safety pharmacology studies as the Technical Rejection Criteria for Study Data will not initially apply to submissions within eCTD module 4.2.1.3 (Safety Pharmacology).**

**The use and creation of simplified ts.xpt files is further explained in the Study Data Technical Conformance Guide (TCG)[3], and information about the Technical Rejection Criteria for Study Data can be found on the Study Data for Submission to CDER and CBER website.[4] The Agency will give industry 90 days' notice on the eCTD web page[5] prior to implementation of the Technical Rejection Criteria for Study Data.**

***Discussion regarding Question 2:*** *There was no discussion regarding Question 2.*

## 2.1. CLINICAL

**Question 3**: Does the Agency agree that the proposed clinical data package provides an adequate basis to support the submission and review of an NDA for the treatment of achondroplasia?

**FDA Response to Question 3:**

**You stated that you believe the vosoritide CDP is consistent with the Agency's recommendations to conduct two randomized, double-blind, placebo-controlled trials in 2 different age groups. While we do not agree with this perspective given the one-year controlled duration in your proposed program, we are open to discussing with you further your proposed data package as outlined below.**

| Principal Efficacy Outcome | Analysis | Data Sources | Type of Control |
|---|---|---|---|
| Primary efficacy | Change from baseline in AGV after 52 weeks of treatment in vosoritide versus placebo arm | 111-901/301 | Placebo |
| Short-term efficacy (up to 2 years) | Change from baseline in AGV and height Z-score over time with vosoritide | 111-901/301/302 | Intra-subject |
| | Change from baseline in AGV and height Z-score over time in vosoritide versus NH control | 111-901/301/302, 111-901/202/205 and RWE data | External control |
| Long-term efficacy (up to 5 years) | Change from baseline in height Z-score and AGV over time in vosoritide | 111-901/202/205 | Intra-subject |
| | Height comparison between active treatment arm versus NH control | 111-901/202/205 and RWE data | External control |

AGV: annualized growth velocity; RWE: real world evidence

[3] https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
[4] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[5] https://www.fda.gov/ectd

**At our meeting please address the following:**

**Your proposed plan to use the retrospective natural history (NH) database for the comparison may be acceptable, provided the data was properly collected, analyzed and matched to study patients' characteristics, i.e., data quality must be ensured, and analyses demonstrating that the NH controls are sufficiently similar to the current ACH population and patients in the Phase 2 and 3 studies will be essential. At our meeting, summarize your proposal to ensure matching of subjects from treatment studies to the retrospective NH database and address previous statistical comments from the Agency. As you noted, we provided a Written Responses Only (WRO) dated July 25, 2019, to your briefing package submitted on June 12, 2019, which detailed the statistical analysis plans for the pivotal study, and the identified NH data sources. However, it does not appear that you have responded to all of our recommendations and comments.**

(b) (4)

**The individual long-term data that we have seen in the 6 patients dosed with the 30 mcg/kg dose is encouraging because it appears that these patients are experiencing growth beyond what would be expected from ACH growth curves. Please discuss the growth observed in these 6 individuals as compared to matched controls. In addition, we note that individual long-term data from study 111-202/111-205 demonstrated better improvement in AGV in patients treated with 30 mcg/kg compared to 15 mcg/kg cohort, while all patients (8 out of 8) in Cohort 4 had improvement in growth velocity over time, 4 (subjects (b) (6) ) out of 10 patients in Cohort 3 (15 mcg/kg) had no/minimal improvement in growth compared to baseline AGV over time. These results, while observed in a small cohort of patients, may indicate that the 30 mcg/kg dose deserves further investigation as a potentially more effective dose. Please clarify how you interpret available data with the 30 mcg/kg dose (b) (4)**

***Discussion regarding Question 3:***

- *Use of NH data for the comparison*

*The primary investigator for the ACH Natural History study (AchNH), discussed key features of the study, noting the large (N=1374), protocol-driven study, conducted at 4 highly specialized US skeletal dysplasia centers, utilizing the RedCAP database with audit trail capabilities.*

*According to BioMarin, the AchNH data source, while collected retrospectively, was highly consistent. Comparability in height across all ages and genders, when compared to two prospectively collected NH studies (study 111-901 and Merkett 2018), were included in the pre-NDA briefing package (Tables 7 and 8, pages 36-37). The sponsor emphasized that the retrospective data represented a much larger data source of patient-level height data, and that the NDA will include patient-level data from the AchNH data source. The sponsor outlined the matching criteria and indicated that subjects height data in the AchNH database would be matched with vosoritide-treated subjects by sex and integer age, as these are two critical components that affect height. According to BioMarin, the matching process ensures subjects in the NH database cannot be matched to more than one active subject. Furthermore, the sponsor stated that the robustness of matching will be assessed by sensitivity analyses conducted with tighter age matching, and summary tables for goodness of matching will be provided in the NDA to determine the similarity of the subjects within the matched groups.*

*In response to the Agency's question regarding differences that may be seen in patients, the sponsor confirmed comparisons of patient characteristics between NH datasets and study 111-901 will be included in the NDA.*

*In response to the Agency's question regarding whether the sponsor has justification that matching on sex and age will be enough to ensure comparability between the treated subjects and those selected from AchNH, the sponsor stated that age and sex are the most important factors and other baseline characteristics will also be explored. The Agency stated that the justification of this position will be a review issue and clarified that the same inclusion/exclusion criteria should be applied to both the treated and AchNH populations first before any matching procedure.*

(b) (4)

- *Extrapolation of short-term linear height measures to FAH increases*

(b) (4)

(b) (4)

*BioMarin indicated that* (b) (4) *FAH would be collected in the post-marketing settings, as recommended by the Advisory Committee during the PAC/EMDAC meeting in 2018.*

*The sponsor also addressed the Agency's question on small changes in height Z-score observed in study 111-301 and confirmed there was an improvement of +0.24 standard deviation in height Z-score after one year of treatment with vosoritide which is consistent with the findings observed over 5 years of treatment in study 111-202/205. The sponsor reported no improvement in Z-score in the placebo arm.*

**BioMarin's post-meeting Clinical comments, March 20, 2020**

- Use of 30 mcg/kg dose in study 111-202 and study 111-205

BioMarin stated that most subjects treated with doses of 15 mcg/kg and 30 mcg/kg in studies 111-202 and 205 demonstrated a sustained improvement in growth resulting in an increase in standing height compared to NH control. As no additional meaningful improvements in AGV were seen with 30 mcg/kg over 15 mcg/kg, 15 mcg/kg was chosen for the active drug arm in study 111-301.

The sponsor stated that within the NDA, it will discuss the growth observed in all cohorts of the 111-205 study, including 8 subjects from Cohort 4, and will compare growth to matched NH controls. Furthermore, important characteristics such as sex, age, compliance and drug exposure, which may potentially influence the growth response to vosoritide, and any potential differences between the cohorts, will be analyzed. Available data from all 111-205 study cohorts, including biomarker data, in addition to the outcomes from study 111-301, will provide a data-driven assessment of efficacy and safety (b) (4)

(b) (4)

[redacted]

**Additional Comments:**

1. **Clarify how many patients in your overall clinical program, and by study, are expected to achieve FAH at time of NDA submission.**

   ***Discussion regarding Additional Comments Question 1:***

   *BioMarin confirmed that at the time of the NDA submission, there would be 3 subjects with 24-month treatment, and 14 subjects with 18-month treatment data. Complete 24-month data would be available in November 2020.*

   **BioMarin's post-meeting comment, March 20, 2020, regarding Additional Comments Question 1:**

   For the purpose of the vosoritide clinical program, FAH is defined as the height achieved by 16 years of age. The age of 16 years has been selected as children with ACH will have completed the majority of their growth potential by this age. At the time of the NDA submission, there will be 5 patients who will have reached the FAH criteria (4 subjects in study 111-205, and 1 subject in study 111-302 with limited exposure to vosoritide).

2. **We noted a discrepancy in the changes in mean and individual average growth velocity (AGV) overtime in the Phase 2 study 111-202/111-205. There is a downward trend for the mean AGV over time in Cohort 3 (15 mcg/kg dose cohort) (month 12 to months 60) and Cohort 4 (30 mcg/kg dose Cohort) (month 12 to month 48) (Table 32, page 154). However, the individual growth charts of patients in these 2 Cohorts (3 and 4) (included in the response to our information request dated February 18, 2020) show an increase in growth velocity over time (i.e., minimal or no improvement in growth within the first 1-2 years and increasing growth velocity after longer drug exposure). Comment on the overall downward trend in AGV observed in study 111-202/111-205 and explain the discrepancy noted above.**

   ***Discussion regarding Additional Comments Question 2:***
   *BioMarin indicated, there was a small standard deviation, with little variability year-to-year (ranging from 1.10 to 1.34 in Cohort 3), and all patients appeared to progressively depart upward from their growth trajectory compared to NH. BioMarin committed to provide individual growth charts for all subjects in the planned NDA.*

3. **Explain the differences in the drug effect in the subgroup analysis in study 111-301, with the largest increase in AGV from baseline observed in age group > 8 to< 11 years old (2.32 cm/yr.) and in patients with less severe disease at baseline (2.9 cm/yr. in patients with height Z-scores > -4) as per Figure 2 in your briefing package (p.58).**

   ***Discussion:*** *There was no discussion regarding Additional Comments Question 3.*

   **BioMarin's post-meeting comment, March 20, 2020, regarding Additional Comments Question 3:**
   The sponsor stated that a consistent treatment effect in favor of vosoritide was observed in all subjects with overlapping 95% confidence intervals, and the analyses demonstrate a highly consistent treatment effect across all subgroups. Based on the small numbers and multiplicity considerations, the results should be interpreted with caution. Details of analysis will be provided in the NDA.

4. **Provide available information pertaining to body and limb segment proportionality changes and the effect of your drug on ACH-related comorbidities after long term (i.e., 48 – 60 months) exposure to BMN 111 in study 111-202/111-205.**

**Discussion regarding Additional Comments Question 4:**

*BioMarin confirmed proportionality including upper to lower body segment ratios, upper arm to forearm length, and upper leg to lower leg length is collected and analyzed in study 111-205. The sponsor stated that these data will be included in the NDA as of the cut-off date for the study report. BioMarin stated that the data showed a favorable trend in change in upper to lower body ratio over time with mean change from baseline to Month 60 in Cohorts 1, 2 and 3 being -0.15, -0.18 and -0.12, respectively. In Cohort 4 the data available to Month 48 similarly indicated a positive trend with a mean change from baseline of -0.20. In the sponsor's view, these data confirm that long-term treatment effect on growth with vosoritide is not associated with negative effect on body proportions.*

*The sponsor acknowledged the comparison of functional improvements to the change in height is not easily captured in a NH study, the sponsor confirmed the measures of function being collected in study 111-302 and that change may be seen over longer periods. The sponsor confirmed the measures of function were also being collected in the 111-206/208 studies.*

5. **Address the following issues noted in study 111-901:**

   a) **Patients in 111-901 who were later enrolled in any of the drug studies should be clearly delineated in the dataset. Inclusion of patients in both the NH data and treated population can lead to uninterpretable results for some analyses.**

***Discussion**: The was no discussion regarding Additional Comments, Question 5a.*

**BioMarin's post-meeting comments, March 20, 2020, regarding Additional Comments Question 5a:**
The sponsor indicated that subjects in study 111-901 are included either for intra-subject comparisons or for the external control arm within the NH supportive comparative analyses. No subject is included in both the NH comparative arm and the active arm within analyses.

   b) **You indicated that 3 patients in study 111-901 have completed the study. Provide the criteria defining these patients as "completers" (e.g., achieved final height, received other therapies).**

***Discussion***: *The was no discussion regarding Additional Comments, Question 5b.*

**BioMarin's post-meeting comment, March 20, 2020, regarding Additional Comments Question 5b:**
The sponsor indicated that these patients met the 5-year protocol defined end of study.

c) **We noted that more than 50% of the subjects in study 111-901 who were not enrolled in any of the drug studies have discontinued the study. Provide the detailed reasons for the early termination of the study in these subjects.**

***Discussion regarding Additional Comments, Question 5c:***
*The sponsor stated that most discontinuations were due to withdrawal by the subject (54 subjects, 69.2% of all discontinuations from the study). The majority of these were due to personal reasons, such as lack of time, family/child decision, lack of interest, and fear of blood draws given lack of prospect of benefit. Furthermore, many of the patients who never enrolled in the interventional studies were due to competitive enrollment at sites. Some are also in study 111-901 as they are waiting to enroll in study 111-206. All discontinuation will be outlined in the 111-901 study report to be submitted with the NDA.*

d) **Clarify whether subjects in study 111-901 who were not enrolled in any of the drug studies were allowed to have and/or were administered any growth promoting procedures/treatments during the study.**

***Discussion:*** *The was no discussion regarding Additional Comments, Question 5d.*

**BioMarin's post-meeting comment, March 20, 2020, regarding Additional Comments Question 5d:**
Subjects enrolled in study 111-901 were not allowed to have and did not receive any growth promoting procedures/treatments during the study. Furthermore, subjects were not allowed to participate in the 111-901 study if they had treatment with a growth-promoting therapy within 6 months before enrollment or if they had been treated with a growth-promoting therapy for more than 3 months at any time in the past. Subjects with previous limb-lengthening surgery could be enrolled only if a surgery took place at least 18 months prior to the study and healing was complete without sequelae.

**Question 4:**

**a)** Does the Agency agree with the proposed approach for inclusion and evaluation of efficacy and safety data from vosoritide studies? Specifically, the proposed pooling of studies for the integrated summary of safety (ISS) integrated summary of efficacy (ISE), and integrated summary of immunogenicity (ISI)

**FDA Response to Question 4a:**

**Given that we have not come to agreement on the clinical data requirements for your NDA, this question is premature. However, the studies to be included in the proposed pooled groups have different design (i.e., randomized, double-blind vs. single arm, open label), different patient populations, different study durations, etc., hence, a simple pooling of data from these studies may not be informative and could be misleading.**

**b)** The proposed integrated analyses for inclusion in the ISE/ISS/ISI

**FDA Response to Question 4b:**

**Refer to the response to Question 4a.**

**c)** The proposed format of the ISE/ISS/ISI in eCTD

**FDA Response to Question 4c:**

**Refer to the response to Question 4a.**

**d)** The proposed individual study, pooled groups, and NH datasets

**FDA Response to Question 4d:**
**Refer to the response to Question 4a. Additionally, we do not agree with the proposed pooling of the NH studies. The proposed supportive NH data source includes prospective, cross-sectional, and retrospective study designs. You should analyze the data in these studies separately. Particularly, the comparison to the prospective NH data source from 111-901 study should be done separately.**

**e)** The proposed NH analyses, and format for inclusion in the comparative NH report

**FDA Response to Question 4e:**

**Refer to the response to Question 4d.**

***Discussion regarding Question 4:*** *There was no discussion regarding Question 4.*

**BioMarin's post-meeting comments, March 20, 2020**

1. **Regarding FDA responses to Questions 4a,b and c:**
   The sponsor acknowledged the Agency's comment and stated that within the NDA, the data will be presented by study, as well as pooled groups, and justification for pooling will be provided.

2. **Regarding FDA responses to Questions 4d and e:**
   The sponsor acknowledged the Agency's comment and will take the recommendation into consideration for the pooling of the NH studies.

**Question 5:** Does the Agency agree with the proposed content and clinical cut-off date of the 120-Day Safety Update Report?

**FDA Response to Question 5:**
**Given that we have not come to agreement on the clinical data requirements for your NDA, this question is premature.**

***Discussion regarding Question 5:***
*Based on the June, 2020 data cutoff, BioMarin is committed to working with the Agency to provide additional data requested for inclusion in the Safety Update Report.*

**BioMarin's post-meeting comments, March 20, 2020**
The sponsor acknowledged the Agency's comment. As included in the Pre-NDA Meeting briefing package, BioMarin plans to submit a Safety Update Report approximately 120 days following the NDA submission. This safety update report will include additional data relevant to safety from the four ongoing studies, 111-205, 111-206, 111-208, and 111-302.

The safety update report will present both incremental (i.e., data collected post the NDA data cut-off dates) and cumulative data collected through a 120-day safety update data cut-off date in June, 2020. The data cut-off is planned for June, 2020, in order to include more than 6 months of additional safety information from each ongoing study. The safety update data will be analyzed using the same statistical analyses as performed for the clinical study reports (CSRs) and submitted in the format of an integrated summary.

**Question 6:** Does the Agency have comments regarding BioMarin's proposed plans to provide additional clinical data, including FAH, in a post approval setting from subjects currently enrolled in the extension studies?

**FDA Response to Question 6:**
**See our response to question 2. We recommend further discussion of the NDA data package before discussion of any postmarketing submissions or requirements.**

***Discussion regarding Question 6:***
*BioMarin confirmed that FAH would continue to be collected in the post-approval setting. This plan is in line with the Joint PAC and EMDAC meeting on May 11, 2018, where the Advisory Committee members were supportive of generating evidence on FAH that would require many years of evaluation in the post-approval setting in order to avoid delaying access to treatment. The sponsor stated that further details on the post-market plan will be included in the NDA.*

## 2.2. REGULATORY

**Question 7:** Is the Agency amenable to scheduling an applicant orientation/technical walk through meeting with the Sponsor after the submission of the NDA?

**FDA Response to Question 7:**
**A decision as to whether a meeting is needed will be made after NDA submission.**

***Discussion regarding Question 7:*** *There was no discussion regarding Question 7.*

**Question 8:** Does the Agency agree that the proposed eCTD structure of the NDA, adequately meets criteria for an acceptable file for review?

**FDA Response to Question 8:**
**From a technical perspective, the organization of the proposed eCTD structure of the NDA is acceptable.**

***Discussion regarding Question 8:*** *There was no discussion regarding Question 8.*

## 2.3. CLINICAL PHARMACOLOGY

**Additional Clinical Pharmacology Comment:**

**Confirm that you used the final to-be-marketed (TBM) product of vosoritide in the phase 3 trials. If formulations other than TBM formulation were used in Phase 3 trials, appropriate bridging studies will need to be conducted prior to the submission of the NDA.**

***Discussion regarding Additional Clinical Pharmacology Comment:***
*There was no discussion regarding the Additional Clinical Pharmacology Comment.*

**Sponsor's post-meeting comments, March 20, 2020**
BioMarin confirms that the to-be-marketed commercial formulation of vosoritide was used in the Phase 3 trials, including the dosage form (lyophilized), peptide and excipient concentrations.

## 3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

- There were no agreements for late submission of application components within 30 days after submission of the original application; therefore, the application is expected to be complete at the time of submission.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- In addition, we note that chemistry pre-submission written responses were granted. Refer to those written responses for any additional agreements that may have been reached.

## 4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues were identified that would require further discussion. Refer to the Action Item below.

## 5.0 ACTION ITEMS

BioMarin agreed to respond to the Additional Clinical Comments (refer to Preliminary Comments, pp. 7-8) in an amendment to the IND. BioMarin's response was submitted and received March 20, 2020.

## 6.0 ATTACHMENTS AND HANDOUTS

BioMarin submitted slides and statements from the patient segment of the meeting along with Pre-NDA meeting slides on March 17, 2020.

## 7.0 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 (January 17, 2013), you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

## 8.0 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[6] and Pregnancy and Lactation Labeling Final Rule[7] 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling.

[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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

## 9.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

## 10.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |

## 11.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

[8] https://www.fda.gov/media/85061/download

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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LINDA V GALGAY
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