CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214938Orig1s000

OTHER REVIEW(S)

Memo to file re: vosoritide and device interface issues and proposed PMR

November 19, 2021

Naomi Lowy (DGE)

Jason Flint, Irene Chan (DMEPA 1)

NDA 214938 (vosoritide)

The purpose of this memorandum is to summarize scientific and regulatory discussion, rationale and recommendations related to user interface issues identified during review of the vosoritide NDA.

In the review of this NDA (see DARRTS dated November 18, 2021), DMEPA concluded that the Human Factors (HF) validation study demonstrated that the user interface is not optimized for safe and effective use. DMEPA is concerned that use errors and use difficulties will occur with the introduction of this product to the market that could result in under- or overdosing of the drug. Although DMEPA suggested multiple changes to the labels and labeling to mitigate the use issues seen in the HF validation study, they also acknowledged that meaningful risk mitigation would also require changes to the product design. Therefore, DMEPA recommended a post-marketing requirement or commitment that the Applicant "develop a validated user interface that better supports the safe and effective use of the product by the intended users, for intended uses, in the intended use environments".

However, the Clinical and Clinical Pharmacology reviewers performed multiple analyses and concluded that it would be unlikely that the magnitude of either over- or underdosing observed in the HF study would meaningfully impact efficacy or safety.

To fulfill the commitment of timely communication about possible PMRs to Applicants, while this issue was under discussion by the review team, DGE notified the Applicant of a potential PMR as follows: *Conduct a human factors validation study using a redesigned product user interface that addresses the residual risks identified in your previous human factors validation study.* (b) (4) The Applicant did not have any concerns regarding the proposed PMR.

As the review progressed, feedback from ORP was sought regarding acceptability of the proposed PMR despite the apparent lack of safety issue. During an internal meeting on October 19, 2021, representatives from OCHEN and OSE explained that no "serious risk" has been identified to satisfy the requirements for 505(o)(3).

ORP reviewed the proposed PMR, and Diana Pomeranz provided feedback via email dated October 22, 2021 that a PMR was not appropriate.[1]

(b) (5)

Although DMEPA and DGE remain concerned about a product user interface that has been shown to be prone to use errors, the analyses conducted by the review team reassured us about the impact on efficacy or safety. DMEPA agrees with DGE that the current user interface is acceptable to support the safe and effective use of the product and that the product can be approved in its present form. The team also agreed that availability of an optimized interface, that is, one that minimizes the potential for use errors, should be pursued voluntarily by the sponsor in the postmarket setting. Furthermore, if the Applicant changes the user interface than a new HF validation study would be useful to determine if the design changes were successful in reducing the user errors.

[1] *A PMR under 505(o)(3) is appropriate for the following purposes:*

(i) To assess a known serious risk related to the use of the drug involved.
(ii) To assess signals of serious risk related to the use of the drug.
(iii) *To identify an unexpected serious risk when available data indicates the potential for a serious risk.*

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

PATIENT LABELING REVIEW

Date:	November 5, 2021
To:	Linda Galgay, RN, MSN Senior Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	VOXZOGO (vosoritide)
Dosage Form and Route:	for injection, for subcutaneous use
Application Type/Number:	NDA 214938
Applicant:	BioMarin Pharmaceutical Inc.

1 INTRODUCTION

On August 20, 2020, BioMarin Pharmaceutical Inc. submitted for the Agency's review an original New Drug Application (NDA) 214938 for VOXZOGO (vosoritide). This NDA is proposing an indication for the treatment of achondroplasia in pediatric patients 5 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of General Endocrinology (DGE) on September 6, 2020 and September 7, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for VOXZOGO (vosoritide) for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Revised draft VOXZOGO (vosoritide) PPI and IFU received on September 2, 2021, and received by DMPP and OPDP on October 27, 2021.
- Draft VOXZOGO (vosoritide) Prescribing Information (PI) received on August 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 27, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

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

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

Memorandum

Date: November 3, 2021

To: Geanina Roman-Popoveniuc, M.D., Medical Officer
Division of General Endocrinology (DGE)

Linda Galgay, Project Manager, (DGE)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for VOXZOGO (vosoritide) for injection, for subcutaneous use

NDA 214938

In response to DGE's consult request dated September 7, 2020, OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI), and Instructions for Use (IFU) for VOXZOGO (vosoritide) for injection, for subcutaneous use (Voxzogo). This application is under accelerated approval based on an improvement in linear growth observed in pediatric patients 5 years of age and older with open epiphyses.

PI, PPI, IFU: OPDP's comments on the proposed PI are based on the draft materials sent by DGE on October 25, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed and comments on the proposed PPI and IFU will be sent under separate cover at a later time.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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CHARUNI P SHAH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 13, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214938
Product Name and Strength:	Voxzogo (vosoritide) for injection, 0.4 mg/vial, 0.56 mg/vial, 1.2 mg/vial (b) (4)
Applicant/Sponsor Name:	Biomarin Pharmaceutical Inc
OSE RCM #:	2020-1758-1
DMEPA 1 Safety Evaluator:	Jason Flint, MBA, PMP
DMEPA Team Leader:	Ebony Whaley, PharmD, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 2, 2021 for Voxzgogo. Division of General Endocrinology (DGE) requested that we review the revised instructions for use, container labels and carton labeling for Voxzgogo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Flint, J. Human Factors and Label and Labeling Review for Voxzgogo (NDA 214938). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021Aug04. RCM No.: 2020-1758.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 2, 2021

Response to Recommendations

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Instructions For Use

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Container labels

(b) (4)

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 9, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214938
Product Type:	Combination Product
Drug Constituent Name and Strength	Voxzogo (vosoritide) for injection, 0.4 mg/vial, 0.56 mg/vial, 1.2 mg/vial (b) (4)
Device Constituent:	Vial kit with diluent prefilled syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biomarin Pharmaceutical Inc
Submission Date:	August 20, 2020
OSE RCM #:	2020-1758
DMEPA 1 Human Factors Evaluator:	Jason Flint, MBA, PMP
DMEPA 1 Safety Evaluator:	Melina Fanari, RPh.
DMEPA Associate Director for Human Factors (acting):	Lolita White, PharmD
DMEPA 1 Director (Acting):	Irene Z. Chan, PharmD, BCPS

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 214938 for vosoritide.

1.1 PRODUCT DESCRIPTION

The Voxzogo (vosoritide) injection product consists of vosoritide lyophilized powder (0.4 mg/vial, 0.56 mg/vial, 1.2 mg/vial (b) (4) prefilled diluent syringes (0.5 mL, 0.6 mL or 0.7 mL), diluent syringe needles, and administration syringes. Per the Applicant, the commercial product will be provided to patients in shipments (b) (4) . Voxzogo is intended for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed.

(b) (4)

1.2 REGULATORY HISTORY

We previously reviewed the HF validation study protocol and the proposed labeling under IND 111299[1] and provided recommendations to Biomarin on December 21, 2019. On August 20, 2020, the Applicant submitted their NDA with results from the HF validation study to support their vosoritide user interface design, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide more information regarding each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

[1] Purcell, J and Fanari, M, HF Study Protocol and Labels and Labeling Review for BMN 111 (IND 111299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Dec 17. RCM No: 2019-2220 and 2019-2221

2. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results support the safe and effective use of the proposed product. The applicant provided two HF validation studies. The first HF validation study included untrained healthcare providers (HCP), and trained and untrained Adult Caregivers of children with chronic conditions, and the second HF validation study included trained and untrained Adult caregivers of children with achondroplasia (ACH) and untrained pediatric patients with ACH. Our analysis includes the results and details for both studies so that we could address use of the product by all intended users.

2.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants – Study 1	15 Untrained healthcare providers (HCP) 15 Trained Adult Caregivers (CG-T) of children with chronic conditions 15 Untrained Adult Caregivers (CG-U) of children with chronic conditions
Participants – Study 2	15 Trained Adult Caregivers of children with achondroplasia (ACH) 15 Untrained Adult Caregivers of children with ACH 15 Untrained pediatric patients with ACH aged 11 to 18 years
Training	The applicant provided up to 90 minutes of training for two adult caregiver groups.
Test Environment	Testing was conducted in an observation room made to approximate a home environment. The testing was observed via one-way mirror supplemented by video cameras.
Sequence of Study	HCP- One study session with three simulated injections, knowledge tasks, and root cause analyses
	CG-U- Two sessions ~24 hours apart. One simulated injection on day one, and two simulated injections on day 2, followed by knowledge tasks and root cause analyses upon completion of all simulated injections.
	CG-T- Three sessions ~24 hours apart. Training on day one, one simulated injection on day two, and two simulated injections on day three, followed by knowledge tasks and root cause analyses upon completion of all simulated injections.

3. RESULTS AND ANALYSES

The Identified Issues and DMEPA's Findings table describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations. We evaluate the use errors, close calls, and use difficulties associated with tasks that we determined to be critical tasks in the table below.

Overall, we note the root cause analysis for several of the identified use errors are incomplete. In some cases our analysis determined that the root cause analysis did not probe further to identify what elements of the user interface may have contributed to the use errors. Furthermore, in these cases, the applicant has not proposed mitigations to address these use errors. See the table below for additional details.

Table 3. Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	**DMEPA's Analysis and Findings**
1.	For the task "Slowly inject all of the sWFI PFS into the BMN 111 vial", there were 12 use errors (4 failures and 8 close calls). For example, some participants did not inject all the diluent into the vial, and some expelled some diluent before injecting into the vial but restarted the preparation process. The reported subjective data and the Applicant's root cause analysis indicated: Perceptual Error – One participant didn't realize that the diluent syringe had diluent in it and emptied the syringe before attempting to draw up the contents of the vial. Information Oversight – Participants indicated that they were not paying attention to the instructions, or that they missed a step in the instructions. Slip – Some participants indicated they accidentally put their thumb on the plunger and expelled some of the diluent. We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly, there is risk of overdose, acute/Mild physiological effect (e.g., hypotension, dizziness, tachycardia) Our review of the study results identified that the subjective feedback did not identify elements of the user interface that may have contributed to the use errors, and the participants did not propose any mitigation strategies. Our review of the labels and labeling (user interface, etc.) finds that the image in step 4 of the IFU shows the diluent syringe in a person's hand with their thumb on the plunger. This may have contributed to the use errors that occurred when participants placed their thumb on the plunger and inadvertently expelled some of the diluent (slip). Based on our overall assessment, we find the user interface can be improved. **We provide recommendations in the Identified Issues and Recommendations for Biomarin Table to address this concern**.
2.	For the task "Gently swirl mixture until BMN 111 powder has completely dissolved" there were 9 use errors (8 failures, 1 close call) involving participants inadequately swirling the medication in the vial.	Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. Our review of the study results identified subjective feedback that indicated that participants may be prone to rely on previous experience or mental

	The subjective data and the Applicant's root cause analysis stated: Lapse/slip – participants understood the requirement to "swirl" the mixture but did not or shook the vial instead. Information Oversight – Participant read the instructions but misinterpreted them Negative Transfer – Participant felt it was more natural to shake the vial. We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address these use errors.	models and shake the vial instead of swirling it gently. We discussed the concept of shaking versus swirling of the vials for reconstitution with our colleagues in the Office of Pharmaceutical Quality (OPQ) and they stated that there was no data to determine whether shaking the vial was worse than swirling the vial. As such, it is unclear whether this difference may impact homogeneity or other factors that may impact the safe and effective use of the product. Our review of the labels and labeling (user interface, etc.) finds that step 6 in the IFU "Gently swirl" provides an image and text to support completion of this task, however, because this use error seems to be related to participant's mental model of needing to shake the vial, it may be necessary to place this important information on other labeling such as the carton to ensure that users do not shake the vial while mixing. Based on our overall assessment, we find the user interface can be improved. **We provide recommendations in the Identified Issues and Recommendations for Biomarin Table to address this concern**.
3.	For the task "Determine injection site" there was one close call during the first injection, and 19 failures for the second injection. For example, two users injected, and one almost injected into an unspecified injection site, and 17 users failed to rotate the injection site for the second injection. The subjective data and the Applicant's root cause analysis indicated: Negative transfer/Mental Model – Participants had preconceptions about where to inject, and reinjected into the same site or into the arm based on those preconceptions. Study Artifact – Participants stated that in real-life they would pay more attention, or that it wasn't clear whether the second injection scenario was intended to represent a different day.	Based on the URRA, if this task is omitted or not performed correctly there is risk of lipodystrophy. Our review of the study results identified that the subjective feedback did not identify elements of the user interface that may have contributed to the use errors. Our review of the labels and labeling (user interface, etc.) finds that Step 13 in the IFU "Select and prepare injection site" provides an image and text to support completion of this task; however, we note that the instruction to rotate the injection site can be improved. Based on our overall assessment, we find the user interface can be improved. **We provide recommendations in the Identified Issues and Recommendations for Biomarin Table to address this concern**.

	The applicant indicated that they made changes to the IFU based on formative testing, but have not proposed any additional mitigations.	
4.	For the task "Pull plunger back to withdraw slightly more than prescribed dose" there were 8 use errors (4 failures, 4 close calls). For example, some participants removed the plunger from the syringe, tried to withdraw medication from the vial using the diluent syringe, or were unable to withdraw medication from the vial. The subjective data and the Applicant's root cause analysis stated: Mistake or Perceptual Error – participants drew air into the syringe We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. We disagree with the Applicant that the root cause of these use errors were "mistakes" because it is generally unacceptable to blame the user without investigating further how the user interface design may have contributed to the error. The subjective feedback indicated that these errors were users not adding diluent, trying to withdraw medication from the vial using the diluent syringe, and inadvertently bending the needle, which prevented them from withdrawing the medication from the vial. Most users recognized their errors, started the process over, and were successful, however, these types of use errors would deplete the user's supply of diluent syringes. Additionally, we noted fewer errors on the second injection, which could indicate a learning effect. Our review of the labels and labeling (user interface, etc.) finds that Step 7 does not clearly indicate that the user should switch from the diluent syringe to the injection syringe. Based on our overall assessment, we find the user interface can be improved. **We provide recommendation in the Identified Issues and Recommendations for Biomarin Table to address this concern**.
5.	For the task "Gently tap syringe with needle pointed upward so that any air bubbles rise to the top" there were 79 use errors (75 failures, 4 close calls) The subjective data and the Applicant's root cause analysis stated:	Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. We agree with the Applicant that participant perception may have played a role in these use errors, however, we are concerned that this use error occurred in trained and untrained participants, and HCPs. Additionally, the occurrence of this error did not improve on the second injection attempt.

	Mistake, Perceptual Error, and Assumption – Participants generally assumed that they had removed "enough" air bubbles to give "close enough to a full dose". The applicant has not proposed mitigations to address these use errors.	Our review of the study results identified that the applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use errors. Our review of the labels and labeling (user interface, etc.) finds that Step 10 in the IFU "Remove large air bubbles" provides an image and text to support completion of this task. We discussed this finding with the clinical and clinical pharmacology reviewers, and their feedback indicates that there are no clinical or safety concerns with this use error. We find the residual risk acceptable and have no recommendations at this time.
6.	For the task "Verify administration syringe plunger is at the prescribed dose" there were 13 use errors (12 failures, 1 close call). For example, participants verified dose volumes that were not within the allowed 0.02 mL margin. The subjective data and the Applicant's root cause analysis stated: Negative Transfer – some participants measured the dose that they remembered from training, instead of the dose that they were instructed to measure. Mistake – Some participants measured incorrectly because of air in the syringe, or just measured the wrong dose. Perceptual Error – Participants did not know what part of the rubber stopper to use for measurement. For example, two participants used the top of the rubber stopper to measure their dose. The applicant has not proposed mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of overdose, acute / Mild physiological effect (e.g. hypotension, dizziness, tachycardia) We agree with the Applicant that negative transfer contributed to some of these use errors, however, some participants indicated that syringe design and the small volume required also contributed to dose inaccuracy. Our review of the study results identified subjective feedback that indicated some participants used the top of the plunger to measure their dose, resulting in overdose. It is not clear what was meant by the "top of the plunger", and there was no additional clarification provided. Additionally, several users indicated difficulty measuring an accurate dose because of the small volumes involved. In response to an information request, the applicant indicated that while they didn't record how much extra each participant measured, most appeared to be "one or two minor tick marks" or 0.01 to 0.02 mL. Our review of the labels and labeling (user interface, etc.) finds that while step 11 of the IFU indicates which part of the syringe should be used to measure the dose, participants indicated that the syringe design may have contributed to the use errors. In particular, based on the syringe image in the IFU, participants may have used a part of the syringe used to activate the needle retraction (shown as [redacted] (b) (4)" below) to measure their dose, which would lead to overdose.

		(b) (4) Based on our overall assessment, we find the user interface can be improved. **We provide recommendation in the Identified Issues and Recommendations for Biomarin Table to address this concern**.
7.	For the task "Pinch skin at injection site" there were 23 use errors (19 failures, 4 close calls). The subjective data and the Applicant's root cause analysis stated: Mistake – several ACH participants attempted to give the injection on their arms and were unable to pinch the skin because their arms were too short. Slip/Lapse – Participants knew they should pinch the skin, but did not. We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of intramuscular injection (leading to variable bioavailability)/Mild physiological effect (e.g. hypotension, dizziness tachycardia) We disagree with the Applicant that users made a mistake that led to this use error. Particularly, ACH users may have difficulty injecting into their own arms as a result of their condition. Our review of the study results identified that the subjective feedback did not identify elements of the user interface that may have contributed to the use errors. Our review of the labels and labeling (user interface, etc.) finds that step 13 in the IFU "select and prepare injection site" provides an image and text indicating that the back of the upper arm is an acceptable location for injection. This location may be acceptable for HCP and Caregiver administration, but the data indicates that it may be difficult for some ACH patients to reach the back of their upper arms. Based on our overall assessment, we find the user interface can be improved. **We provide recommendation in the Identified Issues and Recommendations for Biomarin Table to address this concern**.

8.	For the task "Hold syringe at 45 degrees to the skin" there were 8 failures, for example, the participants injected at a 90 degree angle. The subjective data and the Applicant's root cause analysis stated: Negative Transfer – One HCP participant indicated that she would change the angle depending on the characteristics of the patient to ensure that they were delivering the medication subcutaneously. Slip – participants knew they should inject at 45 degrees, but did not. We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of intramuscular injection (leading to variable bioavailability) / Mild physiological effect (e.g., hypotension, dizziness tachycardia) Our review of the study results identified that the subjective feedback did not identify elements of the user interface that may have contributed to the use errors; however, our review of the labels and labeling (user interface, etc.) finds that step 16 in the IFU "insert the needle at a 45-degree angle" provides an image and text that supports this use task and, based on our expert review, additional labeling mitigations in the IFU are unlikely to further mitigate the risk associated with this use error. We find the residual risk acceptable in this case and do not have further recommendations.
9.	For the task "Slowly push in syringe plunger until full dose is injected" there were 52 use errors (51 failures, 1 close calls). For example, participants did not continue depressing the plunger until the needle guard activated. Per the manufacturer's instructions for the (b) (4) syringe, a full dose is only administered when the needle retraction is activated. The subjective data and the Applicant's root cause analysis stated: Slip/Mistake/Perceptual Error- Participants thought that they pressed down all the way, but the needle didn't retract. Physical Limitation – Some ACH patients were unable to press hard enough to get the needle to retract	Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. We disagree with the Applicant that the use errors were due to user mistakes or physical limitations. The product should be designed to accommodate the intended users, including any physical limitations they may have. Our review of the study results identified that subjective feedback indicated that some ACH patients had difficulty performing this task because they "couldn't squeeze it hard enough", which indicates that the user interface is not optimized for this patient population. Additionally, caregivers indicated that mental models (Stopping the injection when the plunger reached the end of the syringe) and tactile or audible cues (feeling or hearing a "click" or "pop") were perceived as signals that the injection was complete. In an information request response, the applicant indicated that this use error would result in an underdose of approximately 0.01 mL.

	The applicant has not proposed mitigations to address these use errors.	Our review of the labels and labeling (user interface, etc.) finds that step 17 in the IFU "Push the plunger rod all the way" provides images and text that supports this use task. However, we note feedback from some participants that experienced this use error that indicate that they were unable to press the plunger hard enough to get the needle to retract, which indicates that the user interface is not optimized for this user population. Discussion with the clinical team indicates that the level of underdose that could arise from this use error may not be a clinical concern, however, the sponsor should consider using a different administration syringe to further mitigate this use error. Based on our overall assessment, we find the user interface can be improved. **We provide recommendation in the Identified Issues and Recommendations for Biomarin Table to address this concern**.
10.	For the tasks: • Insert administration syringe needle straight through the center of the BMN 111 vial's stopper • Remove administration syringe from vial There were six use errors in total that resulted in a bent needle. The subjective data and the Applicant's root cause analysis stated that these were "mistakes". We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address this use error.	Based on the URRA, failure to perform these tasks could result in a bent needle, which would lead to bruising if used. The subjective feedback indicated that participants indicated that they were uncomfortable or not confident in their ability to insert the needle into the vial, but that they expected to become more confident with more experience. Our review of the labels and labeling indicate that the IFU contains text and images to support these two tasks and to "be careful not to bend needle". Based on our expert review, additional labeling mitigations in the IFU are unlikely to further reduce the residual risk associated with these use errors.

11.	For the task “Store out of the reach of Children” there was 1 use error; a participant misunderstood a question about how they should store the product when small children were present in the home to be about storage conditions. Instead of stating to keep the product out of reach of children, the participant gave storage temperatures. The subjective data and the Applicant’s root cause analysis stated that this was an information oversight. We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of overdose, acute / Mild physiological effect (e.g. hypotension, dizziness, tachycardia) We disagree with the Applicant that this error was an information oversight, as it appears to be a test artifact. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains the bolded text “Store VOXZOGO and all other medicines out of the reach of children” which supports this knowledge task. Based on our expert review, additional labeling mitigations in the IFU are unlikely to further reduce the residual risk associated with this use error.
12.	For the task “Inspect BMN 111 and components for signs of contamination / damage” there was 1 use error; one participant indicated that a cloudy appearance was acceptable. The subjective data and the Applicant’s root cause analysis stated that this use error was attributed to information oversight. We note the root cause analysis for these errors are incomplete, for example the root cause analysis does not indicate what elements of the user interface may have contributed to the use errors. The applicant has not proposed mitigations to address these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of contamination / Systemic infection. Our review of the study results identified that the applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use error. Our review of the labels and labeling (user interface, etc.) finds that step 6 contains the text “Make sure medicine is clear to yellow, not cloudy and essentially particle-free”, which supports this knowledge task and we have not identified additional labeling changes in the IFU that are likely to further reduce the residual risk associated with this use error.
13.	For the task “Clean top of BMN 111 vial with alcohol wipe” there were 9 use errors. The subjective data and the Applicant’s root cause analysis stated that this use error was attributed to test artifact and slips.	Based on the URRA, if this task is omitted or not performed correctly, there is a risk of infection. Our review of the study results identified that the applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use error.

	The applicant has not proposed mitigations to address these use errors.	Our review of the labels and labeling (user interface, etc.) finds that step 1 contains the text "On a clean flat surface, flip off the cap and wipe the top with an alcohol pad". Additionally, step 1 contains a corresponding image showing the vial being wiped with an alcohol pad. We have not identified additional labeling changes in the IFU that are likely to further reduce the residual risk associated with this use error.
14.	For the task "Dispose the used sWFI PFS and diluent needle in the sharps container" and the task ""Dispose of used vial and syringe in sharps container"" nine participants disposed of the vial in the trash, and one disposed of the syringe in the trash. The subjective data and the Applicant's root cause analysis stated that this use error was attributed to negative transfer – participants thought that the sharps container was only for needles. The applicant has not proposed mitigations to address this use error.	Based on the URRA, if this task is omitted or not performed correctly, there is a risk of needle stick injury. Our review of the study results identified that the applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use error. Our review of the labels and labeling (user interface, etc.) finds that step 18 contains the text "Throw away the used vial, syringes, and needles in a sharps container". Additionally, step 18 contains a corresponding image showing the vial and syringes into a sharps container. We have not identified additional labeling changes in the IFU that are likely to further reduce the residual risk associated with this use error.
15.	For the task "Press needle retracting safety tab to retract needle from BMN 111 vial" there were 8 use errors. The subjective data and the Applicant's root cause analysis stated that this use error was attributed to "slips". The participants knew that the needle guard was there, and that they should engage it, but didn't. The applicant has not proposed mitigations to address this use error.	Based on the URRA, if this task is omitted or not performed correctly, there is a risk of needle stick injury. Our review of the study results identified that the applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use error. Our review of the labels and labeling (user interface, etc.) finds that step 5 contains the text "Remove the needle from the vial, then press the blue tab for the needle to pull back (retract). Throw away the needle and syringe in a sharps container. See step 18 and "How to Throw Away (Dispose of) VOXZOGO." Do not use the diluent syringe to administer the injection." Additionally, step 5 contains a corresponding image showing the needle retraction step.

		We have not identified additional labeling changes in the IFU that are likely to further reduce the residual risk associated with this use error.

3.1 ANALYSIS OF OTHER TASK ERRORS

The HF validation study showed use errors, (e.g., failures, difficulties, and close calls) with the following non-critical tasks. We reviewed the available participants' subjective feedback, and the Applicant's root cause analysis to determine acceptability. Our assessment of these user errors finds the residual risk is acceptable, and we have no recommendations to further address the use errors related to the following non-critical use tasks:

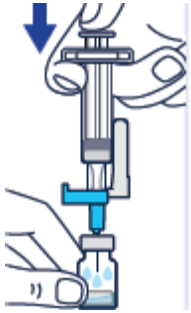
- Wash hands
- Remove flip off cap from BMN 111 vial
- Crack and remove end cap from sWFI PFS
- Attach diluent needle to sWFI PFS
- Let skin air dry (after cleaning)
- Remove 1mL administration syringe from packaging
- Remove needle cap from administration syringe
- Release pinch

3.2 LABELS AND LABELING

Tables 4 and 5 below include the identified medication error issues with the submitted Prescribing Information (PI), Patient Prescribing Information (PPI), Instruction for Use (IFU), carton labels and container labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Of note, the labels and labeling submitted by the Applicant in the NDA submission incorporated a majority of the recommendations previously provided by DMEPA and the Division of Medical Policy Programs[2].

[2] Purcell, J and Fanari, M, HF Study Protocol and Labels and Labeling Review for BMN 111 (IND 111299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Dec 17. RCM No: 2019-2220 and 2019-2221

Table 4. Identified Issues and Recommendations for Division of General Endocrinology			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Patient Prescribing Information			
1.	Post reconstitution storage instructions are not included.	Decrease risk of administering expired products.	The post reconstitution storage conditions should be added to the section entitled "How should I store Voxzogo?" to be consistent with all labeling.
General Issues			
1.	Product strength expression (mg) does not match unit of measure described recommended dosing under Dosage and Administration section (mcg).	Minimize wrong dose medication errors.	Revise the weight-based dosing information (b) (4)
Full Prescribing Information (Section 16)			
1.	Post reconstitution storage instructions are not included.	Decrease risk of administering expired products.	The post reconstitution storage conditions should be added to section 16.2 and to be consistent with all labeling.
Container Label (Drug)			
1.	The package type statement is "Single Dose Vial".	We are concerned that this statement may increase the risk of the entire contents of the vial being given as a single dose.	We defer to CMC to determine the correct package type term; however, we recommend revising the statement 'Single-Dose Vial' to read 'Single-Dose Vial-Discard Unused Portion'.

Table 5. Identified Issues and Recommendations for Biomarin (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instruction for Use (IFU)			
1.	The image in step 4 can be improved. We note that some participants in the HF validation study inadvertently expelled some diluent from the diluent syringe, and that the IFU contains an image of the syringe already inserted into the vial, with a thumb on top of the plunger.	We are concerned that the image in step 4 may have contributed to this use error. 	Consider adding an image or step to indicate to the user that they should first insert the diluent PFS needle into the vial *without* their thumb on the plunger. In this instance we find that you do not need to submit additional HF data if you choose to implement this change.
2.	The instructions for step 7 can be improved. We note that some participants in the HF validation study attempted to use the diluent syringe to withdraw the medication.	We are concerned that Step 7 does not clearly indicate that the user should switch to the injection syringe.	Consider adding a step or language to clearly indicate to the participants that they should use the injection syringe. For example “Retrieve the injection syringe. Pull off the needle cap...” In this instance we find that you do not need to submit additional HF data if you choose to implement this change.

3.	The acceptable injection sites can be better presented. We note that some participants in the HF validation study attempted to inject into their own arm as indicated in the IFU, but were unable to pinch their skin for the injection.	We are concerned that the IFU indicates that the back of the upper arm is an acceptable location for self-injection.	Clarify in Step 13 that injection into the upper arm would only be acceptable for HCP or caregiver administration. In this instance we find that you do not need to submit additional HF data after implementing this change.
4.	The instruction to not use the same injection sites can be improved. We note that some participants in the HF validation study did not rotate the injection site between injections.	We are concerned that users will miss the instruction to change injection sites, because it is in the middle of a list.	Revise step 13 of the IFU to make the warning "Do not inject the same site two times in a row" more easily identifiable. For example, you may consider relocating this text under the text "VOXZOGO should be injected into the fatty layer under the skin (subcutaneous) only" or other means to make this important information stand out.
5.	We note that some participants in the HF validation study were unable to generate the force required to activate the needle guard upon injection, and had difficulty measuring their dose accurately because	We are concerned that the user interface is not optimized for this user group, and that consistent underdose or overdose may result in suboptimal treatment or adverse events.	We advise developing or providing an administration syringe that optimizes safe and effective use of this product for the intended user populations and reduces the risk of underdose or overdose in patients.

	they measured their dose using a design element for needle activation instead of the syringe plunger. These use errors would lead to underdose or overdose.		
Container Labels and Carton Labeling (All)			
1.	Expiration date not defined.	We are unable to assess the acceptability of the proposed expiration date format which may pose risk of administering expired products.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
Container Labels and Carton Labeling (Diluent Syringe)			
1.	Word 'Diluent' lacks prominence compared to other information on label.	We are concerned that the lack of prominence may pose risk of wrong drug medication errors.	Increase the prominence of the word 'Diluent' so that it is the most prominent word on the label.
Outer Carton Labeling (10 vials)			

1.	Post-reconstitution storage statement is not prominently placed and may be overlooked.	We are concerned this placement poses risk of administering expired products.	The post reconstitution storage conditions should be relocated to follow the carton storage conditions.
2.	Usual dosage statement requires revisions.	Per 21 CFR 201.55	Add the following statement to the side panel: "Recommended Dosage: See prescribing information." This statement should replace (b) (4) .
3.	'Date removed from refrigerator' statement requires revisions.	We are concerned the current presentation poses risk of administering expired products.	Revise the statements 'Date removed from refrigerator __/__/__ to read: 'Date removed from refrigerator __/__/__. Discard unused portion 90 days after removal from refrigerator' in bold font.
4.	We note that some users in the HF validation study shook the vial during the reconstitution step.	We are concerned that some users may experience difficulty with recalling that they should swirl the vial during reconstitution instead of shaking it.	We recommend including a statement on the carton that indicates to the user that they should swirl the vial to reconstitute it. For example, "Swirl vial with diluent to reconstitute. Do not shake."

4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrate that trained and untrained participants continue to experience use errors and use difficulties with this product, indicating that the user interface is not optimized for safe and effective use. Thus, DMEPA is concerned that use errors will occur with the introduction of this product to the market.

Changes to the labels and labeling alone are unlikely to meaningfully further reduce the residual risk associated with the observed use errors and use difficulties. n order to meaningfully further mitigate residual risk, it would likely require changes to the product design that that may not be practicable at this point in time if the division intends to approve this product in consideration of the public health need to provide a treatment for achondroplasia. A presentation that better supports the safe and effective use of the product by the intended users, in the intended use environments, may need to be developed. As part of our evaluation, we considered that this patient population may have the benefit of closer patient interaction such as training, skill verification, and more frequent monitoring; however, we note that the sponsor has not developed specific training materials for validation. Furthermore, we note that in the human factors validation study, trained participants experienced similar use errors as untrained participants.

Furthermore, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 4 for the Division and Table 5 for the Applicant. We again emphasize it is unlikely that labeling alone will address the types of use errors seen in the HF validation study. If the division intends to pursue an approval action based on a determination that the overall public health benefit outweigh the residual known risks, at a minimum we request that the Division convey Table 5 in its entirety to the Applicant, and that these recommendations are implemented prior to approval of this NDA. Additionally, we request a post-marketing requirement or commitment that the Applicant develop a validated user interface that better supports the safe and effective use of the product by the intended users, for intended uses, in the intended use environments.

4.1 RECOMMENDATIONS FOR BIOMARIN

The results of the HF validation study demonstrate that trained and untrained participants continue to experience use errors, close calls, and use difficulties with the use of your product, indicating that the user interface is not optimized for safe and effective use. Changes to the labels and labeling alone are unlikely to adequately reduce the residual risks associated with the observed use errors and use difficulties. Additionally, in order to meaningfully further mitigate residual risk, it would likely require developing a different user interface that better supports the safe and effective use of the product by the intended users, in the intended use environments.

Furthermore, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 5 and we recommend that you implement these recommendations prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Voxzogo that Biomarin submitted on August 20, 2020.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Modified recombinant human C-type natriuretic peptide
Active Ingredient (Drug or Biologic)	vosoritide
Indication	For the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed
Route of Administration	subcutaneous
Dosage Form	Injection
Strength	0.4 mg/vial, 0.56 mg/vial, 1.2 mg/vial (b) (4)
Dose and Frequency	(b) (4) given as a single daily dose
How Supplied	Supplied in 0.4 mg, 0.56 mg, 1.2 mg (b) (4) of vosoritide lyophilized powder for reconstitution
Storage	Refrigerate VOXZOGO vials at 36°F to 46°F (2°C to 8°C). Do not freeze. VOXZOGO can be stored at room temperature 68°F to 77°F (20°C to 25°C); excursions permitted to 15°C to 30°C (59°F to 86°F) for 90 days. Do not return VOXZOGO to the refrigerator once stored at room temperature.
Container Closure/Device Constituent	Co-pack which includes ten; sterile, single-dose 2 mL glass vials containing VOXZOGO, either 0.5 mL, 0.6 mL or 0.7 mL diluent (Sterile Water for Injection, USP) in a single-dose prefilled syringe, diluent transfer needles (23 gauge) and single-dose administration syringes (30 gauge) both with needle retraction safety devices
Intended Users	Adult caregivers, Healthcare Providers (HCPs)
Intended Use Environment	Home use, pediatric care setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On December 1, 2020, we searched the L:drive and AIMS using the terms, vosoritide to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[3] and we confirmed that our previous recommendations were implemented.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:
\\CDSESUB1\evsprod\nda214938\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\achondroplasia\5354-other-stud-rep\hfe-ue\hf-report.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\NDA214938\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\achondroplasia\5354-other-stud-rep\hfe-ue

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

The clinical team requested additional information in the 74 day letter to clarify whether the administration syringe used in the clinical trial and in the HF validation studies were the same. The Applicant responded with the following IR:

\\CDSESUB1\evsprod\nda214938\0022\m1\us\111-information-amendment\1111-quality-information-amendment\quality.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Voxzogo labels and labeling submitted by Biomarin.

- Container labels received on August 20, 2020
- Carton labeling received on August 20, 2020
- Instructions for Use received on August 20, 2020;
  \\CDSESUB1\evsprod\NDA214938\0001\m1\us\114-labeling\1141-draft-labeling\11413-draft-labeling-text

[3] Purcell, J and Fanari, M, HF Study Protocol and Labels and Labeling Review for BMN 111 (IND 111299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Dec 17. RCM No: 2019-2220 and 2019-2221

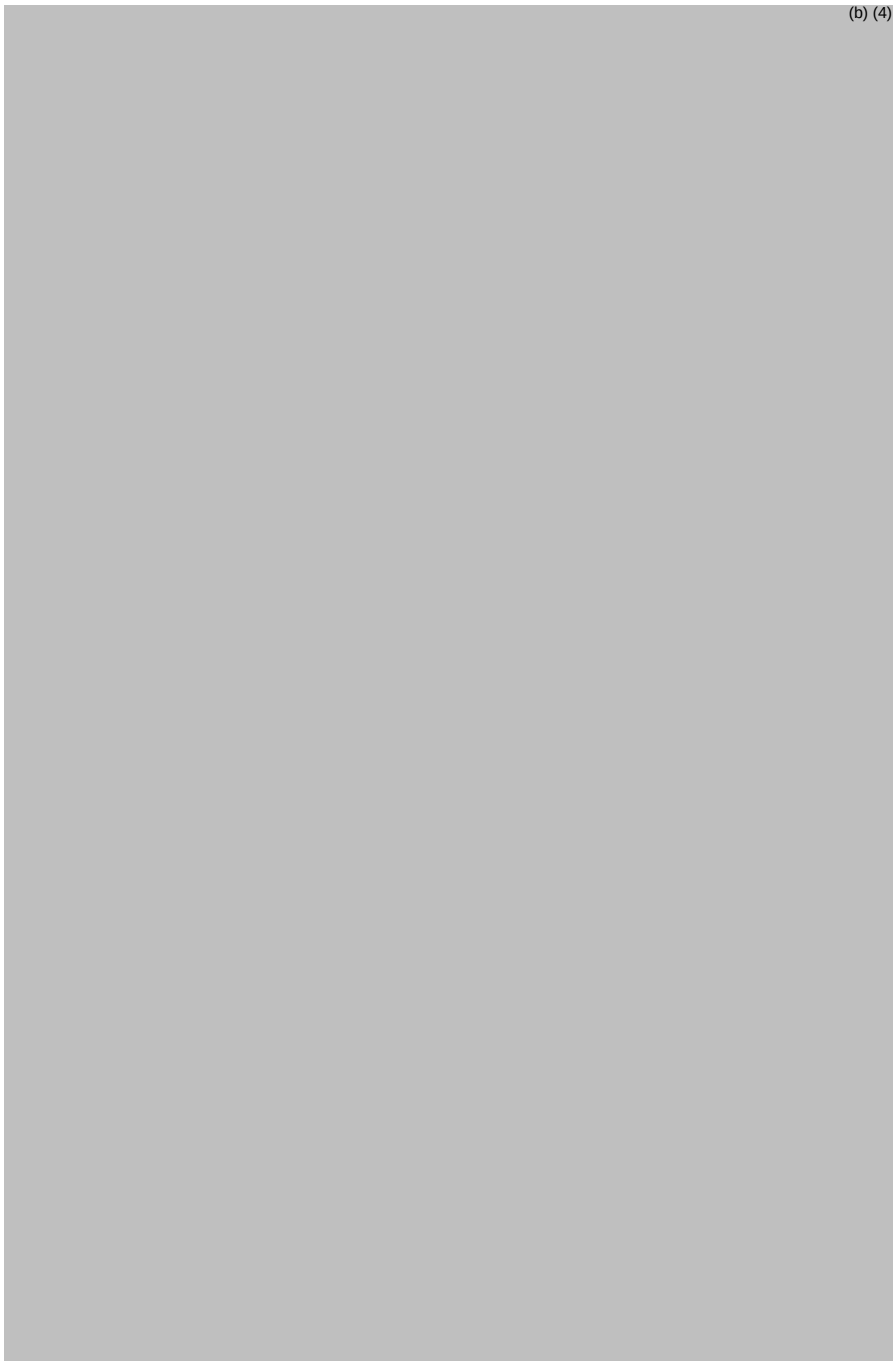
[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Prescribing Information and Patient Prescribing Information(Images not shown) received on August 20, 2020; \\CDSESUB1\evsprod\NDA214938\0001\m1\us\114-labeling\1141-draft-labeling\11413-draft-labeling-text

E.2 Label and Labeling Images

Container Labels (Drug product)

(b) (4)



8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

JASON A FLINT
08/11/2021 10:37:45 AM

MELINA N FANARI
08/11/2021 11:09:11 AM

LOLITA G WHITE
08/11/2021 03:22:14 PM

IRENE Z CHAN
08/11/2021 03:49:15 PM

Memorandum (Pediatric Ethics Consultation)

To: Geanina Roman-Popoveniuc, MD, Medical Officer
Marina Zemskova, MD, Clinical Team Leader
Linda Galgay, Regulatory Project Manager

Division of General Endocrinology (DGE)
Office of New Drugs
Center for Drug Evaluation and Research

From: Elizabeth L. Durmowicz, MD
Medical Officer, Office of Pediatric Therapeutics (OPT)
Office of Clinical Policy and Programs (OCPP)/Office of the Commissioner (OC)

Through: Donna L. Snyder, MD, MBE
Senior Pediatric Ethicist and Team Leader, OPT/OCPP/OC

Dionna J. Green, MD
Deputy Director, OPT/OCPP/OC

Date: August 5, 2021

Subject: NDA 214938; vosoritide (IND 111299, BMN 111)

MATERIALS REVIEWED:

1. Sponsor's Response to IR Issued by FDA on July 19, 2021 submitted to NDA 214938 on July 23, 2021 (eCTD Seq# 0055)
2. Ethics Consultative Request, NDA 214938, vosoritide, dated June 28, 2021, DARRTS Reference ID: 4818145
3. Clinical Review of a Priority Review Request, NDA: 214938, vosoritide, dated September 3, 2020. DARRTS Reference ID: 4666402
4. Synopsis of Study 111-301 and Study 111-206 and 111-208 submitted to NDA 214938 on August 20, 2020 (eCTD Seq #: 0001)
5. Investigator's Brochure (IB), Version 12.0, Release date: April 22, 2020 submitted to the NDA (eCTD Seq#: 0004)
6. Background Document for the Closed Session, and the Background Document and Meeting Minutes for the Open Session of the Joint Meeting of the Pediatric Advisory Committee (PAC) and Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), May 11, 2018
7. Clinical Study Protocol, Study 111-206, Amendment Date February 8, 2019 submitted to IND 111299 on February 19, 2019 (eCTD Seq#: 0107)
8. Pediatric Cluster Teleconference Meeting Notes, December 5, 2017

9. OPT Consults, IND 111299, BMN 111, dated February 23, 2017, DARRTS Reference ID: 4059931, and November 2, 2016, DARRTS Reference ID: 4008016
10. European Medicines Agency (EMA) documents: Protocol Assistance (April 28, 2016), EMA/Pediatric Committee (PDCO) Summary Report (2016), EMA/PDCO Modification Summary Report (December 2017).

Published Literature
The reference list is included at the end of the consultation, following the recommendations.

CONSULT REQUEST
OPT received a consultative request from DGE on June 28, 2021 requesting OPT input on the acceptability of a 2-year placebo control arm in patients with achondroplasia 3 months to 5 years of age after approval of vosoritide in patients ≥ 5 years of age with achondroplasia, and whether placebo control arms should be used in other clinical development programs for treatments of achondroplasia after approval of vosoritide. The following was included in the consult request:

> "The Sponsor (BioMarin) has submitted an NDA application on 08/20/2020 for vosoritide for treatment of achondroplasia in children (b) (4) whose epiphyses are not closed. The Division intends to approve the drug for children with achondroplasia 5 years of age and older with the indication of treatment of short stature (b) (4) The Sponsor is currently conducting a phase 2 study, 206, in children with achondroplasia age 3 month to 5 years, double-blind, placebo-controlled, of 1 year duration, followed by extension study 208, open-label, single arm study, where all children in study 206 will be treated with vosoritide until they reach near final adult height. The Agency would like the Sponsor to extend the study to 2 years using placebo group (as was recommended by Advisory Committee from July 2018) in this younger patient population in order to evaluate durability of the response and potential long-term safety. Please comment on the following issues:
>
> 1) Is it ethically acceptable to use placebo control arm of 2 years duration in younger group of patients enrolled in study 206, once vosoritide would be approved and available on the market for treatment of short stature in older children 5 years of age and older?
>
> 2) Once vosoritide would be approved on the market, is it ethically acceptable to use placebo control arms in other clinical development programs of drugs intended for treatment of achondroplasia or active control arm should be used instead?"

BACKGROUND
Achondroplasia (ACH) is an inherited, autosomal dominant, short-stature skeletal dysplasia caused by a gain of function mutation in the fibroblast growth factor-3 (FGFR3) gene, a negative regulator of endochondral bone formation. Because of abnormal bone growth, patients with ACH are at risk for complications in multiple organ systems, especially the neurological, musculoskeletal, cardiorespiratory, and ear, nose and throat systems. In general, neurological conditions represent the most severe physical complications and are usually related to a decreased size/diameter of the cranio-cervical junction and spinal canal. Age-specific mortality in patients with ACH is increased at all ages. Increased mortality in infants and toddlers is primarily due to sudden death, most often a result of central apnea, a complication of foramen magnum and cervico-spinal stenosis. Individuals with achondroplasia also

experience challenges in mobility, performing activities of daily living and school performance. Altered body schema can result in psychosocial stress.

Although data on the natural history of growth velocity in children with ACH is limited, patterns of growth in children with ACH are different than average stature children: lower rates of growth in children with ACH have been identified during infancy and puberty, periods of rapid linear growth in average stature children. Infants with ACH have shorter birth lengths (i.e., -1.6 standard deviations (SD) below the mean for an average stature infant) and a significant difference in growth rates has been identified (i.e., approximately 20 cm/year in infants with ACH compared to 44 cm/year in average stature infants). Although by 2 years of age, the stature of children with ACH is approximately -5 SD below the mean compared to the average stature children, the growth rates in children 2 years to 10 years of age with ACH (i.e., 3-5 cm/year) are similar to those in average stature children (5-7 cm/year).[1] However, after 10 years of age growth rates in average stature children range from 5.5 cm to < 7 cm/year whereas growth rates remain at 4-5 cm/year in children with ACH. Median height velocities during puberty in children with ACH remain at approximately 5 cm/year in boys and girls. In contrast, median height velocity in average stature boys is 9.3 cm/year aged 13.5 years and 8.3 cm/year in girls aged 12 years.

(b) (4)

no therapeutic is FDA-approved for ACH and treatment is focused on supportive care.

Important elements of drug development programs for products intended for the treatment of ACH were discussed during the open session of the Joint Meeting of the PAC and EMDAC in May 2018. During this session the Committee:

- Stated that studying the sub-population of children < 2 years of age with ACH should be the priority.
- Suggested that the greatest benefit for patients with ACH may be through improvement in early growth parameters.
- Emphasized that conducting trials in younger children during a critical period of growth may be the most informative and impactful noting that if annualized growth velocity (AGV) is targeted, the duration of study may be shorter and sample sizes smaller, given that growth occurs rapidly.
- Stressed the importance of collecting comprehensive and consistent postmarket data to assess long-term safety.
- Agreed that a randomized, blinded, placebo-control trial design is critical for the evaluation of efficacy and safety for products intended to treat ACH, noting that a randomized, controlled trial would ultimately be necessary in patients < 2 years of age.
- Agreed that the duration of study should be at least 2 years to obtain adequate growth data.

Product Description

Vosoritide (BMN 111), a lyophilized powder for solution for daily subcutaneous (SC) injection, is a modified recombinant human C-Type natriuretic protein (CNP) that stimulates proliferation of

[1] Physical Growth of Infants and Children. Merck Manual. Available at: https://www.merckmanuals.com/professional/pediatrics/growth-and-development/physical-growth-of-infants-and-children. Accessed July 2, 2021.

chondrocytes in growth plates and, as such, is hypothesized to result in long bone growth in patients with ACH. (b) (4)

In August 2020, the Applicant submitted the NDA for vosoritide seeking an indication for the treatment of ACH in patients (b) (4) whose epiphyses are not closed. The NDA includes data from the completed trial in patients ≥ 5 years (Study 111-301) and preliminary results from patients 2 years to < 5 years in the ongoing Study 111-206 (See "Evidence to Support Prospect of Direct Benefit" and "Brief Synopsis of Studies 111-206 and 111-208", below).

The Sponsor's vosoritide development program is multinational, and FDA discussed the program at a Pediatric Cluster Teleconference (December 2017). The European Medicines Agency (EMA) provided protocol assistance to the Sponsor in April 2016, adopted a pediatric investigation plan (PIP) in December 2017 and accepted a modification of an agreed PIP in February 2020.[2] The modification request included changes to the Statistical Analysis Plan and an extension to the agreed completion date for Study 111-301.

> ***Reviewer Comment:***
> *Based on the review of these EMA documents and the Pediatric Cluster Minutes from 2017, FDA and EMA's positions on the development of vosoritide for treatment of ACH appeared, in general, to be aligned; however, EMA has considered annualized growth velocity (AGV) a "sufficient endpoint." In contrast, DGE has expressed concerns that 1-year AGV may not be clinically meaningful, a concern that is consistent with opinions shared by Little People of America suggesting that height increase, or final height may not be as important an outcome compared to other outcomes such as spinal stenosis and quality of life.*
>
> *Of note, in contrast to DGE's planned age of vosoritide approval, the EMA appears to be planning to approve vosoritide in a younger patient population (see Brief Synopsis of Studies 111-206 and 111-208, below)*

Evidence to Support Prospect of Direct Benefit

The Applicant's vosoritide development program in patients with ACH includes completed Study 111-202, a phase 2, up to 24 month, open-label, dose-escalation trial in patients 5 years to 14 years of age, and completed Study 111-301, a multinational, phase 3, 52-week, double-blind, placebo-controlled trial in patients 5 years to < 17 years of age evaluating change from baseline in AGV. Secondary endpoints included change from baseline height Z-score, change from baseline in upper to lower segment body ratio, effects on bone morphology and pathology by radiographs and dual X-ray absorptiometry (DXA), change in health-related quality of life, and change in functional independence (see Appendix II: Study 111-301 Objectives). Long-term safety and efficacy extension trials, Studies 111-205 (for Study 111-202) and Study 111-302 (for Study 111-301), are ongoing. Additional ongoing vosoritide trials for treatment of ACH include trials in patients from birth to < 60 months of age (see Brief Synopsis of Studies 111-206 and 111-208 (below) and Appendix III: Listing of Clinical Studies).

[2] European Medicines Agency decision P/0060/2020 (EMEA-002033-PIP01-16-M01). Available at: https://www.ema.europa.eu/en/documents/pip-decision/p/0060/2020-ema-decision-10-february-2020-acceptance-modification-agreed-paediatric-investigation-plan_en.pdf. Accessed July 16, 2021

Per the Applicant, Study 111-301 demonstrated that after 52 weeks, the difference in AGV in vosoritide treated patients compared to placebo was 1.57 cm/year (95% confidence interval (CI): 1.22, 1.93, with a two-sided p<0.0001) and these results are supported by the long-term data from Studies 111-202 and 111-205, which demonstrated a sustained treatment effect (i.e., improvement in height of over 9 cm) with vosoritide during 5 years of follow-up. Key secondary endpoints supporting vosoritide efficacy included change from baseline in height Z-score (0.28, 95% CI 0.17, 0.39, two-sided p-value <0.0001) and change from baseline in upper to lower body segment ratio (-0.01, 95% CI:-0.05, 0.02, two-sided p-value = 0.5060).[3]

The clinical program completed to date has not evaluated the effects of vosoritide on serious aspects of ACH, including physical manifestations (e.g., final adult height or improvement in disproportional growth), complications (e.g., foramen magnum stenosis, spinal stenosis), comorbidities (e.g., otitis media, hearing loss, sleep apnea, dental abnormalities), or survival.

> ***Reviewer Comment****:*
> *We note FDA raised concerns with the Applicant during the vosoritide development program that data from a 1-year trial may not be adequate to demonstrate a clinically meaningful benefit and encouraged the Applicant to conduct a 2-year placebo-controlled trial to evaluate the duration of effect and long-term safety.*
>
> *Although the changes in AGV and height Z-scores in the phase-3 trial in patients ≥ 5 years are statistically significant, the increase in AGV identified with vosoritide treatment seems modest over a 1-year period; however, this gain in height if sustained over multiple years may be clinically meaningful, especially in patients with ACH who may reach a height that improves their ability to perform activities of daily living.*
>
> *DGE has determined that the 1-year placebo-controlled data submitted from Study 111-301 are adequate to support an accelerated approval for treatment of "short stature" in patients ≥ 5 years of age with ACH based on growth velocity as a surrogate endpoint. The confirmatory clinical trial in patients ≥ 5 years of age will require evaluation of final adult height to confirm efficacy.*

Safety

The safety data from the clinical trials do not appear to reveal a major safety signal with vosoritide treatment. Adverse events (AEs) of special interest include injection site reactions and hypotension (likely related to CNP being a natriuretic peptide that causes natriuresis and vasodilatation). No deaths were reported in the clinical program.

Brief Synopsis of Studies 111-206 and 111-208

The Applicant is currently conducting Study 111-206, a phase 2, multinational, 52-week, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of vosoritide in approximately 70 patients with ACH from birth to 5 years of age, and Study 111-208, an open-label, long-term extension trial of Study 111-206, to evaluate the safety and efficacy of vosoritide until the patient attains near final adult height (NFAH). The primary objectives of both trials are to evaluate the safety and tolerability of

[3] Per the Applicant, the nonsignificant change in body segment ratio indicates that the positive change in growth velocity was not associated with a negative impact on body proportions.

vosoritide and to evaluate the effect of vosoritide on change from baseline in length/height Z-scores. Secondary objectives include evaluations of vosoritide on quality-of-life measures, incidence of surgical and medical interventions related to ACH, sleep disordered breathing and skull and brain morphology (See Appendix IV: Objectives Study 111-206). Study 111-206 has three planned cohorts: Cohort 1 (patients ≥ 24 to <60 months of age), Cohort 2 (patients 6 to <24 months of age), and Cohort 3 (patients birth to <6 months of age). Patients in Cohorts 1 and 2 must have at least 6 months of pretreatment growth assessment immediately prior to study entry, and subjects in Cohort 3 must have at least 3 months of pretreatment growth assessment.[4]

[4] These data are being collected in Study 111-901, a prospective, observational study collecting growth measurements on patients being considered for enrollment in a vosoritide treatment trial.

[5] (b) (4)

(b) (4)

ANALYSIS/RESPONSE/RECOMMENDATIONS

The Additional Safeguards for Children (21 CFR 50 subpart D) must be considered when pediatric patients will be enrolled in a clinical trial. Unless the risks of an investigational agent are no more than a minor increase over minimal risk (21 CFR 50.53), the administration of an investigational agent in children must offer a prospect of direct clinical benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52). Additionally, adequate provisions must be made to obtain the permission of the parents and the assent of the child (21 CFR 50.55).

We note that patients who are receiving placebo in a trial do not directly benefit from participation in the trial. Therefore, the risks of patients receiving placebo in this trial must not exceed a "minor increase over minimal risk" (21 CFR 50.53), and the risks of placebo administration must be considered. Although the trial procedures in Study 111-206 do not exceed a minor increase over minimal risk, considerations regarding the risks of placebo include the method of administration of the placebo (e.g., oral versus injection), the frequency and duration of placebo administration, and the risks of withholding therapy while placebo is administered. FDA has precedent for allowing daily intramuscular placebo injections for 2 years in pediatric trials of multiple sclerosis.[6]

Given that (b) (4) current standard of care (SOC) does not include vosoritide, inclusion of a placebo-control group in patients < 2 years of age would not be considered withholding therapy. As such, if DGE determines that a placebo-control design is scientifically necessary in patients < 2 years of age (b) (4) then a trial that includes SC placebo injections for 2-years duration would be acceptable under subpart D, if participation in the trial also contributes to generalizable knowledge for understanding or ameliorating ACH (21 CFR 50.53). However, DGE must consider the feasibility of a 2-year placebo-controlled trial: there may be a perception in the community that vosoritide is beneficial in the pediatric population overall, and equipoise no longer exists.

[6] Per the United States Prescribing Information (USPI) December 2019 and the Cross Team Leader Review (April 15, 2018) for fingolimod (Gilenya®, NDA 022527) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022527s031lbl.pdf and https://www.fda.gov/media/114305/download, respectively. Accessed on July 14, 2021

OPT'S RESPONSES TO DGE'S CONSULT QUESTIONS

DGE Question 1:
"Is it ethically acceptable to use placebo control arm of 2 years duration in younger group of patients enrolled in study 206, once vosoritide would be approved and available on the market for treatment of short stature in older children 5 years of age and older?"

OPT Response:
Given that Study 111-206 is fully enrolled, we do not agree with trying to extend this trial for an additional year.

However, even if this trial had not been initiated, given the similarity of growth in patients 2 years to < 5 years of age compared to patients ≥ 5 years of age, and that DGE intends to approve vosoritide in patients ≥ 5 years of age for treatment of short stature in patients with ACH based on 1-year of placebo-controlled data, a strong scientific rationale for requiring 2-year placebo-controlled data in this age cohort does not appear to exist and a 2-year trial would likely not be feasible, especially in the setting of an ex-US approval of vosoritide in patients ≥ 2 years of age.

If DGE has strong scientific justification to support that a 2-year placebo-controlled trial of vosoritide in patients < 2 years of age with ACH is necessary to evaluate long-term safety and effectiveness of vosoritide, a daily, placebo SC injection control arm for this duration in this patient population in which vosoritide is not approved is acceptable under subpart D, with the caveat that participation in the trial also contributes to generalizable knowledge for understanding or ameliorating ACH (21 CFR 50.53).

DGE Question 2:
Once vosoritide would be approved on the market, is it ethically acceptable to use placebo control arms in other clinical development programs of drugs intended for treatment of achondroplasia or active control arm should be used instead?"

OPT Response:
Yes, it may be acceptable to use placebo control arms in other clinical development programs for ACH after vosoritide is approved. However, we note the distinction between the use of placebo in the setting of an accelerated approval vs. a full approval. If DGE issues a full approval of vosoritide, new products would need to be compared to vosoritide if the new product is seeking the same indication in the same age group in which vosoritide receives full approval (see discussion below).

However, we anticipate a placebo control arm may raise problems of trial acceptability and enrollment may be challenging, especially for products seeking the same indication as vosoritide and in patients in the age cohort(s) in which vosoritide will receive accelerated approval in the US and approval ex-US. Given that the pediatric ACH development programs appear to be primarily multinational trials, use of placebo in age groups in which vosoritide is likely to be fully approved in other countries (i.e., patients ≥ 2 years of age), will likely not only impact the ability to collect placebo-controlled data in the age cohort in which vosoritide is approved in the US, but also in patients down to 2 years of age.

For clinical investigations involving serious conditions, placebo alone is generally only acceptable as a

comparator when there is no established standard of care,[7] and in general, new interventions, especially those targeting the same indication, must be tested against the best proven treatment.[8] In the setting where the only available product has been approved via accelerated approval, such as the anticipated approval of vosoritide, a degree of uncertainty of the product's ability to result in a clinically meaningful benefit remains. As such, this uncertainty may provide scientific support for including a placebo control arm. In situations in which a placebo is necessary for scientific reasons to determine the safety or efficacy of the intervention, conducting a placebo-controlled trial may be acceptable if the patient will not be exposed to serious or irreversible harm as a result of not receiving the best proven intervention. Although DGE has determined that delaying growth hormone therapy in patients with growth hormone deficiency for 1- year will not result in irreversible harm, DGE must determine whether delaying or withholding vosoritide treatment in patients with ACH for 1 or 2 years, or the proposed duration of the placebo control, may result in irreversible harm. We note that the informed consent documents (ICDs) must adequately communicate the potential risks of withholding or delaying administration of the best proven intervention.[9,10]

The acceptability of placebo will likely be dependent on the age cohort being evaluated:

- Patients ≥ 5 years of age
  Given that DGE will likely approve vosoritide via the accelerated approval pathway for treatment of short stature in patients with ACH which reflects uncertainty about whether vosoritide will offer patients a clinically meaningful benefit, a placebo control arm may be scientifically acceptable for clinical trials of other therapeutics; however, the ability of a placebo-controlled trial to enroll may be limited given that vosoritide will likely be available outside of a clinical trial in this age cohort.

- Patients 2 years to < 5 years of age
  If off-label use of vosoritide (or another to-be-approved therapeutic) is not considered standard of care (SOC), a placebo-controlled trial in the US in this age cohort would be ethically acceptable. However, given that clinical trials of ACH have generally been multinational trials and the EMA appears to be planning to approve vosoritide in patients down to 2 years of age,[11] enrollment in a multinational, placebo-controlled trial in this age cohort may not be feasible.

- Patients < 2 years of age
  Including a placebo control arm in this age cohort in which vosoritide is not approved (in any country) would likely not be withholding SOC, and likely less challenging than including a placebo control in the older pediatric age cohorts.

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[7] Council for International Organizations of Medical Sciences (CIOMS), "International Ethical Guidelines for Health-related Research Involving Humans", Guideline 5, dated 2016, available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf
[8] Declaration of Helsinki (2013)
[9] Ibid
[10] The International Conference on Harmonization "Choice of Control Group and Related Issues in Clinical Trials" (ICH E10)
[11] Summary of opinion (initial authorization) vosoritide (Voxzogo). June 24, 2021. Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-voxzogo_en.pdf. Accessed July 16, 2021.

A trial in which a placebo control arm may be more likely to be feasible may include a trial in a patient population who refuse an injectable medication, in a patient population in which vosoritide is contraindicated, evaluating an indication other than improved AGV, in patients who reside in a country in which vosoritide is not approved (if the Applicant will make the product available in the country after completion of the trials) and in age cohorts of patients in which vosoritide is not approved. (b) (4)

(b) (4)

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Appendix II: Study 111-301 Objectives

Primary objective

- Evaluate change from baseline in AGV at 52 weeks in patients treated with vosoritide compared with controls

Secondary objectives:

- Evaluate change from baseline in height Z-score in patients treated with vosoritide compared with controls at 52 weeks
- Evaluate change from baseline in upper to lower segment body ratio in patients treated with vosoritide compared with controls at 52 weeks
- Evaluate change from baseline in body proportion ratios of the extremities
- Evaluate the effect of vosoritide on bone morphology and pathology by X-ray and DXA
- Evaluate potential changes in health-related quality of life (HRQoL) as measured by the Quality of Life in Short Stature Youth (QoLISSY) and Pediatric Quality of Life Inventory (PedsQL) questionnaires
- Evaluate potential changes in functional independence as measured by the Functional Independence Measure for Children (WeeFIM) clinician-reported outcome
- Evaluate safety and tolerability of vosoritide in children with ACH
- Evaluate the pharmacokinetics (PK) of vosoritide
- Evaluate the immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures
- Evaluate change from baseline in bone metabolism biomarkers

Exploratory objectives:

- Evaluate sleep study scores by polysomnography in a subset of subjects
- Evaluate biomarkers of vosoritide activity
- Evaluate genomic biomarkers

Appendix III: Listing of Clinical Studies[12]

Study Identifier/ Location	Primary Objective(s)	Study Design and Type of Control	Dosage Regimen	Subjects Enrolled	Study Population	Duration of Follow-Up	Date of Study Initiation	Status at time of MA	Report data included in MA
111-101 5.3.3.1	To evaluate the safety and tolerability of single and escalating, and multiple and escalating SC injections of vosoritide compared with placebo in healthy adult male volunteers	Phase 1, double-blinded, placebo-controlled	Part 1: Single SC doses of vosoritide at 5, 10, or 15 µg/kg Part 2: Multiple SC doses of vosoritide ranging from 0.5 to 8 µg/kg	48	Healthy male volunteers	Part 1: 9 days Part 2: 25 days	14FEB2012	Completed	Full complete CSR
111-901 5.3.5.4	To collect consistent baseline growth measurements on pediatric subjects being considered for subsequent enrollment in 111-202, 111-301, and 111-206	Prospective, non-interventional	NA	342	Pediatric subjects with ACH from birth to <17 years of age	Observation period of up to 7 years	20APR2012	Ongoing	Interim full CSR (data cut-off date 31MAY2019)
111-202 5.3.5.2	To evaluate the safety and tolerability of daily SC injections of vosoritide administered to children with ACH	Phase 2, open-label, sequential cohort dose-escalation, global, multicenter	Daily SC dose of vosoritide at 2.5, 7.5, 15, or 30 µg/kg	35	Pediatric subjects 5-14 years old with ACH	Up to 24 months (initial 6-month and optional 18 months extension)	13JAN2014	Completed	Full complete CSR
111-205 5.3.5.2	To assess the long-term safety, tolerability, and efficacy of daily SC injections of vosoritide in children with ACH	Phase 2 open-label extension of 111-202	Daily SC dose of vosoritide at 15 or 30 µg/kg	30	Subjects with ACH who completed 2 years of vosoritide treatment in 111-202	5 years, or until subject attains NFAH (evidence of growth plate closure and 6 month interval AGV <1.5 cm/year), whichever comes later	26JAN2016	Ongoing	Interim full CSR (data cut-off date 20NOV2019)
111-301 5.3.5.1	To evaluate the efficacy and safety of daily SC injections of vosoritide in children with ACH	Phase 3, double-blinded, placebo-controlled	Daily SC dose of vosoritide at 15 µg/kg	121	Pediatric subjects 5-<18 years old with ACH	60 weeks (4 weeks screening 52 weeks of treatment with an additional 4 weeks of safety follow-up)	12DEC2016	Completed	Full complete CSR
111-302 5.3.5.2	To assess the long-term safety, tolerability, and efficacy of daily SC injections of vosoritide in subjects with ACH	Phase 3 open-label extension of 111-301	Daily SC dose of vosoritide at 15 µg/kg	119	Subjects with ACH who completed 111-301	5 years, or until subject attains NFAH (evidence of growth plate closure and 6 month interval AGV <1.5 cm/year), whichever comes later	12DEC2017	Ongoing	Interim full CSR (data cut-off date 31OCT2019)
111-206 5.3.5.1	To assess the safety and efficacy of daily SC injections of vosoritide in younger children with ACH	Phase 2, randomized, double-blind, placebo-controlled, global, multicenter	Age appropriate daily dose for subjects <5 years or 15.0 µg/kg in subjects ≥5 years	44	Pediatric subjects from birth to <60 months old with ACH	60 to 72 weeks (4 weeks screening 52 weeks of treatment with an additional 4 weeks of safety follow-up; Cohort 3 had a 12 week observational period after screening)	13JUN2018	Ongoing	Interim full CSR (data cut-off date 12SEP2019)
111-208 5.3.5.2	To assess the long-term safety, tolerability, and efficacy of daily SC injections of vosoritide in children with ACH	Phase 2 open-label extension of 111-206	Age appropriate daily dose for subjects <5 years or 15.0 µg/kg in subjects ≥5 years	4	Pediatric subjects with ACH who completed 111-206	Until subject attains NFAH (evidence of growth plate closure and 6 month interval AGV <1.5 cm/year)	13JUN2019	Ongoing	Interim full CSR (data cut-off date 12SEP2019)

ACH: achondroplasia; AGV: annual growth velocity; CSR: Clinical Study Report; MA: Marketing Application; NFAH: near final adult height; NA: not applicable; SC: subcutaneous.

[12] Tabular Listing of Clinical Studies (5.2) from the original NDA submission.

Appendix IV: Objectives Study 111-206

Primary objectives:

- Evaluate the safety and tolerability of vosoritide in children age 0 to < 60 months with ACH
- Evaluate the effect of vosoritide on change from baseline in length/height Z-score

Secondary objectives:

- Evaluate the effect of vosoritide on change from baseline in AGV
- Evaluate the effect of vosoritide on bone morphology/quality by X-ray and DXA
- Evaluate the PK of vosoritide in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of vosoritide on HRQoL, developmental status, and /functional independence using age-specific Qo) and functional independence questionnaires/QOL status (Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III]), Wee-FIM, Infant Toddler Quality of Life Questionnaire (ITQOL), Child Behavior Checklist (CBCL)
- Evaluate immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of vosoritide on bone metabolism and vosoritide pharmacodynamic biomarkers
- Evaluate the effect of vosoritide on growth parameters and body proportions, including change from baseline in upper to lower body segment ratio
- Evaluate the effect of vosoritide on sleep apnea
- Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

Exploratory objectives:

- Document physical and phenotypic changes with clinical photography (optional)
- Evaluate genomic biomarkers (optional)

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/s/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

U.S. FOOD & DRUG ADMINISTRATION

Memorandum
(Immunogenicity Assay Review)

Date:	August 3, 2021
To:	File for NDA 214938/SDN1
From:	Milos Dokmanovic, Ph.D., RAC, Product Quality Reviewer, DBRRI/OBP
Through:	Brian Janelsins, Ph.D., Team Leader, DBRRI/OBP
Product:	Vosoritide, also known as BMN111, is a modified recombinant human C-type natriuretic peptide (CNP)
Indication(s):	Treatment of achondroplasia in patients (b) (4) whose epiphysis are not closed
Dose regimen:	BMN111 is proposed to be administered subcutaneously (s.c.) once daily (b) (4)
Product stage:	New NDA submission
Sponsor:	BioMarin Pharmaceutical, Inc.
Received by FDA:	August 20, 2020
PDUFA Due date:	November 20, 2021
Consult received by OBP:	March 2, 2021
Consult due:	July 21, 2021

Recommendation: From OBP's perspective, the assays proposed for immunogenicity testing are sufficiently evaluated and suitable to support the marketing application.

Note: Figures were copied directly from the submission. Assessor comments are emphasized in *italics*.

Background

Vosoritide (BMN 111) is a 39-amino acid analogue (4kDa) that includes two amino acids (Pro-Gly) on the N-terminus for half-life extension followed by 37-amino acid sequence derived from human CNP53 peptide. Vosoritide is manufactured in E.coli and commercial drug product is provided as a lyophilized powder for

solution in [redacted] strengths (0.4mg/vial, 0.56mg/vial, 1.2mg/vial, [redacted] Prior to administration, the drug product is reconstituted with sterile water for injection to obtain 2mg/mL solution for injection.

Evaluation of immunogenicity was planned in four phase 2 and phase 3 studies (111-202, 111-205, 111-301 and 111-302) and included a tiered approach: any sample that screened and confirmed positive for total anti-drug antibodies (TAb) was analyzed for Tab titer, neutralizing antibody (NAb) and NAb titer, and potential for cross-reactivity to endogenous natriuretic peptide molecules (NP, atrial NP [ANP], B-type NP [BNP], and CNP). Additionally, in case of a pre-defined qualifying event (e.g. anaphylaxis, hypersensitivity reaction), the clinical sample would be also analyzed for anti-drug IgE antibodies pre- and post-treatment. The conclusions from the clinical studies are summarized below:

- There were up to 38% of all subjects (59/156) who developed TAbs with titers within 14-18500 range.
- The NAbs developed in 2% (3/156) of patients, however, all NAb incidences were transient and were resolved at subsequent time-points.
- The % of TAb samples who showed cross-reactivity to ANP, BNP and CNP was 30%, 3% and 19%, respectively; however, detected cross-reactivity did not correlate with any safety signals in any of the studies.
- There was no grade 3 hypersensitivity or anaphylaxis adverse events reported to-date in the study and therefore testing of anti-drug IgE antibodies was only included in the pre-treatment samples.

Assessor comment: *Importantly, the analysis of clinical studies 111-205 and 111-302 is still ongoing and it appears that at least some of the initially analyzed samples would require additional analysis, because of the updates in the cut points used (see details in the memo). The final results are expected in the CSR for 111-301/302.*

Section 5.3.1 (Reports of Biopharmaceutical Studies)

I. Detection of Anti-BMN 111 (ProCNP38) Total Antibodies in Human Serum Validation report (BMN111-12-022)

Validation approach included assessment of screening, confirmation and titer cut-point, confirmation cut-point for cross-reactivity to endogenous proteins (ANP, BNP, and CNP), inter- and intra-assay precision, sensitivity (LOD), drug tolerance, robustness, specificity, selectivity, stability and QC acceptance ranges.

Assessor comment*: A total of four validation studies were conducted to support method suitability:*

- *The original validation study (BMN111-12-022) did not include assessment of cross-reactivity to endogenous proteins and was only used to support a Phase 1 study in the healthy male subjects; however, the evaluation was not used to support conclusions regarding overall immunogenicity rate.*
- *Amendment 1 included all relevant validation parameters (including cross-reactivity to endogenous proteins) and was intended to support the analysis of Phase 2 study samples from male and female*

subjects. However, because of inconsistent and unexpected assay performance due to implementation of new assay reagents, all results from amendment 1 were rejected, and were not included in the final validation report. Follow-up investigation showed that the likely cause for discrepancy was that the assay reagents were not sufficiently optimized and could cause a drift in assay performance.

- *Amendment 2 (also referred as BMN111-12-022 A2) re-evaluated all validation parameters (except for robustness) using optimized reagents (e.g. labelled reagent concentrations) and the results were used to support the analysis of phase 2 and 3 study samples in male and female subjects.*
- *Amendment 3 included evaluation of lower LPC at 40 and 50 ng/mL; however, these consistently generated 0% screen failure rate which was not a desired 1% failure rate. To enable determination of an LPC that would be more appropriate (e.g. targeting 1% failure rate), re-evaluation was performed on additional lower LPC concentration levels (1, 3 and 20 ng/mL) and therefore amendment 3 included only selected validation parameter (LOQ, inter-and intra-assay precision, reagent stability, and new HQC qualification) to support the analysis of Phase 2 and 3 study samples using adjusted LQC.*

A total of 48 runs was performed in the original validation study, 158 runs in amendment 2 and 29 in amendment 3; all validation runs were successfully completed, and no failures were noted. Deviations from all studies were primarily related to the editorial and technical mistakes (pipette calibration, incubation times, expired reagents). A single deviation PR159487 is related to the use of LQC concentrations of 40 and 50ng/mL to confirm their adequacy to target the 1% failure rate, however, that deviation was addressed in amendment 3 and it was determined that the results support lower LQC concentration at 20ng/mL . Overall, there was no impact of any deviation on the study validity, except for the deviation related to comparability in the QC ranges which resulted in invalidation of amendment 1 study results.

This review memo will primarily focus on the results from amendments 2 and 3 for all evaluated validation parameters and will also include the results from the original study, where appropriate, to support assay suitability for intended use (e.g. analysis of precision, reagent stability, robustness, etc.).

Analytical method

The analytical method, based on electrochemiluminescence (ECL)-based bridging assay, was used for screening and confirmation, and for determination of titer and cross-reactivity to endogenous NP proteins (ANP, BNP and CNP). The assay reagents (biotin-and ruthenium-tagged BMN 111) were prepared and incubated in equal concentrations with 1:10 diluted human serum samples. Following incubation, the mixture was incubated onto streptavidin-coated plates to capture any drug-antibody complexes. After the final wash, the MSD read buffer T was added, followed by tripropylamine -based reaction to generate electrochemiluminescence signal. In the screening assay, all samples that screened above the screening cut-point were considered to be potentially positive and were analyzed in confirmatory assay.

For sample confirmation, the same assay procedures are followed as in screening assay, except that all samples (test and control) are either pre-treated or not with 10 µg/ml unlabeled BMN111. The final result from

confirmation assay is reported as the percentage signal inhibition (%SI) according to the following formula: %SI=[1-mean confirmation signal/mean screen signal]x100. All samples with %SI greater or equal than the confirmation cut point were determined to be positive.

For titration assay, same procedures were followed as in screening assay except that test and control samples are serially diluted and the sample titer was interpolated at the signal value of the dilution curve crossing the titer cut point. The final concentration is calculated by multiplying the result of assay by MRD (minimum required dilution) of 1:10 to determine the concentration.

For cross-reactivity to endogenous NP proteins, the assay procedures were the same, except that the 1:10 diluted human serum samples were either spiked or not with recombinant human ANP, BNP, or CNP-22 (10 µg/ml) . The result for cross-reactivity (%SI) was calculated similar as in confirmation assay (see above). The samples with signal inhibition greater than or equal to the cross-reactivity cut-point were reported as positive for cross-reactive ADA.

Materials (all included studies: original validation study and amendments 2 and 3)

a) Reference material (BMN 111 (b) (4) (2 lots: lot P2204-11002 in original validation and lot P2204-13101 in amendments 2 and 3; (b) (4)
b) Positive control source: protein A-purified rabbit IgG polyclonal antibody against CNP (3 lots: lot 10498 in original validation, lot A12525 in amendment 2 and lot A16047 in amendment 3; see details in table below).
c) Biotin -labelled BMN 111 (2 lots: lot BAS-R12-080 in original validation and lot BAS-R14-0021 in amendments 2 and 3)

Implemented control	PC concentration	Number of PC lots	NHS matrix used in control preparation
Negative quality control (NQC): normal human pooled serum (NHPS)			
NQC	0 ng/mL	N/A	(b) (4) sourced lot BAS-R12-527 (the same lot used in all three studies)
Cut point control (CC): normal human pooled serum (NHPS)			
CC	0ng/mL	N/A	(b) (4) -sourced lot BAS-R12-526 (the same lot used

d) Ruthenium-labelled BMN 111 (2 lots: lot BAS-R12-081 in original validation and lot BAS-R14-0022 in amendments 2 and 3)
e) Positive and negative controls (summarized below):

			in all three studies)
Positive quality control: affinity purified rabbit anti-CNP polyclonal antibody diluted in NHPS			
HQC (high quality control) TQC (titer quality control)	10000ng/mL	3 lots (lot BAS-P12-1045 in original validation, lot BAS-P14-1207 in amendment 2 and lot BAS-P17-1681 in amendment 3)	Lots BRH1281057 and BAS-R12-526 (b) (4)
LQC (low quality control)	200ng/mL	2 lots (lot BAS-P14-1046 in original validation and lot BAS-P14-1208 in amendment-2)	Lot BAS-R12-526 (b) (4)
	1ng/mL	1 lot (lot BAS-P18-0044 in amendment 3)	
	20ng/mL	1 lot (lot BAS-P18-0205 in amendment-3)	Lots BRH1281057
	3ng/mL	1 lot (lot BAS-P18-0043 in amendment 3)	
	40ng/mL	1 lot (lot BAS-P17-1683 in amendment 3)	
	50ng/mL	1 lot (lot BAS-P17-1682 in	

		amendment 3)	

Assessor comment: *It is not clear of the immunogen used to derive the positive control (PC) for the validation study is appropriate. The information included in Table 8.1.2 of validation report identifies C-type natriuretic peptide (CNP, 32-53) as immunogen; however, this description is not consistent with vosoritide drug description which is a 39 amino acid recombinant peptide which includes native human CNP and additional Pro-Gly amino acid extension on the amino terminus (Section 3.2.S.2.1). In principle, the positive control used in validation study should be derived against BMN111 drug, or alternatively, appropriate justification should be included to support that the immunogen chosen for derivation of positive control is sufficiently representative of BMN111 drug (e.g. presence of major epitope regions, etc.) and derived positive control is appropriate for evaluation of assay suitability. IR was conveyed to clarify the source of immunogen used to derive the positive control, and if appropriate, provide justification to support the use of CNP-based peptide to derive respective positive control used in validation study. The Sponsor clarified that the immunogen used for derivation of PC was derived from CNP-22 protein, which is a predominant form of CNP in human peripheral blood and includes functional and immunogenic domains of vosoritide drug. The concern with the use of CNP-22 protein is that the ability of the assay to detect ADAs against all drug domains may not be adequately evaluated in the validation study. However, although the approach is not optimal, the assay design includes appropriate capturing reagent (biotin-tagged BMN111) which can bind to ADAs from all potential immunogenic regions and confirmatory assay is in place to confirm vosoritide-specific interaction; importantly, clinical sample analysis showed that ADAs can be detected in the screening and confirmatory assays.*

The information included in clinical study reports (Section 5.3.1.4) indicates that there were additional QC lots that were used in analysis of clinical samples that were not evaluated in the validation study. For example, clinical study report for study 111-202 lists lot BAS-095-P15-0797 for HQC/TQC, and lot BAS-095-P15-0798 for LQC, clinical study report for study 111-301 lists BAS-P17-0666, BAS-P17-2074, and BAS-P19-1608 for QC. Furthermore, footnote 2 to Table 8.3.1. indicates that due to antibody lot-to-lot variability, the PC concentrations in the respective QC lots (e.g. BAS-095-P15-0797 and BAS-095-P15-0798) were optimized to match the signal and performance of the original lot. Importantly, it appears that the reagent lots for ruthenium and biotin -labelled drug were the same between the amendment-2, -3 and clinical sample analysis. However, the use of different QC lots raises potential concerns because of potential impact on assay performance for the analysis of clinical samples. IR was conveyed to provide details on the lot qualification requirements for the introduction of new lots that were not validated or included in robustness study to ensure consistent assay performance. The Sponsor provided details on the requirements for the qualification of new critical reagent lots (SOP-(b) (4)) and included relevant reagent qualification reports to support introduction of new PC control lots (lots BAS-095-P15-0797 and -0798 prepared from lot A14389, and labelled BMN-11 reagent lots). The requirements for the new lot introduction appear appropriate (evaluation from a minimum of 6 runs by at least 2 analysts over at least 3 days; the range for new positive control lots within 3 SD of the old range; and the 99% confidence interval for negative control below assay cut-point, and above matrix background). Furthermore, the adjustment to PC concentration was undertaken to minimize potential risk for assay drift due to differences in PC lots, and the new labelled reagent lots (e.g. Bio-BMN111 and Ru-BMN111) were re-evaluated to support shelf-life extension.

Overall, the final trending data (e.g. Figures 1-7 in the qualification report M201015-01) support consistent assay performance, and within pre-specified ranges. This is acceptable.

Validation run acceptance criteria: All data from each plate must be reported unless a plate contained a known error, or the CC failed the %CV requirement (%CV must be ≤20% for CC).

For each plate, the following controls were included in the validation studies:

- Screening and confirmation: ≥2LQC(low quality control), ≥2HQC (high quality control) and ≥2NQC (negative quality control) assayed in duplicate wells, and 1 CC (cut-point control) assayed in 4 or 8 wells. The LQC was screened and confirmed on all confirmatory assay plates.
- Titration: ≥1 LQC and ≥1NQC assayed in duplicate wells, 1CC assayed on 4 or 8 wells and ≥1 TQD (titration quality control) dilution series (1:10 MRD plus 7 serial 1:3 dilutions in 10% NHPS), assayed in duplicate wells.

Assessor comment: *The controls implemented for the validation assay runs appear appropriate.*

Summary of validation study

1) Cut point and cut-point factors

Assessor comment: *The results for cut-point determination were obtained from amendment-2, because they included cross-reactivity determination and were intended for the analysis of phase 2 and 3 study samples. The results from the original validation study are not reviewed.*

Testing was performed on a total of 48 drug-naïve normal subject serum samples on six plates in each of 6 runs, and each plate included 8 samples. The analysis was performed by two analysts, for≥ 3 days; with samples were processed in rotating order on each of the 3 days. Details on the datapoints and data analysis are summarized below:

Cut-point type	Datapoint set/ transformation /data distribution	Excluded datapoints (inter-quartile ranges based)	Cut point (CP) type/calculation/value
Screening (SCP) cut point	N=288/Log_{10} RLU/Normal distribution confirmed	No datapoints excluded (Table 16.4)	Floating to target 5% false positive rate SCP=1.11(CPF) x mean plate CC (RLU)

			CPF=Cut point (RLU)/grand mean CC (RLU)
Titration cut point (TCP)	The same as for screening cut point (Table 16.4)		Floating to target 0.1% false positive rate TCP=1.24 (CPF) x CC (RLU) CPF=Cut point (RLU)/CC Grand mean (RLU)
BMN111 specificity confirmatory cut-point (CCP)	N=286/%SI/Normal distribution confirmed	Two outliers (Table 16.3)	Floating to target 1% false positive rate CCP=23.2% SI
ANP cross-reactivity cut-point (ANP XCP)	N=282/%SI /Normal distribution confirmed	Six outliers (Table 16.5)	Fixed to target 0.1% false positive rate ANP XCP=30.8% SI
BNP cross-reactivity (BNPXCP)	N=287/Log_{10} (spiked/unspiked)/Normal distribution confirmed	One outlier (Table 16.6)	Fixed to target 0.1% false positive rate BNP XCP=21.9% SI
CNP cross-reactivity (CNP XCP)	N=282/Log_{10} (spiked/unspiked)/Normal distribution confirmed	Six outliers (Table 16.7)	Fixed to target 0.1% false positive rate CNP XCP=21.6% SI

Assessor comment: *The cut-points in the amendment 2 study do not appear appropriate because of potential impact of patient-specific matrix on the signal output. That was confirmed by the evaluation of the pre-treatment study samples (baseline positive rate), and in both clinical studies intended to support approval, 0% positive rate was detected based on screening, confirmation and cross-reactivity cut-points determined from the amendment-2 validation study (see below). This raises concerns that these validated cut-points may not identify clinical samples with low levels of ADAs. It is possible that the cut-points may be impacted by the differences in the serum matrix*

between the adult human samples used in validation and pediatric population intended for the clinical sample analysis. Also, the cross-reactivity cut-points target 0.1% false positive rate and not 1% false positive rate, and this may be too high and inappropriate. As a result, study-specific cut-points were implemented following the analysis of the pre-dose clinical study samples; see below.

Study-specific cut-points

Study-specific cut points were implemented because it was determined that the initial cut-points, based on commercial normal human serum samples, were not appropriate. The mathematical approach used (analysis software, outlier exclusion based on Dixon Q test and inter-quartile ranges) was similar to that described above, except that the samples were obtained from studies 111-202 and 111-301 (details on the study population included in the table); the summary is provided below:

Evaluated cut-point	Baseline positive rate based on validation cut point	Study-specific cut-point	False positive rate based on study specific cut-point
Study 111-202: • A total of 35 pediatric subjects' (5-14 years age) samples were analyzed, one sample was assayed twice in TAb screening and confirmatory assays, and two samples were assayed twice in ANP, BNP and CNP cross-reactivity assays. • Comparison of the data distribution indicated that the means from the screening, confirmation and BNP and CNP cross-reactivity assays were lower in the clinical study compared to validation study dataset. • The implemented cut-points target 5% false-positive rate for TAb screening, and 1% false positive rate for TAb titer, confirmation and TAb cross-reactivity assays.			
TAb screening cut-point	0%	Screening cut-point factor (SCPF)=mean (RLU/CC)+1.645xSD= 1.01(CPF) x mean plate CC (RLU)	5.6%
TAb titration cut point	N/A	1.05 (CPF) x mean plate CC (RLU)	N/A

TAb BMN111 confirmation cut point	0%	Confirmatory cut-point (CCP)=mean %SI+2.33xSD= 14.7% SI	0%
TAb ANP cross-reactivity cut-point	5.4%	Cross-reactivity cut-point (XCP)=mean %SI+2.33SD= 35.4%SI	2.7%
TAb BNP cross-reactivity cut-point	0%	XCP=99th percentile from empirical data= 9.1%SI	2.7%
TAb CNP cross-reactivity cut-point	0%	XCP=mean %SI+2.33SD= 14.7%SI	0%
Study 111-301: • A total of 120 pediatric subjects' (5-18 years age) samples were analyzed, and one sample was assayed twice in TAb screen and cross-reactivity assays • Comparison of the data distribution indicated that the means from the screening and cross-reactivity assays were lower in the clinical study sample compared to validation study dataset; the means from %SI from confirmatory assays were similar, but the variance was higher in the clinical dataset compared to the validation study dataset. • The cut-points were defined to target 5% false-positive rate for TAb screening, and 1% false positive rate for TAb titer, confirmation and TAb cross-reactivity assays.			
TAb screening cut-point	0%	95th percentile from empirical data: 1.02 XCC	5.0%
TAb titration cut point	N/A	1.05 (CPF) x mean plate CC (RLU)	N/A

TAb confirmation cut point	0%	CCP=mean %SI+(2.33xSD)= 15.3% SI	2.5%
TAb ANP cross-reactivity cut-point	0%	XCP= Mean%SI+(2.33SD)= 14.1% SI	7.4%
TAb BNP cross-reactivity cut-point	0%	XCP= Mean%SI+(2.33SD)= 7.1% SI	0.8%
TAb CNP cross-reactivity cut-point	0%	XCP= Mean%SI+(2.33SD)= 9.7%SI	1.7%

Assessor comment: *Of note, the TAb titration study-specific cut-points were implemented based on 1% false positive rate (1.05 xCC); the cut-point based on screening cut-point factor which targets 5% false positive rate, was too low, and it appears that diluted samples did not cross the screening threshold (memo M112519-03). This is acceptable considering that the assay is sufficiently sensitive (~7-8 ng/mL) and not a risk for misidentifying samples in the clinically relevant range (<100ng/mL).*

Overall, the results for %false positive rate in the study pre-treatment samples are acceptable and the study-specific cut-points appears acceptable to support the clinical sample analysis.

2) Precision

The results from all three studies are summarized below:

Evaluated control (concentration level, ng/mL)	Lot numbers	Dataset	Intra-run precision (within one plate, %CV)	Inter-run precision (between multiple plates, %CV)

Original validation study: all controls were evaluated on at least 6 plates by two analysts over 3 days in screening and titration assays.				
HQC (10000ng/mL)	BAS-P12-1045	N=6 runs Each sample in 6 replicates (Tables 16.15, 16.17 and 16.19)	≤2.7%	≤14.0%
LQC (200ng/mL)	BAS-P12-1046		≤1.7%	≤9.9%
NQC (0ng/mL)	BAS-R12-527		≤2.7%	≤10.4%
TQC (10000ng/mL, Log_3 titer)	BAS-P12-1045	N=6 runs Each sample in 5 replicates (Table 16.22)	≤4.8%	≤6.2%
Amendment-2; all controls were evaluated on at least 6 plates by two analysts over 3 days in screening, confirmatory, and titration assays.				
HQC (10000ng/mL)/CC	BAS-P14-1207/BAS-R12-526	N=7 runs Each sample in 6 replicates (Tables 16.14, 16.16, 16.18, 16.20)	≤12.6%	≤24.2%
LQC(200ng/mL)/CC	BAS-P14-1208/ BAS-R12-526		≤7.1%	≤12.2%
NQC(0ng/mL)/CC	BAS-R12-527/ BAS-R12-526		≤3.7%	≤5.1%
LQC %SI (200ng/mL)	BAS-P14-1208/		≤5.1%	≤7.7%

	BAS-R12-526			
TQC(10000ng/mL)	BAS-P14-1207/BAS-R12-526	N=6 runs Each sample in 5 replicates (Table 16.21)	≤2.7%	≤3.9%
Mean titer and Limit of Detection (LOD)			2670/37.5ng/mL	
Amendment-3; all controls were evaluated on at least 6 plates by two analysts over 3 days in screening, confirmatory and titration assays.				
HQC (10000ng/mL); HQC/CC	BAS-P17-1681/ BAS-R12-526	N=6-12 runs Each samples evaluated in at least 3 replicates (Figures 15.25-15.29)	≤11.1%;	≤16.81%
LQC;LQC/CC (50, 40, 20, 3, and 1 ng/mL)	BAS-P18-0044 (1ng/mL) BAS-P18-0043 (3ng/mL) BAS-P18-0205 (20ng/mL) BAS-P17-1683 (40ng/mL) BAS-P17-1682 (50ng/mL)		≤10.4%	≤12.8%

NQC (0ng/mL);NQC/CC	BAS-R12-527/ BAS-R12-526		≤6.5%	≤11.5%
TQC (10000ng/mL)	BAS-P17-1681/ BAS-R12-526		≤3.2%	≤6.0%
LQC %SI (50, 40, 20, 3, and 1 ng/mL)	See section on LQC above for details		≤8.6%	≤17.3%

Assessor comment: *Overall, the results support acceptable inter- and intra-assay precision in all validation studies.*

3) Evaluation of additional LQC level (Amendment-3, Tables 16.36 and 16.37)

In addition to the LQC at 40 and 50ng/mL, lower concentration levels (1, 3, and 20ng/mL) were evaluated in the screening and confirmatory assay, and the % negative samples for each concentration level was reported. The evaluation was done to determine if any lower concentration level may be appropriate to target the 1% false positive rate for LQC. The results are summarized in the table below:

Evaluated LQC level (ng/mL)	Screening assay result (%negative) Cut point used: 1.11xCC	Confirmatory assay result (%negative)
1	17% (4/24)	38% (9/24)
3	8.3% (2/24)	54.2% (13/24)
20	0% (0/18)	0% (0/18)
40	0% (0/24)	0% (0/17)
50	0% (0/20)	0% (0/16)

Assessor comment: *The information in the clinical study reports indicates that the controls used in clinical sample analysis include 3ng/mL (for screening assay) and 20ng/mL (for confirmation assay). This appears appropriate, however, the plate-specific screening cut point used for all evaluations (1.11xCC) was based on the normal human serum samples, and not on the study-specific samples. However, the study-specific screening and confirmation cut-points (1.01-1.02xCC and 14.7-15.3%, respectively) are lower than those based on validation study (1.11xCC and 23.2%), and all LPC samples (a total of 24) even at the lowest evaluated level (1ng/mL), would screen and confirm positive, thus supporting the use of LPC at 3ng/mL and 20ng/mL level for the clinical sample analysis.*

4) Quality control acceptance criteria for in-study testing use

The results for acceptance ranges for QC samples from all acceptable validation runs are summarized in the table below:

Evaluated control sample	Formula	Final range
Original validation study (Table 16.11, 16.13, and 16.22)		
HQC/CC	99% CI	19.4-47
LQC/CC	99% CI	1.28-1.92
NQC/CC	Upper 99% CL	≤1.08
TQC	$\log_3$ and mean titer value	6.81-8.81 $\log_3$ Values: 1780-16000
Amendment-2 (Table 16.10, 16.12, and 16.21)		
HQC/CC	99% CI	27.3-96.0
LQC/CC	99%CI	1.61-2.95
NQC/CC	Upper 99% CL	≤1.08
TQC	$\log_3$ and mean titer value	6.18-8.18 $\log_3$ Values: 888-8000
Amendment-3 (Table 16.38 and 16.40)		

HQC/CC	99%CI	32.3-80.4
LQC (3ng/mL)/CC	99%CI	1.05-1.24
NQC/CC	Upper 99% CL	≤1.16
Titer values	Log_3 and mean titer value	Values 1680-15100

Assessor comment: *For any information related to the use of different PC reagent lots in the validation and clinical sample analysis, see also section of the materials and methods and IR conveyed.*

5) Limit of detection/sensitivity

Limit of detection (LOD) was defined as the lowest analyte concentration in the neat serum that would generate result ≥screening cut point (i.e. screen positive). The LOD was determined in 6 runs, using TQC precision data from at least 3 replicates, by interpolation of the result at the screening cut-point. The LOD in the original validation study was determined at 18.8ng/mL (Table 16.22) and in amendment-2 at 37.5ng/mL (Table 16.21); both values were based on the original screening cut-points from the normal human samples. However, because the cut-points were revised and study-specific screening cut-point was implemented, the revised LOD was determined at 7.69ng/mL.

Assessor comment: *The cut-point used for LOD determination (1.05xCC) is titration cut point and not the screening cut point (1.05xCC versus 1.02xCC, see also memo M112519-03). This was done because diluted samples did not cross the screening cut point and dilution curve was plateauing above the respective screening cut-point. This could be due to differences in the serum matrix, and slight adjustments to the cut point are therefore acceptable to support the LOD within clinically relevant range. Overall, however, considering that the assay sensitivity is in the range sufficiently below the 100ng/mL level, the approach is acceptable.*

6) Specificity

Specificity was determined by spiking non-specific IgG or HQC (10µg/mL) to NHPS and evaluating samples in screening and confirmatory assay using cut-points from the amendment 2 validation study (Table 16.26). Overall, most results were as expected, and the assay was specific to detect anti-BMN111 Ab and not the non-specific Ab. The following exception are noted: a single (out of three) unspiked NHPC samples screened positive, and 2/3 NHPS samples spiked with non-specific IgG screened positive but were confirmed negative.

Assessor comment: *It is not clear if the implemented cut-points, based on the validation study, are appropriate to support assay specificity. However, the re-evaluation using the study-specific screening and confirmatory cut-points (1.02-1.02xCC, and 14.7%-15.3%, respectively) would likely not change the sample status, except that two out of three unspiked samples would now screen positive (instead of one out of three), and that all NHPS samples spiked with non-specific IgG would now screen positive (instead of two out of three); however, all samples would be eventually confirmed negative. This is likely due to differences in the sample matrix between the samples used in the validation study and the samples used for clinical analysis (lower background in the clinical samples). Overall, however, considering the results from confirmation, and the use of appropriate LPC which are not at risk to be impacted by the revised study-specific cut-points, totality of data support that the assay is sufficiently specific to detect anti-BMN111 antibodies in the presence of all relevant matrix components.*

7) Selectivity

Assay selectivity was evaluated by preparing LQC/HQC in the presence of either hemolytic or lipemic serum (lipemic: visual confirmation; hemolytic level: 35-1100mg/dL), followed by evaluation in the screening and confirmatory assays. The results from Tables 16.23 and 16.24 are summarized in the table below:

Evaluated PC	Matrix	Screening	Confirmatory
Amendment 2 (cut-points based on normal human samples); the samples were evaluated by two analysts over one day.			
Unspiked sample	Normal	8/8/ negative	
LQC (200ng/mL)		8/8/ positive	8/8 positive
Unspiked sample	Lipemic	2/2 negative	
LQC (200ng/mL)		2/2 positive	2/2 positive
Unspiked sample	Hemolyzed (35-1100 mg/mL)	6/6/ negative	N/A
LQC (200ng/mL)		3/6 positive	
HQC (10µg/mL)		6/6/ positive	

Assessor comment: *Overall, the results support that hemolysis may interfere with sample detection and therefore the hemolyzed samples should be interpreted with caution.. IR was conveyed to provide information on the measures implemented during clinical sample analysis to ensure that all samples are appropriately evaluated, and to clarify if any clinical samples with hemolysis levels at or above what was tested in the validation study were positive for ADAs. The Sponsor clarified that only up to 9.96% of samples could be at risk because of >140mg/mL hemolysis levels that could interfere with sample detection in the validation study. However, although the levels of hemolysis above 140mg/mL level were detected in the clinical samples, nonetheless up to 16 samples from that group (~8.5%) still screened positive which further mitigates any concerns that hemolysis level >140mg/mL could preclude sample analysis. To further mitigate concerns, the level of hemolysis is descriptively assessed for all clinical samples (assessment chart included in response). This is acceptable.*

8) Drug tolerance (Amendment-2)

Drug tolerance was evaluated in screening assay in NHPS, LQC and HPC samples that were either spiked or not with BMN111 at the following concentration range: 10pg/mL-1µg/mL. All samples were analyzed in the screening assay by at least one analyst over one day. The results from Table 16.28: all NHPS samples were negative, while all LQC and HQC were positive. Regarding signal interference, there was no interference with detection of LQC and HQC up to 1000ng/mL of BMN111.

Assessor comment: *The results support assay tolerance with up to 1000ng/mL of BMN111 drug. Furthermore, the concern over potential for interference is greatly reduced because of short BMN111 half-life, up to 70 min, and low levels of interfering drug levels (<100pg/mL range) as early as 24 hours after dosing. Therefore, re-validation of the assay drug tolerance using study-specific cut-points is not warranted.*

9) Stability

The evaluated samples included labelled drug (biotynilated and ruthenylated BMN111) and QC samples (NQC, LQC and HQC). For the labelled BMN111 drug, the evaluated condition included 1 and 2-hour storage on wet ice. For the QC samples, the evaluated conditions included overnight storage at 2-8ºC, 4 and 24-hour storage at room temperature, and up to 4 cycles of freeze and thaw cycles. All samples were evaluated in the screening assay and included sample status (positive/negative) and QC ranges (indicated before in the review memo). The results are summarized in the table below:

Evaluated sample	Evaluated condition	Result summary (screening assay)
Original validation study (performed by one analysts over one day; Table 16.31-33)		

Labelled BMN111/biotinylated and ruthenilated BMN111	1 and 2-hour storage at wet ice NQC;LQC;HQC	All samples met the respective acceptance criteria for sample status (positive/negative) and QC range, except for 2/3 HQC and 1/3 NQC samples that did not meet the relevant QC ranges
NQC LQC HQC	2-8^{o}C overnight 4- and 4-hour at room temperature 4x Freeze/thaw (F/T)cycle	All samples met the respective acceptance criteria for sample status except for 1/3 NQC stored at 2-8^{o}C overnight condition which screened positive.
Amaendment-2 (performed by one analysts over one day; Table 16.30)		
Labelled BMN111/ biotinylated and ruthenilated BMN111	Up to 4 hours storage at wet ice NQC;LQC;HQC	All samples met the respective acceptance criteria for the sample status (positive/negative).

Assessor comment: *It is not clear if the acceptance ranges are appropriate to support indication-specific screening and confirmation cut-points and the evaluation included only short-term storage conditions. IR was conveyed to provide data to support that the LQC/HQC samples are sufficiently stabile for the intended use in the confirmatory assay, or to provide appropriate justification for why such evaluation may not be necessary. The Sponsor clarified that the long-term stability of rabbit polyclonal antibody preparations at the <-20^{o}C is supported by the public literature data (Michaut, 2014, Boridy, 2019). Regarding the short-term stability, it was clarified that the evaluation in the screening assay should be sufficient to support all assay components (e.g. labeled BMN-111), because the procedures between screening and confirmation assays are identical except for the addition of confirmatory reagent in confirmation assay. Considering however that the confirmatory reagent stability is a low risk, the overall approach is acceptable.*

10) Robustness

Assay robustness was evaluated in the original validation study only, and included the following assay parameters: MSD plate blocking (105-135 min), QC sample pre-incubation in master mix (105-135min), transfer of pre-incubated MSD SA plate (50-70 min), plate read (up to 10 min). The evaluated samples included NQC, LQC and HPC. All results met the respective acceptance criteria for the relevant QC ranges (Table 16.34 and 16.35).

Assessor comment: *The QC ranges were based on the original validation study, and the evaluation was not performed with updated study reagents or acceptance ranges. However, the assay robustness is intended to evaluate the impact of deliberate variations on the study data reproducibility, and all acceptance ranges, derived in the original validation by 99% CI, should be acceptable to support that the impact of any deliberate assay variations is minimal under the specified conditions. This is acceptable.*

11) Prozone analysis

Prozone effect was investigated on 2 study samples (study 111202) within 10-21810 dilution range (Table 16.41 and Figure 15.30). Both dilution curves showed a hook effect however, the lowest concentration samples in both curves were still above the titration cut point and not a concern for being misclassified as false negative.

Assessor comment: *The results are acceptable and support that the impact of hook effect on sample analysis is unlikely.*

Assessor comment regarding validation study for TAb: *Overall, the results provided support that the binding assay for detection of total antibodies against BMN111 is suitable for intended use.*

II. **Cell-Based assay to Measure BMN 111-Neutralizing Antibodies in Human Serum (BMN111-13-044)**

Validation study included the following parameters: screening, confirmation and titration cut-point determination, intra and inter-assay precision, quality control acceptance ranges, sensitivity/limit of detection, selectivity, specificity, drug tolerance, robustness, and bench-top, freeze/thaw and long-term stability.

Assessor comment: *A total of three validation studies were included, highlighted below:*

- *The original study evaluated all relevant assay parameter (except for the long-term reagent stability), however, an inappropriate reagent was used for confirmation (protein A/G coupled sepharose beads) which resulted in higher than expected % of false positive samples (12.5% of drug-naïve samples).*
- *In amendment 1, the confirmatory cut-point was re-evaluated using more appropriate reagent, BMN111-conjugated sepharose beads, which resulted in a total of 1% of drug naïve samples which screened and confirmed positive. In addition to the revised cut-points, the evaluation in amendment-1 included also inter-and intra-assay precision, and additional lots of critical reagents (PC, confirmation reagent), additional LQC levels (400ng/mL and 500ng/mL) and associated QC acceptance ranges.*
- *To enable continued use of critical assay reagents, amendment-2 completed the assessment of long-term stability for the following: NIH3T3 cells, BMN111 working stock, BMN111-conjugated sepharose resin, PC lots, assay kit for cGMP analysis etc. Of note, the specified critical reagents were the same as in amendment-1 and there were no other changes implemented.*

Overall, there were up to 142 validation runs conducted; 16 runs (11%) were deleted, and 6 runs (4%) were rejected. The reasons for deletion were administrative, as some runs which were erroneously created, but were

not needed in the analysis, as the samples were already processed in other runs. The other reasons for rejection were primarily related to the control samples which did not meet the pre-specified requirements or respective QC ranges; the rejected runs were repeated, and all validation assay requirements were met. Additionally, minor deviations were also noted- typographical and technical mistakes (incubation time, wrong formulae, not adding appropriate buffer etc.), and none was found to impact the study validity. Overall, although the number of deleted/rejected runs is slightly higher than usual, the impact on study validity is unlikely, and all follow up actions (SOP updates, investigations) are appropriate.

Analytical method

A tiered testing strategy is used and included screening, confirmation and titration assays. The samples are prepared by 1:5 dilution, mixed with BMN111 drug and assayed on the NIH3T3 cells. The incubation with BMN111 cells results in increase in intracellular cGMP levels which is then detected by a competitive colorimetric enzyme immunoassay (EIA). The production of cGMP is inhibited in the presence of neutralizing antibodies from the human serum samples, and the absorbance signal in EIA assay is directly correlated with the neutralizing antibody levels (the higher the inhibition, the stronger the binding of the competing labelled cGMP [cGMP-AChE] and the stronger the assay signal). For the screening assay, all samples that are above the screening cut-point are designated as screen positive. For the confirmation assay, the same procedures were followed as in screening assay except that all samples that are screen positive are either treated or not with protein A/G 50:50 mixture (updated in amendment-1, to include more appropriate confirmation agent, BMN111-conjugated protein A/G sepharose beads). For the titration assay, the same procedures were followed as in screening assay except that test and control samples are serially diluted and the sample titer is reported as the sample dilution factor (DF) where the dilution curve crosses the titer cut point; of note, the final concentration result, if appropriate, also includes the MRD and the DF .

Materials (Critical reagents; all studies)

a) Cells: NIH3T3 cells (lot 14-003654)
b) Drug product: Biomartin supplied BMN111 (b) (4) (lot P2204-13101 at 2 mg/mL)
c) Drug working stock: BMN111 (b) (4) diluted in formulation buffer to 2µg/mL
d) Positive control: Protein A purified mouse anti-BMN111 monoclonal IgG1 (explained below)
e) Matrix: Normal individual and normal pooled human serum (NHPS, (b) (4) see below for details)
f) Immunodepletion material: Protein A/G beads (original validation study) and BMN111-conjugated protein A/G beads (lots CRG#251520, amendment-1 and lots CRG#251520, CRG262084 and CRG#369491, amendment-2).
g) Assay buffer component: Tween 20 (lot B0531553)
h) cGMP detection kit (b) (4)
i) Validation controls prepared in NHPS (summarized below):

Control	PC concentration (µg/mL	PC lot number	NHPS lot number
CC (cut point negative control)	0	BAS-P17-0412 (amendment-1 and amendment-2) BAS-R13-2114 (original validation study)	BRH788818 (amendment-1 and amendment-2) BAS-R13-2114 (original validation study)
HQC	3	BAS-P18-0504/BAS-300-P15-0566 (amendment-1 and amendment-2) BAS-P14-0167 (original validation study)	BRH788818 (amendment-1 and amendment-2) BAS-R13-2114 (original validation study)
LQC	0.4, 0.5 (amendment 1) 0.6 (original validation study, amendment-1, and amendment-2)	BAS-P17-0360/BAS-P17-0359 (amendment-1 for 0.4 and 0.5µg/mL level) BAS-300-P15-0567/BAS-300-P18-0505 (amendment -1 and amendment-2 for 0.6µg/mL level) BAS-P14-0168 (original validation study for 0.6µg/mL level)	BRH788818 (amendment-1 and amendment-2) BAS-R13-2114 (original validation study)
NQC (assay negative control)	0	BAS-P17-0362 (amendment-1 and amendment-2)	BRH1281054 (amendment-1, and amendment-2)

		BAS-R13-1716 (original validation study)	BAS-R13-1716 (original validation study)
TQC	10	BAS-P300-P15-0565 (amendment-1) BAS-P13-2098 (original validation study)	BRH788818 (amendment 1) BAS-R13-1476 (original validation study)

Assessor comment: *The NIH3T3 cell line is a critical reagent in the assay used to detect neutralizing antibodies and should be appropriately controlled to ensure consistent assay performance. Insufficient information was included to enable determination of the adequacy of the assay design and associated controls (e.g. cell passage level) to ensure consistency throughout validation and clinical sample analysis. IR was conveyed to provide additional information on evaluated assay conditions (e.g. cell age, plating number, drug concentration etc.) for the BMN111 dose response curve in NIH3T3 cells, and to clarify how the passage level was controlled during validation and clinical sample analysis. The Sponsor provided data (Figure 3 and 4 in response) that support that the chosen BMN111 concentration for 3T3 cell response (at 2.5ng/mL) is within assay linear range and appropriate to support assay sensitivity at 600ng/mL. Regarding passage level, the Sponsor clarified that the validated range support up to 11 passage levels and included qualification reports for the introduction of new NIH3T3 cell lots (e.g. 3T3 WCB4 and WCB5 qualification reports). All cells used in the same experiment were derived from the same WCB lot which was prepared at the same passage level. The qualification of the new lots is controlled by SOP (SOP (b) (4)), and the acceptance criteria at the time of qualification of new WCB lots include pre-specified ranges for HQC/CC, LQC/CC and NQC/CC and %CV below 20%. This is acceptable.*

It appears that the QC and BMN111-conjugated protein A/G sepharose beads lots used throughout validation studies were consistent, while there were additional BMN111-conjugated protein A/G sepharose bead lots that were introduced for the analysis of clinical samples (e.g., lots CRG#450731, and CRG#502469, clinical study 111-301). The results from trending analysis (Figures 15.1-15.3, amendment -2) indicate that several QC/CC results were outliers and there were several rejected runs during in-study analysis. The root cause for these discrepancies is not clear and IR was conveyed to provide additional information to support consistent assay performance, including but not limited to, the results from qualification studies for any new reagent lots, investigations into the root causes of QC/CC result discrepancies etc. The Sponsor provided detail on the requirements for the qualification of new critical reagent lots (SOP- (b) (4)) and included reagent qualification reports to support introduction of new BMN11-conjugated sepharose beads (lots CRG#450731, and CRG#502469). Overall, the requirements for the new lot introduction appear appropriate (evaluation from a minimum of 6 runs by at least 2 analysts over at least 3 days; the range for new positive control lots within 3 SD of the old range; and the 99% confidence interval for negative control below assay cutpoint, and above matrix

background), and the results from trending analysis (Figures 5 and 6) support consistent NQC and LQC performance within pre-specified ranges , notwithstanding few outliers due to technical errors, analyst errors or equipment malfunctions. This is acceptable.

Validation run acceptance criteria: All data from each plate must be reported unless a plate contained a known error, or the CC failed the %CV requirement (%CV must be ≤20%).

Summary of validation study

The controls used on each plate in validation study include ≥2 sets of positive and negative controls and no drug control (NHPS assayed in the absence of BMN111). Additionally, conformation assay plates included 2 sets of LQC in duplicate wells, and titration assay plates included 3 sets of at least 6 dilutions of TQC in duplicate wells.

Assessor comment: *The controls used in assay validation runs appear appropriate.*

1) Cut point and cut-point factors

Assessor comment: *Because of inappropriate confirmation regent, the results from the original validation study will not be further elaborated here, and the focus will be on the results from amendment 1, with more appropriate confirmatory reagent.*

Experimental design

Testing was performed on a total of 48 drug-naïve healthy subject samples (24 male and 24 female) on three plates in each run (a total of 6 runs); the CC was assayed in 8 wells per plate and the LQC was included in 4 wells per plate for screening and confirmation assays. The analysis was performed by two analysts, for≥ 3 days; with samples processed in rotating order on each of the 3 days. For each day a fresh serum and cell thaw vial was used. Details on the datapoints and data analysis are summarized below:

Cut-point type	Datapoint set/ transformation /normality distribution	Excluded datapoints (inter-quartile ranges-based)	Cut point (CP) type/calculation
Screening cut-point (SCP)	N=288/No transformation (AU results)/confirmed	Five outliers (Table 16.4)	Floating to target 5% false positive rate Additive SCPF=Cut point – CC Grand mean =0.470-0.4=0.00663AU SCP=Grand mean + 1.645xpooled SD=0.470
Titration cut point (TCP)			
Confirmatory cut-point (CCP)	N=288/%SI/confirmed	Four outliers (Table 16.3)	Fixed to target 1% false positive rate CCP=mean +2.33 SD= upper 99th CL=16.0% SI

Study-specific cut-points

Study -specific cut points were implemented because it was determined that the initial cut-points, based on normal human serum samples were not appropriate. The approach used was similar to that described above (analysis software, normality distribution, outlier exclusion by Dixon's Q test), except that the samples were obtained from study 111-202 and 111-301; the summary is provided below:

Assessed cut-point	Baseline positive rate based on validation cut point from amendment 1	Study-specific cut-point	False positive rate based on study specific cut-point
Study 111-202: • A total of 35 subjects was analyzed; four samples were assayed twice • Comparison of the data distribution indicated similar means between the validation and clinical study samples, while the confirmation %SI was lower in the validation study compared to the clinical study samples.			

• The cut-points were defined to target 5% false-positive rate for NAb screening assay and 1% false positive rate for NAb confirmation assays.			
NAb screening/titration cut point	76.9%	SCPF=mean (RLU-CC)+(1.645xSD)= mean of CC +0.2129	**2.6%**
NAb BMN111 confirmation cut point	2.6%	CCP=mean %SI+(2.33xSD)= 13.2%	**2.6%**
Study 111-301: • A total of 120 subjects were analyzed in the screening and confirmatory assays. • Comparison of the data distribution indicated that the means from the screening datasets for the clinical and validation studies are similar, but the variances were different; the means from the confirmatory are lower in in the clinical compared to the validation dataset. • The cut-points were defined to target 5% false-positive rate for NAb screening, and 1% false positive rate for NAb confirmation assays.			
NAb screening/titration cut point	30.8%	SCPF=mean (RLU-CC)+(1.645xSD)= mean of CC+ 0.1913	**3.3%**
NAb BMN111 confirmation cut point	0%	Mean %SI+2.33(SD)=7.1%	**0%**

Assessor comment: *Overall, the results for % false positive in pre-treatment drug-naïve clinical study samples are acceptable and support the use of the revised study-specific cut points for clinical sample analysis.*

2) Precision

The evaluations in both studies included ≥2 sets of QCs, on at least 6 plates, over at least 3 days by at least two analysts. The results are summarized below:

Evaluated control	Dataset	Intra-assay precision	Inter-assay precision
Original validation study: screening, confirmation and titration assay (Tables 16.9-16.12A)			
HQC (3µg/mL)	N=32 runs Each sample in n≥2 replicates	3.5%	8.3%
LQC (0.6 µg/mL)		5.1%	9.8%
NQC (0 µg/mL)		6.3%	14.7%
TQC (3µg/mL , Log_3(titer))	N=6 runs Each sample in n=4 replicates	4.5%	8.1%
LQC (0.6 µg/mL, %SI)	N=19 runs Each sample in n=2 replicates	12.3%	18.5%
Amendment 1-screening assay (Tables 16.5-16.10)			
LQC/CC (600ng/mL)	N=6 runs Each sample in n=3 replicates	7.3%	10.6%
LQC/CC (500ng/mL)		9.8%	9.5%
LQC/CC (400ng/mL)		9.4%	10.5%

Assessor comment: *The validation study should evaluate all assay reagents in the screening, confirmatory and titration assays to determine relevant validation parameters to support suitability for the intended use. It appears that only limited validation parameters (e.g. screening, confirmation, and titration cut-points) were evaluated in amendment 1 using updated and more appropriate confirmatory reagent (BMN111-conjugated sepharose beads). This is not sufficient, and additional validation parameters, such as inter- and intra-assay precision, selectivity and assay robustness, should be evaluated in screening, confirmatory and titration assays using updated critical reagent lots. IR was conveyed to provide data to support that the assay is sufficiently precise, selective and robust*

following update in critical reagent or a justification for why this analysis is not needed. The Sponsor clarified that the intra-assay precision for confirmatory assay with appropriate reagent (BMN11-conjugated sepharose beads) was 16.3%CV and inter-assay precision 18.8%CV. The inter-and intra-assay precision for the screening and titration assays is not impacted by the change in confirmation reagent (e.g. confirmatory reagent is not used) and was evaluated in the original study and amendment 1 (included in the table above). Overall, the inter-and intra-assay precision is acceptable for all assays.

3) Quality control acceptance criteria for in-study testing use

The evaluation of QC acceptance ranges from control samples is summarized in the table below:

Evaluated control sample	Mathematical method	Final range
Original validation study (Tables 16.9-16.14); the QC samples were evaluated in duplicates in all validation plates, except for robustness and stability studies.		
HQC	99% CI	0.722-1.12
LQC (600ng/mL)	99%CI	0.571-0.970
NQC	Upper 99% CL	≤0.744
TQC	Mean titier±1 dilution step (1:3)	Log_3 (titer): 3.74-5.74 Dilution factor values: 61.1-550
Amendment 1 (Tables 16.11-16.15)		
HQC/CC	99% CI	1.3-1.92
LQC (600ng/mL)/CC		0.995-1.53
NQC/CC		0.864

Assessor comment: *Of note, it is indicated (Table 11.5.1) that the QC acceptance ranges used for the analysis of clinical samples will be those derived in amendment 1. Importantly, however, the clinical study reports (e.g. 111-206, 111-202, 111-301-302) reference also reagent qualification memo M071218-01 for the introduction of slightly adjusted acceptance criteria. See section on QC samples for IR and Sponsor's response regarding qualification of any new lots of critical reagents for in-study analysis..*

4) Limit of detection; LOD/Sensitivity

The evaluation of LOD in original validation was performed in six runs over 4 days by 2 analysts; each run included 4 TQC dilution series (each series in duplicate wells, Table 16.15). The mean dilution factor at which each TQC crossed the respective plate specific SCP was interpolated, and the DF was converted to the LOD. The final LQC was set at 600ng/mL, based on the mean LOD (227ng/mL) and the 99%CI (508ng/mL).

The amendment 1 evaluated lower concentration levels (400ng/mL and 500ng/mL), in parallel with 600ng/mL to determine which LQC would be most appropriate to match the 1% failure rate in the screening and conformation assays. The evaluation was performed in a total of 36 replicates, on 24 plates, over 6 days by two analysts. The results support that the LQC at 600ng/mL level had a 13.9% failure rate in the screening assay and 0% failure rate in the confirmatory assay (Tables 16.11-16.13). The LQC samples at 500ng/mL and 400ng/mL had a higher %failures in the screening and confirmatory assays .

Assessor comment: *The updated study-specific screening cut-points were not used for LQC evaluation. This is acceptable, because the %SI from the confirmation results is within the 16.3-34.8%, and above the study-specific cut points (7.1% and 13.2%). Overall, the results support the final implemented LQC at 600ng/mL for the analysis of clinical samples.*

5) Selectivity (original validation study)

Ten individual drug-naïve normal human serum samples were either spiked or not with LQC and HQC and analyzed in the screening assay on 3 plates by 2 analysts over 2 days. The individual human's serum samples included 2 visually lipemic samples, and 4 hemolytic samples (2 with low level and 2 with high level). The results from Tables 16.16-16.19 are summarized in the table below:

Evaluated PC	Matrix	Screening
Original validation study		
Unspiked sample	Normal	10/10 negative
LQC (0.6µg/mL)		10/10 positive
HQC (3.0 µg/mL)		10/10 positive
Unspiked sample	Lipemic	2/2 negative
LQC (0.6µg/mL)		2/2 positive
HQC (3.0 µg/mL)		2/2 positive
Unspiked sample	Hemolyzed	2/4 negative
LQC (0.6µg/mL)		4/4 positive
HQC (3.0 µg/mL)		4/4 positive

Assessor comment: *Although some unspiked samples showed up positive, the results could be still used to support assay selectivity and higher false positive rates due to hemolysis are acceptable. Furthermore, the Sponsor is monitoring and visually assessing hemolysis in clinical samples (see IR and response for the binding ADA assay). This is acceptable.*

6) Drug tolerance

Drug tolerance was evaluated in the screening assay using LQC samples that were either spiked or not with BMN111 (0.04-270 ng/mL). The results are included in Table 16.21, and support that the LQC sample screened positive in the presence of up to 10ng/mL of BMN111 drug.

Assessor comment: *The results support assay tolerance with up to 10ng/mL of BMN111 drug. Furthermore, the concern over potential for interference is greatly reduced because of short BMN111 half-life, up to 70 min, and the BMN111 level 24 hours after the dosing is within <100pg/mL range. Therefore, re-validation of the assay drug tolerance using study-specific cut-points is not warranted.*

7) Robustness (original validation study)

The evaluation of robustness included the following assay parameters: incubation time (cell plate[17-23 hours], immunodepletion incubation[60-90min], sample incubation[60-90min], cell stimulation incubation[13017min], EIA incubation[17-19 hours], and EIA development time[3hour;20min-3 hour:40min]) and NIH cell number

[9000-11000cells/well]. The evaluation included the following samples: HQC, LQC, NQC; and the analysis was performed on 2 plates by 1 analyst on 1 day.

Overall, most samples met the requirements for robustness analysis (screening assay: test positive for LQC and HQC, test negative for NQC; ≥66.7% of samples within QC range and %CV≤20%; confirmatory assay: sample reading results within QC range and %SI≥CCP). Noted exceptions include the results from confirmatory analysis for the minimum incubation time where up to 50% of LQC samples did not perform as expected (results <CCP) and the results from the screening assay performed with minimum and maximum cell numbers which did not meet the screening assay requirements with multiple plates failing (Tables 16.23-16.28).

Assessor comment: *The minimum and target incubation time were adjusted (e.g., from 17 hours to 19 hours for cell plate incubation, from 60 to 70 min for immunodepletion incubation time, and from 70 to 90 for sample incubation time) to ensure adequate assay performance. Additionally, the cell concentration number was limited to the target value to minimize any impact on assay performance. It appears however that although confirmatory assay was used for evaluation of robustness, there was the wrong confirmatory reagent. IR was therefore conveyed to provide data to support confirmatory assay robustness with the correct confirmatory reagent. In their response the Sponsor clarified that although assay robustness did not include appropriate confirmation reagent, most of assay procedures are identical between screening and confirmation assay, and any additional confirmation assay procedures (e.g. incubation with unlabeled BMN-111) are a low risk for assay robustness. This is acceptable.*

8) Stability

The evaluation included short-term (original validation) and long-term storage conditions (amendment 2); the evaluation was performed using the screening assay/confirmatory assays and included QC ranges and sample status (positive/negative). The QC samples (NQC, LQC and HQC) were evaluated in the short-term study (6-hour storage on ice [bench top] and multiple freeze/thaw cycles), and during long-term storage (up to 2 y at -60-(-80)^{o}C). Additionally, all other assay reagents (NIH3T3 cells, BMN111, BMN111-conjuagted sepharose immunodepletion reagent, and kit components) were evaluated in the long-term stability study (amendment-2), and the results are analyzed by Levey Jennings QC trending charts (per deviation PR229877). The results are summarized in the table below:

Evaluated sample	Evaluated condition	Result summary
Original validation study (Table 16.29)		
NQC	6-hour at ice 6x Freeze/thaw	All samples met the respective requirements for sample status (positive/negative) and the QC acceptance ranges in the screening
LQC		

<table>
<tr><td>HQC</td><td>(F/T)cycle</td><td>assay.</td></tr>
<tr><td colspan="3">Amendment-2 (Table 10.1.1)</td></tr>
<tr><td>NQC/CC
LQC/CC
HQC/CC
LQC-%SI
NQC-%SI</td><td>NIH3T3 cells: up to 44 months at -140-(-200)^{o}C

QC: up to 2-year storage at -60-(-80)^{o}C

BMN111 working stock: up to 16 months storage at -60-(-80)^{o}C

cGMP ELISA kit reagents: Up to 20 months storage at -10-(-30)^{o}C.

BMN111-sepharose conjugated immunodepletion reagent: Up to 9-months storage at -10-(-30)^{o}C.</td><td>The results from stability evaluation within March 2017 -July 2018 period are plotted on Figures 15.1-15.4. All QC and QC/CC parameters show consistent performance in validation study (see reviewer comment and Sponsor’s response in QC section).</td></tr>
</table>

Assessor comment: *Overall, the results support short-term and long-term assay reagent stability and consistent assay performance.*

Assessor comment regarding validation study for NAb assay: *Overall, the results provided support that the cell-based assay for detection of neutralizing antibodies against BMN111 is suitable for intended use.*

III. Detection of Anti-BMN111 IgE Antibodies in Human Serum using the ImmunoCAP Platform (21120.5955)

Assessor comment: *In addition to ImmunoCAP platform-based assay, there was also a conventional RAST-based (RadioAllergoSorbent test) assay which was used for evaluation of samples from phase 1 and is not discussed here.*

Validation study included the following parameters: screening and confirmation cut-point determination, intra and inter-assay precision, quality control acceptance ranges, sensitivity(limit of detection, LOD, and limit of quantitation, LOQ), selectivity (sample matrix interference), specificity (specific IgG and total IgE interference), and short-term stability.

Assessor comment: *A total of 15 runs were conducted as part of validation study, and all runs were acceptable.*

Analytical method

The assay is based on ImmunoCAP-based platform in which BMN111-coupled to ImmunoCAP streptavidin reagent is reacted with human serum samples to bind to BMN1111-specific antibodies. After washing step, anti-IgE mouse monoclonal antibody coupled to beta-galactosidase is added to form a ternary complex. The signal is generated by the addition of fluorogenic substrate for beta-galactosidase, and the signal is read on ImmunoCAP1000 instrument. Sample fluorescence is directly proportional to the drug specific IgE concentration in the sample. Assay design is similar for both screening and confirmation analysis, except that in confirmation analysis, the samples are additionally incubated with 200µg/mL of BMN111.

Critical reagents:

- BMN111 coupled ImmunoCAP streptavidin reagent
- Positive control: Surrogate IgE antibody control: affinity -purified rabbit polyclonal anti-BMN111 IgG chemically conjugated to myeloma-derived human IgE antibody.
- BMN111 drug
- Anti BMN111 QC samples:

QC sample	PC concentration	Matrix
HQC	882 ng/mL (6kUA/L)	Normal human serum pool
IQC	441 ng/mL (3kUA/L)	
LQC	57.3ng/mL (0.35 kUA/L)	
NQC	Normal human serum pool (<0.1kUA/L)	
LQC-C (Confirmation LQC)	LQC spiked with 200µg/mL BMN111 (inhibited) or without spike (uninhibited)	

Assessor comment: *Insufficient information was included in the assay description to enable evaluation of the adequacy of the method procedures to support that the assay is suitable for intended use. IR was conveyed to provide information on the minimum required dilution (MRD) used for sample analysis and whether MRD is included in the reported titer for the IgE antibodies, and to include detailed information on the type of analysis used for outlier exclusion for the screening and confirmatory cut-point determination. The Sponsor clarified that the samples used for analysis were not diluted (neat) and included details on the approach for sample exclusion (JMP software with box plot, incorporated in review memo). This is acceptable.*

The use of surrogate antibody control coupled to IgE is acceptable considering that the commercial generation of IgE antibody is not feasible and therefore not readily available. Because of the surrogate nature of the control, the values for the protein amount of surrogate control are additionally correlated with relative IgE activity units (e.g. kUA/L), which are included next to the surrogate control amounts. For the purpose of discussion, all assay results, where appropriate, will include the relative IgE activity units. Based on public information search, it appears that the activity units are based on WHO standards for total IgE determination.

1) Screening cut point (SCP) determination

Screening cut-point was established using 50 drug-naïve healthy human subject samples in two runs, a total of 100 samples (Table 4A). It was determined that the dataset does not follow normal distribution after outlier exclusion (inter-quartile ranges by box plot analysis, 6 outliers in both runs). The screening cut-point was determined non-parametrically at 95th percentile (63RU, corresponding to 0.13kUA/L) to target 5% false positive rate. All samples that screen above SCP are considered positive.

Assessor comment: *It is not clear if the cut points used for analysis is appropriate. It is stated that all day 1, pre-treatment, samples are negative for IgE (Section 2.7.4.2.1.10.3). However, it is not clear if this was at the screening or following confirmation analysis. The expectation is that, if the screening cut point is appropriate, between 2-11% of samples should screen initially positive. To ensure that the cut points are appropriate, IR was conveyed to provide the results from screening and confirmation analysis for day 1, pre-treatment samples. The Sponsor clarified that although no samples screened positive, this was likely due to small sample size, and not due to inadequate cut-point. Considering that there were no qualifying events that would warrant evaluation of IgE type of antibodies, the approach is acceptable and the risk for clinical sample evaluation is low.*

2) Confirmatory cut point (CCP) determination

Confirmation cut-point was established using 50 drug-naïve healthy subject samples in two runs; a total of 100 samples (Table 4C). It was determined that the dataset is normally distributed after outlier exclusion (2 in each run by inter-quartile ranges). The screening cut-point was determined parametrically to target 1% false positive rate at 56.8% SI. The %SI is calculated as 100x (uninhibited sample-inhibited sample/uninhibited sample). All samples that are above the CCP ae confirmed as positive.

Assessor comment: *See the section on the screening cut point.*

3) Inter-and intra-assay precision

For the analysis of precision, three replicates of QC samples (HQC, IQC, LQC and NQC) were evaluated in six independent runs over six days across two instruments (Tables 6-9). The results are summarized in the table below:

QC sample	Inter-assay precision	Intra-assay precision
HQC	7.35%	0.76-8.74%
IQC	4.60%	1.98-3.57%
LQC	5.13%	1.42-6.04%
NQC	22.17%	1.59-4.72%

Assessor comment: *It appears that the precision analysis was limited to the screening assay only, and no data were provided to support precision analysis for confirmatory assay (Tables 6-9). This is not appropriate as the assay is intended to support both screening and confirmatory analyses. IR was conveyed to provide data to support inter and intra-assay precision for the confirmation of IgE-type of antibodies using relevant assay reagents and controls or provide justification why such analysis is not necessary. The Sponsor clarified that the inter-assay precision for the confirmation assay was calculated at 13.5% CV (Table 4 in response). This is acceptable.*

4) QC acceptance ranges

The QC acceptance ranges for the clinical testing were derived from the QC results from all validation runs (Table 10). The QC acceptance ranges specify that at least two out of three QC controls should be within 2SD and the third QC control should be within 3SD, while the NQC must be <0.13 kUA/L. The 2 and 3 SD ranges for the QC samples are included in the table below:

QC	2SD ranges (kUA/L)	3SD ranges (kUA/L)
HQC	4.41-5.93	4.03-6.31
IQC	2.37-2.85	2.25-2.97
LQC	0.35-0.43	0.33-0.45
NQC	<0.13	<0.13

Assessor comment: *The QC acceptance ranges appear acceptable.*

5) Selectivity: Matrix interference

For the analysis of matrix interference, a total of 10 samples were either spiked or not with LPC and analyzed in the screening and confirmatory assays; of 10 samples, 5 were visually confirmed as lipemic and 5 had different extent of hemolysis. All lipemic and hemolytic spiked samples screened positive, and all, but one hemolytic sample, confirmed positive (Table 12).

Assessor comment: *Overall, the results support that there is no major matrix impact on assay selectivity.*

6) Specificity:

- IgG interference

IgG interference was evaluated by either spiking or not, a rabbit polyclonal anti-human CNP IgG1 antibody (1-100µg/mL range) to either LQC or IQC and evaluating the samples in the screening assay (Table 13A). All samples screened positive and no interference was detected.

- Total IgE interference

The analyzed samples included human sera with varying levels of total IgE (0.1-0.48kUA/L). Four out of five samples screened positive; however, all samples were confirmed negative in the BMN111-specific confirmatory assay.

Assessor comment: *The results support that the interference from anti-CNP antibody or total IgE antibody on specific detection of anti-BMN111 IgE antibodies is unlikely.*

7) Drug tolerance

Assessor comment: *The results to support assay tolerance were not provided. This is acceptable, considering that the concern over potential for interference is greatly reduced because of short BMN111 half-life, up to 70 min, and the BMN111 level 24 hours after the dosing were within <100pg/mL range.*

8) Sensitivity

- Lower limit of quantitation (LLOQ)

The LLOQ was determined in a serial dilution experiment. For the analysis, the HQC and IQC was serially diluted (3.81-882ng/mL and 3.81-8.23ng/mL range) and each sample was evaluated in triplicate over three runs (Tables 3A and 3B). The LLOQ was defined as the lowest analyte concentration which can be measured with CV≤25% and can generate the response above that of the 0.1kUA/L. The results show that any PC levels above 9.86ng/mL generated a consistent signal above the 0.1kUA/L value.

Assessor comment: *In addition to LLOQ, the Sponsor also included LOD evaluation from the analysis of 50 drug naïve normal human serum samples in one run, by calculating the 2SD from the mean response, at 59 RU, which corresponds to 0.12 kU/L activity (Table 2). Although this does not indicate the true LOD for detection of BMN111-specific IgE antibody, it nonetheless shows that the any signal above 0.12kUA/L would be acceptable to distinguish the presence of anti-BMN11 IgE antibodies, if detectable. Therefore, the LLOQ was set at the SCP, at 0.13kUA/L. IR was conveyed to provide data from real-life evaluation of basal clinical samples to confirm the adequacy of the proposed LPC at 0.13 kUa/L. The Sponsor clarified that the implemented LPC across in-study analysis was higher, between 0.32-0.48 kU/L. This is still acceptable as it corresponds to IgE levels of ~55.1 ng/mL (Table 3A) and close to clinically relevant level at 0.39 kU/L.*

9) Stability

Stability was evaluated under the following conditions: 6 hours, 24 hours and 1 week at room temperature, 6 hour, 24 hours and 1 week at 2-8^{o}C, and up to 3 cycle of freeze/thaw (Tables 11A, 11B, 11C, and 11D). The evaluated samples included duplicates of all QCs in the screening assay (HQC, IQC,LQC and NQC). Overall, the mean results from all samples were within 20% of the baseline control samples and all results for %CV were <20%.

Assessor comment: *The results support short-term, long-term and freeze/thaw stability under the specified conditions.*

No data are provided to support assay robustness for the screening and confirmation evaluation of clinical samples. IR was conveyed to provide data to support that the assay performance is not impacted by the deliberate variation in assay procedures to ensure consistent assay performance for the clinical sample analysis. The Sponsor clarified that the assay for the analysis IgE is an automated robotic system and that there is minimal potential for assay variability to built-in instrument controls. This is acceptable.

Assessor comment regarding validation study for IgE antibody detection assay: *Overall, the results support that the assay for detection of IgE type of antibodies is suitable for intended use.*

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Real World Evidence

Date:	July 23, 2021
Reviewer:	Christian Hampp, PhD, FISPE Division of Epidemiology I
Team Leader	Yandong Qiang, MD, PhD, MPH, MHS Division of Epidemiology I
Division Director	Simone P. Pinheiro, ScD, MSc, ALM Division of Epidemiology I
Subject	Review of Natural History Studies in Vosoritide NDA
Drug Name:	vosoritide
Application Type/Number:	NDA 214938
Submission Number:	multiple
Applicant/applicant:	Biomarin
OSE RCM #:	2021-76

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EXECUTIVE SUMMARY

This Division of Epidemiology-I (DEPI-I) review evaluates the appropriateness of comparing subjects exposed to vosoritide in single-arm extensions of clinical trials with subjects from a real-world, external natural history (NH) control group to support long-term effectiveness claims for vosoritide in the treatment of achondroplasia (ACH).

On August 20, 2020, Biomarin submitted NDA 214938 for vosoritide, an analog of C-type Natriuretic Peptide (CNP), intended for the treatment of pediatric patients with ACH, (b) (4) whose epiphyses are not closed. The vosoritide clinical development program consists of 7 interventional studies, 1 noninterventional observational study, and real-world data from NH data sources. To support long-term effectiveness claims, the applicant submitted analyses based on NH data to provide external controls as a comparator to subjects from the ongoing phase 2 long-term extension study 111-205, with follow-up through 5 years of continuous treatment, and the ongoing study 111-302, which is a long-term extension study of the pivotal phase-3 trial 111-301.

The applicant obtained NH data from 4 different studies of ACH patients, with the primary NH data source (AchNH study) providing the majority of patients. The AchNH study is a protocol-driven, multicenter registry designed to primarily characterize growth in patients with ACH. Anthropometric data were collected as part of routine specialist care in 4 established skeletal dysplasia centers across the United States. The 3 remaining data sources were pooled to provide a supportive NH control pool.

The applicant compared height measurements between patients exposed to vosoritide (consisting of several treatment groups from studies 111-202/205 and 111-301) and age- and sex-matched subjects from untreated ACH subjects in the AchNH database. The pre-specified primary analysis was a 5-year cross-sectional analysis to compare the difference between height at 5-years' follow-up and at baseline between the vosoritide group and the NH control group. Supportive analyses include 5-year longitudinal analyses, 4-year cross-sectional and longitudinal analyses, and 2-year longitudinal analyses, and comparisons with other NH data sources. In addition, the applicant compared the 1-year height increase between vosoritide patients and placebo patients in Study 111-301 and matched NH controls to demonstrate the appropriateness of using external controls.

In the primary, 5-year cross-sectional analysis, the baseline-adjusted mean height difference between subjects exposed to vosoritide (n=10) and the matched external AchNH control (n=360 at Year 5) was 9.08 cm (95% CI: 5.77 – 12.38). The 5-year longitudinal analysis yielded a mean difference in baseline-adjusted height between subjects exposed to vosoritide (Cohort 3, n=10) and the matched external AchNH control (n=98) of 8.40 cm (95% CI: 6.13 – 10.67). Sensitivity analyses were generally consistent with results from the primary analysis, with baseline-adjusted height differences after 5 years ranging from 7.50 cm to 9.08 cm across these analyses. The 4-year and 2-year analyses were generally supportive.

In addition, per FDA's request, the applicant repeated these analyses after excluding a vosoritide subject who underwent limb-lengthening surgery prior to study entry, and matching vosoritide subjects with AchNH controls on baseline height and annualized

growth velocity (AGV), in addition to age and sex. In the updated 5-year cross-sectional analysis, the baseline-adjusted mean height difference between subjects exposed to vosoritide (n=9) and the matched external AchNH control (n=346 at Year 5) was 8.15 cm (95% CI: 4.83 – 11.47). The 5-year longitudinal analysis yielded a baseline adjusted height difference of 7.46 cm (95% CI: 4.82 – 10.10).

The results of the applicant's calculations show a high degree of consistency across primary, secondary, and sensitivity analyses. *Post-hoc* analyses requested by the FDA yielded slightly attenuated estimates of treatment effect. In addition, review of the applicant's analyses, and analyses conducted by the FDA, suggest that measurement bias, confounding, and selection bias are unlikely to explain the observed height gain associated with 5 years of vosoritide treatment, compared with matched NH control patients.

1 INTRODUCTION

This DEPI-I review evaluates the appropriateness of comparing subjects exposed to vosoritide in single-arm extensions of clinical trials with subjects from a real-world, external NH control group to support long-term effectiveness claims for vosoritide in the treatment of ACH.

1.1 BACKGROUND

On August 20, 2020, Biomarin submitted NDA 214938 for vosoritide, an analog of C-type Natriuretic Peptide (CNP), intended for the treatment of pediatric patients with ACH (b) (4) whose epiphyses are not closed. Achondroplasia is a rare genetic disorder that is characterized by severe short stature (-6 standard deviation score [SDS] versus average stature) and results in short-limb skeletal dysplasia. The proposed dosage for vosoritide is (b) (4) once daily, via subcutaneous injection.

The vosoritide clinical development program consists of 7 interventional studies (111-101, 111-202, 111-205, 111 301, 111-302, 111-206, and 111-208), 1 noninterventional observational study (111-901), and real-world data from natural history (NH) data sources. To support long-term effectiveness claims, the applicant submitted analyses based on NH data to provide external controls as a comparator to subjects from the ongoing phase 2 long-term extension study 111-205, with follow-up through 5 years of continuous treatment, and the ongoing study 111-302, which is a long-term extension study of the pivotal phase-3 trial 111-301.

On January 8, 2021, the Division of General Endocrinology (DGE) consulted DEPI-I to advise regarding the adequacy of the 4 NH data sources used to support efficacy evaluation for vosoritide, with regards to data collection procedures, quality of the collected data (i.e. demographics; height data: completeness, contemporaneousness, longitudinal assessment, comparability to prospectively collected data sources, limitations of data), adequacy of the matching process, and the proposed methods of analysis for comparison.

2 REVIEW METHODS AND MATERIALS

This review is based on following submissions by the applicant:

Study reports:

- The primary focus of this review was on the "Natural History Integrated Analyses Report," dated June 16, 2020
- Study report for Study 111-901 "A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia," dated December 12, 2019
- Study report for Study 111-501 "The Impact of Achondroplasia on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial state of the Individual. Lifetime Impact of Achondroplasia Study in Europe (LIAISE)," dated November 19, 2020
- The "synoptic reports" for the AchNH study, dated May 26, 2020, and the KAISER study, dated May 26, 2020, contain insufficient information to support a review

Study protocols and statistical analysis plans:

- Statistical Analysis Plan "Planned Natural History Data Analysis and Comparative Analysis of Effect of BMN 111 versus Natural History Growth Data in Pediatric Subjects with Achondroplasia", dated April 27, 2020, submitted as Appendix to NH study report
- Study protocol for "Achondroplasia Natural History: multi-center clinical study," dated December 2015, included as Appendix 1 in "The AchNH Synoptic Report," dated May 26, 2020
- Study protocol for Study 111-501, dated January 30, 2017, included as Appendix 1 in "Synoptic Report Study 111-501: The Impact of Achondroplasia on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial State of the Individual," date of latest amendment was February, 5, 2018
- Study protocol for KAISER study Natural History of Achondroplasia: A Retrospective Study of Patients Managed by a Multispecialty Program Protocol Version 1.3, dated November 20, 2016
- Study protocol for Study 111-901 "A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia" original protocol, dated December 22, 2011, date of latest amendment was August 29, 2018

In addition, this review incorporates the applicant's responses to multiple information requests by DGE, DEPI-I, and the Division of Biometrics-II (DB-II), which include clarifications as well as important *post-hoc* analyses.

Finally, this review reports on the results of several *post-hoc* analyses conducted by Dr. Jiwei He, Statistical Reviewer in DB-II.

These materials were reviewed under consideration of the FDA Guidance for Conducting and Reporting Pharmacoepidemiologic Safety Studies, (1) the FDA Framework for Real-World Evidence Program, (2) the International Society for Pharmacoepidemiology

(ISPE) Guidelines for Good Pharmacoepidemiology Practices,(3) and a recent ISPE publication on external control groups for single arm trials or long-term extensions.(4)

3 REVIEW RESULTS

The applicant compared increase in height, changes in height Z-score, and AGV among patients exposed to vosoritide for up to 5 years in clinical trials to age- and sex-matched subjects from an external, NH pool of patients with ACH. This section lists overall study objectives, describes data sources for patients exposed to vosoritide in clinical trials, the methods of each NH data source, the methods used to compare data between active treatment and NH controls, and results of this comparison.

3.1 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

Primary Objective

- Durability of treatment effect: To demonstrate the effect of BMN 111 on height after 5 years of treatment follow up on 15 μg/kg as compared to the NH control

Secondary Objectives

- To demonstrate durability of BMN 111 treatment effect up to 5 years of treatment as compared to NH control
- To demonstrate whether the treatment effect observed on 15 μg/kg at one year in the BMN 111-301 study is maintained for up to 2 years, as compared to the NH control
- To describe the distribution of growth parameters for untreated ACH subjects from NH control

Exploratory Objectives

- Impact of treatment on near final adult height (NFAH): To gain understanding of the potential treatment effect on height at 16 years of age, as compared to the NH control
- To assess the impact of using a randomized versus non-randomized control arm

3.2 STUDY METHODS

3.2.1 Patients Exposed to Vosoritide in Clinical Trials

Patients exposed to vosoritide were selected from the following clinical trials:

- **Study BMN 111-202**
  BMN 111-202 was a phase 2, open-label, sequential cohort dose-escalation study of vosoritide in children with ACH. Study duration was up to 2 years and a total of 35 subjects were treated. The study was completed in October 2017.
- **Study BMN 111-205**
  BMN 111-205 is an extension study of Study 111-202. A total of 30 subjects were treated. Subjects are followed either until they reach NFAH or for 5 years if

NFAH occurs prior to the end of the 5-year period. The study is ongoing, and the data cutoff date was November 20, 2019.

The applicant categorized patients from Studies 111-202/205 into the following cohorts:

- Cohort 1: Subjects assigned to receive 2.5 µg/kg in 111-202 who were dose-escalated to receive 15 µg/kg
- Cohort 2: Subjects assigned to receive 7.5 µg/kg in 111-202 who were dose-escalated to receive 15 µg/kg
- Cohort 3: Subjects assigned to receive 15 µg/kg in 111-202 and 111-205
- Cohort 4: Subjects assigned to receive 30 µg/kg in 111-202 and 111-205

- **Study BMN 111-301**
  BMN 111-301 was a phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vosoritide in children with ACH. The study duration was 1 year and a total of 121 subjects were treated. The study was completed in October 2019.
- **Study BMN 111-302**
  BMN 111-302 is an extension study of Study 111-301. Subjects are followed either until they reach NFAH, or for 5 years if NFAH occurs prior to the end of the 5-year period. The study is ongoing, and the data cutoff date was October 31, 2019. All subjects from 111-301 except for 2 discontinued subjects were entered to 111-302 as of the cutoff date.

3.2.2 Natural History Data Sources

The applicant obtained NH data from 4 different studies of ACH patients. The primary NH data source is the AchNH study and the 3 additional studies (111-501 ("LIAISE"), 111-901, KAISER) were used to substantiate the primary analyses. The study methods of all 4 NH data sources are briefly described in this section, focusing primarily on study objectives, subject selection, and on methods to collect and analyze anthropometric measures.

3.2.2.1 AchNH Study

Study Design and Setting

The Achondroplasia Natural History Multi-Center Clinical Study is a protocol-driven, multicenter registry designed to primarily characterize growth in patients with ACH. It was conducted across 4 established skeletal dysplasia centers across the United States: Johns Hopkins University, AI DuPont Hospital for Children, University of Texas, and University of Wisconsin-Madison. The planned study duration was 2 years,[a] and the investigators expected to enroll between 1,000 and 1,500 patients. The AchNH database

[a] The calendar year range of height measurements was not provided.

includes 1,374 patients, of whom 791 met all criteria[b] for inclusion into the NH descriptive population (Appendix, Table 2.1.1.1).

Study Objectives

1.) Mixed longitudinal anthropometry of patients with ACH:
To characterize growth (e.g., height, height velocity, weight) in this ACH cohort and compare these parameters to previously published populations whenever possible. New or augmented reference growth charts for ACH (by age and gender) will be created.

2.) Surgical burden in ACH:
To quantify the total number, type, age, indications, and complications of all surgical interventions of a cohort of patients with ACH.

3.) Sleep disordered breathing in ACH:
To quantify the prevalence and characteristics of sleep disordered breathing in a cohort of patients with ACH.

4.) Imaging available for future study:
To record the type, the date/age the imaging was performed and the location of the images for future interrogation.

Selection, Inclusion, and Exclusion Criteria

All patients with a molecular or clinical diagnosis of ACH were eligible for enrollment if they were a prior or current clinical patient at one of the participating study sites.

Inclusion Criteria

- Molecular or clinical diagnosis of ACH (as confirmed by physical exam and/or radiograph review by the PI, one of the co-PIs or other qualified clinical geneticists)
- Subjects must have been seen for a clinical genetics visit at Johns Hopkins, AI DuPont Hospital for Children, University of Wisconsin-Madison or University of Texas
- Subjects may be active clinical patients at the above sites or no longer treated at a given site but with sufficient retrospective clinical data for extraction as determined by the PI or co-PIs

Exclusion Criteria

- Skeletal dysplasia diagnosis other than heterozygous ACH

Outcomes

The outcome that is most relevant for the analyses to support NDA 214938 is the primary outcome under the primary objective, for subjects <20 years: growth (i.e., height, height velocity, weight, and BMI).

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[b] Included were subjects with at least 1 height assessment between age 5-16 years, excluded were subjects enrolled in an interventional study, without a height assessment measured at a known age, or who received growth hormone or underwent limb-lengthening surgery

Secondary outcomes are numerous and include age at which linear growth ceases, secular trends in weight and BMI for age over decades, stages/landmarks of pubertal development, and others.

Additional primary and secondary outcomes were selected to address Objectives 2-4. These are not listed here to maintain focus on the analyses that are relevant for the NDA.

Outcome Assessment and Data Curation

Data from the following domains were abstracted from medical charts at each available time point for each subject:
1. Demographics, means of diagnosis, inheritance
2. Anthropometric measures: height, weight, head circumference, and parental height
3. Number, type, age at, and complications, of all surgical interventions
4. Results of sleep studies
5. Results of any imaging studies

On January 13, 2021, FDA requested additional detail regarding the collection of anthropometric measurements in the AchNH study. The applicant responded with an explanation that all anthropometry (height, length, weight and head circumference) was collected by multiple providers in their individual clinic settings as part of routine specialist care and recorded in the hard copy or electronic medical record. Single assessments were performed at each time point. Length was obtained in a supine position until at least 2 years of age when most individuals with ACH could participate in a standing height measurement with a stadiometer.

To clean data, the investigators planned to assess intra-subject variability by visually examining data points for outliers and implausibility by plotting each parameter (i.e., length/height) over time on individual and cohort liner plots. In addition, algorithms flagged length/height differences greater than 10 cm between 2 values obtained within 2 months, length/height differences greater than 5 cm between any 2 data points and height over 139.9 cm. Discrepancies were resolved by checking the value in question against the primary data source. Physiologically implausible values were deleted.

3.2.2.2 LIAISE (Study 111-501): The Impact of Achondroplasia on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial State of the Individual.

Study Design and Setting

Study 111-501 was a multinational, epidemiological, observational, retrospective, cross-sectional study of individuals with ACH. The investigators planned to enroll up to 300 subjects in up to approximately 20 sites in European countries during the planned study period from 2017 through 2020. The LIAISE database include 128 patients, of whom 56 met all criteria[b] for inclusion into the NH descriptive population (Appendix, Table 2.2.4.1).

Study Objectives

The objectives of the study were to describe the impact on the following in individuals with ACH on:

- Quality of life (QoL)
- Clinical burden (functional impact, comorbidities, complications, medical and surgical care)
- Healthcare resource use
- Socio-economic burden (educational, personal, employment and financial impact)
- Psychosocial burden (psychological and socialization impact)

Selection, Inclusion, and Exclusion Criteria

Subjects were enrolled during routine hospital visits, from patient lists of those previously treated but no longer followed at the study site, and through collaboration of the PI with ACH patient organizations, other ACH-related organizations, other healthcare professionals in their country, and ACH-related social media sites.

Inclusion Criteria

- Individuals with a documented diagnosis of ACH based on genetic confirmation and/or clinical diagnosis (clinical examination or radiological assessment) of ACH
- At least 5 years of age at the time of enrolment
- Cognitive and linguistic capacities necessary to complete questionnaires in the language of his/her country (and/or parents/legally acceptable representatives, as applicable)
- Agree to participate in the study
- Medical records available for at least the 5 years prior to the date of enrolment.

Exclusion Criteria:

- Currently participating, or participated within the last 6 months, in a clinical trial of a medicinal product or medical device or other non-clinical, low interventional studies
- Currently participating or participated in any BioMarin study at any time.

Outcomes

The study endpoints include results QoL and symptom specific questionnaires/assessments, clinical burden of disease including results of clinical assessments, comorbidities/complications, investigations and results surgical procedures, and treatments.

The study endpoints did not include anthropometric measures. However, the investigators planned to collect data on the following growth characteristics at different ages: height, weight, head circumference, proportionality of body parts.

3.2.2.3 Study 111-901: A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia

Study Design and Setting

Study 111-901 was designed as a prospective, multicenter, multinational study to collect specific growth measurements on pediatric subjects with ACH at approximately 45 multinational sites.[c] The study duration was planned for up to 7 years. The investigators anticipated the enrollment of approximately 500 subjects from birth to ≤ 17 years of age at study entry. The 111-901 database includes 352 patients, of whom 242 met all criteria[b] for inclusion into the NH descriptive population (Appendix, Table 2.2.4.1).

Study Objective

The objective of this study was to collect consistent baseline growth measurements on pediatric subjects being considered for subsequent enrollment in other future studies by BioMarin.

Selection, Inclusion, and Exclusion Criteria

Inclusion Criteria:

- Informed consent
- Birth to ≤ 17 years of age, at study entry.
- Have ACH, documented by clinical diagnosis
- Are ambulatory and able to stand without assistance (not applicable for children who are younger than 5 years of age and less than 104 cm in length)
- Are willing and able to perform all study procedures as physically possible

Exclusion Criteria:

- Hypochondroplasia or short stature condition other than ACH
- Any of the following disorders: Hypothyroidism, insulin-requiring diabetes mellitus, autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others), inflammatory bowel disease, autonomic neuropathy
- Unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression
- History of growth plate closure, renal insufficiency, anemia, cardiac dysfunction, hypertrophic cardiomyopathy, congenital heart disease, cerebrovascular disease, aortic insufficiency, clinically significant atrial or ventricular arrhythmias
- Current treatment with antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, any medication

[c] The study was conducted at 27 study centers in 8 countries: US (50.9%), Australia (14.3), Spain (12.9%), UK (10.5%), Japan (4.4%), Germany (2.9%), France (2.3%), and Turkey (1.8%).

that may impair or enhance compensatory tachycardia, drugs known to alter renal function that is expected to continue for the duration of the study

- Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the previous 6 months or long-term treatment (> 3 months) at any time. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids are acceptable) in the previous 12 months
- Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever is longer, before the screening visit
- Have used any other investigational product or investigational medical device for the treatment of ACH or short stature
- Planned or expected bone-related surgery (i.e., surgery involving disruption of bone cortex), during the study period. Subjects with previous bone-related surgery may enroll if surgery occurred at least 12 months prior to the study and healing is complete without sequelae.
- Planned or expected to have limb-lengthening surgery during the study period. Subjects with previous limb-lengthening surgery may enroll if surgery occurred at least 18 months prior to the study and healing is complete without sequelae.
- Have any condition that, in the view of the Investigator, places the subject at high risk of poor compliance with the visit schedule or of not completing the study.
- Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation

Study Outcomes and Anthropometric Outcome Assessment

Anthropometric measurements included growth parameters (height, standing height, sitting height, weight, upper and lower arm and leg length, and arm span) and body proportion measurements. Following baseline measurements, subjects undergo growth measurements at subsequent 3-month intervals.

The appendix of the study protocol includes detailed anthropometric measurement guidelines. They specify that growth measures were to be collected approximately at the same time (± 2 hours) during each visit by a trained study staff member. Each measurement (excluding weight) was to be taken in triplicate using standardized measuring equipment techniques.

Statistical analysis

The investigators planned to calculate descriptive statistics (mean, standard deviation, median, minimum, and maximum) to summarize growth velocity and absolute growth based on growth measures at each scheduled time point. Growth measurements were planned to be converted to standard deviations or Z-scores, corrected for age and sex, and compared with standardized pediatric growth curves.

3.2.2.4 KAISER

Study Design and Setting

The KAISER study is an observational, retrospective single-cohort study (case series), incorporating cross-sectional and retrospective longitudinal data in the Kaiser Permanente of Northern California (KPNC) database. The KAISER database included 114 patients, of whom 61 met all criteria[b] for inclusion into the NH descriptive population (Appendix, Table 2.2.4.1).

Study Objectives

The study has two co-primary objectives:

1. To determine the baseline characteristics of ACH patients followed in the KPNC Skeletal Dysplasia Program
2. To determine the natural history and longitudinal progression of ACH among patients followed in the KPNC Skeletal Dysplasia Program.

Selection, Inclusion, and Exclusion Criteria

The investigators aimed to include all KPNC members with a diagnosis of ACH and at least one visit to the KPNC Skeletal Dysplasia Clinics at any time (approximately 100).

Inclusion Criteria

- Active or former member of the KPNC Health Plan
- Confirmed diagnosis of ACH
- Availability of clinical data (either clinic shadow charts, EMR data, or both)

Exclusion Criteria

According to the protocol, since a census of all current and former patients of the KPNC Skeletal Dysplasia Clinic was to be included in this study (i.e., no subject sampling), no exclusion criteria were applied to the patients in this study.

Outcome Assessment and Data Curation

Outcomes were extracted from medical charts. The study protocol included an extensive list of variables to be collected, including those relevant for the present analysis: height, age, means of ACH diagnosis, related diagnoses, surgery, and medication use.

Potential outlier observations were planned to be identified by inspection, as well as by common quantitative rules (e.g., > 3 standard deviations above or below the mean). They were then investigated for possible data recording or entry errors.

An overview of the 4 NH data sources is provided in Table 2.1.

Table 2.1: Overview of Natural History Sources

Study ID	Design	Number of Sites	Study Objective	Study Population[a]	Type of Data Collection	Protocol Date	Date Data Received/Data Cut-off	Subjects Enrolled
AchNH	Observational	4	Investigator-sponsored study to characterize growth (ie, height, height velocity, weight and BMI) in ACH.	All prior or current clinical subjects of all ages at participating study sites with a diagnosis of ACH	Retrospective from medical charts	DEC2015	21NOV2019	1374
111-901	Observational	27	To collect baseline growth measurements on subjects being considered for subsequent enrollment in studies 111-202, 111-301 and 111-206	Pediatric subjects with ACH from birth to ≤ 17 years of age	Prospective; observation period of up to 7 years	22DEC2011	30NOV2019	352
LIAISE	Observational	11	Track impact on QoL, clinical burden, healthcare resource use, socio-economic burden, and psychosocial burden in ACH	ACH subjects of all ages at participating EU study sites	Retrospective from medical charts	30JAN2017	01NOV2019	128
KAISER	Observational	1	Investigator-sponsored study to determine baseline characteristics and natural history in ACH	ACH Subjects in Kaiser Permanente, Northern California Skeletal Dysplasia Program	Retrospective from medical charts	20JUN2016	21JUL2019	114

ACH, achondroplasia; AchNH, Achondroplasia Natural History: multicenter clinical study (Principal Investigator Julie Hoover Fong, MD, PhD); BMI, body mass index; EU, European Union; ID, identification; KAISER, Natural History of Achondroplasia: A Retrospective Study of Patients Managed by a Multispecialty Program (Principal Investigator Ericka Okenfuss, MS, LCGC); LIAISE, The Impact of Achondroplasia on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial State of the Individual (Study 111-501); QoL, quality of life.

[a] Study population at study entry.

The data cut-off date is provided for 111-901 and LIAISE, and the date on which the data were received are provided for AchNH and KAISER.

3.2.3 Comparative Analysis Methods Using Clinical Trial Data and NH Data Sources

The investigators compared height measurements between patients exposed to vosoritide (several treatment groups from studies 111-202/205 and 111-301) and age- and sex-matched subjects from the external control group (untreated ACH subjects).

The pre-specified primary analysis was a 5-year cross-sectional analysis to compare the difference between height at 5-years' follow-up and at baseline between the vosoritide group and the NH control group. Supportive analyses include 5-year longitudinal analyses, 4-year cross-sectional and longitudinal analyses, and 2-year longitudinal analyses, and comparisons with other NH data sources (Table 3.1). A 1-year analysis that compared baseline and 1-year height between the placebo group and external NH patients and between the active treatment arm and external NH patients was designed to demonstrate the impact of using a randomized versus non-randomized control arm. Sensitivity analyses include simulations, a tighter age matching time interval, and analyses using an external control without matching.

Patient Selection

The NH control arm comprises a subset of subjects from the NH data source who met the following criteria:

- Subject must have a confirmed diagnosis of ACH
- Sex must be available
- Subject must have ≥ 1 standing height measure available taken at a known age

For those subjects who received BMN-111 or growth hormone, or underwent any limb lengthening surgery, post-event height assessments were excluded for analysis. When the time of the event was not available, all data for that subject were excluded.

Primary Analysis: 5-Year Comparative Analysis (Table 3.1)

- **Active Treatment Arm**
  Subjects in Study 111-202 Cohort 3 (15 μg/kg) who continued to Study 111-205 with at least 5 years of total follow-up (N=10).

- **NH Control Arms**

  Cross-Sectional Analyses:
  At baseline: all subjects from the NH data source who are matched by sex and age to at baseline to subjects in the active treatment arm.
  At Year 5: all subjects from the NH data source who are matched by sex and age at Year 5 (i.e., Month 60) to subjects in the active treatment arm.

  Longitudinal Analysis:
  Subset of NH control arm for 5-year cross-sectional analysis who are matched by sex and age at baseline and had at least one height assessment at 60 +/- 3 months after baseline.

Secondary Analysis Populations: 4-Year Comparative Analysis

- **Active Treatment Arm**
  Subjects in Study 111-202 Cohorts 1, 2, or 3 (maximum dose 15 μg/kg) who continued to Study 111-205 with at least 4 years of total follow-up (N=20). Follow-up for Cohorts 1 and 2 was counted from the first time when a vosoritide dose of 15 μg/kg was received ("re-baselined").

- **NH Control Arms**

  Cross-Sectional Analyses:
  At baseline: all subjects from the NH data source who are matched by sex and age at baseline to subjects in the active treatment arm.
  At Year 4: all subjects from the NH data source who are matched by sex and age at Year 4 (i.e., Month 48) to subjects in the active treatment arm.

  For Longitudinal Analysis:
  Subset of NH control arm for the 4-year cross-sectional analysis who are matched by sex and age at baseline and had at least one height assessment at 48 +/-3 months after baseline.

Secondary Analysis Populations: 2-Year Comparative Analysis (longitudinal)

- **Active Treatment Arm**
  Subjects in the active treatment arm in Study 111-301 (15 μg/kg) who continued to Study 111-302 with at least 2 years of total follow-up and subjects in Study 111-202 Cohorts 1, 2, or 3 (maximum dose 15 μg/kg) with 2 years of follow-up (N=25: 22 from 111-202 + 3 from 111-301). Follow-up for Cohorts 1 and 2 was counted from the first time when a vosoritide dose of 15 μg/kg was received ("re-baselined").

- **NH Control Arm**
  Subjects of the NH control arm with at least one height assessment between 6 to 12 months prior to the identified baseline and at least one height assessment at 12 +/- 3 months and 24 +/- 3 months after the identified baseline.

Supportive Analysis Population #1: 5-Year Comparative Analysis

- **Active Treatment Arm**
  For both cross-sectional and longitudinal analyses:
  Subjects in Study 111-202 Cohorts 1, 2, or 3 (maximum dose 15 μg/kg vosoritide) who continued to Study 111-205 with at least 5 years of total follow-up (N=20). Follow-up for Cohorts 1 and 2 is counted from receipt of the first vosoritide dose ("not re-baselined").

- **NH Control Arms**
  As in primary analysis

Supportive Analysis Populations #2: 4-Year Comparative Analysis

- **Active Treatment Arm**
  Subjects in Study 111-202 Cohort 4 (30 µg/kg) who continued to Study 111-205 with at least 4 years of total follow-up (N=8).
- **NH Control Arms**
  As in secondary, 4-year analysis

Analysis Populations to Assess the Impact of Using a Randomized vs. Non-Randomized Control Arm

1. **111-301 Active vs. NH Control Arm**

- **Active Treatment Arm**
  Subjects on active treatment (15 µg/kg) in Study 111-301 who had at least 1 year of follow-up (N=58).
- **NH Control Arm**
  As in secondary, 2-year analysis

2. **111-301 Placebo vs. NH Control Arm**

- **111-301 Placebo**
  Subjects who receive placebo in Study 111-301 and had at least 1 year of follow-up (N=61).
- **NH Control Arm**
  As in secondary, 2-year analysis

Matching

Subjects from the BMN 111 treated population were matched with subjects from the NH population by sex and age (age in integer) by selecting subjects from the NH controls of the same sex who have a height assessment at the same age as an active treatment subject. This step was repeated for all active treatment subjects.

Since NH subjects could have height assessments at different ages, they could be matched with more than one subject from the active arm with a different age. In this case, the active treatment subject was randomly assigned to one of the groups with an equal probability (Appendix, Figure 3.1.1).[d] When there were multiple subjects in the active arm with the same sex and age, the algorithm matched them to the same set of subjects in the NH control arm. This algorithm resulted in each subject in the vosoritide group being matched to a unique group of subjects from the NH control pool with a different number of NH subjects in each matched set.

[d] A sensitivity analysis included 5,000 iterations of this random selection step.

For the cross-sectional analyses, the matching algorithm was applied separately for the baseline assessment and the post-baseline assessment. Thus, the external control group for the post-baseline comparison and the external control group for the baseline comparison comprises a different, yet potentially overlapping, set of subjects.

Study Outcomes

- **Cross-sectional analyses:** Height and height Z-score
- **Longitudinal analyses:** Change from baseline in height, change in height Z-Score, change from baseline in cumulative AGV (primary endpoint in 1-year and 2-year comparative longitudinal analyses).

Statistical analysis

Validity of height measurements in the AchNH database

To examine whether there is a temporal trend in height measurements in the AchNH database, the applicant provided age- and sex-specific mean height measurements stratified by birth prior to or after the Year 2000. In addition, to examine the validity of retrospectively collected height data in the primary AchNH control group, the applicant contrasted its age-specific height measurements with prospectively collected measurements in the 111-901 study and a published data source.

Baseline patient characteristics

The applicant provided "goodness of matching" analyses to compare baseline age, race, baseline height, baseline height Z-Score between the vosoritide treatment arm and NH controls, using descriptive statistics.[e]

Height

The cross-sectional and longitudinal analyses compared changes in height between the active treatment arm and the NH control arm. The difference between the height of each subject from the active treatment arm and the average height of subjects who were matched to this subject from the NH control arm were calculated at Year 5 (or Year 4 or Year 2, depending on the analysis), and at baseline, using the matched sets at each timepoint. The difference between the difference of height at Year 5 and at baseline was calculated using one sample t-test. Supportive analyses used an ANCOVA model that included the fixed effects of treatment (active arm vs. NH arm) and indicator variables for the matching based on sex and age combination.

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[e] In its response to FDA's November 17, 2020, information request, the applicant stated that the baseline tables are not an accurate reflection of how closely the subjects are matched because more younger NH subjects were matched to the younger vosoritide subjects and fewer to the older ones. Because this tends to reduce the overall mean height for the NH controls, the applicant recommended to evaluate baseline characteristics using the "goodness of matching" summary tables. Yet, as evident in subsequent responses to information request, goodness of matching analyses did not account for the variable ratio matching. Per FDA's request from April 6, 2021, the applicant calculated LS mean difference in baseline measures adjusting for matching ID in the regression model, which account for the variable matching ratio.

Height Z-score

The applicant converted each measurement of height to age- and sex-appropriate height Z-score by comparison with normal reference standards (not ACH reference standards) as published by the CDC.

Annualized growth velocity

AGV for a given interval was calculated as follows:

$$\text{AGV} = \frac{Standing\ Height\ at\ Date\ 2 - Standing\ Height\ at\ Date\ 1}{Interval\ Length\ (Days)} \text{ x } 365.25$$

Exploratory extrapolation of the effect of vosoritide on final adult height

In an exploratory analysis, the applicant extrapolated subjects' height from last height assessment at the data cutoff to the time when the subject will reach 16 years of age. The following assumptions were made in separate analyses to project a range of scenarios:

- Assumption: AGV is the same as for untreated subjects with ACH of the same age and sex:
    - For each subject, the yearly AGV following last height assessment on treatment was determined from the NH AGV estimates. Extrapolation by assuming 50% of NH AGV was also be conducted.
- Assumption: AGV reverts back to the subject's individual baseline AGV as observed in 111-901 (baseline GV)
    - For each subject, the baseline AGV was used to extrapolate from last height on treatment to height at 16 years of age. Extrapolation by assuming 50% of baseline AGV was also be conducted.
- Assumption: subjects continue to grow at the same AGV observed on BMN 111 (active AGV):
    - For each subject, the AGV observed over last year of treatment was used to extrapolate from last height on treatment to height at 16 years of age. Extrapolation by assuming 50% of active AGV was also be conducted.
- Assumption: no further growth after last assessment on BMN 111 treatment:
    - For each subject, the last height observed on treatment was considered as the height observed at 16 years of age (LOCF – last observation carried forward).

Table 3.1: Summary of Primary and Supportive Comparative Analyses

	Type of Analysis[a,b]	Analysis Population for Vosoritide Group	Analysis Population for External Control Group	Location in Report
Primary	**5-year cross-sectional** analysis on height at 5-years follow up between vosoritide group and external control	Cohort 3 of 111-202/205 *(subjects who received 15 µg/kg)*	Primary NH source[c]	Section 3.3
Supportive	**5-year longitudinal** analysis on height at 5-years follow-up between vosoritide group and external control	Cohort 3 of 111-202/205 *(subjects who received 15 µg/kg)*	Primary NH source[d]	Section 3.3.2
	5-year cross-sectional and **longitudinal** analysis on height at 5-years follow up between vosoritide group and external control	Cohorts 1, 2 and 3 of 111-202/205 *(including all data for subjects who were assigned to receive 2.5 µg/kg, 7.5 µg/kg or 15 µg/kg, respectively)*	Primary NH source[c]	Section 3.4 and 3.4.2
	4-year cross-sectional and **longitudinal** analysis on height at 4-years follow up between vosoritide group and external control	Cohorts 1, 2 and 3 re-baselined of 111-202/205[e] *(only including data for subjects while receiving 15 µg/kg)*	Primary NH source[c]	Section 3.6.1 and Section 3.6.2
	4-year cross-sectional and **longitudinal** analysis on height at 4-years follow up between vosoritide group and external control	Cohort 4 of 111-202/205 *(subjects who received 30 µg/kg)*	Primary NH source[c]	Section 3.7 and Section 3.7.2
	2-year longitudinal analysis on AGV at 2-years follow up between vosoritide group and external control	Cohort 1, 2, 3 of 111-202[e] *(only including data for subjects while receiving 15 µg/kg)* combined with vosoritide group of 111-301 *(subjects who received 15 µg/kg)*	Primary NH source	Section 3.9

AGV, annualized growth velocity; NH, natural history.

[a] Cross-sectional analyses compared the difference between height at Year 5 or Year 4 follow-up and at baseline between the vosoritide group and the external control group. All analyses were repeated for height Z-score.

[b] Longitudinal analyses compared the change from baseline in height at Year 5 or Year 4 (all analyses were repeated for height Z-score) or the change from baseline in AGV at Year 2 (all analyses were repeated for height and height Z-score).

[c] The cross-sectional analysis was repeated using the supportive pooled NH sources. Supportive pooled NH sources were used for cross-sectional analyses only because there were not sufficient subjects from the external control group to match with subjects in the vosoritide group

3.3 STUDY RESULTS

This section describes findings included in the original NDA submission. Separate subsections summarize findings from *post-hoc* analyses requested by the FDA.

Validity of height measurements in the AchNH database

To examine whether there is a temporal trend in height measurements in the AchNH database, the applicant provided age- and sex-specific mean height measurements stratified by birth prior to or after the Year 2000 (Table 2.1.1.3.1). Sex-specific height measurements were comparable in both periods up to Age 11. Among older children, mean height measurements trended lower among girls born after 2000, while the reverse was the case for boys. However, this may reflect random error, as the higher age-strata among children born after 2000 included few individuals.

Table 2.1.1.3.1: Height in Subjects Born Before versus After Year 2000 by Sex and Age (Analysis Population: Primary NH Descriptive Population)

Age (years)	Female				Male			
	Subjects Born Before 2000 (N = 464)		Subjects Born After 2000 (N = 327)		Subjects Born Before 2000 (N = 464)		Subjects Born After 2000 (N = 327)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
5	220	86.78 (4.75)	167	87.05 (4.73)	177	87.57 (4.10)	251	87.87 (4.19)
6	161	91.03 (4.63)	135	91.77 (6.13)	130	92.09 (4.53)	173	93.38 (4.60)
7	149	95.89 (4.83)	91	95.23 (5.99)	118	96.29 (5.44)	134	96.79 (5.84)
8	128	99.20 (5.36)	86	99.06 (5.85)	113	100.10 (5.42)	118	101.96 (4.82)
9	146	103.25 (6.16)	73	104.30 (5.33)	115	104.53 (6.10)	80	104.45 (5.84)
10	118	106.09 (6.48)	53	106.60 (5.76)	103	107.32 (6.13)	77	108.44 (5.12)
11	119	110.66 (6.43)	50	110.53 (5.51)	105	110.30 (6.13)	68	110.79 (5.55)
12	88	112.59 (7.97)	24	112.28 (5.34)	89	113.91 (6.43)	58	115.06 (5.29)
13	94	117.72 (5.89)	34	116.03 (6.35)	71	118.49 (6.78)	44	121.25 (6.42)
14	88	118.17 (6.30)	14	115.06 (5.66)	72	121.99 (7.04)	26	126.25 (6.69)
15	79	120.05 (6.24)	4	115.78 (4.17)	79	124.53 (6.37)	4	124.55 (6.92)
16	64	121.50 (5.87)	7	117.79 (2.23)	60	125.76 (7.27)	2	129.20 (2.69)

To examine the validity of retrospectively collected height data in the primary AchNH control group, the applicant contrasted its age-specific height measurements with prospectively collected measurements in the 111-901 study and a published data source

(Tables 2.1.1.5.1 and 2.1.1.5.2). Age-specific height measurements were comparable, albeit with some random variation in older age strata based on fewer individuals.

Table 2.1.1.5.1: Comparison of Mean Height (Retrospective Primary NH Descriptive Population versus Prospective 111-901 and Published Merker Study) – Females

	Data Collected Retrospectively		Data Collected Prospectively		Data Collected Prospectively and Retrospectively	
	Primary NH Descriptive Population		111-901[a]		Published Source (Merker 2018)[b]	
Age (years)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)
5	242	86.46 (4.44)	56	86.84 (3.91)	122	85.7 (3.9)
6	199	90.82 (4.73)	59	91.51 (4.44)	85	90.2 (4.3)
7	168	95.53 (5.17)	49	96.14 (4.56)	78	94.4 (4.5)
8	148	98.84 (5.30)	40	99.21 (6.29)	75	98.3 (4.7)
9	141	102.93 (5.94)	36	102.54 (6.64)	65	102.0 (4.9)
10	121	105.99 (5.94)	36	105.58 (7.24)	67	105.7 (5.0)
11	112	110.25 (6.15)	16	111.86 (8.13)	52	109.5 (5.2)
12	90	112.70 (7.20)	7	113.92 (9.36)	50	113.3 (5.3)
13	93	117.06 (6.11)	3	118.23 (11.07)	49	116.7 (5.3)
14	71	118.75 (5.78)	3	120.43 (9.75)	34	119.6 (5.2)
15	61	120.13 (6.35)	0	-	33	121.9 (5.1)
16	49	120.68 (5.97)	0	-	22	123.3 (4.9)

NH, natural history; SD, standard deviation.

[a] In 111-901, specific growth measurements on pediatric subjects with ACH were collected prospectively using eCRF.

[b] In the Merker study (2018), the dataset was a mixture of cross-sectional and longitudinal data of children of European origin. Most of the height measurements were collected prospectively in the Merker study, and further measurements were collected retrospectively from birth records, child heath, and school records.

Height assessments after subjects received limb lengthening or growth hormone treatment in the dataset of the primary NH source and 111-901 were excluded.

Source: Table 1.3.1 and Merker (2018)

Table 2.1.1.5.2: Comparison of Mean Height (Retrospective Primary NH Descriptive Population versus Prospective 111-901 and Published Merker Study) – Males

	Data Collected Retrospectively		Data Collected Prospectively		Data Collected Prospectively and Retrospectively	
	Primary NH Descriptive Population		111-901[a]		Published Source (Merker 2018)[b]	
Age (years)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)
5	259	87.51 (4.27)	51	87.79 (3.57)	83	87.2 (3.1)
6	208	92.47 (4.60)	53	92.63 (4.50)	84	91.6 (3.4)
7	165	96.55 (5.20)	49	97.34 (4.93)	72	95.8 (3.8)
8	158	100.74 (4.76)	42	101.37 (4.82)	59	99.6 (4.1)
9	143	104.92 (5.62)	39	104.97 (5.67)	59	103.1 (4.3)
10	129	107.94 (5.33)	26	108.33 (7.79)	55	106.2 (4.4)
11	119	110.70 (5.74)	20	112.48 (8.37)	47	109.8 (4.6)
12	112	113.93 (6.30)	12	115.08 (6.76)	43	113.6 (4.7)
13	81	118.58 (6.63)	7	119.77 (7.32)	30	117.0 (4.9)
14	75	122.56 (6.94)	1	118.00 (NA)	37	120.2 (5.0)
15	55	124.03 (6.87)	0	-	25	123.5 (5.1)
16	49	126.29 (7.43)	0	-	23	126.9 (5.1)

NH, natural history; SD, standard deviation.

[a] In 111-901, specific growth measurements on pediatric subjects with ACH were collected prospectively using eCRF.

[b] In the Merker study (2018), the dataset was a mixture of cross-sectional and longitudinal data of children of European origin. Most of the height measurements were collected prospectively in the Merker study, and further measurements were collected retrospectively from birth records, child heath, and school records.

Height assessments after subjects received limb lengthening or growth hormone treatment in the dataset of the primary NH source and 111-901 were excluded.

Source: Table 1.3.1 and Merker (2018)

Matching and baseline characteristics

The primary, 5-year cross-sectional comparison included 10 patients exposed to vosoritide (Cohort 3, subjects assigned to receive 15 µg/kg in 111-202 and 111-205), matched to 360 patients in the primary AchNH control pool (range, 21 to 75 matches per vosoritide subject), and to 84 patients in the supportive control pool at Year 5 (Table 3.3.2). In the longitudinal analysis, 10 vosoritide patients were matched to 98 external control patients (range, 4 to 17 matches per vosoritide subject) from the AchNH pool. The mean age at baseline among the 10 vosoritide exposed patients was 8.49 years, 6 were female, 5 were White and 3 were Asian. Control patients were of similar mean age at baseline, similarly likely to be female (approximately 53%), and more likely to be White, especially in the AchNH control pool (approximately 78%, cross-sectional, and 87%, longitudinal analysis).

Table 3.3.2: Demographics for Cohort 3 of 111-202/205 versus External Controls (Analysis Population: 5-Year Comparative Analysis)

Demographic Variable	Vosoritide 15 µg/kg (N = 10)	Cross-Sectional Analyses: External Control (Primary at Year 5) (N = 360)	Cross-Sectional Analyses: External Control (Primary at Baseline) (N = 559)	Longitudinal Analyses: External Control (Primary) (N = 98)	Cross-Sectional Analyses: External Control (Supportive Pooled at Year 5) (N = 84)	Cross-Sectional Analyses: External Control (Supportive Pooled at Baseline) (N = 236)
Age at baseline, years						
n	10	-	559	98	-	236
Mean (SD)	8.49 (1.53)	-	8.45 (1.64)	8.30 (1.60)	-	8.38 (1.53)
Median	8.33	-	8.11	7.95	-	8.01
25th, 75th Percentile	7.90, 9.46	-	7.21, 9.57	7.07, 9.14	-	7.31, 9.50
Min, Max	6.2, 11.1	-	6.0, 12.0	6.1, 12.0	-	6.0, 11.9
Age at baseline, n (%)[a]						
≥ 5 to < 8 years	4 (40.0)	-	262 (46.9)	51 (52.0)	-	118 (50.0)
≥ 8 to < 11 years	5 (50.0)	-	233 (41.7)	37 (37.8)	-	95 (40.3)
≥ 11 to < 16 years	1 (10.0)	-	64 (11.4)	10 (10.2)	-	23 (9.7)
Age at Year 5, years						
n	10	360	-	98	84	-
Mean (SD)	13.53 (1.53)	13.22 (1.50)	-	13.29 (1.57)	13.07 (1.45)	-
Median	13.42	12.92	-	13.02	12.64	-
25th, 75th Percentile	12.89, 14.46	12.20, 13.97	-	12.07, 14.13	12.13, 13.75	-
Min, Max	11.3, 16.1	11.0, 17.0	-	11.0, 17.1	11.0, 16.8	-
Age at Year 5, n (%)[a]						
≥ 8 to < 11 years	0	0	-	1 (1.0)	0	-
≥ 11 to < 16 years	9 (90.0)	334 (92.8)	-	87 (88.8)	79 (94.0)	-
≥ 16 years	1 (10.0)	26 (7.2)	-	10 (10.2)	5 (6.0)	-
Sex, n (%)[a]						
Male	4 (40.0)	168 (46.7)	269 (48.1)	46 (46.9)	39 (46.4)	114 (48.3)
Female	6 (60.0)	192 (53.3)	290 (51.9)	52 (53.1)	45 (53.6)	122 (51.7)
Race, n (%)[a]						
Asian	3 (30.0)	15 (4.2)	38 (6.8)	2 (2.0)	9 (10.7)	28 (11.9)
Black or African American	1 (10.0)	15 (4.2)	24 (4.3)	1 (1.0)	2 (2.4)	12 (5.1)

Demographic Variable		Cross-Sectional Analyses		Longitudinal Analyses	Cross-Sectional Analyses	
	Vosoritide 15 µg/kg	External Control (Primary at Year 5)	External Control (Primary at Baseline)	External Control (Primary)	External Control (Supportive Pooled at Year 5)	External Control (Supportive Pooled at Baseline)
	(N = 10)	(N = 360)	(N = 559)	(N = 98)	(N = 84)	(N = 236)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.2)	0	0	0
Other	1 (10.0)	44 (12.2)	55 (9.8)	8 (8.2)	17 (20.2)	26 (11.0)
White	5 (50.0)	280 (77.8)	433 (77.5)	85 (86.7)	40 (47.6)	139 (58.9)
Unknown	0	5 (1.4)	8 (1.4)	2 (2.0)	16 (19.0)	31 (13.1)

Max, maximum; Min, minimum; SD, standard deviation.

[a] Percentages were calculated using the total number of subjects for each analysis population as the denominator.

Source: Table 2.2.1 and Table 2.2.2

Patients exposed to vosoritide had a mean baseline height of 104.61 cm, which exceeded the mean baseline height of subjects from the AchNH pool in in the cross-sectional analysis (99.70 cm, Tables 3.3.3 and 3.3.4), the longitudinal analysis (99.98 cm), and from the supportive external control pool in the cross-sectional analysis (100.15 cm).[f] A similar imbalance was present in height Z-score.

[f] The applicant argued that is principally due to one subject in the vosoritide group who had undergone limb-lengthening prior to entry into 111-202. *Post-hoc* analyses presented later in this section provide additional context.

Table 3.3.3: Baseline Growth Measures for Cohort 3 of 111-202/205 versus External Controls (Analysis Population: 5-Year Comparative Analysis)

		Cross-Sectional Analyses	Longitudinal Analyses	Cross-Sectional Analyses
Baseline Growth Measure	**Vosoritide 15 µg/kg**	**External Control (Primary at Baseline)**	**External Control (Primary)**	**External Control (Supportive Pooled at Baseline)**
	(N = 10)	**(N = 559)**	**(N = 98)**	**(N = 236)**
Height, cm				
Mean (SD)	104.61 (8.75)	99.70 (8.06)	99.98 (7.90)	100.15 (8.60)
Median	103.95	99.35	100.25	99.53
25th, 75th percentile	100.90, 106.55	93.35, 105.00	93.50, 105.60	94.30, 105.54
Min, Max	93.6, 126.1	81.3, 120.9	84.3, 118.2	59.0, 137.3
Height Z-score				
Mean (SD)	-4.61 (1.14)	-5.56 (1.07)	-5.39 (1.06)	-5.41 (1.29)
Median	-4.85	-5.50	-5.27	-5.37
25th, 75th percentile	-5.42, -3.68	-6.22, -4.83	-5.99, -4.57	-6.18, -4.60
Min, Max	-6.3, -2.6	-9.1, -1.8	-7.9, -3.0	-14.5, -1.0

Max, maximum; Min, minimum; SD, standard deviation.

Z-Scores were derived using age sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

Source: Table 2.3.1 and Table 2.3.2

Table 3.3.4: Goodness of Matching for Cohort 3 of 111-202/205 versus External Controls (Analysis Population: 5-Year Comparative Analysis)

	Cross-Sectional Analyses		Longitudinal Analyses	Cross-Sectional Analyses	
	External Control (Primary at Year 5)	External Control (Primary at Baseline)	External Control (Primary)	External Control (Pooled at Year 5)	External Control (Supportive Pooled at Baseline)
	(N = 360)	(N = 559)	(N = 98)	(N = 84)	(N = 236)
Number of matched subjects					
n	10	10	10	10	10
Mean (SD)	36.0 (15.8)	55.9 (19.3)	9.8 (4.2)	8.4 (4.8)	23.6 (10.8)
Median	34.5	55.0	9.0	7.5	21.0
25th, 75th Percentile	26.0, 39.0	51.0, 71.0	7.0, 12.0	5.0, 14.0	18.0, 28.0
Min, Max	21, 75	25, 83	4, 17	2, 16	11, 45
Age difference from vosoritide 15 µg/kg group (years)					
n	360	559	98	84	236
Mean (SD)	-0.13 (0.39)	-0.06 (0.41)	-0.09 (0.45)	-0.18 (0.39)	-0.09 (0.38)
Median	-0.13	-0.06	-0.10	-0.22	-0.05
25th, 75th Percentile	-0.42, 0.13	-0.36, 0.24	-0.42, 0.23	-0.44, 0.09	-0.37, 0.21
Min, Max	-0.9, 0.9	-0.9, 0.9	-0.9, 0.9	-0.9, 0.7	-0.9, 0.9
Baseline height difference from vosoritide 15 µg/kg group					
n	-	559	98	-	236
Mean (SD)	-	-5.34 (8.35)	-4.77 (8.81)	-	-4.82 (8.61)
Median	-	-5.50	-5.85	-	-4.93
25th, 75th Percentile	-	-11.60, 0.70	-11.40, 1.50	-	-10.26, 1.05
Min, Max	-	-28.6, 15.6	-22.6, 15.6	-	-46.6, 19.9
Baseline height Z-score difference from vosoritide 15 µg/kg group	-				
N	-	559	98	-	236
Mean (SD)	-	-1.01 (1.57)	-0.87 (1.64)	-	-0.88 (1.60)
Median	-	-1.04	-0.88	-	-0.72
25th, 75th Percentile	-	-2.16, 0.07	-2.20, 0.34	-	-1.89, 0.30
Min, Max	-	-5.0, 3.2	-4.3, 3.2	-	-8.9, 3.6
Race compared to vosoritide 15 µg/kg group, n(%)					
Yes	145 (40.3%)	261 (46.7%)	46 (46.9%)	23 (27.4%)	70 (29.7%)
No	209 (58.1%)	286 (51.2%)	50 (51.0%)	59 (70.2%)	166 (70.3%)
Unknown	5 (1.4%)	8 (1.4%)	2 (2.0%)	1 (1.2%)	0
Other	1 (0.3%)	4 (0.7%)	0	1 (1.2%)	0
Duration of follow-up (month)					
n	-	-	98	-	-
Mean (SD)	-	-	59.87 (1.51)	-	-
Median	-	-	59.81	-	-
25th, 75th Percentile	-	-	58.80, 61.02	-	-
Min, Max	-	-	57.1, 63.0	-	-

Max, maximum; Min, minimum; SD, standard deviation.

The difference in demographic and baseline growth characteristics is between each subject from the external control group of the NH source and their matched vosoritide subject.

Height Z-Scores were derived using age sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

Impact of using a non-randomized external control versus randomized controls

The applicant conducted two comparisons to examine the adequacy of using an external control arm.

First, the treatment effect (measured as 1-year AGV) based on the comparison of vosoritide with placebo was contrasted with the treatment effect based on the comparison of vosoritide with external controls. In Study 111-301, the mean differences in AGV between vosoritide (N=58) and placebo (N=61), in the subjects who completed treatment, was 1.62 cm/year (95% CI: 1.27 - 1.98) after 52 weeks. Comparing the vosoritide subjects to the external AchNH control group (N = 295) yielded a mean difference of 1.70 cm/year (95% CI: 1.23 - 2.16).

Second, they compared changes in AGV between the randomized, placebo control group from 111-301 to a sex- and age-matched non-randomized, external control group from the primary NH descriptive population. The mean difference in AGV between the placebo group in 111-301 and the external control (N = 292) was 0.11 cm/year (95% CI: -0.35 - 0.56). Analyses of height and height Z-score showed similar findings.

Height difference at Year 5

In the primary, 5-year cross-sectional analysis, vosoritide patients (Cohort 3, n=10, Appendix Table 3.3.1.1) were on average 4.97 cm taller than AchNH control patients (n=559) at baseline. At Year 5, the mean difference in height between the two groups reached 14.04 cm. The baseline-adjusted mean height difference between subjects exposed to vosoritide and the matched external AchNH control (n=360 at Year 5) was 9.08 cm (95% CI: 5.77 – 12.38). Using the secondary external control pool (n=84 at Year 5) yielded a similar height difference 8.74 (95% CI: 5.37 – 12.11).

Table 3.3.1.1: TTEST of Height Difference at Year 5 and at Baseline (Cross-Sectional) (Analysis Population: 5-Year Cross-Sectional Comparative Analysis (111-205/202 versus Primary and Supportive Pooled External Controls)

	Primary Analysis		Supportive Pooled	
	Vosoritide 15 µg/kg	External Control (Primary)	Vosoritide 15 µg/kg	External Control (Supportive Pooled)
Height (cm) at Year 5				
N	10	360	10	84
Mean (SD)	130.94 (10.77)	116.90 (5.44)	130.94 (10.77)	117.88 (5.32)
Median (min, max)	130.53 (115.8, 158.0)	116.76 (110.2, 126.6)	130.53 (115.8, 158.0)	117.08 (111.9, 129.2)
25th, 75th percentile	124.65, 131.70	112.16, 119.29	124.65, 131.70	112.98, 121.11
Means difference (95% CI)	14.04 (7.29, 20.79)		13.06 (6.49, 19.62)	
2-sided p-value	0.0011		0.0015	
Height (cm) at Baseline				
N	10	559	10	236
Mean (SD)	104.61 (8.75)	99.64 (6.53)	104.61 (8.75)	100.29 (6.33)
Median (min, max)	103.95 (93.6, 126.1)	99.44 (90.8, 110.7)	103.95 (93.6, 126.1)	100.37 (91.2, 112.3)
25th, 75th percentile	100.90, 106.55	95.91, 102.77	100.90, 106.55	96.72, 104.00
Means difference (95% CI)	4.97 (0.19, 9.74)		4.32 (0.13, 8.51)	
2-sided p-value	0.0431		0.0447	
Height (cm) Difference (Year 5 – Baseline)				
Means (95 CI)	**9.08 (5.77, 12.38)**		8.74 (5.37, 12.11)	
2-sided p-value	**0.0002**		0.0002	

CI, confidence interval; max, maximum; min, minimum; SD, standard deviation.

Bolded numbers are the results for the primary analysis.

Results from the primary and supportive pooled analyses are from two separate models.

Source: Table 2.4.1.1, Table 2.4.1.2, Table 2.5.1.1, Table 2.5.1.2, Table 2.6.1.1, Table 2.6.1.2

The 5-year longitudinal analysis utilized an ANCOVA model, with fixed effects for treatment and indicator variables for matching factors of sex and age (Table 3.3.2.1). The mean difference in change from baseline height between subjects exposed to vosoritide (Cohort 3, n=10) and the matched external AchNH control (n=98) was 8.40 cm (95% CI: 6.13 – 10.67).

Table 3.3.2.1: Longitudinal Analysis of Covariance of Change from Baseline in Height for Cohort 3 of 111-202/205 (Analysis Population: 5-Year Longitudinal Comparative Analysis versus Primary External Control)

Change from Baseline in Height at Year 5	External Control (Primary) (N = 98)	Vosoritide 15 µg/kg (N = 10)
Mean (SD)	17.91 (3.43)	26.33 (4.70)
Median (min, max)	17.80 (7.8, 26.0)	27.12 (18.1, 32.0)
25th, 75th percentile	15.70, 20.20	23.70, 30.15
LS means change from baseline (95% CI)	17.91 (17.22, 18.59)	26.31 (24.15, 28.47)
Difference in LS means change from baseline	8.40 (6.13, 10.67)	
2-sided p-value	< 0.0001	

CI, confidence interval; LS, least square; max, maximum; min, minimum; SD, standard deviation.

Results were based on an ANCOVA model with fixed effects of treatment and indicator variables for matching.

Source: Table 2.10.1

Table 1 includes a synopsis of the 5-year analyses created by this reviewer. In addition to the aforementioned analyses, it includes results from a 5-year longitudinal sensitivity analysis without matching, and a 5-year cross-sectional and a 5-year longitudinal analysis with 20 vosoritide patients from Cohorts 1, 2, and 3 (Appendix Table 3.4.2.1). Point estimates of baseline-adjusted height differences after 5 years range from 7.50 cm to 9.08 cm across these analyses. The table further includes results from 3 sensitivity analyses that were consistent with the primary analyses. Differences in height Z-scores ranged from 0.75 to 0.85 (Appendix Tables 3.3.4.1 and 3.3.5.1).

Table 1. Synopsis of results – 5-year analyses

	Analysis	Vosoritide exposure cohort	NH Control	Mean height difference (cm)	Height Z-score difference
Primary Analysis	Cross-sectional	Cohort 3: Vosoritide 15 µg/kg N=10	AchNH N=360*	9.08 (5.77 – 12.38)	0.77 (0.40 – 1.14)
	Cross-sectional	Cohort 3: Vosoritide 15 µg/kg N=10	Supportive Pool N=84*	8.74 (5.37 – 12.11)	0.75 (0.35 – 1.15)
	Longitudinal	Cohort 3: Vosoritide 15 µg/kg N=10	AchNH N=98*	8.40 (6.13 – 10.67)	0.78 (0.44 – 1.11)
	Cross-sectional	Cohorts 1,2,3 Vosoritide 15 µg/kg N=20	AchNH**	8.36 (6.38 – 10.33)	0.85 (0.59 – 1.10)
	Longitudinal	Cohorts 1,2,3 Vosoritide 15 µg/kg N=20	AchNH N=97*	7.50 (5.83 – 9.17)	
Sensitivity Analysis 1: 5,000 iterations	Cross-sectional	Cohort 3: Vosoritide 15 µg/kg N=10	AchNH	9.05 (5.60 – 12.50)	
Sensitivity Analysis 1: 5,000 iterations	Longitudinal	Cohort 3: Vosoritide 15 µg/kg N=10	AchNH	8.72 (6.57 – 10.87)	
Sensitivity Analysis 2: Age-matching by 6 months	Cross-sectional	Cohort 3: Vosoritide 15 µg/kg N=10	AchNH	8.55 (4.95 – 12.14)	
Sensitivity Analysis 2: Age-matching by 6 months	Longitudinal	Cohort 3: Vosoritide 15 µg/kg N=10	AchNH	8.36 (6.21 – 10.50)	
Sensitivity Analysis 3: without matching	Longitudinal	Cohort 3: Vosoritide 15 µg/kg N=10	AchNH N=217*	8.57 (6.50 – 10.63)	

*At Year 5

** The number of matched subjects was not provided

Height difference at Year 4

The 4-year analyses were based on 20 vosoritide exposed patients from Cohorts 1, 2, and 3. They were matched to 439 patients in the primary, AchNH control pool, and to 140 patients in the supportive control pool at Year 4 in the cross-sectional analysis. In the longitudinal analysis, 20 vosoritide patients were matched to 108 external control patients from the AchNH pool.

The mean age at baseline among the 20 vosoritide exposed patients was 8.91 years, 10 were female, 14 were White, 4 were Asian, 1 was Black, and 1 "Other". AchNH control patients were of slightly lower mean age (8.45 years) and had a comparable sex and race distribution.

Patients' height measurements were "re-baselined," that is, measured from the time when a patient's vosoritide dose reached 15 µg/kg. In the 4-year cross-sectional analysis, the baseline-adjusted mean height difference between subjects exposed to vosoritide (Cohorts 1, 2, 3, n=20, Table 2, Appendix, Table 3.6.1.1) and the matched external AchNH control (n=439 at Year 4) was 7.06 cm (95% CI: 5.39 – 8.73). Comparisons with the secondary external control pool (n=140 at Year 4) yielded a height difference of 7.32 cm (95% CI: 5.20 – 9.44).

The 4-year longitudinal analysis yielded a mean difference in change from baseline height between subjects exposed to vosoritide (Cohorts 1, 2, 3, n=20, Table 2, Appendix, Table 3.6.2.1) and the matched external AchNH control (n=108) of 6.95 cm (95% CI: 5.61 – 8.29).

Cross-sectional and longitudinal analyses based on Cohort 4, with a higher, 30 µg/kg dose of vosoritide (n=8), yielded point estimates for mean height difference and height Z-score difference that exceeded those from the cohorts exposed to 15 µg/kg (Table 2 and Appendix Tables 3.7.1.1 and 3.7.2.1).

Table 2. Synopsis of results – 4-year analyses

Analysis	Vosoritide exposure cohort	NH Control	Mean height difference (cm)	Height Z-score difference
Cross-sectional	Cohorts 1,2,3 Vosoritide 15 µg/kg N=20	AchNH N=439*	7.06 (5.39 – 8.73)	0.71 (0.51 – 0.91)
Cross-sectional	Cohorts 1,2,3 Vosoritide 15 µg/kg N=20	Supportive Pool N=140*	7.32 (5.20 – 9.44)	0.78 (0.52 – 1.04)
Longitudinal	Cohorts 1,2,3 Vosoritide 15 µg/kg N=20	AchNH N=108*	6.95 (5.61 – 8.29)	0.72 (0.48 – 0.95)
Cross-sectional	Cohort 4 Vosoritide 30 µg/kg N=8	AchNH**	9.01 (5.46 – 12.56)	1.28 (1.00 – 1.55)
Longitudinal	Cohort 4 Vosoritide 30 µg/kg N=8	AchNH N=116*	8.61 (6.67 – 10.56)	1.19 (0.82 – 1.56)

**At Year 4*

*** The number of matched subjects was not provided*

Height difference at Year 2

The applicant conducted analyses to determine if the AGV after 1 year for subjects treated with vosoritide was maintained at Year 2. This analysis included 25 subjects from the vosoritide group (22 subjects from 111-202/205 and 3 subjects from 111-301/302), and 159 subjects from the external control group (Appendix, Tables 3.9.1 and 3.9.2). Notably, the mean age of subjects in the vosoritide group (7.77 years) was lower than in the untreated ACH subjects in the external control (8.71 years). Sex and race distributions were balanced. While baseline AGV was comparable (3.96 cm/year vs. 4.29 cm/year), mean baseline height was approximately 6 cm larger in the vosoritide group (102.83 cm) compared with the external control group (96.97 cm).

Based on a longitudinal ANCOVA model with fixed effects of baseline AGV and baseline height Z score, treatment, sex and age matching indicator variables, the change in AGV from baseline at Year 1 (1.54 cm/year, Table 3.9.1) was maintained in Year 2 (1.61 cm/year).

Table 3.9.1.1: Longitudinal Analysis of Covariance of Change from Baseline in Annualized Growth Velocity at Year 1 and 2 for Cohorts 1, 2 and 3 Re-baselined of 111-202/205 and 111-301/302 versus Primary External Control (Analysis Population: 2-Year Longitudinal Comparative Analysis)

	External Control (Primary) (N = 159)	Vosoritide 15 µg/kg (N = 25)
Change from Baseline in AGV at Year 1		
Mean (SD)	-0.49 (3.60)	2.05 (1.32)
Median (min, max)	-0.42 (-14.3, 9.7)	2.15 (-0.7, 5.2)
25th, 75th percentile	-1.80, 1.29	1.25, 2.78
LS mean change from baseline (95 CI)	-0.35 (-0.57, -0.14)	1.19 (0.62, 1.75)
Difference in LS means change from baseline	1.54 (0.93, 2.15)	
2-sided p-value	< 0.0001	
Change from Baseline in AGV at Year 2		
Mean (SD)	-0.53 (3.08)	1.89 (1.14)
Median (min, max)	-0.46 (-11.1, 10.7)	1.94 (0.0, 4.2)
25th, 75th percentile	-1.81, 0.69	0.94, 2.47
LS mean change from baseline (95 CI)	-0.42 (-0.56, -0.28)	1.19 (0.82, 1.56)
Difference in LS means change from baseline	1.61 (1.21, 2.01)	
2-sided p-value	< 0.0001	

AGV, annualized growth velocity; CI, confidence interval; max, maximum; min, minimum; LS, least square; SD, standard deviation.

Source: Table 4.4.1 and Table 4.5.1

Exploratory analysis of height at Age 16

Table 4.1 summarizes findings of the applicant's exploratory analyses of extrapolated NFAH at Age 16, under various assumptions. The estimates for mean difference in NFAH between patients exposed to vosoritide compared with external control patients ranged from 8.71 cm based on last height observed (assuming no further growth), to 20.17 cm, assuming continuing growth at the last observed AGV.

Table 4.1: Summary of Extrapolated Near Final Adult Height at Age of 16 Years Old (Analysis Population: 111-202/205 Cohort 3 and Primary NH Descriptive Population)

	Vosoritide 15 µg/kg (N = 10)	External Control (N = 72)
Mean based on active AGV (95% CI)	142.86 (137.73, 147.98)	122.69 (120.78, 124.59)
Difference in mean based on active AGV (95% CI)	20.17 (14.70, 25.64)	
Mean based on 50% of active AGV (95% CI)	137.12 (132.16, 142.08)	122.68 (120.84, 124.53)
Difference in mean based on 50% of active AGV (95% CI)	14.44 (9.14, 19.73)	
Mean based on baseline AGV (95% CI)	142.49 (137.35, 147.63)	122.69 (120.78, 124.60)
Difference in mean based on baseline AGV (95% CI)	19.80 (14.31, 25.29)	
Mean based on 50% of baseline AGV (95% CI)	136.94 (131.95, 141.92)	122.68 (120.83, 124.54)
Difference in mean based on 50% of baseline AGV (95% CI)	14.25 (8.93, 19.58)	
Mean based on NH AGV (95% CI)	136.97 (132.14, 141.80)	122.67 (120.88, 124.47)
Difference in mean based on NH AGV (95% CI)	14.29 (9.14, 19.45)	
Mean based on 50% of NH AGV (95% CI)	134.18 (129.29, 139.06)	122.68 (120.86, 124.49)
Difference in mean based on 50% of NH AGV (95% CI)	11.50 (6.29, 16.71)	
Mean based on last height observed (95% CI)	131.38 (126.40, 136.37)	122.68 (120.82, 124.53)
Difference in mean based on last height observed (95% CI)	8.71 (3.39, 14.03)	

AGV, annualized growth velocity; CI, confidence interval; NH, natural history.

Source: Table 5.1

FDA requested *post-hoc* analyses

On November 17, 2020, and on January 13, 2021, FDA requested the following from the applicant, among other items:

1. Explanation of the applicant's assertion that height difference between the study groups is principally due to one subject in Cohort 3 who had limb-lengthening prior to entry into the vosoritide study.
2. *Post-hoc* analyses with the following conditions:
    a. Exclude subject in Cohort 3 who had limb-lengthening prior to entry into the vosoritide study
    b. Match vosoritide subjects with controls on baseline height and AGV, in addition to sex and age.
    c. Not "re-baselining" height measures in 4-year analyses.

3. Explanation about the potential bias resulting from missing information on baseline characteristics

Subject with limb-lengthening surgery prior to entry into the vosoritide study

The applicant provided information on Subject (b) (6) from Cohort 3 of Study 111-205 who had limb-lengthening surgery on (b) (6), more than 3 years prior to entry into Study 111-202 on (b) (6). At baseline of Study 111-202, this subject wa (b) (6) years old, with a standing height of 126.05 cm, and baseline AGV of 3.67 cm/year. On treatment, the subject's cumulative AGV over a 5-year treatment period was 6.39 cm/year, resulting in a height increase of 31.9 cm.

After removing Subject (b) (6), the applicant matched the 9 remaining vosoritide subjects to 535 AchNH subjects on age and sex, resulting in a baseline height difference of -3.64 cm. Because this difference was smaller than the mean difference in the original NDA (-4.97 cm) and no longer statistically significant (p=0.0855), the applicant concluded that the baseline height difference observed between the two groups was principally due to this one subject.

In response the FDA's request, the applicant repeated the 5-year cross-sectional analyses (matched on age and sex) after excluding Subject (b) (6). In this analysis, the 5-year, baseline-adjusted height difference between the vosoritide arm and the AchNH control arm was 8.15 cm (Appendix, Table 2.3), which is somewhat attenuated compared with the primary analyses based on 10 vosoritide subjects (mean height difference, 9.08 cm).

***Post-hoc* analyses**

The calculation of baseline AGV required the presence of at least 2 baseline height assessments, thus reducing the size of eligible controls. In addition, the number of controls eligible to be matched to each vosoritide patient depended on the width of the matching caliper. The applicant explored three matching calipers for baseline height (within 10, 8, or 6 cm) and baseline AGV (within 2, 1.5, or 1 cm/year). Of these, the applicant selected the widest matching caliber (baseline height within 10 cm and baseline AGV within 2 cm/year) to maximize the size of the control pool (Table 4.3).[g] Table 4.4. shows that this selection was conservative, that is, it resulted in the smallest treatment effect estimate among three caliper options.

[g] Notably, vosoritide Subject (b) (6), was matched with 22 controls, amid a mean number of 7 controls per vosoritide patient. This large proportion of relatively young control patients may have contributed to baseline height imbalances in descriptive analyses that did not account for variable ratio matching.

Table 4.3: Number of NH Subjects Matched to Each Active Subject Under Different Threshold Values for Baseline Height and AGV (Analysis Population: 5-Year Longitudinal Comparative Analysis [111-205 Cohort 3 Exclude Subject (b) (6) vs. AchNH])

			Number of Matched Natural History Subjects					
			Baseline Height = 10 cm and Baseline AGV = 2 cm/year (N=63)		Baseline Height = 8 cm and Baseline AGV = 1.5 cm/year (N=50)		Baseline Height = 6 cm and Baseline AGV = 1 cm/year (N=39)	
Subjects	Sex	Age (Year) (b) (6)	Frequency	Percent	Frequency	Percent	Frequency	Percent
			5	7.9	3	6.0	2	5.1
			22	34.9	19	38.0	14	35.9
			4	6.3	4	8.0	4	10.3
			2	3.2	3	6.0	2	5.1
			8	12.7	6	12.0	7	17.9
			3	4.8	1	2.0	1	2.6
			5	7.9	4	8.0	4	10.3
			11	17.5	8	16.0	4	10.3
			3	4.8	2	4.0	1	2.6

Source: Table ir201117.q04.2
AGV: annualized growth velocity; F: female; M: male

Table 4.4: Estimate of Treatment Effects and P-Values from Longitudinal Analyses Under Different Threshold Values for Matching (Analysis Population: 5-Year Longitudinal Comparative Analysis)

Variable	Mean Estimates (95% CI) of Treatment Effects and P-values					
	Baseline Height = 10 cm and AGV = 2 cm/year		Baseline Height = 8 cm and AGV = 1.5 cm/year		Baseline Height = 6 cm and AGV = 1 cm/year	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Change from Baseline in AGV (cm/yr)	1.60 (0.75, 2.44)	0.0003	1.67 (0.91, 2.43)	<.0001	1.65 (0.97, 2.32)	<.0001
Change from Baseline in Height (cm)	7.46 (4.82, 10.1)	<.0001	7.67 (4.93, 10.41)	<.0001	7.97 (5.31, 10.63)	<.0001

Source: Table ir201117.q05.2.10.1, Table ir201117.q05.2.10.2, Table ir201117.q05.2.10.1.t1, Table ir201117.q05.2.10.2.t1, Table ir201117.q05.2.10.1.t2 and Table ir201117.q05.2.10.2.t2
AGV: annualized growth velocity; CI: confidence interval.

In the 5-year longitudinal analysis, 9 vosoritide patients were matched with 63 AchNH controls on age, sex, baseline height, and baseline AGV. The goodness of matching analysis of baseline characteristics showed a smaller, but persistent baseline mean difference in height of -1.98 cm (Table 5.2). In an FDA-requested analysis that accounted for the variable matching ratio, the mean difference in baseline height was -2.39 cm.

Table 5.2: Goodness of Matching for 5-Year Comparative Analyses for Cohort 3 vs. External Control (Analysis Population: 5-Year Comparative Analysis)

	External Control (Primary)[b] (N=63)
Number of Matched AchNH Subjects / Active Control	
n	9
Mean (SD)	7.0 (6.3)
Median (min, max)	5.0 (2.0, 22.0)
25th, 75th percentile	3.0, 8.0
Baseline Age Difference from Active Treatment Arm (Year)[a]	
N	63
Mean (SD)	-0.01 (0.40)
Median (min, max)	-0.13 (-0.8, 0.7)
25th, 75th percentile	-0.25, 0.33
Baseline AGV Difference from Active Treatment Arm (cm/year)[a]	
n	63
Mean (SD)	0.15 (1.11)
Median (min, max)	0.29 (-2.0, 2.0)
25th, 75th percentile	-0.83, 1.16
Baseline Height Difference from Active Treatment Arm (cm)[a]	
n	63
Mean (SD)	-1.98 (4.82)
Median (min, max)	-1.80 (-9.9, 9.1)
25th, 75th percentile	-5.65, 1.30
Baseline Height Z-Score Difference from Active Treatment Arm[a]	
n	63
Mean (SD)	-0.47 (1.06)
Median (min, max)	-0.49 (-2.5, 2.0)
25th, 75th percentile	-1.27, 0.23
Race Identical to Active Treatment Arm [a], n (%)	
Yes	35 (55.6%)
No	27 (42.9%)
Other	1 (1.6%)
Duration of Follow-up (Month)[c]	
n	63
Mean (SD)	59.94 (1.78)
Median (min, max)	59.81 (57.2, 63.0)
25th, 75th percentile	58.44, 61.29

Source: Table ir201117.q05.2.1.2.1
AGV: annualized growth velocity; max: maximum; min, minimum; SD: standard deviation
a Active Treatment Arm includes all subjects in Study 111-202 Cohort 3 (15 ug/kg BMN 111) who continued to Study 111-205 with at least 5 years of total follow-up after excluding Subject (b) (6) who had limb-lengthening prior to entry into the study.
b AchNH Control Arm for 5-Year Longitudinal Comparative Analysis includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex, baseline AGV, baseline height, and age to the sex, baseline AGV, baseline height, and age at Baseline

After 5 years, vosoritide exposure was associated with a mean change in AGV from baseline of 1.60 cm/year and a mean difference in change in height of 7.46 cm, compared with AchNH controls (Table 5.3). As reference, the primary longitudinal analysis with 10 vosoritide subjects matched on age and sex yielded a difference in change in height of 8.40 cm after 5 years.

Table 5.3: Longitudinal Analysis of Covariance of Change from Baseline in AGV and Height for Cohort 3 of 111-205 (Analysis Population: 5-Year Longitudinal Comparative Analysis vs. Primary External Control)

	External Control (Primary)[a] (N=63)	Vosoritide[b] (N=9)
Change from Baseline in AGV at Year 5		
Mean (SD)	-0.44 (1.24)	1.02 (1.28)
Median (min, max)	-0.60 (-3.3, 2.2)	0.99 (-0.8, 3.4)
25th, 75th percentile	-1.19, 0.24	-0.01, 1.96
LS means change from baseline (95% CI)	-0.58 (-0.94, -0.23)	1.02 (0.25, 1.78)
Difference in LS means change from baseline[c]	**1.60 (0.75, 2.44)**	
2-sided p-value	**0.0003**	
Change from Baseline in Height at Year 5		
Mean (SD)	18.59 (3.60)	25.71 (4.52)
Median (min, max)	18.10 (11.0, 26.0)	25.95 (18.1, 31.1)
25th, 75th percentile	15.70, 20.90	23.70, 29.20
LS means change from baseline (95% CI)	18.24 (17.13, 19.36)	25.71 (23.31, 28.10)
Difference in LS means change from baseline[c]	**7.46 (4.82, 10.10)**	
2-sided p-value	**<.0001**	

Source: Table ir201117.q05.2.10.1 and Table ir201117.q05.2.10.2
AGV: annualized growth velocity; CI: confidence interval; max: maximum; min, minimum; SD: standard deviation.
a AchNH Control Arm for 5-Year Longitudinal Comparative Analysis includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex, baseline AGV, baseline height, and age to the sex, baseline AGV, baseline height, and age at Baseline from subjects in the Active Treatment Arm who had at least one height assessment between 6 to 12 months prior to the baseline and at least one height assessment at 60+/-3 months relative to the baseline.
b Active Treatment Arm for 5-Year Longitudinal Comparative Analysis includes all subjects in Study 111-202 Cohort 3 (15 ug/kg BMN 111) who continued to Study 111-205 with at least 5 years of total follow-up after excluding Subject (b) (6) who had limb-lengthening prior to entry into the study.
c Difference is Active Treatment Arm minus AchNH Control Arm from ANCOVA model with fixed effects of treatment and matching ID.
AGV at baseline is defined as [(Height at Baseline - Height at 6 Months Prior to Baseline)/(Date of Baseline - Date of 6 Months Prior to Baseline Assessment)] x 365.25.
AGV at Year 5 is defined as ((Height at Month 60 - Height at Baseline)/(Date of Month 60 - Date at Baseline)) x 365.25.

The applicant also conducted 4-year *post-hoc* analyses, matched on age, sex, baseline height, and baseline AGV, which were not rebaselined, that is, the analysis included height measurements of vosoritide subjects while their dose was not yet increased to 15 µg/kg. The 4-year longitudinal analysis with 21 subjects from vosoritide Cohorts 1, 2, and 3 yielded a height difference of 5.86 cm (95% CI: 4.47 – 7.26, Appendix, Table 8.3). Results of these analyses and additional *post-hoc* analyses are summarized in Table 3. Across 3 *post-hoc* longitudinal analyses, difference in AGV ranged from 1.54 cm/year to 1.74 cm/year, favoring vosoritide.

Table 3. Synopsis of *post-hoc* results in response to FDA information request

	Analysis	Match	Vosoritide exposure cohort	NH Control	Mean height difference (cm)	Difference in change in AGV (cm/year)
5-Year	Cross-sectional	Age, sex	Cohort 3: Vosoritide 15 µg/kg N=9	AchNH N=346*	8.15 (4.83 – 11.47)	
5-Year	Cross-sectional	Age, sex	Cohort 3: Vosoritide 15 µg/kg N=9	Supportive Pool N=83*	7.95 (4.81 – 11.10)	
5-Year	Longitudinal	Age, sex, height, AGV	Cohort 3: Vosoritide 15 µg/kg N=9	AchNH N=63*	7.46 (4.82 – 10.10)	1.60 (0.75 – 2.44)
4-Year**	Longitudinal	Age, sex, height, AGV	Cohorts 1,2,3 Vosoritide 15 µg/kg N=21	AchNH N=125*	5.86 (4.47 – 7.26)	1.54 (0.96 – 2.12
4-Year	Longitudinal	Age, sex, height, AGV	Cohort 3: Vosoritide 15 µg/kg N=9	AchNH N=83*	6.71 (4.80 – 8.63)	1.74 (1.03 – 2.46)
4-Year*	Cross-sectional	Age, sex, height, AGV	Cohorts 1,2,3 Vosoritide 15 µg/kg N=21	AchNH N=461*	6.06 (4.41 – 7.72)	

**At Year 4*

***Not rebaselined*

Questions about confounding and selection bias

In response to FDA's question about the potential for confounding due to absence of randomization and matching only on age and sex, the applicant conceded that information on other medical history and concomitant medications (except growth hormone analogs) was not consistently entered into the AchNH study database, thus limiting the ability to control for, or even evaluate, potential imbalances. The applicant also stated that exclusion criteria in terms of medical conditions at baseline, and especially medication use at baseline, were substantially narrower in the AchNH study, compared with vosoritide Study 111-202/205 (Table 4).

Table 4. Excluded medical conditions and medications at baseline in Studies 111-202/205 and AchNH

	111-202/205	AchNH study
Excluded medical conditions at baseline	hypochondroplasia or other short stature conditions, hypo/hyperthyroidism, diabetes mellitus, autoimmune disease, renal insufficiency, cardiac or vascular disease, and bone-related surgery	hypochondroplasia, compound heterozygosity, homozygosity or double heterozygosity for two bone growth disorders
Excluded medications at baseline	growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids, ACE inhibitors, cardiac glycosides, calcium channel blockers, beta blockers, or antihypertensive medications, diuretics, probenecid, or other drugs known to alter renal or tubular function, concomitant medication that prolongs the QT/QTc-F interval, any other investigational product for the treatment of ACH or short stature	none

The applicant argued that, since vosoritide studies excluded medical conditions that are likely to affect growth, only inclusion of medical conditions that result in slowing of growth in the NH control could potentially bias the comparison in favor of vosoritide. The applicant cited the examples of hypothyroidism, pediatric autoimmune disorders, and renal insufficiency but reasoned that these conditions are not frequent enough to have meaningfully impacted the study results.

Similarly, because children receiving growth hormone were excluded from the comparative analyses, any bias in favor of vosoritide would require a substantially higher use of concomitant medications that have a materially negative impact growth in the AchNH population, compared to the vosoritide clinical trial population. The applicant cited examples of systemic corticosteroids and treatments for attention-deficit hyperactivity disorder (ADHD). Yet, according to the applicant, the data on the long-term effect of ADHD medications on growth are controversial, and the prevalence of ADHD in the AchNH population is likely too low to introduce meaningful bias.

Finally, the applicant provided data on surgeries reported in the AchNH database. Almost 80% of patients had at least 1 ACH-related surgery. These included 21.2% with extremity surgery, which can impact standing height. The applicant argued that, because

they would only increase height in the control arm and not in the vosoritide arm, any effects of surgery would disadvantage the vosoritide arm.

3.4 STUDY CONCLUSIONS

The applicant concluded that vosoritide showed consistent and sustained improvement in AGV over time, compared to the natural growth in children with ACH, as confirmed by multiple analyses and using different NH sources.

According to the applicant, the primary analysis from the AchNH database confirmed durable year-on-year height gain with up to 5 years of treatment with vosoritide 15 ug/kg daily, resulting in a clinically meaningful improvement in height of 9.08 cm compared to a sex and age matched untreated ACH population.

3.5 FDA ANALYSIS

Two *post-hoc* analyses conducted by the FDA explored whether having a control group that includes children born well before those in the vosoritide trials could bias the RWE comparisons, and whether selection bias could have impacted height measurements in the NH control subjects.

Contemporaneousness of control group

Per request by DEPI-I, Dr. Jiwei He, Statistical Reviewer in DB-II, analyzed the distribution of birth years among AchNH control patients to provide insight into the contemporaneous nature of the NH control data.

All patients in Cohort 3 of the vosoritide study 111-202/205 (N=10) were born in the decade following the Year 2000 (Table 5). In contrast, the AchNH sample, prior to applying inclusion and exclusion criteria, included a relatively even distribution of birth decades between the 1970s and the 2010s. After applying inclusion and exclusion criteria and matching on age and sex in the primary 5-year, cross-sectional analysis, approximately one-third of AchNH control patients at baseline were born in the 1990s and slightly more than one-third in the 2000s. However, among controls who were matched at Year 5, the largest group was born in the 1990s (41.4%). A similar distribution was observed in the primary and *post-hoc* 5-year longitudinal analyses.

Of note, only height measurements taken between ages 5 and 16 were included in the analysis. Also, matching patients on age and sex at Year 5 required controls who had height measurements at relatively older age (effectively, >10 years of age), which explains that these analyses primarily included patients born prior to the 2000s, and none born in the 2010s. Similar considerations apply to those included in the longitudinal analyses.

Table 5. Comparison of birth decades among vosoritide patients and various matched sets of AchNH control patients, based on analysis by Dr. Jiwei He, DB-II

	Cohort 3, Study 111-202/205	Entire AchNH database	5-year cross-sectional analysis, at baseline	5-year cross-sectional analysis, at Year 5	5-year longitudinal analysis, primary	5-year longitudinal analysis, *post-hoc*
Matching factors		-	Age, sex	Age, sex	Age, sex	Age, sex, height, AGV
Cohort size	N=10	N=1374	N=559	N=360	N=98	N=63
Birth decade (%):						
1970		17.0	9.3	12.2	8.2	9.5
1980		16.8	18.4	22.5	24.5	20.6
1990		22.9	32.4	41.4	41.8	42.9
2000	100.0	25.9	36.1	23.9	25.5	27.0
2010		17.4	3.8			

Dr. He conducted additional analyses to provide insight as to whether having a control cohort with a blend of historic and contemporaneous data could bias the results. She compared results from analyses that adjust vs. do not adjust for birth period (<2000 versus >=2000).

- In the original, 5-year longitudinal analysis, matched on sex and integer age only, the treatment effect was 8.40 cm (95% CI: 6.13-10.67). With additional adjustment for birth period (<2000 versus >=2000), the estimated treatment effect was 9.46 cm (95% CI: 6.91-12.01)
- In the 5-year longitudinal analysis matched on sex, integer age, baseline height and AGV (FDA requested *post-hoc* analysis) the treatment effect was 7.46 cm (95% CI: 4.82-10.10). With additional adjustment for birth period (<2000 versus >=2000), the estimated treatment effect was 7.45 cm (95% CI: 4.30-10.60).

These analyses do not suggest that having a control cohort with a blend of historic and contemporaneous data introduced bias in the results.

Potential selection bias if slow growth is associated with more height measurements among controls

If children in the AchNH with slower than average growth, even for children with ACH, have more height measurements than children with average or above average growth, they may be more likely to be selected as controls both the in the cross-sectional and longitudinal analyses. In this case, average growth among controls would be underestimated, resulting in bias favoring vosoritide.

To understand whether selection bias is present, FDA conducted the following 3 analyses in the AchNH database:

1. A comparison of mean baseline height by the number of years until the last height measurement

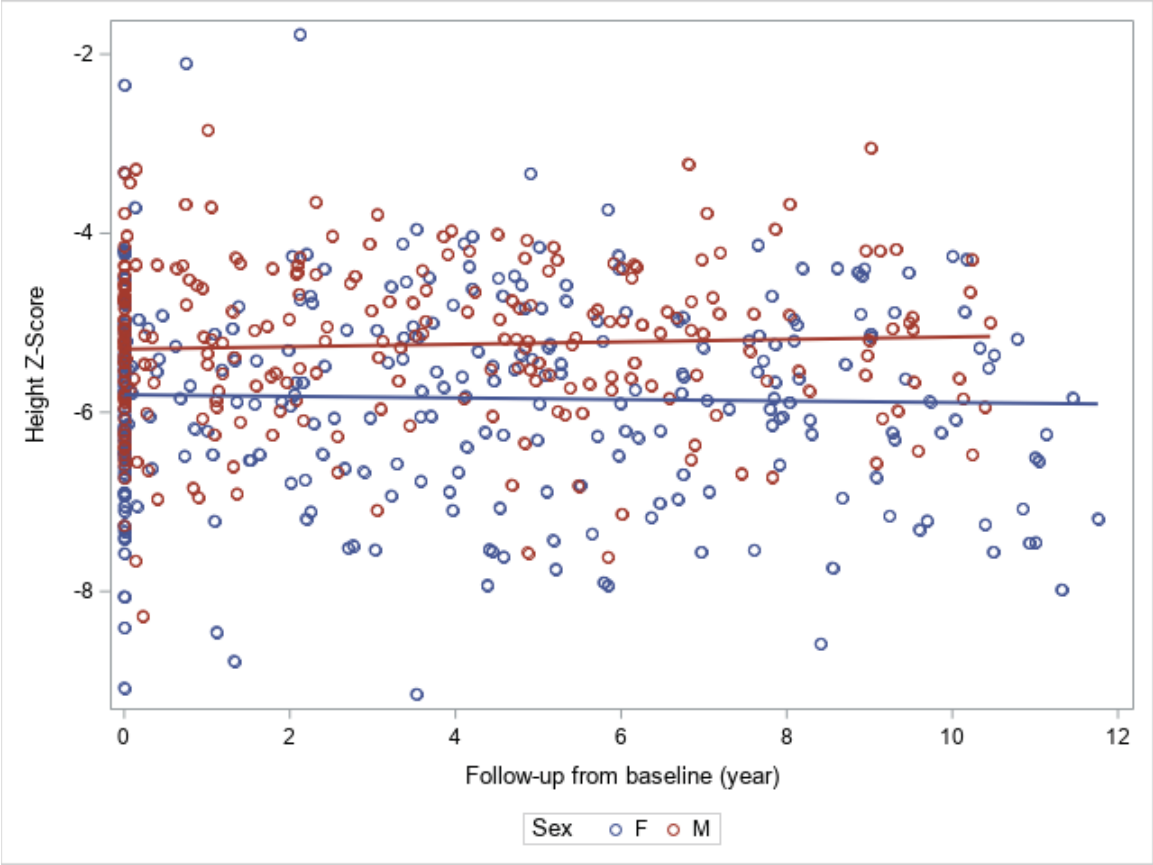
2. An analysis to test whether there are height differences at Year 2 of follow-up between subjects who have height measurements at Year 5 vs. those who do not have height measurements at Year 5

3. An analysis to explore whether the number of previous height assessments is associated with subjects' height prior to reaching final adult height

The first analysis, conducted by Dr. Jiwei He, DB-II, explored the question whether subjects with longer follow-up tend to have a lower baseline height than subjects with shorter follow-up duration. The analysis included 559 AchNH subjects from the cross-sectional analysis who were matched at baseline by sex and integer age to vosoritide subjects. Height measurements since baseline and up to 18 years old were included. Figure 1 shows, for each subject, the baseline height Z-score (Y-axis), according to the number of years until their last height measurement in the AchNH (prior to Age 18, X-axis). It was notable that a large proportion of subjects did not have measurements after

their baseline measurement. Regardless, there was not an association, among males or females, between baseline height and duration of follow-up.

Figure 1. Baseline height Z-score versus follow-up time from baseline by sex – AchNH subjects from 5-year cross-sectional analysis



Note: A linear regression line was fit for each sex group. The flat slope suggests no association.

The second analysis, also conducted by Dr. Jiwei He, DB-II, included AchNH subjects who were matched to vosoritide subjects on age and integer sex at baseline in the applicant's primary cross-sectional analysis. This analysis was only conducted among AchNH subjects with available height measurements at 2 year +/-6 months. Among them, height at Year 2 was compared between subjects who had, and who did not have, another height measurement at Year 5 (Analysis 1), or at Year 5 or later (Analysis 2), while adjusting for baseline age. Results in Table 6 indicate that in Analysis 1, males who had Year-5 height measurements available were on average 1.45 cm shorter at Year 2 than those who did not have Year-5 height measurements. Yet, the reverse was the case in Analysis 2: males who had height measurements at Year 5 or later were on average 2.04 cm taller at Year 2 than those who did not have Year-5 or later height measurements. Differences in height were less pronounced among female subjects, and none of the height differences among males or females were statistically significant.

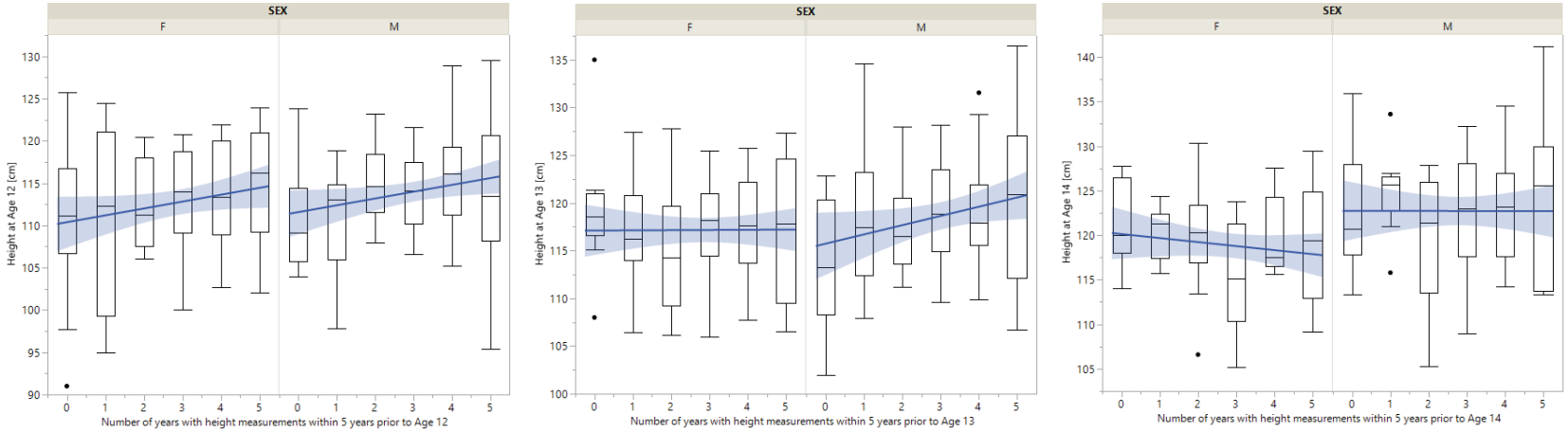
Table 6. Comparison of height at year 2 between subjects with 5-year follow-up versus those without - AchNH subjects from 5-year cross-sectional analysis with height assessment at year 2

	Sex	5-Year height available	N	Height at Year 2 [cm]	Difference between groups [cm]
Analysis 1	Male	Yes	58	110.08	-1.45 (p=0.20)
		No	47	111.53	
	Female	Yes	77	105.09	-0.70 (p=0.49)
		No	53	104.39	
Analysis 2		**≥ 5-Year height available**	**N**	**Height at Year 2 [cm]**	**Difference between groups [cm]**
	Male	Yes	30	112.19	2.04 (p=0.10)
		No	75	110.15	
	Female	Yes	36	104.69	0.03 (p=0.98)
		No	94	104.66	

The third analysis, conducted by this DEPI-I reviewer, explored whether the number of previous height assessments is associated with subjects' height prior to reaching final adult height. The analysis was conducted using a dataset comprised of subject-level data from the AchNH database with height measurements for each year of age. The database included, for each subject and age year, a missingness indicator when no height measurement was available, the height in cm when a single height measurement was available, and the median when multiple height measurements were available in a subject for a given age year. Figure 2 displays, by sex, the height at Age 12 (and Age 13, 14 in separate analyses), according to the number of years with height measurements during the 5 years prior to Age 12 (and Age 13, 14, accordingly). In the analysis of height at Age 12, there was a slight increase in height according to the number of years with height measurements. Only among females in the analysis at Age 14, did we observe a trend toward lower height with increasing number of prior years with height measurements.

These three FDA analyses suggest that 1) baseline height is not associated with the duration of follow-up, 2) subjects with 5 years' of follow-up are not consistently shorter at Year 2 of follow-up compared to subjects without 5 years' of follow-up, and 3) subjects with more frequent previous height measurements are not consistently shorter at Ages 12, 13, or 14 than subjects with less frequent height measurements. Thus, we did not find evidence for selection bias whereby AchNH control subjects with more height measurements during follow-up and thus, a higher likelihood to be selected at controls in the longitudinal analysis or at Year 5 in the cross-sectional analysis, have a shorter than average height.

Figure 2. Height at age 12, 13, 14 years old versus number of years with height measurements within 5 years prior to 12 years old by sex – AchNH subjects



4 DISCUSSION

The applicant provided a comparison of height gain between subjects exposed to vosoritide for up to 5 years and an external NH control. The primary analysis, a 5-year cross-sectional comparison with AchNH controls matched on age and sex at baseline and after 5 years yielded an improvement in height gain of 9.08 cm, associated with vosoritide treatment. Various secondary, sensitivity, and *post-hoc* analyses, including those requested by the FDA, yielded effectiveness point estimates that were somewhat attenuated, but still relatively consistent, with a 5-year baseline-corrected height difference of approximately 7.50 to 9.00 cm (Tables 1 and 3).

The following observations provide context to help evaluate the validity of these findings.

Impact of using a of non-randomized external control versus randomized controls

The applicant conducted two related analyses to examine the adequacy of using an external control arm, based on the 1-year AGV observed in vosoritide (N=58) and placebo (N=61) subjects in Study 111-301, and matched controls from the AchNH study. Using the AchNH controls matched to vosoritide patients yielded a similar vosoritide treatment effect (difference in 1-year AGV) as observed in the placebo comparison. In addition, an analysis that matched placebo subjects with AchNH patients, thus not including any vosoritide patients, showed an expected null association after 1 year. These analyses demonstrate that the AchNH controls performed similarly to randomized placebo controls, with the important limitation that follow-up was only for 1 year and it is not certain that this relative comparability would hold up for the 5-year follow-up in the primary analysis.

Consistency of results

Point estimates for differences in growth between vosoritide patients and matched controls were largely consistent, across various analyses. They ranged from 7.46 cm to 9.08 cm after 5 years. As expected, the difference in height gained after 4 years, and after 2 years, was proportionally lower, however, with comparable increase in AGV of approximately 1.60 cm/year. Yet, even though they were close to the height difference estimated in the primary analysis (9.08 cm after 5 years), estimates in secondary, sensitivity, and *post-hoc* analyses tended to be slightly lower, albeit typically still exceeding 7.50 cm. Some are expectedly lower than the corresponding primary results, including those resulting from 4-year analyses that were not rebaselined. Because analyses that were not re-baselined include a period when patients were exposed to lower vosoritide doses prior to escalation to 15 μg/kg, they are more conservative than the rebaselined 4-year analyses, which measure baseline height at the time of dose escalation to 15 μg/kg. In addition, height increases in longitudinal analyses and in *post-hoc* analyses that matched on baseline height and AGV (in addition to age and sex), and when the vosoritide subject with limb lengthening surgery was excluded, tended to be slightly lower than those from the primary, 5-year cross-sectional analysis, matched on age and sex. The reasons for this particular discrepancy are unclear.

Longitudinal and cross-sectional analyses

Having both longitudinal and cross-sectional analyses strengthens the study. Cross-sectional analyses compared heights of vosoritide patients to two different sets of matched controls at baseline and at Year 5, while longitudinal analyses selected controls who had height data at both baseline and Year 5 and compared their height gains with those of vosoritide patients. Therefore, longitudinal analyses included fewer control patients and their selection was conditional on the availability of future data (i.e., they were only matched at baseline if they had height measurements available 5 years later). While conditioning on future events in a "complete case analysis" raises theoretical concerns about selection bias,(4) it is unclear to which extent this would have introduced meaningful bias, especially considering the relative consistency in treatment effect between longitudinal and cross-sectional analyses.

Theoretically, if children with slower growth were more likely to have 5-year height data, this would disadvantage the control group and could explain the slight attenuation in treatment effect when comparing longitudinal with cross-sectional analyses. However, FDA analyses did not find evidence that children with slower growth tended to have more height measurements.

Potential for confounding

The non-randomized design and the use of an external control group, combined with matching only on age and sex (and baseline height and AGV in *post-hoc* analyses), raise concerns about the potential for confounding.

Any confounding effect that biases analyses of height or AGV in favor of vosoritide either requires a higher prevalence of conditions or medications that promote growth in the vosoritide arm or a higher prevalence of conditions or medications that slow growth in the AchNH control arm. The applicant argued that, because vosoritide studies excluded medical conditions that are likely to affect growth, only medical conditions or medications that result in slowing of growth in the NH control arm could potentially bias the comparison in favor of vosoritide. This argument has merit and this section will focus on the latter.

Medical conditions that may slow growth include diabetes and renal disease (and rare conditions, including genetic abnormalities and cancer). Medications that have been associated with slower growth include stimulants used in the treatment of ADHD and systemic, long-term use of corticosteroids.

While patients with ACH may be at increased risk to develop diabetes, the prevalence of diabetes (type 1 or type 2) in pediatric patients with ACH is not expected to be large. In addition, whether diabetes affects growth at all is controversial.(5) Similarly, renal disease is not a known complication of ACH and its prevalence in the AchNH database may not be large enough to have a meaningful impact on overall growth.

Studies of the effects of stimulants on growth have either found a small extent of slowed growth,(6, 7) or no effect at all.(8-10) Even if there is an association between stimulants and growth as suggest by some studies, this effect is smaller (2.0-2.7 cm in one study (6)) than the height increase associated with vosoritide. In addition, the prevalence of ADHD in patients with ACH is not known; however, the statistical probably of co-occurrence is

low,(11) making it unlikely that the number of AchNH patients who are affected by ADHD and who are treated with stimulants have a meaningful impact on overall growth trajectory.

Inhaled corticosteroids in the treatment of childhood asthma have been associated with a small decrease in AGV of approximately 0.20 cm/year (12) to 0.48 cm/year.(13) Similar considerations apply as with stimulants in the treatment of ADHD: the expected small prevalence of use, combined with the modest association, is unlikely to have a meaningful confounding effect.

In addition, comparisons in age- and sex-specific mean height measurements between the retrospective AchNH data and prospectively collected data from Study 111-901, with similar inclusion/exclusion criteria as in the vosoritide trials, showed a high level of consistency in height measurements (Tables 2.1.1.5.1 and 2.1.1.5.2). This comparison does not suggest the presence of a meaningful amount of confounding that would result in slower growth among subjects included in the AchNH database.

The following section on baseline height differences provides additional context relevant to potential confounding.

Baseline height differences

In the primary, 5-year cross-sectional analysis, vosoritide patients (Cohort 3, n=10, Table 3.3.1.1) were on average 4.97 cm taller than AchNH control patients (n=559) at baseline. The applicant later argued that this difference was principally due to inclusion of one subject who had limb-lengthening surgery prior to entry into Study 111-202. Removing this subject from subsequent analyses resulted in a small attenuation of the baseline height difference, yet a difference of 3.64 cm remained. Based on FDA's request, the applicant matched patients on baseline height (using a caliper of 10 cm) and AGV (in addition to age and sex), which further attenuated the baseline height difference to 1.98 cm. In an FDA-requested analysis that accounted for the variable matching ratio, the mean difference in baseline height was -2.39 cm. Ultimately, the difference in baseline height is only partially explained. Because the vosoritide effectiveness analyses focus on *increase* in height, the small but present baseline difference in height does not necessarily introduce bias.

Measurement

The absence of a prespecified, consistent height measurement approach in the AchNH database raises concern about the potential for measurement bias. The following considerations are made to assess the presence and potential impact of measurement bias. First, a systematic measurement error (e.g., an approach that consistently under- or overestimates height) would not necessarily be expected to result in biased estimates of AGV or height increase, because they are a function of *difference* in height, not *absolute* height. Second, inconsistent use of height measurement approaches would increase random error, possibly even resulting in instances where a subsequent measurement indicates a height decrease, as seen in the AchNH database, or an overestimated height increase, but due to its random nature, this would not be expected to systematically favor or disfavor the active treatment arm vs. external control. Third, concern about measurement bias would exist in a scenario where a measurement approach or device is

replaced, such that all measurements prior to replacement are taken differently from measurements after replacement. If the new approach or device yield consistently higher or lower height measurements than the previous approach, bias could be introduced. However, to result in meaningful bias, such an approach would have to be implemented at several study sites, affecting a large proportion of patients, for which there is no indication that this occurred.

The applicant provided data that showed relatively consistent AchNH height trends between subjects born prior to or after 2000 (Table 2.1.1.3.1) and consistency in retrospective height measures obtained in AchNH and prospectively collected measurements in the 111-901 study and a published data source (Tables 2.1.1.5.1 and 2.1.1.5.2). These data, together with information regarding the contemporaneous/historical nature of control data presented in the section below, do not provide evidence for measurement bias, to an extent and directionality that could plausibly explain the observed treatment effect.

Contemporaneous/historical control data

Analyses conducted by Dr. He, DB-II, suggest that the AchNH control group is best described as a blend of contemporaneous and historical. While all 10 vosoritide subjects from Study 111-202/205, Cohort 3 were born in the decade following the Year 2000, this is the case for only approximately one-quarter to one-third of matched AchNH control subjects, depending on the analysis. More than 40% of control subjects were born in the decade following the Year 1990 in the 5-year longitudinal analyses, and the remainder were born in the 1970s and 1980s. *Post-hoc* inferential analyses conducted by Dr. He suggest that lack of adjustment for birth period in the primary analysis did not result in bias favoring vosoritide. In contrast, there may have been bias favoring controls in the analyses that only adjusted for age and sex. However, when analyses were also adjusted for baseline height and AGV (as requested by FDA), additional adjustment for birth decade made virtually no difference.

Exploratory analyses of final height

The applicant's projections in exploratory analyses for mean difference in NFAH between patients exposed to vosoritide compared with external control patients ranged from 8.71 cm to 20.17 cm under various assumptions. Because these analyses are exploratory and the projections are highly dependent on underlying assumptions, these findings have limited ability to support regulatory decisions.

5 CONCLUSION

The applicant's analyses based on 5-year on-treatment data from a small sample of vosoritide treated patients and a matched external ACH control group provided evidence that support a sustained height gain associated with vosoritide treatment. The results of the applicant's calculations show a high degree of consistency across primary, secondary, and sensitivity analyses.

Post-hoc analyses requested by the FDA that removed a subject with limb-lengthening surgery and added baseline height and AGV as matching factors in addition to age and sex, yielded slightly attenuated estimates of treatment effect.

A review of the applicant's analyses and analyses conducted by the FDA suggest that measurement bias, confounding, and selection bias are unlikely to explain the observed height gain associated with 5 years of vosoritide treatment, compared with matched NH control patients.

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APPENDIX 1. TABLES

Table 2.1.1.1: Summary of Primary NH Source Dataset (Analysis Population: All Subjects)

	AchNH (N = 1374) n (%)
N of subjects in the dataset	1374 (100.0)
N of subjects included for NH Descriptive Population	1329 (96.7)
N of subjects included for NH Descriptive Population with at least one height assessment between age 5-16 years	791 (57.6)
N of subjects excluded	45 (3.3)
N subjects enrolled into an interventional study	10 (0.7)
N of subjects without a height assessment available that was measured at a known age	28 (2.0)
N of subjects who received growth hormone or underwent limb-lengthening	7 (0.5)

AchNH, Achondroplasia Natural History: multicenter clinical study (Principal Investigator Julie Hoover Fong, MD, PhD); NH, natural history.

This table provides a simplified breakdown of the dataset and is not a complete representation of the external control group from the NH source. Further details on the external control groups are presented in Appendix 2: Natural History Statistical Analysis Plan.

Bolded text refers to the additional criterion for the subset of subjects compared with the previous subset.

Source: Table 1.1

Table 2.2: Goodness of Matching for 5-Year Comparative Analyses for Cohort 3 (Excluding Subject [redacted] (b) (6)) versus External Control (Analysis Population: 5-Year Comparative Analysis)

	External Control (Primary)		External Control (Supportive Pooled)	
	At Year 5[a] (N=346)	At Baseline[b] (N=535)	At Year 5[c] (N=83)	At Baseline[d] (N=227)
Number of Matched AchNH Subjects per Active Control				
N	9	9	9	9
Mean (SD)	38.4 (17.8)	59.4 (23.9)	9.2 (5.4)	25.2 (11.8)
Median (min, max)	35.0 (21, 80)	59.0 (25, 92)	8.0 (2, 17)	27.0 (11, 47)
25th, 75th percentile	30.0, 44.0	51.0, 77.0	7.0, 14.0	18.0, 30.0
Age Difference from Active Treatment Arm (Year)[ae]				
n	346	535	83	227
Mean (SD)	-0.17 (0.36)	-0.12 (0.38)	-0.22 (0.35)	-0.14 (0.36)
Median (min, max)	-0.16 (-0.9, 0.7)	-0.11 (-0.9, 0.7)	-0.24 (-0.9, 0.7)	-0.13 (-0.9, 0.7)
25th, 75th percentile	-0.44, 0.09	-0.40, 0.14	-0.44, 0.03	-0.40, 0.13
Baseline Height Difference from Active Treatment Arm (cm)[ae]				
n		535		227
Mean (SD)		-3.72 (7.81)		-3.40 (8.65)
Median (min, max)		-4.00 (-24.7, 15.6)		-3.40 (-46.6, 29.0)
25th, 75th percentile		-9.40, 2.30		-8.97, 2.10
Baseline Height Z-Score Difference from Active Treatment Arm[e]				
n		535		227
Mean (SD)		-0.73 (1.50)		-0.63 (1.61)
Median (min, max)		-0.69 (-4.9, 3.2)		-0.55 (-8.9, 4.6)
25th, 75th percentile		-1.75, 0.37		-1.69, 0.41

Source: Table ir201117.q02.2.1.2.1 and Table ir201117.q02.2.1.2.2
max: maximum; min, minimum; SD: standard deviation
The external control from the primary source includes untreated ACH subjects from the Achondroplasia Natural History: a multicenter clinical study (referred to as the AchNH study).
The external control from the supportive pooled sources includes untreated ACH subjects from 111-901, 111-501 (referred to as LIAISE), and Natural History of ACH: A Retrospective Study of Patients Managed by a Multispecialty Program (referred to as KAISER) studies.
a AchNH Control Arm for 5-Year Cross-Sectional Comparative Analysis at Year 5 includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex and age to the sex and age at Year 5 from subjects in the Active Treatment Arm.
b AchNH Control Arm for 5-Year Cross-Sectional Comparative Analysis at Baseline includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex and age to the sex and age at Baseline from subjects in the Active Treatment Arm.
c Pooled Other NH Sources Control Arm for 5-Year Cross-Sectional Comparative Analysis at Year 5 includes all subjects from the Pooled Other NH Sources Descriptive Analysis Population who are matched by sex and age to the sex and age at Year 5 from subjects in the Active Treatment Arm.
d Pooled Other NH Sources Control Arm for 5-Year Cross-Sectional Comparative Analysis at Baseline includes all subjects from the Pooled Other NH Sources Descriptive Analysis Population who are matched by sex and age to the sex and age at Baseline from subjects in the Active Treatment Arm.
e Active Treatment Arm for Cross-Sectional Comparative Analysis includes all subjects in Study 111-202 Cohort 3 (15 ug/kg BMN 111) who continued to Study 111-205 with at least 5 years of total follow-up after excluding Subject [redacted] (b) (6) who had limb-lengthening prior to entry into the study
Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention

Table 2.2.4.1: Summary of Supportive NH Source Datasets (Analysis Population: All Subjects)

	111-901 (N = 352)	LIAISE (N = 128)	KAISER (N = 114)	Pooled NH Sources (N = 594)
	n (%)	n (%)	n (%)	n (%)
N of **subjects** in the dataset	352 (100.0)	128 (100.0)	114 (100.0)	594 (100.0)
N of subjects **included for the Descriptive Population**[a]	304 (86.4)	83 (64.8)	110 (96.5)	497 (83.7)
N of subjects included for the Descriptive Population with **at least one height assessment aged between 5-16 years**	242 (68.8)	56 (43.8)	61 (53.5)	359 (60.4)
N of subjects **excluded**	48 (13.6)	45 (35.2)	4 (3.5)	97 (16.3)
N subjects enrolled into an interventional study	0	0	3 (2.6)	3 (0.5)
N of subjects without a height assessment available that was measured at a known age	44 (12.5)	42 (32.8)	1 (0.9)	87 (14.6)
N of subjects who received growth hormone or underwent limb-lengthening	4 (1.1)	3 (2.3)	0	7 (1.2)

NH, natural history; KAISER, Natural History of Achondroplasia: A Retrospective Study of Patients Managed by a Multispecialty Program (Principal Investigator Ericka Okenfuss, MS, LCGC); LIAISE, The Impact of Achondroplasia on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial State of the Individual (Study 111-501).

[a] Percentages were calculated using the total number of subjects enrolled as the denominator.

This table provides a simplified breakdown of the dataset and is not a complete representation of the NH control arm. Further details on the NH control arms are presented in Appendix 2: Natural History Statistical Analysis Plan.

Bolded text refers to the additional criterion for the subset of subjects compared with the previous subset.

Source: Table 1.1

Table 2.3: TTEST of Height Difference at Year 5 and at Baseline (Cross-Sectional) (Analysis Population: 5-Year Cross-Sectional Comparative Analysis (Cohort 3 of 111-205 (Excluding Subject (b) (6)) vs. Primary and Supportive Pooled External Controls)

	Primary Analysis		Other Pooled NH Sources	
	External Control[a] (Primary) (N=9)	Vosoritide[b] (N=9)	External Control[c] (Supportive Pooled) (N=9)	Vosoritide[b] (N=9)
Height (cm) at Year 5				
Mean (SD)	115.95 (4.64)	127.93 (5.37)	116.95 (4.25)	127.93 (5.37)
Median (min, max)	116.17 (110.2, 124.5)	130.45 (115.8, 132.5)	117.00 (111.9, 124.8)	130.45 (115.8, 132.5)
25th, 75th percentile	112.16, 118.91	124.65, 131.00	113.40, 119.38	124.65, 131.00
Means difference (95% CI)	11.99 (5.96, 18.01)		10.99 (5.16, 16.81)	
2-sided p-value	0.0018		0.0024	
Height (cm) at Baseline				
Mean (SD)	98.39 (5.58)	102.23 (4.72)	99.19 (5.41)	102.23 (4.72)
Median (min, max)	98.07 (90.8, 108.1)	103.40 (93.6, 107.3)	98.56 (91.2, 107.6)	103.40 (93.6, 107.3)
25th, 75th percentile	95.91, 101.23	100.90, 105.60	96.72, 102.63	100.90, 105.60
Means difference (95% CI)	3.83 (-0.67, 8.34)		3.04 (-1.17, 7.25)	
2-sided p-value	0.0855		0.1345	
Height (cm) Difference (Year 5 – Baseline)				
Means (95% CI)[d]	**8.15 (4.83, 11.47)**		**7.95 (4.81, 11.10)**	
2-sided p-value	**0.0005**		**0.0004**	

Source: Table ir201117.q02.2.4.1.1, Table ir201117.q02.2.4.1.2, Table ir201117.q02.2.5.1.1, Table ir201117.q02.2.5.1.2, Table ir201117.q02.2.6.1.1 and Table ir201117.q02.2.6.1.2

CI: confidence interval; max: maximum; min, minimum; SD: standard deviation

a N for the external control represents the number of matched groups. .AchNH Control Arm for 5-Year Cross-Sectional Comparative Analysis at Year 5 includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex and age to the sex and age at Year 5 from subjects in the Active Treatment Arm.

b Active Treatment Arm for Cross-Sectional Comparative Analysis includes all subjects in Study 111-202 Cohort 3 (15 ug/kg BMN 111) who continued to Study 111-205 with at least 5 years of total follow-up after excluding Subject (b) (6) who had limb-lengthening prior to entry into the study

c N for the external control represent the number of matched groups. Pooled Other NH Sources Control Arm for 5-Year Cross-Sectional Comparative Analysis at Baseline includes all subjects from the Pooled Other NH Sources Descriptive Analysis Population who are

Table 3.4.1.1: TTEST of Height Between Year 5 and Baseline for Cohorts 1, 2 and 3 of 111-202/205 versus Primary External Control (Analysis Population: 5-Year Cross-Sectional Comparative Analysis)

Height Difference Between Subjects in Vosoritide Treatment Group and Average Height of Matched Subjects in AchNH Control Arm	Baseline (N = 20)	Year 5 (N = 20)
Mean (SD)	2.22 (6.06)	10.58 (8.64)
Median (min, max)	2.82 (-7.2, 15.4)	11.92 (-1.9, 31.5)
25th, 75th percentile	-3.63, 5.40	4.79, 15.51
Means (95% CI)	8.36 (6.38, 10.33)	
2-sided p-value	< 0.0001	

AchNH, multicenter clinical study (Principal Investigator Julie Hoover Fong, MD, PhD); CI, confidence interval; max, maximum; min, minimum; SD, standard deviation.

Source: Table 2.4.1.1.c123

Table 3.4.2.1: Longitudinal Analysis of Covariance of Change from Baseline in Height at Year 5 for Cohorts 1, 2 and 3 of 111-202/205 versus Primary External Control (Analysis Population: 5-Year Longitudinal Comparative Analysis)

Change from Baseline in Height at Year 5	External Control (Primary) (N = 97)	Vosoritide 15 µg/kg (N = 20)
Mean (SD)	18.00 (3.45)	25.19 (4.31)
Median (min, max)	17.50 (7.8, 26.0)	25.48 (18.1, 32.0)
25th, 75th percentile	15.80, 20.20	21.08, 28.57
LS Mean change from baseline (95% CI)	17.94 (17.27, 18.62)	25.44 (23.93, 26.95)
Difference in LS means (95% CI)	7.50 (5.83, 9.17)	
2-sided p-value	< 0.0001	

ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; max, maximum; min, minimum; SD, standard deviation.

Results were based on an ANCOVA model with fixed effects of treatment and indicator variables for matching.

Source: Table 2.10.1.c123

Table 3.3.4.1: TTEST of Height Z-Score Difference at Year 5 and at Baseline for Cohort 3 of 111-202/205 (Analysis Population: 5-Year Cross-Sectional Comparative Analysis versus External Controls)

	Vosoritide 15 µg/kg	External Control (Primary)	Vosoritide 15 µg/kg	External Control (Supportive Pooled)
Height Z-score at Year 5				
N	10	360	10	84
Mean (SD)	-3.80 (1.25)	-5.56 (0.56)	-3.80 (1.25)	-5.41 (0.63)
Median (min, max)	-3.77 (-5.7, -2.0)	-5.47 (-6.5, -4.9)	-3.77 (-5.7, -2.0)	-5.41 (-6.2, -4.4)
25th, 75th percentile	-4.72, -2.90	-6.07, -5.04	-4.72, -2.90	-6.14, -4.78
Means difference (95% CI)	1.76 (0.95, 2.58)		1.61 (0.81, 2.41)	
2-sided p-value	0.0008		0.0014	
Height Z-score at Baseline				
N	10	559	10	236
Mean (SD)	-4.61 (1.14)	-5.61 (0.34)	-4.61 (1.14)	-5.48 (0.35)
Median (min, max)	-4.85 (-6.3, -2.6)	-5.62 (-6.2, -5.2)	-4.85 (-6.3, -2.6)	-5.55 (-6.1, -5.0)
25th, 75th percentile	-5.42, -3.68	-5.87, -5.27	-5.42, -3.68	-5.66, -5.18
Means difference (95% CI)	0.99 (0.13, 1.86)		0.87 (0.12, 1.61)	
2-sided p-value	0.0290		0.0276	
Height Z-score Difference (Year 5 – Baseline)				
Means (95% CI)	**0.77 (0.40, 1.14)**		0.75 (0.35, 1.15)	
2-sided p-value	**0.0012**		0.0022	

CI, confidence interval; max, maximum; min, minimum; SD, standard deviation.
Results from the primary and supportive pooled analyses are from two separate models.

Table 3.3.5.1: Longitudinal Analysis of Covariance of Change from Baseline in Height Z-Score at Year 5 for Cohort 3 of 111-202/205 versus Primary External Control (Analysis Population: 5-Year Longitudinal Comparative Analysis)

Change from Baseline in Height Z-Score at Year 5	External Control (Primary) (N = 98)	Vosoritide 15 µg/kg (N = 10)
Mean (SD)	0.10 (0.73)	0.82 (0.72)
Median (min, max)	0.11 (-2.0, 1.8)	0.88 (-0.7, 2.1)
25th, 75th percentile	-0.41, 0.60	0.56, 1.13
LS means change from baseline (95 CI)	0.10 (-0.00, 0.20)	0.87 (0.55, 1.19)
Difference in LS means change from baseline	0.78 (0.44, 1.11)	
2-sided p-value	< 0.0001	

CI, confidence interval; max, maximum; min, minimum; LS, least square; SD, standard deviation.

Results were based on an ANCOVA model with fixed effects of treatment and indicator variables for matching.

Source: Table 2.10.2

Table 3.6.1.1: TTEST of Height Difference at Year 4 and at Baseline for Cohorts 1, 2 and 3 Re-baselined of 111-202/205 versus External Controls (Analysis Population: 4-Year Comparative Analysis)

	Vosoritide 15 µg/kg	External Control (Primary)	Vosoritide 15 µg/kg	External Control (Supportive Pooled)
Height (cm) at Year 4				
n	20	439	20	140
Mean (SD)	124.25 (9.40)	114.71 (6.43)	124.25 (9.40)	115.59 (7.53)
Median (min, max)	123.80 (112.2, 153.2)	112.66(105.5, 126.6)	123.80 (112.2, 153.2)	114.36 (104.6, 130.6)
25th, 75th percentile	117.43, 126.98	110.62, 120.63	117.43, 126.98	109.91, 120.87
Means (95% CI)	9.54 (5.52, 13.55)		8.65 (4.69, 12.61)	
2-sided p-value	< 0.0001		0.0002	
Height (cm) at Baseline				
n	20	634	20	270
Mean (SD)	103.50 (7.85)	101.02 (7.15)	103.50 (7.85)	102.17 (7.31)
Median (min, max)	102.85 (93.6, 126.1)	99.41 (90.6, 113.1)	102.85 (93.6, 126.1)	101.07 (91.7, 115.3)
25th , 75th percentile	97.03, 106.08	96.43, 108.65	97.03, 106.08	96.64, 106.95
Means (95% CI)	2.48 (-0.56, 5.52)		1.33 (-1.59, 4.25)	
2-sided p-value	0.1043		0.3518	
Height (cm) Difference (Year 4 – Baseline)				
Means (95 CI)	**7.06 (5.39, 8.73)**		7.32 (5.20, 9.44)	
2-sided p-value	**< 0.0001**		< 0.0001	

CI, confidence interval; max, maximum; min, minimum; SD, standard deviation.

Results from the primary and supportive pooled analyses are from two separate models.

Source: Table 3.4.1.1, Table 3.4.1.2, Table 3.5.1.1, Table 3.5.1.2, Table 3.6.1.1, Table 3.6.1.2

Table 3.6.2.1: Longitudinal Analysis of Covariance of Change from Baseline in Height at Year 4 for Cohorts 1, 2 and 3 Re-baselined of 111-202/205 versus Primary External Control (Analysis Population: 4-Year Longitudinal Comparative Analysis)

Change from Baseline in Height at Year 4	External Control (Primary) (N = 108)	Vosoritide 15 µg/kg (N = 20)
Mean (SD)	13.96 (3.32)	20.75 (3.64)
Median (min, max)	14.50 (2.6, 21.0)	19.55 (15.9, 27.1)
25th, 75th percentile	12.65, 15.70	17.40, 23.85
LS mean change from baseline (95 CI)	13.94 (13.42, 14.46)	20.89 (19.66, 22.12)
Difference in LS means change from baseline	6.95 (5.61, 8.29)	
2-sided p-value	< 0.0001	

CI, confidence interval; LS, least square; max, maximum; min, minimum; NH, natural history; SD, standard deviation.

Results were based on an ANCOVA model with fixed effects of treatment and indicator variables for matching.

Source: Table 3.10.1

Table 3.7.1.1: TTEST of Height Between Year 4 and Baseline for Cohort 4 of 111-202/205 versus External Control (Analysis Population: 4-Year Cross-Sectional Comparative Analysis)

Height Difference Between Subjects in Vosoritide Group and Average Height of Matched Subjects in External Control Group	Baseline (N = 8)	Year 5 (N = 8)
Mean (SD)	2.35 (2.53)	11.36 (5.95)
Median (min, max)	2.42 (-0.8, 5.4)	13.18 (3.8, 18.8)
25th, 75th percentile	0.09, 4.63	4.95, 16.01
Means (95 CI)	9.01 (5.46, 12.56)	
2-sided p-value	0.0005	

CI, confidence interval; max, maximum; min, minimum; SD, standard deviation.

Source: Table 3.4.1.1.c4

Table 3.7.2.1: Longitudinal Analysis of Covariance of Change from Baseline in Height at Year 4 for Cohort 4 of 111-202/205 versus Primary External Control (Analysis Population: 4-Year Longitudinal Comparative Analysis)

Change from Baseline in Height at Year 4	External Control (Primary) (N = 116)	Vosoritide 30 µg/kg (N = 8)
Mean (SD)	15.19 (2.79)	23.66 (1.94)
Median (min, max)	15.30 (6.1, 22.1)	24.15 (20.1, 25.6)
25th, 75th percentile	13.40, 16.78	22.42, 25.25
LS mean change from baseline (95 CI)	15.18 (14.69, 15.67)	23.79 (21.91, 25.68)
Difference in LS means change from baseline	8.61 (6.67, 10.56)	
2-sided p-value	< 0.0001	

CI, confidence interval; LS, least square; max, maximum; min, minimum; SD, standard deviation.

Results were based on an ANCOVA model with fixed effects of treatment and indicator variables for matching.

Source: Table 3.10.1.c4

Table 3.9.1: Demographics of Cohorts 1, 2 and 3 Re-baselined of 111-202/205 and 111-301/302 versus Primary External Control (Analysis Population: 2-Year Longitudinal Comparative Analysis)

	External Control (Primary) (N = 159)	Vosoritide 15 µg/kg (N = 25)
Age at baseline, years		
N	159	25
Mean (SD)	7.77 (2.09)	8.71 (1.83)
Median	7.21	8.41
25th, 75th Percentile	6.08, 9.23	7.64, 9.49
Min, Max	5.0, 13.0	5.1, 12.1
Age at baseline, n (%)		
≥ 5 to < 8 years	95 (59.7)	10 (40.0)
≥ 8 to < 11 years	46 (28.9)	10 (40.0)
≥ 11 to < 16 years	18 (11.3)	5 (20.0)
Sex, n (%)		
Male	92 (57.9)	12 (48.0)
Female	67 (42.1)	13 (52.0)
Race, n (%)		
Asian	5 (3.1)	4 (16.0)
Black or African American	6 (3.8)	1 (4.0)
Other	14 (8.8)	1 (4.0)
White	130 (81.8)	19 (76.0)
Not Available	4 (2.5)	0

Max, maximum; Min, minimum; SD, standard deviation.

Source: Table 4.2

Table 3.9.2: Baseline Growth Measures for Cohorts 1, 2 and 3 Re-baselined of 111-202/205 and 111-301/302 versus Primary External Control (Analysis Population: 2-Year Longitudinal Comparative Analysis)

	External Control (Primary) (N = 159)	Vosoritide 15 µg/kg (N = 25)
AGV, cm/yr		
n	159	25
Mean (SD)	4.29 (2.43)	3.69 (1.27)
Median	4.41	3.67
25th, 75th Percentile	2.92, 5.46	2.62, 4.93
Min, Max	-4.2, 12.9	1.6, 6.0
Height, cm		
n	159	25
Mean (SD)	96.87 (9.47)	102.83 (7.49)
Median	94.70	102.30
25th, 75th Percentile	89.50, 104.00	97.05, 104.95
Min, Max	79.6, 122.2	90.2, 126.1
Height Z-Score		
n	159	25
Mean (SD)	-5.36 (1.11)	-4.97 (0.99)
Median	-5.23	-4.93
25th, 75th Percentile	-6.16, -4.51	-5.66, -4.34
Min, Max	-8.7, -2.1	-6.6, -2.6

AGV, annualized growth velocity; Max, maximum; Min, minimum; SD, standard deviation; yr, year.

Source: Table 4.3

Table 8.3: Longitudinal Analysis of Covariance of Change from Baseline in Height and AGV for Cohorts 1, 2 and 3 Not Re-baselined of 111-205 (Analysis Population: 4-Year Longitudinal Comparative Analysis vs. Primary External Control)

	External Control (Primary)[a] (N=125)	Vosoritide[b] (N=21)
Change from Baseline in Height at Year 4		
Mean (SD)	15.08 (2.86)	20.58 (3.37)
Median (min, max)	15.20 (8.1, 27.8)	19.45 (16.0, 25.4)
25th, 75th percentile	13.20, 16.50	17.60, 23.80
LS means change from baseline (95% CI)	14.72 (14.07, 15.36)	20.58 (19.34, 21.81)
Difference in LS means change from baseline[c]	**5.86 (4.47, 7.26)**	
2-sided p-value	**<.0001**	
Change from Baseline in AGV at Year 4		
Mean (SD)	-0.24 (1.45)	1.50 (1.12)
Median (min, max)	-0.38 (-4.3, 6.8)	1.42 (-0.4, 3.5)
25th, 75th percentile	-1.03, 0.29	0.66, 2.27
LS means change from baseline (95% CI)	-0.04 (-0.31, 0.23)	1.50 (0.99, 2.02)
Difference in LS means change from baseline[c]	**1.54 (0.96, 2.12)**	
2-sided p-value	**<.0001**	

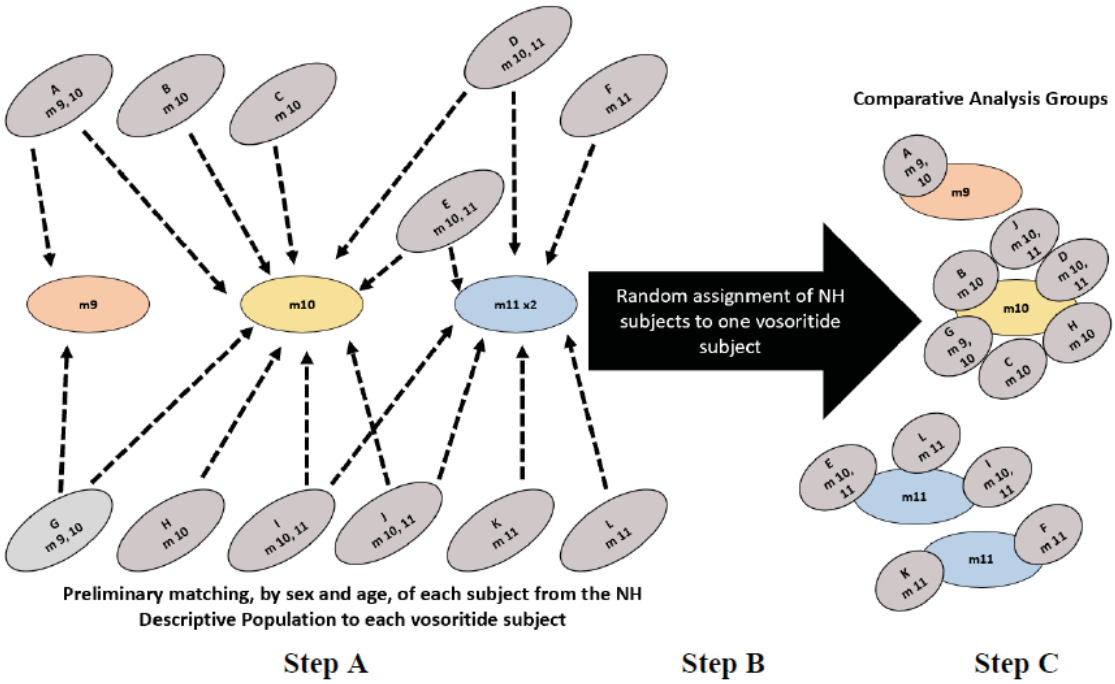
Source: Table ir201117.q08.3.10.1.1 and Table ir201117.q08.3.10.2.1

CI: confidence interval; Max: maximum; min, minimum; SD: standard deviation.

a AchNH Control Arm for 4-Year Longitudinal Comparative Analysis includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex, baseline AGV, baseline height, and age to the sex, baseline AGV, baseline height, and age at Baseline

APPENDIX 2. FIGURES

Figure 3.1.1: Primary Cross-Sectional Matching Approach



NH, natural history.

Grey circles represent the untreated ACH subjects from the NH source.

Peach, yellow and blue circles represent subjects from the vosoritide studies: m9: male subject aged 9 years; m10: male subject aged 10 years; m11 x2: two male subjects aged 11 years

A to L: theoretical subject IDs; m9: male subject aged 9 years; sex; 8: 8 years old; 9: 9 years old; 10: 10 years old; 11: 11 years old

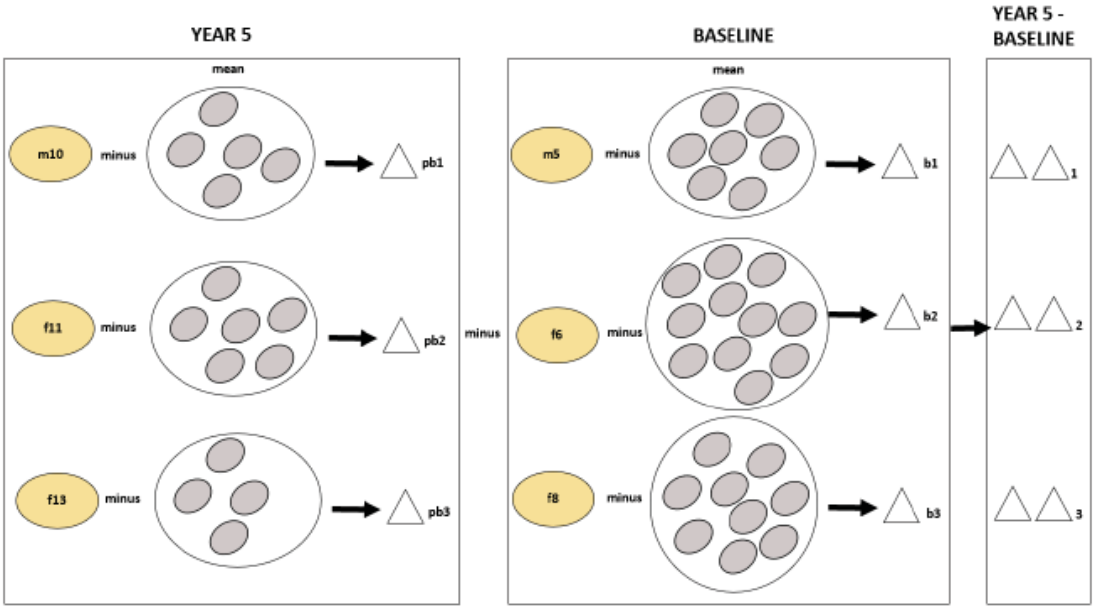
The number and age of subjects is for illustration purposes only and is not representative of the subjects included in the vosoritide or external control groups used in the comparative analyses.

Step A: Dashed arrow shows how subjects from the NH Descriptive Population were preliminarily matched to each vosoritide subject by sex and age.

Step B: Subjects from the NH Descriptive Population were subsequently randomly assigned to one vosoritide subject with equal probability.

Step C: Each subject in the vosoritide group matched to a unique group of subjects from the NH Descriptive Population with a different number of NH subjects in each matched group.

Figure 3.2.1: Illustration of Primary 5-Year Cross Sectional Analysis



NH, natural history.

Yellow circle represents the subject from the vosoritide studies: m10: male subject aged 10 years; m5: male subject aged 5 years who was aged 10 years at Year 5 (m10); f13: female subject aged 13 years; f8: female subject aged 8 years who was aged 13 years at Year 5 (f13); f11: female subject aged 11 years; f6: female subject aged 6 years who was 11 years at Year 5 (f11). Grey circles within the larger circle represents the group of sex and-age matched subjects from the NH source. The number and age of subjects is for illustration purposes only and is not representative of the subjects included in the vosoritide or external control groups used in the comparative analyses.

Δpb: difference at post-baseline; Δb: difference at baseline; ΔΔ: difference of Δpb and Δb; m: male; f: female: 5: 5years old; 6: 6 years old; 8: 8 years old; 10: 10 years old; 11: 11 years old: 13: 13 years old

A: NH subjects who have been matched by sex and age (see Figure 3.1.1) at Year 5; height at Year 5 of the vosoritide subjects (yellow circle) minus the mean height of the sex and age matched group of NH subjects is the difference in height at Year 5 (TTEST on Δpb1, Δpb2, Δpb3)

B: NH subjects who have been matched by sex and age at Baseline; height of the vosoritide subjects (yellow circle) minus the mean height of the sex and age matched group of NH subjects is the difference in height at Baseline (TTEST on Δb1, Δb2, Δb3)

C: The difference in height at Year 5 minus the difference in height at Baseline provided the delta (TTEST on ΔΔ1,ΔΔ2, ΔΔ3)

Note: at baseline, the subjects are 5 years younger than their age at Year 5

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/s/

CHRISTIAN HAMPP
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YANDONG QIANG
07/24/2021 06:00:21 PM

SIMONE P PINHEIRO
07/25/2021 08:29:42 PM

Review and Evaluation of Clinical Data

NDA: 214938
Sponsor: Biomarin Pharmaceutical, Inc.
Drug: Vosoritide for Injection (BMN111)
Proposed Indication: achondroplasia
Date Received by Division:
Date Review Completed: April 6, 2021
Reviewer: Ovidiu A. Galescu, M.D., M.S.

Consult request: The Division of General Endocrinology (DGE) has submitted a consult request for NDA 214938. The NDA holder, Biomarin Pharmaceutical, is currently developing vosoritide (BMN111) for injection as a treatment for short stature in patients with achondroplasia.
The consult requests assistance with the interpretation of changes in bone age compared to chronological age over time after treatment with vosoritide in this patient population. The primary review team noted that in the long-term study 111-202/205 (uncontrolled study) that, while at baseline bone age was behind chronological age, over time, there was an observed trend for bone age potentially exceeding the chronological age (Table 1). As such, DGE would like our input whether the magnitude of observed positive change in the difference between bone age and chronological age over time might potentially suggest accelerated growth and premature final height achievement as a result of vosoritide treatment.

Table 1. Difference between Mean Bone Age and Mean Chronological Age [mean (SD)], Safety population

Mean (SD)	Cohort 1 (2.5 ug/kg)	Cohort 2 (7.5 ug/kg)	Cohort 3 (15 ug/kg)	Cohort 4 (30 ug/kg)	Overall
Baseline (B)	-0.87 (1.56)	-1.05 (1.51)	-0.13 (1.35)	-0.73 (0.81)	-0.62 (1.29)
M 6	-0.9 (1.32)	-1.11 (1.63)	-0.18 (1.36)	-0.28 (1.09)	-0.53 (1.33)
Δ B to M 6 (S)	-0.04 (0.32)	-0.06 (0.45)	-0.04 (0.44)	0.45 (0.38)	0.09 (0.45)
M 12	-0.59 (1.64)	-0.67 (1.16)	-0.24 (1.36)	-0.46 (1.00)	-0.45 (1.22)
Δ B to M 12 (S)	0.29 (0.45)	0.37 (0.80)	-0.10 (0.78)	0.27 (0.36)	0.17 (0.64)
M18	-0.87 (1.61)	-0.51 (1.15)	-0.08 (1.34)	-0.34 (1.12)	- 0.42 (1.26)
Δ B to M 18 (S)	-0.01 (0.58)	0.54 (0.78)	-0.04 (0.48)	0.39 (0.49)	0.21 (0.60)
M 24	-0.70 (1.56)	-0.07 (0.78)	- 0.08 (1.42)	-0.33 (0.90)	-0.28 (1.20)
Δ B to M 24 (S)	0.16 (0.27)	0.60 (1.09) 0.98	0.05 (0.70)	0.40 (0.43)	0.27 (0.65) 0.34
M36	-0.86 (1.30)	-0.28 (0.37)	-0.44 (1.52)	-0.32 (0.71)	-0.47 (1.05)
Δ B to M 36 (S)	0.00 (0.57)	0.39 (1.25) 0.77	0.23 (0.94) -0.31	0.40 (0.58)	0.26 (0.80) 0.15
M 48	-0.82 (1.15)	-0.08 (0.46)	0.04 (1.47)	-0.33 (0.76)	-0.28 (1.06)

Δ B to M 48 (S)	0.04 (0.92)	0.59 (1.65) 0.97	0.58 (0.95) 0.17	0.40 (0.63)	0.41 (0.99) 0.34
M 60	-0.94 (1.34)	0.02 (0.96)	0.16 (1.49)		-0.14 (1.32)
Δ B to M 60 (S)	0.18 (1.17) - 0.07	0.69 (2.12) 1.07	0.70 (0.85) 0.29	N/A	0.57 (1.32) 0.48

Bone age determined using Greulich and Pyle Atlas.
Δ = change; B = baseline; M = month.
Yellow- Sponsor's analysis; Blue- medical reviewer's observed discrepancy in results compared to Sponsor's analysis.
Source: Table 14.3.6.4.1, p. 4564, study 111-202/205

Background:

BMN 111 is a proposed pharmacologic therapeutic option for achondroplasia (ACH).
ACH is an autosomal dominant genetic skeletal disorder caused by a gain-of-function mutation in fibroblast growth factor receptor 3 (FGFR3), a negative regulator of chondrocyte proliferation and differentiation. The most common mutation (98%) in ACH patients is a G380R substitution in the transmembrane domain of FGFR3. The extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) pathway mediates part of FGFR3 inhibition of chondrocyte proliferation and differentiation. The ERK MAPK pathway is modulated by C-type natriuretic peptide (CNP), a positive regulator of chondrocyte proliferation and differentiation. Binding of CNP to the natriuretic peptide-receptor B (NPR-2) antagonizes FGFR3 downstream signaling by inhibiting the MAPK (ERK1/2) pathway at the level of RAF-1.
BMN 111 is a recombinant CNP (rhCNP) analogue that has been engineered to mimic CNP activities in terms of receptor binding and pharmacological activity, and to resist degradation by neutral endopeptidase (NEP), allowing for a longer half-life and an impact on endochondral ossification. Similar to CNP, BMN 111 activates NPR-B signaling with subsequent inhibition of FGFR3 downstream signaling, leading to the promotion of chondrocyte proliferation and differentiation, and subsequent increased endochondral bone formation.

Reviewed Protocols:

Protocol No. 111-205: A Phase 2, Open-Label, Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of BMN 111 in Children with Achondroplasia

This is a multicenter, open-label, Phase 2 extension study to evaluate the long-term safety and efficacy of BMN 111 treatment in children with ACH who had completed Study 111-202. The interim study report includes BMN 111 efficacy and safety data from all subjects enrolled in 111-205, from the time of their first dose of BMN 111 received in 111-202, which was available up to the data cut-off of 20 November 2019.

In study 111-202 subjects with documented achondroplasia, confirmed genetically, were sequentially enrolled into 4 cohorts to receive the daily dosing regimens:

- Cohort 1: Subjects started on dose 2.5 µg/kg; subjects switched from 2.5 µg/kg to 7.5 µg/kg and then to 15 µg/kg during the extension phase of 111-202.
- Cohort 2: Subjects started on dose 7.5 µg/kg; subjects switched from 7.5 µg/kg to 15 µg/kg during the extension phase of 111-202.
- Cohort 3: Subjects started on dose 15 µg/kg; subjects continued to receive 15 µg/kg during the extension phase of 111-202.
- Cohort 4: Subjects started on dose 30 µg/kg; subjects continued to receive 30 µg/kg during the extension phase of 111-202.

Eligible subjects who then completed 2 years of BMN 111 treatment in 111-202 were enrolled in the 111-205 extension study to continue receiving the same stable dose of BMN 111 received upon completion of 111-202 (15 or 30 μg/kg daily).

Pertinent objectives and endpoints:

Secondary objective:
To evaluate the effect of BMN 111 on annualized growth velocity (AGV)
To evaluate the effect of BMN 111 on growth parameters
To evaluate in the effect of BMN 111 on body proportions

Secondary endpoints: Growth parameters (anthropometric measurements) include height, height Z-score, standing height, sitting height, weight, head circumference, upper and lower arm and leg length, and arm span. Body proportion measurements may include but are not limited to upper: lower body segment ratio, upper arm: forearm length ratio, upper leg: lower leg length ratio, and arm span: standing height ratio.

Exploratory endpoints: measures of growth plate, bone age, and BMD

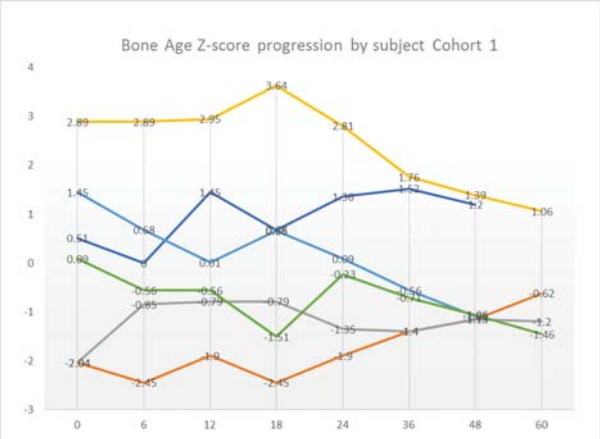
Study Population: Subjects who completed 2 years of BMN 111 treatment in 111-202 were enrolled in the 111-205 extension study. A total of 30/35 subjects from 111-202 enrolled into 111-205 – 6 subjects in 111-202 Cohort 1, 6 subjects in 111-202 Cohort 2, 10 subjects in 111-202 Cohort 3 and 8 subjects in 111-202 Cohort 4. After 6 months of dosing in 111-202, subjects in Cohorts 1 and 2 titrated to receive 15 μg/kg, while subjects in Cohort 3 and 4 subjects continued to receive 15 μg/kg and 30 μg/kg, respectively, therefore, all subjects in 111-205 received either 15 μg/kg or 30 μg/kg.
The mean (SD) age of subjects at Day 1 of 111-202 was between 7.50 (0.95) years (Cohort 4) and 8.54 (1.54) years (Cohort 3), with Cohort 4 having enrolled younger subjects on average, compared to the other 3 Cohorts. Overall, half of the subjects at the time of enrollment were aged ≥ 5 to < 8 years (50%) and the other half ≥ 8 to < 11 years (46.7%); there was only 1 subject aged ≥ 11 to < 15 years who was enrolled in Cohort 3. Overall, a total of 56.7% of subjects enrolled were females, and 43.3% were males;

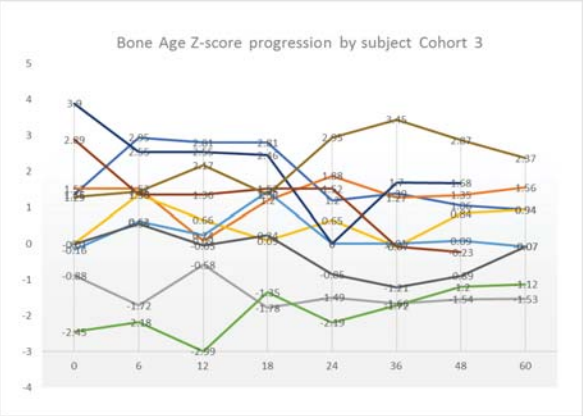
Relevant Results:

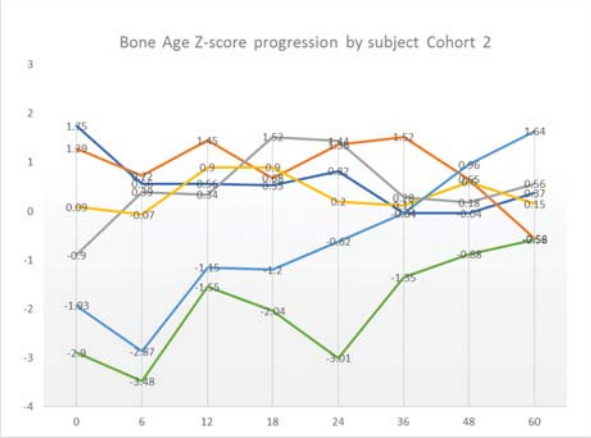
The evaluation of bone age was done by left hand and wrist X-ray, posterior-anterior (PA) view and interpretation was done by the Greulich and Pyle method.
The results were presented as mean measurements. Change from baseline were calculated.

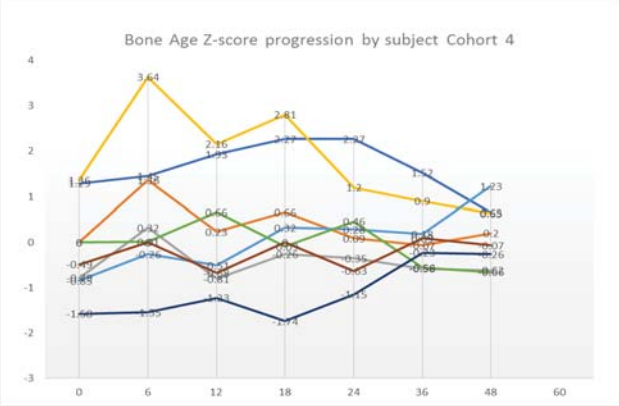
The Sponsor provided individual bone age readings, by subject in Listing 16.2.8.8.1.1. Based on this listing bone age data was available in 6 subjects in the 2.5 ug/kg cohort, 6 subjects in the 7.5 ug/kg cohort, 10 subjects in the 15 ug/kg cohort and 8 subjects in the 30 ug/kg cohort.

To better evaluate the impact on the bone age of the study intervention I evaluated the progression of bone age Z-scores. The Z-scores are a more reliable tool, compared to the (bone age – chronological age) parameter since it accounts for both the age and the sex of the subject.
As such I looked at the progression over time of bone age Z-scores by cohort. See Graphs below.
Although individual variability was observed there is no discernable pattern of bone age progression either by cohort or in the overall study population.

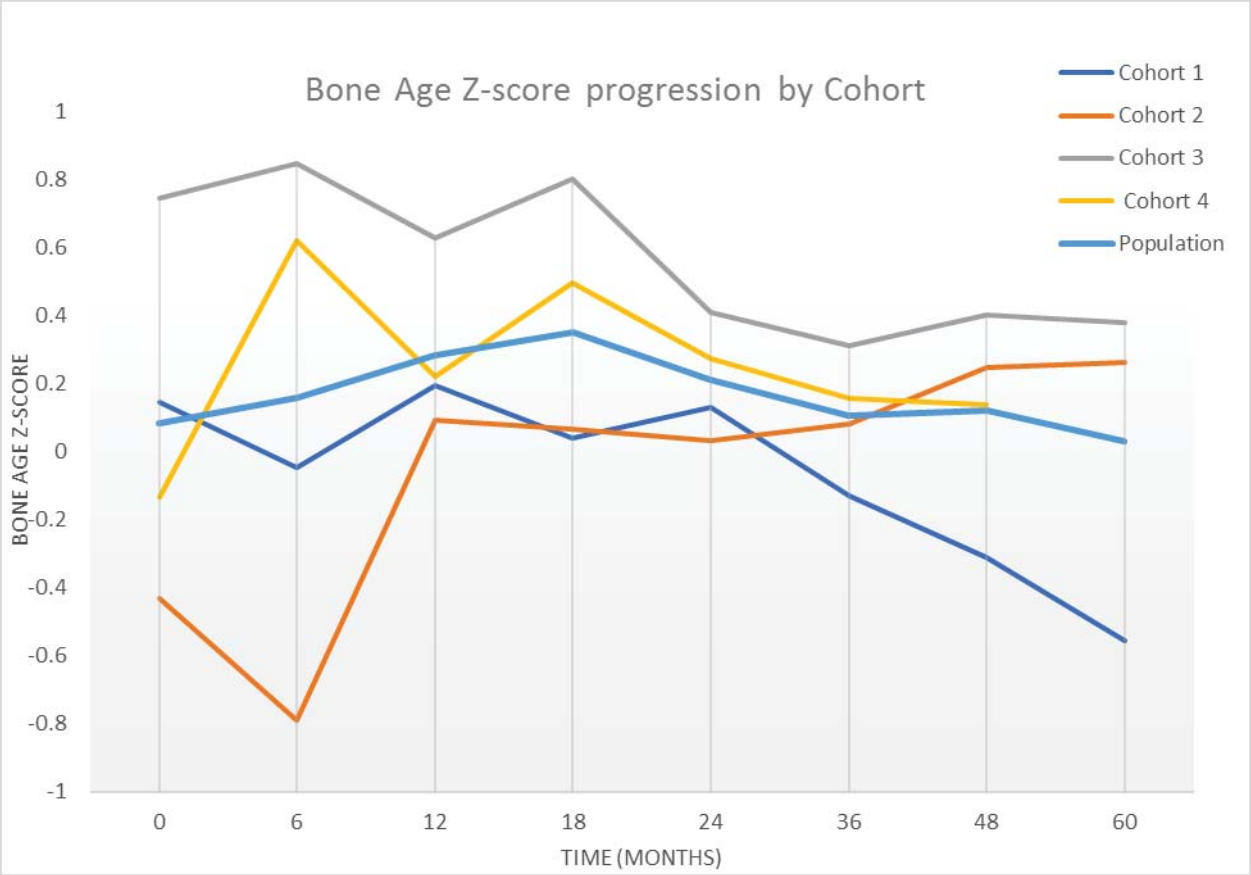




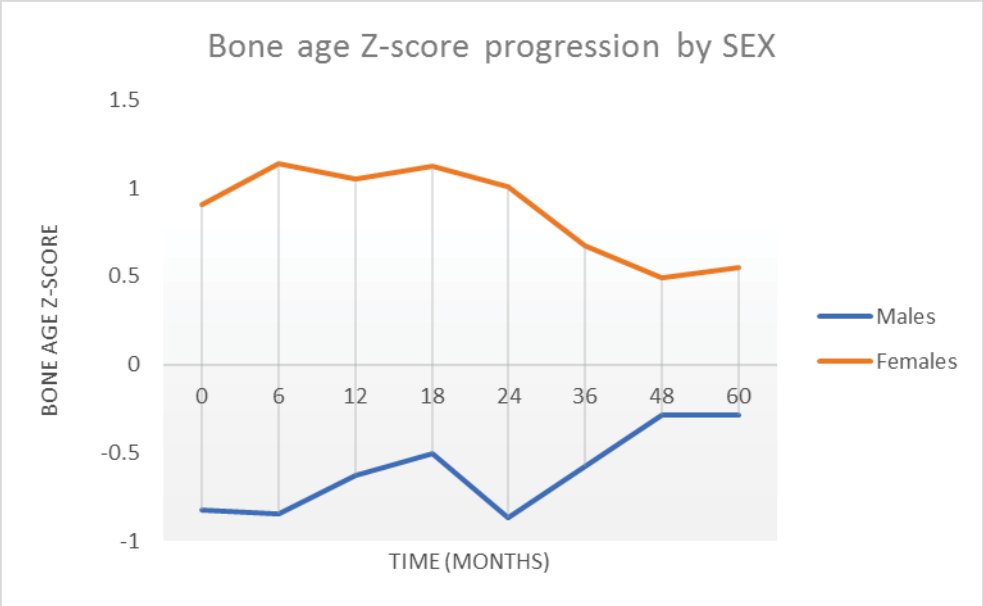




When looking at the average bone age Z-scores by cohort and entire study population no abnormal pattern was observed.



I further looked at the bone age Z-score progression by sex. Based on the Sponsor provided data the female population enrolled tended to have a slightly advanced bone age, when compared to chronological age with a bone age Z-score average of 0.9 (-0.49 to 2.89), compared with the enrolled males who tended to have a slightly delayed bone age, when compared to chronological age with a bone age Z-score average of -0.82(-2.9 to 3.9), At a study population level both females and males tended to normalize their bone age Z-score. See graph below.



Of note the Month 60 data is generated only from 9 of 13 male subjects and 9 of 17 female subjects due to missing data.

Conclusions: Regarding the consult question whether the magnitude of observed positive change in the difference between bone age and chronological age over time might potentially suggest accelerated growth and premature final height achievement as a result of vosoritide treatment, I conclude that based on the available data this is unlikely.

However, this conclusion should be interpreted in the context of the considerable limitations of the data. The Sponsor has not specified the methodology through which the bone age readings were obtained. It is unknown if there was a single central reader or if there are many readers that generated individual bone age assessment readings. With most skeletal age reading methods there is significant inter-reader reliability, which may contribute to the observed pattern. Generally, it is recommended that the bone age interpretation be centralized and read by either a single reader or two readers that average or consolidate their readings.

Furthermore, the Greulich and Pyle atlas, while commonly used for bone age determination was first published in 1950 and subsequently in 1959. The atlas was generated by studying ~800 healthy children from affluent families in the Cleveland, Ohio area. As such, the reliability and validity of this tool may be in question when applied to children with achondroplasia, making bone age in general a difficult parameter to interpret in this population.

Additionally, the data is impacted by the small number of subjects and the relatively heterogeneous baseline characteristics, with Bone Age Z-score outliers from -2.9 to +3.9.

In Listing 16.2.8.8.1.3 the Sponsor also provides a list of subjects where increases or decreases in Bone Age Z-score of more than 2 were observed throughout the study duration. These results are highly variable, do not appear to be dose related and have Bone Age Z-Score Change from Baseline values from -3.12 to +3.57.

The possibility that vosoritide has a direct impact on the bone age cannot be excluded; however, the provided data, as well as the questionable quality of this data, does not support this conclusion at this time. Further evaluation may be necessary to adequately quantify the drug effect on the growth plate.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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MEMORANDUM TO FILE

Version Date:	March 1, 2021
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Shetarra Walker, MD, MSCR, Medical Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director DPMH
NDA Number:	214,938
Applicant:	BioMarin Pharmaceutical, Inc.
Drug:	Voxzogo (Vosoritide, modified recombinant human C-type natriuretic peptide) injection
Indication:	Treatment of achondroplasia (ACH) in patients (b) (4) whose epiphyses are not closed
Dosage Form and Route of Administration:	Lyophilized powder (0.4 mg, 0.56 mg, 1.2 mg (b) (4) single dose vials) for reconstitution in sterile water, and subcutaneous (SC) injection
Proposed Dosing Regimen:	(b) (4) once daily
Division Consult Request:	The Division of General Endocrinology (DGE) requests DPMH assistance in the labeling review for this newly submitted NDA.

Background

Vosoritide, modified recombinant human C-type natriuretic peptide, is under development for treatment of achondroplasia (ACH) in patients (b) (4) whose epiphyses are not closed. Drug development took place under IND 111,299.

On January 17, 2013 vosoritide received orphan designation for treatment of ACH.

No drugs are currently approved for treatment of ACH.

The following brief summary of ACH is taken from the Online Mendelian Inheritance in Man database (OMIM, entry #100,800); search date December 11, 2020. ACH is caused by de novo mutation in the fibroblast growth factor receptor-3 gene (FGFR3) on chromosome 4p16.3. Although FGFR3 normally inhibits bone growth, in patients with achondroplasia, the altered receptor is constitutively active. The altered cartilage formation is pathogenetically linked to abnormal bone formation. While most patients have de novo mutations, rare cases associated with imbalanced translocations from a parent with a balanced translocation have been reported. Conceptuses with two abnormal genes (25% chance of offspring from two affected parents) commonly die in utero or shortly after birth from mechanical respiratory cage dysfunction due to small thoracic cage and multiple rib fractures.

The proposed mechanism of action of vosoritide is by overcoming a gain-of-function mutation in FGFR3 and restoring endochondral bone formation, resulting in sustained normal bone growth over time.

Labeling Review

DPMH's labeling recommendations focus on sections 1 (Indications and Usage), 2 (Dosage and Administration) and 8.4 (Pediatric Usage). Discussion of section 6 is limited to data regarding changes in blood pressure. There are no Warnings and Precautions in the Applicant's draft labeling, which may be amended upon review of the safety data by DGE. Review of the remaining sections [e.g., 6 (Adverse Reactions), and 14 (Clinical Studies)] is deferred to DGE and other consultant disciplines (e.g., Clinical Pharmacology).

For this review, text which DPMH recommends deleting is noted by ~~strike out~~, and any text which DPMH recommends adding is noted in **bold red**. The comments below were provided to DGE on February 25, 2021.

The reader is directed to the final negotiated label which may reflect changes not discussed in this document (e.g., agreed upon trade name of the drug).

1 Indication

Voxzogo is indicated for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed.

Reviewer comment: The indication is consistent with how the drug was studied, and the drug's mechanism of action.

2 Dosage and Administration

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Achondroplasia

The recommended dose of VOXZOGO is (b) (4) once daily by subcutaneous injection.

(b) (4)

(b) (4)

Duration of Use

Treatment with VOXZOGO should be stopped upon confirmation of no further growth potential, indicated by closure of epiphyses.

Missed dose

If a dose of VOXZOGO is missed, it can be administered within 12 hours of the scheduled time of administration. Beyond 12 hours, the missed dose should be skipped and the next daily dose administered according to the usual dosing schedule.

2.2 Growth Monitoring

Monitor and assess patient body weight, growth, and physical development regularly every 3-6 months. Dose should be adjusted according to the patient's body weight *[see Dosage and Administration (2.1)]*.

6 Adverse Reactions (Discussion of blood pressure only)

(b) (4)

(b) (4)

[redacted]

Reviewer comment: Higher blood pressures have been reported in adults with ACH and other short stature skeletal dysplasias.[1] However, DPMH was unable to locate reference values for normative blood pressures adult or pediatric patients with ACH. At the February 25, 2021 team meeting, DAV, DPMH, and members of the Division of Cardiology and Nephrology (DCN) discussed blood pressure findings. DCN concluded the findings did not represent clinically meaningful adverse events. (b) (4) [redacted]

8.4 Pediatric Use

The safety and effectiveness of Voxzogo have been established in pediatric patients aged (b) (4) [redacted]. Use of VOXZOGO for this indication is supported by evidence from adequate and well-controlled studies in pediatric patients aged 5 years and older, (b) (4) [redacted] [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)].

Safety and effectiveness of Voxzogo in pediatric patients with achondroplasia below the age (b) (4) [redacted] have not been established.

Reviewer comment: The passage above, as modified, accurately describes the basis of approval

[1] Hoover-Fong J, Alade AY, Ain M, et al. Blood pressure in adults with short stature skeletal dysplasias. Am J Med Genet A. 2020 Jan;182(1):150-161.

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/s/

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JOHN J ALEXANDER
03/01/2021 03:06:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: 03/1/2021 **Date consulted:** 09/4/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of General Endocrinology (DGE)

Drug: Voxzogo (vosoritide) lyophilized powder for solution for injection

NDA: 214938

Applicant: BioMartin Pharmaceutical Inc.

Subject: new NDA

Proposed Indication: For the treatment of achondroplasia in patients [redacted] (b) (4) whose epiphyses are not closed.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214938
- DGE consult form for DPMH, DARRTS Reference ID 4667107

Consult Question:

- DGE is seeking assistance from DPMH in developing Sections 8.1, 8.2 and 8.3 of the product's labeling.

INTRODUCTION AND BACKGROUND

On August 20, 2020, the applicant (BioMartin Pharmaceutical Inc.) submitted a new original NDA 214938 for vosoritide for injection for approval. The Division of General Endocrinology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) on September 4, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Vosoritide, also known as BMN 111, is a modified recombinant human C-type natriuretic peptide with the proposed indication of treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed.
- Vosoritide has not been approved previously for use in the U.S. or any other country.
- On November 13, 2012, the applicant was granted Orphan Drug designation under IND 111299.
- On January 3, 2017, the applicant was denied Fast Track Designation due to the following reasons:
    - The applicant's human data collected to date did not clearly establish that changes in growth velocity observed were attributable to an effect of BMN 111.
    - It was unclear that the effect can be sustained over several years and result in a change in final standing height.
    - It was unclear that the small magnitude of change in height velocity observed will improve the functional or psychological well-being of patients with achondroplasia.
    - The clinical data did not suggest BMN 111 improves disproportionality or improves morbid complications of the disease attributed to abnormal skeletal development including middle ear, respiratory or neurological complications.
- On August 20, 2020, the applicant submitted an NDA.

Drug Characteristics Based on Applicant's Proposed Labeling

Drug Class	modified recombinant human C-type natriuretic peptide (CNP)
Proposed Mechanism of action	In patients with achondroplasia, endochondral bone growth is negatively regulated due to a gain of function mutation in fibroblast growth factor receptor 3 (FGFR3). Binding of vosoritide to natriuretic peptide receptor-B (NPR-B) antagonizes FGFR3 downstream signaling by inhibiting the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the mitogen-activated protein kinase (MAPK) pathway at the level of rapidly accelerating fibrosarcoma serine/threonine protein kinase (RAF-1). As a result, vosoritide, like CNP, acts as a positive regulator of endochondral bone growth as it promotes chondrocyte proliferation and differentiation (b) (4))[1].
Proposed Dose and Administration	(b) (4) once daily by subcutaneous injection.

[1] Edits by DGE Pharmacology Toxicology Team.

Metabolism	The metabolism of vosoritide is expected to occur via catabolic pathways and be degraded into small peptide fragments and amino acids.
Molecular weight	4.1 kDa
Half life	21 to 27.9 minutes
Protein Binding	NA
Bioavailability	NA
Serious Adverse Reactions	None

Reviewer comment:
The DGE Clinical team, Clinical Pharmacology team, and Pharmacology Toxicology Team are in agreement with the applicant proposed labeling.

REVIEW
PREGNANCY
Achondroplasia and Pregnancy
Achondroplasia is the most common type of skeletal dysplasias that results in marked short stature, and it is often due to a mutation in G380R amino acid substitution of fibroblast growth factor receptors 3 (FGFR 3), which leads to ligand independent activation of FGFR 3 and thus negative regulation of chondrocytic bone growth (though shortening of the proliferative phase and accelerating terminal differentiation).[2] FGFR3 is prevalent on surface of chondrocytes that give rise to cartilaginous bone, calvarial sutures, testes, and the brain.

Prevalence/Incidence: The overall prevalence of achondroplasia is estimated to be 250,000 affected persons worldwide, about 1 in every 25,000-30,000 individuals.[2]

Genetics: Achondroplasia is due to mutations that are autosomal dominant. These mutations are full penetrant and demonstrate modest variability of expression. Approximately 80% of achondroplasia arise from new spontaneous mutations, often in advanced paternal age because FGFR 3 mutant protein products are positively selected for sperm precursor cells (spermatogonia stem cells).[2] Those with homozygous mutations result in a more severe process and are considered lethal in the newborn period.[2]

Clinical features: small stature, short limbs and rhizomelic (proximal) disproportion, macrocephaly, midfacial retrusion, small chest, thoracolumbar kyphosis, lumbar hyper-lordosis, limited elbow extension, short fingers and trident configuration of the hands, hypermobile hips and knees, bowing of the mesial segment of the legs, hypotonia.

Natural history and management: Treatment is usually supportive aimed to prevent or treat complications. There is no treatment that will negate the effects on growth of achondroplasia. Growth hormone and extended limb lengthening has been used in the past to negate some of the effects.

- There are two major concerns:
    - Craniocervical junction constriction which can lead to sudden infant death due to hypoxic damage to the central respirator control centers in the medulla which lead to diminished central respiratory control and apnea.[2]

[2] Paulis R, Achondroplasia: a comprehensive clinical review. Orphanet Journal of Rare Diseases. 2019; 14 (1): 1-49.

    - Restrictive pulmonary disease due to small chests and inefficient chest mechanics which result in chronic hypoxemia.[2]
- Other concerns include obesity, hearing loss, spinal cord compression and stenosis, hydrocephalus, kyphosis and lordosis.

Pregnancy: Published literature consists of case reports and small case series which note that most women with achondroplasia have near-normal trunk size, which allow most women to carry pregnancies to term.

- Prenatal diagnosis, including cell free method, with genetic counseling are available. Prenatal detection rate increased in the recent years and about 1 out of 3 of affected pregnancies were terminated.[3]
- The risk of associated major congenital anomalies was 10%.[3]
- Perinatal mortality was low (0.06 per 100,000).[3]
- All women with achondroplasia must be delivered by C-section due to uniform narrowing of the pelvis and cephalopelvic disproportion.[2]
- Pregnancy-related complications are uncommon, most serious are worsening spinal claudication symptoms and rarely respiratory complications. The greatest cardiorespiratory problems are those with very small stature and with shorter than typical trunks, those with severe spinal deformity and those with apnea-associated complications in the past.[2]

Nonclinical Experience

Applicant proposed labeling:

(b) (4)

The reader is referred to the full Pharmacology/Toxicology review by Dan Minck, Ph.D. and Federica Basso, Ph.D.

Review of Clinical Trials

There were no pregnant women enrolled in the clinical trials.

Review of Literature

DPMH's Review of Literature

DPMH conducted a literature review in Embase, Pubmed, Micromedex,[4] and ReproTox.[5]

[3] Coi A, et al. Epidemiology of achondroplasia: A population-based study in Europe. Am J Med Genet. 2019;179A:1891-1798.

[4] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9/14/2020

[5] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 9/14/2020.

Embase and Pubmed were searched for "vosoritide" and "pregnancy," "vosoritide" and "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage." There is no published literature on the use of vosoritide in pregnancy.

Micromedex[4] and ReproTox[5] contain no information on vosoritide.

Reviewer comment:
Overall, the applicant provided an adequate review of clinical trials regarding vosoritide use in pregnant women. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

LACTATION

Nonclinical Experience

Applicant proposed labeling:

(b) (4)

The reader is referred to the full Pharmacology/Toxicology review by Dan Minck, Ph.D. and Federica Basso, Ph.D.

Review of Clinical Trials

There were no lactating women enrolled in any of the clinical trials, and lactation studies have not been conducted.

Review of Literature

DPMH's Review of Literature

A search was performed using the sources noted below, and the following findings were retrieved:

A search in PubMed and Embase was performed using the search terms "vosoritide" AND "lactation" and "vosoritide" AND "breastfeeding," and no articles were found on the use of vosoritide during lactation.

LactMed,[6] Hale,[7] and Briggs[8] contained no information on vosoritide.

[6] http;//toxnet nlm.nih.gov/newtoxnet/lactmed.htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 2/12/2020.
[7] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.
[8] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 9/14/20

Reviewer comment:
Vosoritide is present in animal milk; therefore, it is likely to be present in human milk. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Applicant proposed labeling:

> In a fertility and reproductive study in male and female rats at dose levels up to 540 mcg/kg/day, vosoritide had no effect on mating performance, fertility, or litter characteristics.
>
> Carcinogenicity and genotoxicity studies have not been performed with vosoritide. (b) (4) .

The reader is referred to the full Pharmacology/Toxicology review by Dan Minck, Ph.D. and Federica Basso, Ph.D.

Review of Clinical Trials

As pregnancy was excluded from the clinical trial, human fertility was not assessed.

Review of Literature

DPMH's Review of Literature

DPMH conducted a published literature review by using the sources noted below, and the following findings were retrieved:

DPMH conducted a published literature review on PubMed and Embase using term "vosoritide" and "fertility," "vosoritide" AND "reproduction," "vosoritide" AND "contraception." No relevant articles were retrieved.

ReproTox[9] contains no information on vosoritide.

Reviewer comment:
Overall, the applicant provided an adequate review of clinical trials regarding vosoritide use in females and males of reproductive potential. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no available data on vosoritide use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies with rats and rabbits, vosoritide did not show any fetal harm.

[9] ReproTox. Accessed 9/14/2020.

The incidence of achondroplasia is about 1 in every 25,000-30,000 people, which represents about 13,178 people in the United States (calculated from US Census 2019 which estimates the US population to be 329.45 million). Vosoritide is not recommended to be used in patients whose epiphyses are closed. Since complete bone fusion happens on average between ages 12 to 18 for girls, vosoritide use during pregnancy is likely to be rare. If a patient were to get pregnant while taking vosoritide, the benefit of taking vosoritide during the entire pregnancy, only to gain an additional 1 to 2cm, is small, and this drug will likely be discontinued if a patient were to get pregnant. For these reasons, a postmarking pregnancy safety study is unlikely to be feasible; therefore, DPMH does not currently recommend a postmarketing pregnancy safety study.

Lactation

It is not known if vosoritide is present in human milk. Vosoritide is present in animal milk and was detected in the blood of one of the rat pups. When a drug is present in animal milk, it is likely to be present in human milk. There are no data on the effects of vosoritide on the breastfed infants or on milk production. DPMH recommends using the standard risk/benefit language in subsection 8.2.

Although vosoritide is likely to be present in human milk based on animal data, vosoritide is a large molecule with a short half-life. Based on its physical properties, vosoritide is not expected to accumulate in breastmilk. Given the small number of adolescents who may become pregnant while taking vosoritide, it will not be feasible to conduct a lactation study in the indicated population. DPMH does not recommend a postmarketing lactation study at this time.

Females and Males of Reproductive Potential

Based on animal fertility studies, vosoritide is not expected to cause infertility. There is no known drug-drug interaction between vosoritide and hormonal birth control. DPMH recommends omitting subsection 8.3.

LABELING RECOMMENDATIONS

DPMH proposes updates to subsections 8.1 and 8.2 of labeling for the new NDA and in compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on vosoritide use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. [Add animal risk summary statement here.]

The estimated background risk of major birth defects for the indicated population is higher than the general population (b) (4) The estimated background risk of miscarriage for the indicated population is

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

Data

Animal Data

[Add animal data here.]

Reviewer comment: The Pharmacology Toxicology edits were not available at the completion of this review.

8.2 Lactation

Risk Summary

There is no information regarding the presence of vosoritide in human milk, the effects on the breastfed child, or the effects on milk production. Vosoritide is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VOXZOGO and any potential adverse effects on the breastfed child from VOXZOGO or from the underlying maternal condition

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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.

/s/

WENJIE SUN
03/01/2021 10:53:31 AM

MIRIAM C DINATALE
03/01/2021 11:01:07 AM

LYNNE P YAO
03/01/2021 11:09:40 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: January 21, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Linda Galgay, RPM
DGE

Subject: QT Consult to NDA-214938 (SDN001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 9/3/2020 regarding the sponsor's QT assessment. We reviewed the following materials:

- Previous IRT review for IND-111299 dated 03/05/2017 in DARRTS (link);
- Previous IRT review for IND-111299 dated 12/06/2018 in DARRTS (link);
- Previous IRT review for IND-111299 dated 04/15/2019 in DARRTS (link);
- Previous IRT review for IND-111299 dated 03/16/2020 in DARRTS (link);
- Sponsor's clinical study protocol # 111-301 (SN0001; link);
- Sponsor's clinical study report # 111-301 (SN0001; link);
- Sponsor's QT assessment report (SN0001; link);
- Sponsor's proposed product label (SN0001; link);
- Investigator's brochure ver. 12.0 (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (Appendix 2; SN0004; link).

1 SUMMARY

No significant QTc prolongation effect of vosoritide was detected in this integrated nonclinical and clinical QT assessment.

The effect of vosoritide was evaluated in a randomized, double-blind, placebo-controlled, multicenter, phase 3 study with children (5 to <18 years) with achondroplasia (Study # 111-301). The highest dose evaluated was 15 µg/kg (as a daily subcutaneous injection for 52 weeks), (b) (4)

(b) (4) Moreover, there are no know clinical scenarios leading to increased exposure of vosoritide than those associated with therapeutic doses (Section 3).

The data were analyzed using the by-time analysis in conjunction with non-clinical assessment, which did not suggest that reltecimod is associated with significant QTc prolonging effect (refer to Appendix). In addition, the IRT performed QT bias assessment by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse. This analysis did not suggest the presence of significant negative treatment bias.

Although the study did not include a separate positive control or required multiples of the clinically relevant exposure, our assessment of the sponsor's non-clinical studies indicates that the sponsor's hERG assay met the best practice according to the new ICH S7B Q&As 2.1 and suggests that vosoritide does not acutely interact with hERG channels at the therapeutic exposure level (hERG safety margin > 8620x).

1.1 Responses to Questions Posed by Sponsor

Not applicable.

1.2 Comments to the Review Division

A nonclinical and clinical QT assessment was used according to draft ICH E14 Q&A 5.1 and ICH S7B Q&A 1.1–1.2.

2 RECOMMENDATIONS

2.1 Additional Studies

Not applicable.

2.2 Proposed Label

No QT labeling language was proposed by the sponsor in the label submitted to SN0001 (link). Our proposal is highlighted (*addition*) below. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At the maximum approved recommended dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 BACKGROUND

BioMarin Pharmaceutical Inc. is developing vosoritide for the treatment of achondroplasia (b) (4) (b) (4) Vosoritide is a modified (Voxzogo, Pro-Gly-CNP37, Pro-CNP38, a 39-amino-acid peptide analog; MW: 4.1 kDa) recombinant human C-type natriuretic peptide (CNP) analog. Similar to endogenous CNP, vosoritide is expected to bind natriuretic peptide receptor (type B and

type C but not to type A) and 1) to promote endochondral bone growth and 2) alter the vascular tone. Vosoritide administration is expected to induce vascular smooth muscle relaxation resulting in decrease in blood pressure with a compensatory increase in heart rate.

The product is formulated as sterile powder (for reconstitution and injection) containing 0.4, 0.56, 1.2, (b) (4) vosoritide (reconstituted as 0.8 and 2 mg/mL solution; single dose vials) for subcutaneous administration. The proposed therapeutic dose for the present indication is (b) (4) once daily as subcutaneous injection. The peak concentrations of 7180 ± 9650 pg/mL (Tmax: ~15 min; half-life: ~0.5 h) are expected at steady-state with the anticipated therapeutic dose (Day 1; Study # 111-301; age: 5 to 18 years). The sponsor expects no significant accumulation at steady-state with the proposed maximum therapeutic dose ((b) (4) . The maximum studied dose is 30 µg/kg once daily (Study # 111-202).

Sponsor claims that vosoritide is not significantly metabolized by the CYP450 enzymes and it has a low drug interaction potential as a victim drug. Vosoritide is expected to be cleared primarily by protease-mediated catabolism (peptide hydrolysis and to some extent NPR-C receptor mediated cellular uptake) and renal elimination. No special population studies (mainly renal impairment or hepatic impairment) have been conducted. However, the sponsor states that the impaired hepatic and renal function is not expected to have a significant impact on vosoritide pharmacokinetics.

Previously, the sponsor requested substitution of thorough QT study based on -

1) the sequence homology between vosoritide and endogenous C type natriuretic peptide (CNP); 2) the large size of this biologic peptide, such that an effect on cardiac ion channels is very unlikely; 3) the low QT prolongation potential characterized in the nonclinical program; 4) a human ether-á-go-go related gene (hERG) assay in which no statistically significant hERG current inhibition was observed at a concentration of vosoritide that is 8620-fold greater than the Cmax in patients treated with 15 µg/kg vosoritide; and 5) lack of any signal in early phase clinical development (electrocardiogram [ECG] data from 111-101 and 111-202).

Considering all these aspects, the IRT proposed an integrated risk assessment based on the planned ECG collection and evaluation of cardiac safety in the Phase 3 clinical studies (Dt: 03/05/2017, 12/06/2018, 04/15/2019, 03/16/2020). This was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study evaluating the efficacy and safety of vosoritide in children (5 to <18 years old) with achondroplasia (Study # 111-301). Subjects received vosoritide 15 µg/kg or placebo as a daily subcutaneous injection for 52 weeks (n=121; RN 1:1).

Triplicate 12-lead ECGs were collected according to the following schedule. ECG assessments were performed post-dose on study day visits at which a dose was given; in addition, on Day 1, ECGs were collected pre-dose also. On days when PK samples were drawn, ECGs were performed within a 5-minute window prior to 30-minute PK assessment:

- Screening
- Day 1, pre-dose; 30 minutes post-dose
- Day 10, 30 minutes post-dose
- Week 13, 30 minutes post-dose
- Week 26, 30 minutes post-dose
- Week 39, 30 minutes post-dose
- Week 52, 30 minutes post-dose

- Week 56 safety follow-up (off-treatment time point; waived if subject enters the 111-302 long-term extension study)
- Early termination (if applicable)

Blood samples for pharmacokinetic (PK) analysis were collected according to the following schedule:

- Full PK Samples on Day 1, Week 26, Week 52
  - Pre-dose and post-dose 5, 15, 30, 45, 60, 90, and 120 minutes
- Partial PK Samples on Week 13, Week 39
  - Pre-dose and post-dose 15, 30, and 60 minutes

The peak concentration (Cmax: ~5800 ng/mL Week 52) observed with highest dose studied (i.e., 15 µg/kg; once daily SC injection) represents the therapeutic exposures in the target population.

3.1 Nonclinical Cardiac Safety

In the current submission, the sponsor provided raw data from Study BMN-111-11-023. FDA's independent analysis of the submitted electrophysiology data shows that vosoritide inhibited hERG current by ~6% at 50 µg/mL. IC50 is far greater than 50 µg/mL and the hERG safety margin of vosoritide is expected to be greater than 8620x (refer to Appendix for a detailed review of sponsor's submission).

In summary, results from experiments that conducted by sponsor suggest that vosoritide does not acutely interact with hERG channels at the therapeutic exposure level.

3.2 Safety Analysis

Most subjects in both placebo (60/61; 98.4%) and vosoritide (59/60; 98.3%) groups experienced at least 1 AE during the study. Ten subjects in each group (16.4% in the placebo and 16.7% in the vosoritide groups) experienced AEs that led to dose interruption. In the vosoritide group, 1 (1.7%) subject experienced an AE (anxiety related to injections) that led to permanent discontinuation of study drug. No subject in the placebo group discontinued from study drug or the study due to an AE. The majority of AEs reported in the study were Grade 1 (mild) or Grade 2 in both groups (96.7% and 39.3% of subjects in the placebo group, respectively, 96.7% and 31.7% of subjects in the vosoritide group, respectively). Grade 3 AEs were reported less frequently in 4.9% and 5.0% of subjects in the placebo and vosoritide groups, respectively. No Grade 4 AEs or deaths were reported. SAEs were reported more frequently in in the placebo group (4/61 [6.6%] subjects) than in the vosoritide group (3/60 [5.0%] subjects) which led to dose interruption in 2 (3.3%) subjects in each group. No SAEs were attributed to the study drug by the investigators, and none led to discontinuation of study drug or the study. In the placebo group, 5 SAEs were reported; appendicitis, adenoidal hypertrophy, dyspnea, intracranial pressure increased, and spinal cord compression. In the vosoritide group, 4 SAEs were reported; influenza, radius fracture, adenoidal hypertrophy and sleep apnea syndrome. No notable changes were seen in mean systolic blood pressure (SBP) in either the vosoritide or placebo group. The mean changes in DBP and HR in the vosoritide group were minimal and not considered clinically significant.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.

4 Appendix: Review of Supporting Nonclinical Data

Vosoritide (BMN 111) is a 39 amino acid, modified recombinant C-type natriuretic peptide (CNP) that is indicated for the treatment of achondroplasia (ACH) in patients (b) (4) whose epiphyses are not closed. The nonclinical cardiovascular safety pharmacology data and in vitro hERG data were reviewed to assess its QT prolongation potential.

4.1 Cardiovascular safety pharmacology evaluation

4.1.1 Sponsor's submission

The in vivo cardiovascular pharmacology Study (Study ID: BMN111-11-040, link) assessed effects of subcutaneous administrations of vosoritide (BMN111) on ECG parameters and cardiovascular hemodynamic in 8 telemetered monkeys. Each animal received one of the four dosages (in a predetermined order) on Days 1, 4, 8, and 11. On each dosing day, animals were given the vehicle control article or test article at a dose level of 10, 50, or 200 µg/kg body weight at a dose volume of 1 mL/kg. Following a single 200 µg/kg SC dose in cynomolgus monkeys, the mean Cmax observed were 52.5 ng/mL. At dose of 200 µg/kg, vosoritide caused decreases in systolic (-16%), diastolic (-9%), mean arterial (-12%), and arterial pulse (-34%) pressures with complete recovery to control levels within 19 hours of dosing. A compensatory increase in heart rate (+49%) was observed. In addition, vosoritide caused time- and dose-dependent shortening of the PR (maximum -15%) and heart rate-corrected QTc [QTcB, using the Bazett correction (maximum -8%)] intervals, but did not affect QRS duration. No positive control drug was included in this study.

In another in vivo toxicology study (link), the sponsor reported that subcutaneous administration of vosoritide at 300 µg/kg caused an increase in heart rate (maximum +42%) in telemetered monkeys. Daily SC administration of vosoritide to cynomolgus monkeys for 28 days at 300 µg/kg resulted in a mean Cmax of 132ng/mL. The sponsor also indicated that administration of vosoritide at 300 µg/kg via SC injection had no effects on blood pressure and showed no ECG abnormalities.

4.1.2 Reviewer's assessment

The sponsor evaluated the effects of subcutaneous administrations of vosoritide (BMN111) on ECG parameters (PR, QRS, QT intervals) in conscious telemetered monkey. The Cmax (52.5 ng/mL) of the highest dose (200 µg/kg) of study BMN111-11-040 exceeded the therapeutic exposure level in humans (5.8 ng/ml). Vosoritide caused time- and dose- dependent shortening of the PR (maximum -15%) and heart rate-corrected QTc (maximum -8%) intervals. An individual rate-corrected QT (QTca) should be used for QT correction since this drug significantly increased the heart rate. In addition, there was no positive control in the study.

4.2 The hERG assay assessment

4.2.1 Sponsor's submission

The sponsor evaluated the effects of vosoritide (BMN111) on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The GLP hERG study report (Study ID:BMN-111-11-023, link) describes the potential effects of vosoritide on the hERG current in HEK293 cells.

The hERG current was assessed at near-physiological temperature, and was evoked by depolarizing the cell from -80 mV to +20 mV for 1 s, followed by a repolarizing ramp down to -80 mV (-0.5 V/s). The voltage waveform was repeated every 5 seconds. and the peak current was measured during ramp down voltage step. In the presence of test or positive control article, peak current was monitored until a new steady state emerged. One test article concentration was tested per cell, followed by E-4031 application to eliminate hERG current completely. The residual current was subtracted offline from the recorded current to isolate the hERG component for drug inhibition assessment. Solution samples were collected from the outflow of the perfusion apparatus for concentration verification analysis. There were negligible deviations (<10 % max difference) from the nominal concentrations. Hence nominal concentrations were used to describe drug effects.

Vosoritide at 50 µg/mL inhibited hERG current by (Mean ± SEM) 1.8 ± 1.2%. Testing was also attempted at concentrations of 300, 2500 and 5000 µg/mL. However, useable data could not be obtained at these concentrations due to disruption of the giga-ohm seal.

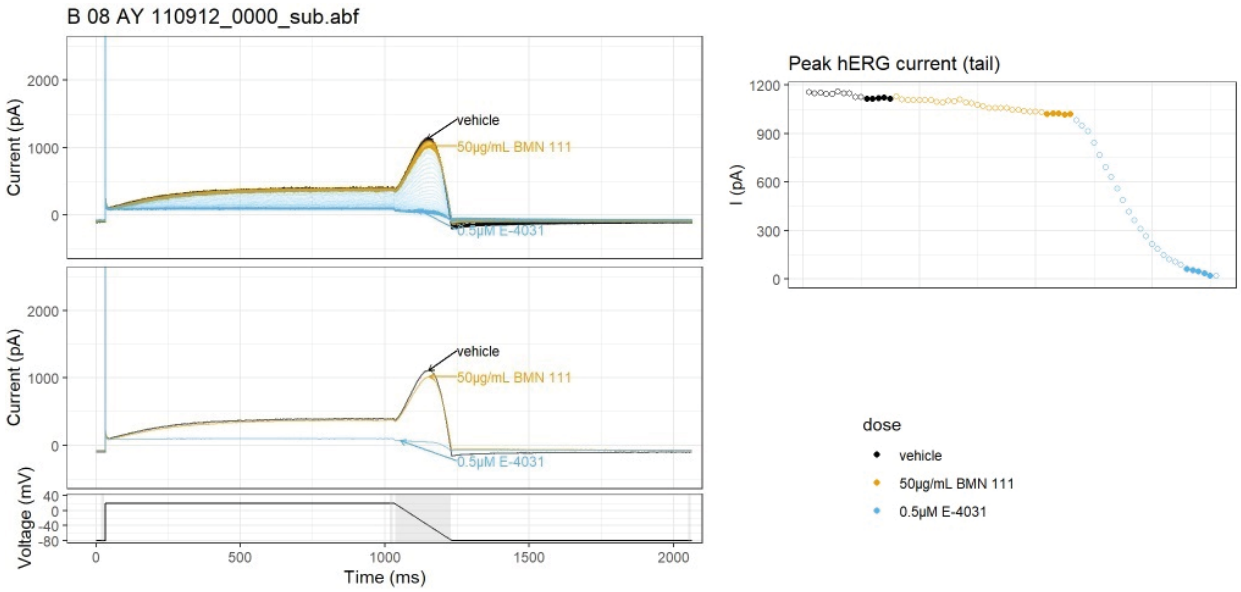
4.2.2 Reviewer's assessment and data reanalysis

Original electrophysiology records for hERG study were provided by the sponsor. We reanalyzed these records to assess data quality and verify study report conclusions. For data quality assessment, holding current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

The voltage protocols used and stimulation frequencies are quite similar to that recommended by the FDA (link), and the reviewer does not anticipate protocol differences to impact hERG current pharmacology.

Representative analysis from one cell of MSP-2017-1059 is shown in **Figure 1**. The top left panel shows all recorded traces from this cell; the middle panel, averaged traces for the last 5 recordings in control and in drug solutions; and the bottom left panel, voltage waveform used to evoke hERG current (shaded gray region highlights where peak hERG tail current was measured). Traces recorded in control solution are shown in black, following 0.3µM etripamil application in orange; and following application of E-4031, a selective hERG blocker, in blue. Time course plot of hERG current is shown on the right panel.

Figure 1: Representative hERG experiment from cell B 08 AY_11092_0000



HERG current amplitudes from the last 5 traces acquired in control (black solid circles) and in drug solutions were then averaged to calculate % inhibition by that concentration. E-4031 subtraction was not performed since the residual current was negligible. Drug concentration verification analysis showed that there were negligible deviations (<10 % max difference) from the nominal concentrations. Nominal concentration-inhibition were used to describe the drug pharmacology. Vosoritide at 50 µg/mL inhibited hERG current by (Mean ± SEM) 6.6 ± 1.4%.

While there are numerical differences in the results from FDA's independent analysis compared to the sponsor's, these do not change overall interpretation and conclusions. That is, FDA's independent analysis of the submitted electrophysiology data shows that vosoritide acutely inhibited hERG current by ~6% at 50 µg/mL. Thus, IC50 is far greater than 50 µg/mL and cannot be determined from this study. The Cmax (steady-state) of vosoritide at therapeutic dose was 5.8 ng/mL. The hERG safety margin of vosoritide is expected to be greater than 8620x.

Summary

In summary, the in vitro hERG assay met the best practices according to the new ICH S7B Q&As (link). The safety margin of vosoritide against hERG channel far exceeds 8620x. The results suggest that vosoritide does not acutely interact with hERG channels at the therapeutic exposure level. The observed PR and QTc shortenings in monkeys after SC administration of vosoritide may result from the increased heart rate.

5 Appendix II: Review of Supporting Clinical Data

5.1 ECG assessments

5.1.1 Overall

Review of the ECG waveforms submitted to the ECG warehouse showed that 11% (339 out of 2962) ECG waveforms were potentially digitized in study 111301. There were 21 (35%) and 31 (51%) subjects that have at least 1 digitized ECG in treatment and placebo arms, respectively. Without the original digital ECG waveforms, it cannot be determined whether the re-digitization process may have increased the variance in the QT, which would have reduced the power to detect a treatment effect (Stockbridge, N., J Electrocardiol 2005; 38, 319-20). Thus, while the rest of quality metrics looked overall acceptable, the potential impact of measures from potentially digitized ECG waveforms was also assessed in FDA sensitivity analyses.

5.1.2 QT Bias Assessment

QT bias assessment was conducted by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (vosoritide/placebo/overall) is presented for QTcF (Table 1). This analysis does not suggest the presence of significant negative treatment bias.

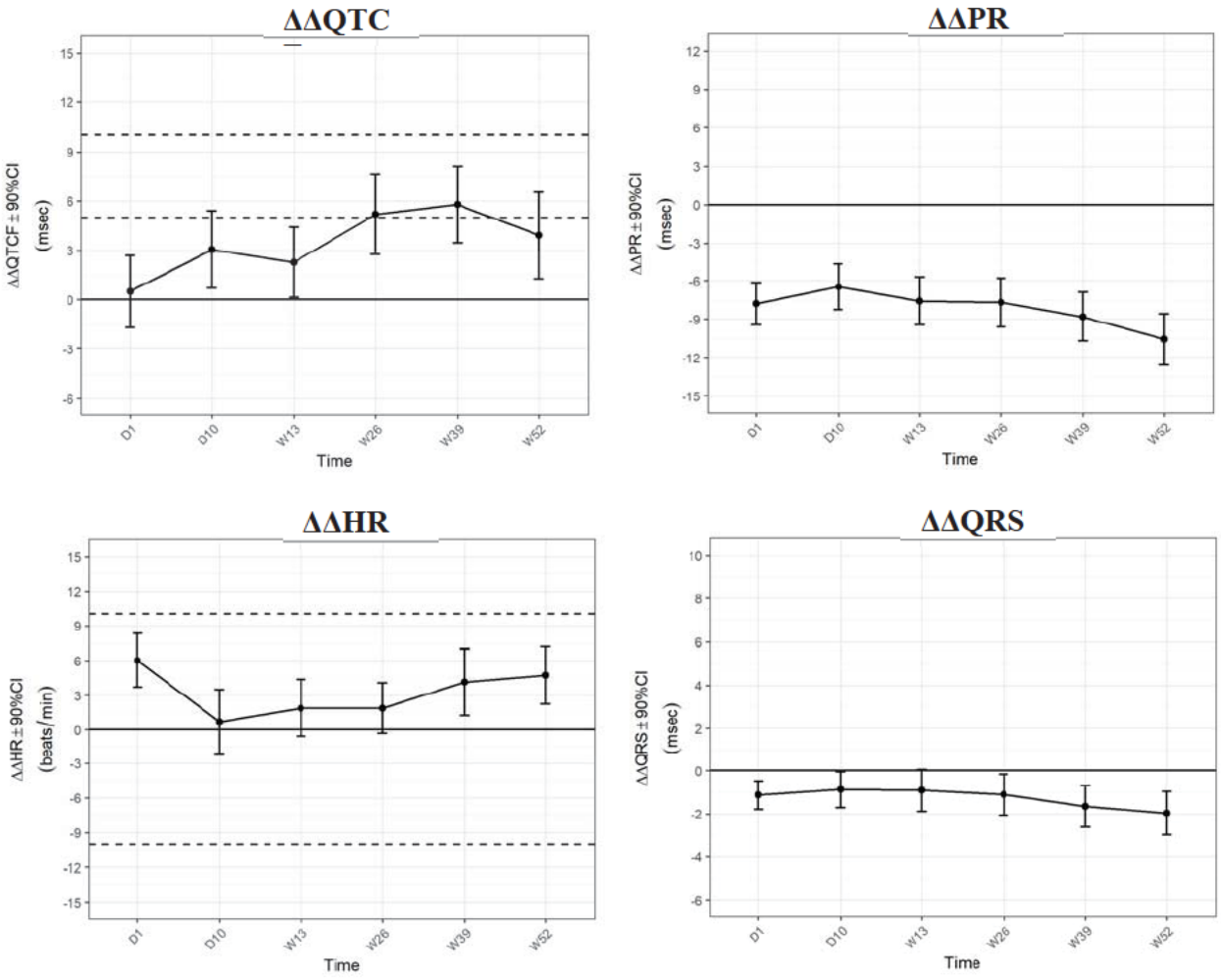
Table 1: QTcF bias assessment by treatment

Treatment	# of ECGs	mean (sd), msec	Slope [95% CI], msec per 100 msec
All	1972	-1.65 (8.77)	-5.3 [-7.37 to -3.23]
Vosoritide	1011	-1.55 (9.6)	-4.84 [-8 to -1.69]
Placebo	961	-1.76 (7.8)	-5.76 [-8.52 to -2.99]

5.2 By-Time Analysis

The statistical reviewer evaluated the ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS effect using descriptive statistics. Figure 2 displays the time profile of these four intervals. The by-time profiles do not suggest significant change of ECG parameters over time. Sensitivity analyses for QTcF excluding subjects with digitized ECG waveforms showed similar results and did not change interpretation of the overall study findings.

Figure 2: Mean and 90% CI Timecourses (unadjusted CIs).



5.3 Categorical analysis

No subjects experienced QTcF above 450 msec or ΔQTcF above 60 msec. No subjects experienced PR above 220 msec. No subjects experienced QRS above 120 msec.

Table 2 lists the categorical analysis results for HR (<100 beats/min and >100 beats/min). 65% subjects received test drug experienced HR above 100 bpm. Because the study subjects are children, the averaged HR is expected to be higher than adults.

Table 2: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Vosoritide 15 mcg/kg	60	352	21 (35.0%)	252 (71.6%)	39 (65.0%)	100 (28.4%)
Placebo	61	370	36 (59.0%)	312 (84.3%)	25 (41.0%)	58 (15.7%)

5.4 Exposure-Response Analysis

Exploratory exposure-response analysis was performed to assess the relationship between plasma concentration of vosoritide and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

An evaluation of the time-course of vosoritide concentration and changes in ΔΔQTcF is shown in **Figure 3**. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of vosoritide indicating no significant hysteresis.

Figure 3: Time course of vosoritide concentration (top) and QTc (bottom)

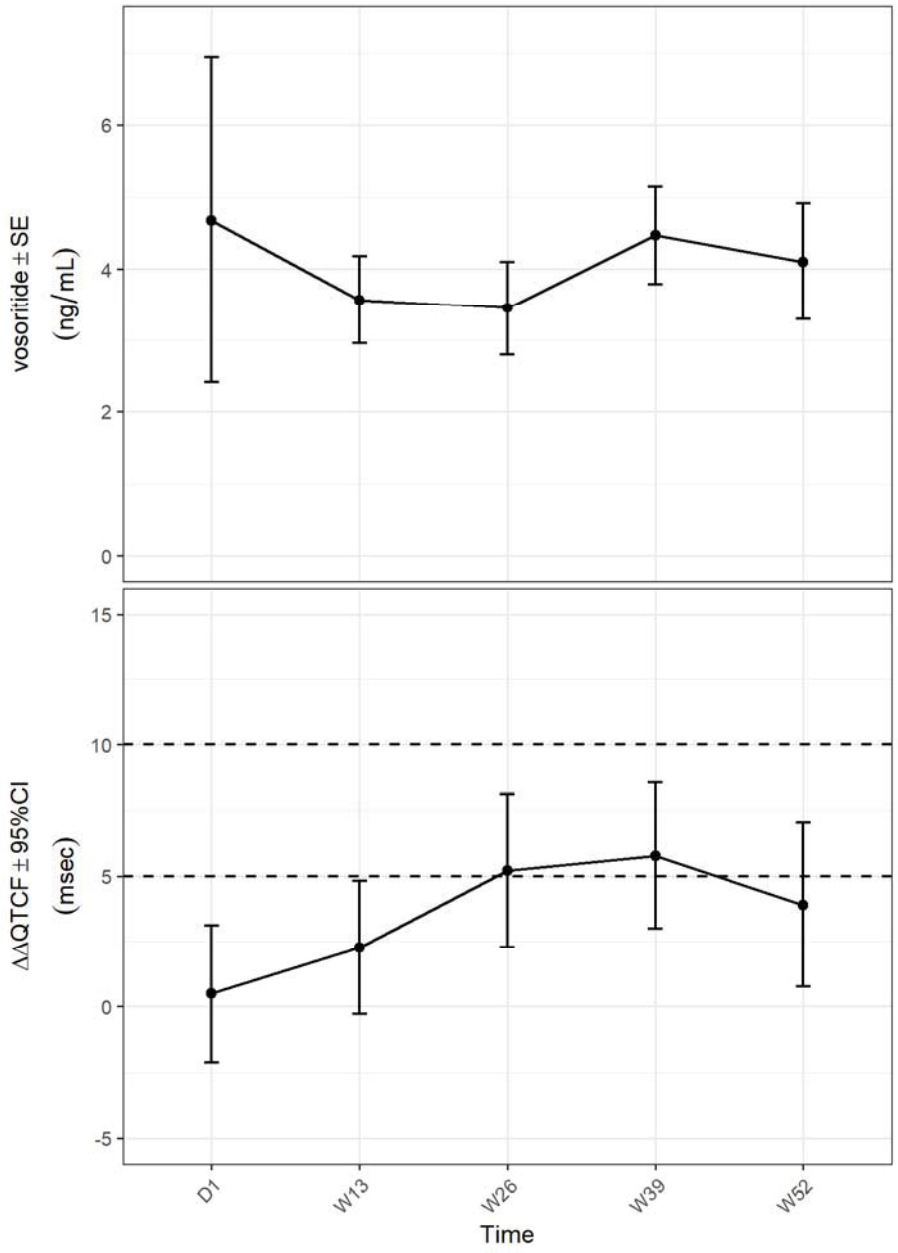
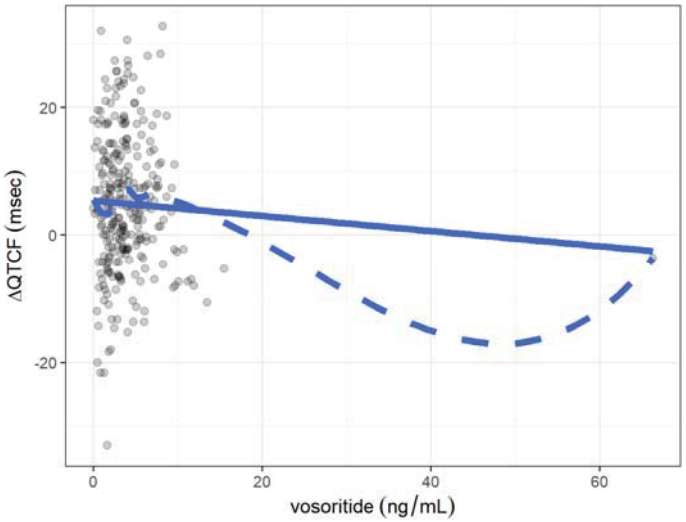


Figure 4 shows the relationship between vosoritide concentration and ΔQTc using a linear model.

Figure 4: Assessment of linearity of vosoritide concentration-QTc relationship



The linear model was applied to the data and the goodness-of-fit plot is shown in **Figure 5**. Predictions from the concentration-QTc model are provide in Table 3.

Figure 5: Goodness-of-fit plot for QTc

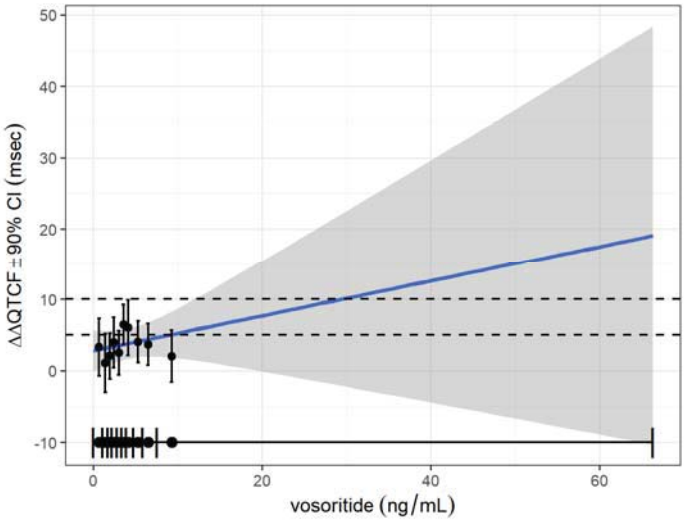


Table 3: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Vosoritide (15 µg/mL)	5.7	4.2	(1.9 to 6.5)

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.

/s/

GIRISH K BENDE
01/21/2021 10:35:34 AM

YU YI HSU
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DALONG HUANG
01/21/2021 12:58:59 PM

DONGLIN GUO
01/21/2021 01:00:00 PM

JOSE VICENTE RUIZ
01/21/2021 01:35:25 PM

CHRISTINE E GARNETT
01/21/2021 01:36:53 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	1/4/2021		
To:	Hamet Toure, FDA/OC/CDER/OPQ/OPRO/DRBPMI/RBPMB1		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	Other
From	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, MS, RAC, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, MS, RAC, Acting Director OPEQ/OHT3/DHT3C		
Subject	NDA 214938, Vosoritide (BMN 111) ICC2000721 Case 00026467		
Recommendation	**Filing Recommendation Date: 10/8/2020** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies		
	Mid-Cycle Recommendation Date: 1/4/2021 ☐ CDRH did not provide a Mid-Cycle Recommendation ☑ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 1/4/2021 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Digitally signed by Florencia T. Wilson -S Date: 2021.01.04 16:54:02 -05'00'		Rumi Young -S Digitally signed by Rumi Young -S Date: 2021.01.08 11:19:04 -05'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 214938
Sponsor	BioMarin Pharmaceutical, Inc.
Drug/Biologic	Vosoritide (BMN 111)
Indications for Use	Vosoritide, also known as BMN 111 Achondroplasia in patients (b) (4) whose epiphyses are not closed
Device Constituent	Co-Packaged Syringe
Related Files	

Important Dates	
Filing Meeting	10/8/2020
74-Day Letter	10/16/2020
Filing	10/19/2020
Internal Mid-cycle Meeting	1/7/2021
Midcycle Meeting/IRs due	
Mid-Cycle Communication to Bio-Marin	2/8/2021
Internal Late-Cycle Meeting/Wrap-up	4/12/2021
Final Lead Device Review Memo Due	4/20/2021
PDUFA Date	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐

CDRH does not have Post-Market Commitments or Requirements	☑

3. PURPOSE/BACKGROUND

3.1. Scope

BioMarin Pharmaceutical, Inc. is requesting approval of Vosoritide (BMN 111) . The device constituent of the combination product is a Co-Packaged Syringe.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

We request your review of NDA 214938. Please review device related data and information in sections 3.2P.7 and 3.2.R including user requirements, design control and verification, 510K clearance, biocompatibility, dose accuracy of administration syringe, biocompatibility, and risk management.

The assigned CDRH assessors will be invited to OPQ meetings and milestone dates will be communicated when the review timeline has been confirmed.

The deliverable/milestone items are the filing review and final review. We request your participation in the OPQ kick-off meeting, OPQ mid-cycle meeting, OPQ wrap-up meeting, and additional OPQ team meetings.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

☒ Device performance
☐ Biocompatibility of the patient contacting components
☐ Sterility
☒ Stability – device performance on stability
☒ Essential Performance Requirements (EPR) Control strategy
☒ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

N/A

3.2.1. Related Files

N/A

3.3. Indications for Use

Combination Product	Indications for Use
Vosoritide (BMN 111)	achondroplasia in patients [redacted] whose epiphyses are not closed. Dosage: - For injection: 0.4 mg, 0.56 mg, 1.2 mg, [redacted] lyophilized powder in a single-dose vial for reconstitution
Co-Packaged Syringe	**Delivery of the Drug Product**
PFS (1.5 mL syringe) (with sterile for water injection (sWFI) as diluent) • Syringe barrel – DMF [redacted] • Rubber stopper – DMF [redacted] • [redacted]	The PFS with sWFI to dilute the DP Diluent volume per dose: - 0.4 mg / 0.5 mL - 0.56 mg / 0.7 mL - 1.2 mg / 0.6 mL [redacted]
[redacted] Needle [redacted]	Diluent needle to be attached to the sWFI PFS for reconstitution
[redacted] syringe needle [redacted]	Delivery of drug product 1 mL [redacted] syringe with 30G [redacted] retractable needle [redacted]

(b) (4)

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	1, 3

0015	1

4. DEVICE DESCRIPTION

4.1. Device Description

The following are taken from Sequence 0001/1.14.1.1 Draft Carton and container Labels:

(b) (4)

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(b) (4)

4.2. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Administered by care-givers in non-clinical (home) settings in patients (b) (4) whose epiphyses have not closed (e.g., still have the potential to grow)
Injection Site	Subcutaneous (back of upper arm, thighs, abdomen [2 inches from belly button], buttocks)
Injection tissue and depth of injection	Subcutaneous tissue
Type of Use (e.g. single use, disposable, reusable, other)	Single use
Environments of use (e.g. home, clinic)	Home
Storage conditions and expiry	• in the refrigerator between 36°F to 46°F (2°C to 8°C) • may be stored (before mixing) at room temperature 68°F to 77°F (20°C to 25°C) for 90 days. • DP – 2 year shelf life • (b) (4) shelf life for sWFI PFS
Needle connection (e.g. luer, slip tip, staked)	Diluent needle - (b) (4) Administration needle – staked to the syringe, but after administration, the safety feature retracts the needle inside the syringe when the plunger is fully depressed
Syringe Volume	Dosage in vial / volume of sWFI PFS - 0.4 mg / 0.5 mL - 0.56 mg / 0.7 mL - 1.2 mg / 0.6 mL (b) (4)

Device materials including lubricant that are drug product contacting	(b) (4) glass, (b) (4) (b) (4) rubber

Additional Syringe Description/Requirements

Requirement	Reviewer Comment	
Hypodermic Needle: length, gauge, and configuration of the tip.	Diluent needle	Administration syringe/needle
	(b) (4) Needle – (b) (4)	1 mL (b) (4) syringe with 30G (b) (4) retractable needle (b) (4) (b) (4)
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	Administration Syringe: 1 mL (b) (4) syringe with 30G (b) (4) retractable needle (b) (4) (b) (4)	
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	N/A	
Safety Features (e.g. Needle safety component/device)	(b) (4) (b) (4) Syringe	
Automated Functions	N/A	
Sterilization method	(b) (4)	

*See Design Verification Section for verification of design requirements

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments
The Sponsor provided an adequate device description.
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ **Yes** ☑ **No**

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		x		
Device Constituent Labeling		x		
Letters of Authorization		x		
Essential Performance Requirements defined by the application Sponsor		x		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		x		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		x		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		x		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		x		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	x		
	Reliability			x
	Biocompatibility			x
	Sterility	x		
	Shelf Life, Aging and Transportation of EPRs	x		
Quality Systems/ Manufacturing Controls Check	Description of Quality Systems	x		
	Control Strategy provided for EPRs	x		

5.2. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☐ Yes ☐ No ☐ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☐ Post-Approval Inspection ☐ Routine Surveillance ☑ No Inspection Needed ☐ N/A
CDRH completed a review of the Quality Systems	☐ Yes ☐ No ☑ N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in Appendix B

5.3. Filing Recommendation

FILING REVIEW CONCLUSION
Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☑ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☑ No Inspection ☐ N/A **Site(s) needing inspection:**
Reviewer Comments The Sponsor provided adequate information, therefore, it is acceptable for filing. In addition, Facilities inspection and Quality Systems review are not applicable because the co-package combination product is not use for emergency.
Refuse to File Deficiencies: ☐ Yes ☐ No ☑ N/A **74-Day Letter Deficiencies:** ☐ Yes ☑ No ☐ N/A

☑ **No Additional Information Requests to add**

6. DEVICE PERFORMANCE REVIEW

6.1. Design Verification/Validation

6.1.1. Device Specification Standards and Guidance Documents

Syringe		**Data Adequate**		
		Yes	**No**	**N/A**
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☑	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☑	☐	☐
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☑
Needle/Sharps		**Data Adequate**		
		Yes	**No**	**N/A**
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☑	☐	☐
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☑	☐	☐
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☑	☐	☐
Luer Lock		**Data Adequate**		
		Yes	**No**	**N/A**

Connection	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications **(replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 2: Lock fittings	☑	☐	☐
Other		**Data Adequate**		
		Yes	**No**	**N/A**
[Other]	[Other]	☑	☐	☐

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3.2.R.2.5 Design Verification

For the PFS design verification on functional requirements has been performed considering the FDA draft Guidance "Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4. The performed tests are given in Table 3.2.R.2.5.1.

Table 3.2.R.2.5.1: Design Verification Tests for the sWFI PFS

Test	Test performed according to:	Results
Seal integrity test to assess dye ingress (container closure integrity)	(b) (4) Procedure (Blue dye Test)	Conforms
Seal integrity test to assess liquid leakage	ISO 594-2[1], 5.2	Conforms
Seal integrity test to assess air leakage	ISO 594-2[1] 5.3	Conforms
Gliding force	(b) (4) procedure	Conforms
Break-loose force	(b) (4) procedure	Conforms
Separation force	ISO 594-2[1], 5.4	Conforms
Ease of assembly	ISO 594-2[1], 5.6	Conforms
Stress cracking	ISO 594-2[1], 5.8	Conforms
Tip cap removal force	(b) (4) procedure	Conforms
Piston seal blowback (ability of syringe with tip cap to hold a certain pressure on the piston)	ISO 11040-4 6.5.3.3 Annex G.2 + H	Conforms

[1] valid at time of performance

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Table 3.2.P.5.1.1: Product Specification and Tests for Release

Test Parameter	Analytical Procedure	Specification
Extractable volume / Volume in container	Ph. Eur. 2.9.17 USP-NF <697> JP 6.05	(b) (4) mL [5] mL [6] mL [7]

[5] Acceptance criteria for the sWFI pre-filled syringe with (b) (4) mL filling volume
[6] Acceptance criteria for the sWFI pre-filled syringe with mL filling volume
[7] Acceptance criteria for the sWFI pre-filled syringe with mL filling volume

3.2.P.5.3.1 Release Test Methods

All release test methods used to test the sWFI pre-filled syringes are compendial methods described in the current European Pharmacopoeia (Ph. Eur.) or US Pharmacopoeia – National Formulary (USP-NF) or Japanese Pharmacopoeia (JP) with the exception of Container Closure Integrity and Break-loose / Glide Force testing. These tests are performed according to valid (b) (4) SOPs. The validation of the Container Closure Integrity and the Break-loose / Glide Force method is described below. Product-specific method suitability tests have only been carried out for the sterility test as well as the bacterial endotoxin test. Suitability of these tests has been completed and all acceptance criteria have been met.

(b) (4)

(b) (4)

Diluent Needle and Diluent Syringe design Verification testing of after distribution cycle 13 per ASTM D4169-16:

6 Tested Performance Requirements

Table 6.1: Tested Performance Requirements

Requirement	Source of Requirement	Report Section
Diluent Syringe cap removal	DVVP-240000	9.2
Rigid Needle Shield (RNS) removal force	DVVP-240000	9.3
Injection force not to exceed (b) (4)	DIR	9.4
Luer Compatibility per ISO-80369-7	DIR	9.4
Safety feature actuation	DIR	9.5

Sample Size and Justification

7.1 The 0.7mL SKU 2 sWFI Diluent Syringe was chosen for this report as it represents the largest injection volume. This is considered worst-case because it has the largest plunger rod throw distance.

- *BioMarin Item Number: P71906*

- *Lot Number: BKSJ43AB*
- *Expiration Date: 10/2024*

7.2 The 23Gx1" Diluent Needle was also used in this report

- (b) (4)
- *Lot Number:* (b) (4)
- *Expiration Date: 2024-04-28*

7.3 Testing was performed using samples that passed ASTM D4169-16 testing, using distribution cycle 13.
7.4 The sample sizes were determined using a risk base approach to determine the confidence and reliability levels. ***Table 7.1-7.3*** *indicates the minimum sample size to achieve the confidence and reliability levels for attribute data, per ISO 16269-6.*

Table 7.1: Diluent Needle Samples Size

Study Description	Sample Size	Confidence	Reliability
RNS Removal Force	22	90%	90
Safety Device Actuation	59	95%	95

Table 7.2: Diluent Syringe Samples Size

Study Description	Sample Size	Confidence	Reliability
Cap Removal	22	90%	90

Table 7.3: Diluent Needle attached to Diluent Syringe Samples Size

Study Description	Sample Size	Confidence	Reliability
Injection Force	22	90%	90
Luer Compatibility	22	90%	90

Table 10.1: Functional Performance Results

Tested Device	**Diluent Needle**		**Diluent Syringe**	**Assembled Diluent Syringe and Needle**	
Attribute	RNS Removal Force (N)	Safety Device Actuation	Cap Removal	Injection Force (N)	Luer Compatibility (No leakage observed)
Sample Size	22	59	22	22	22
Maximum Value	7.18 N	N/A	N/A	10.4 N	N/A
Minimum Value	4.31 N	N/A	N/A	5.4 N	N/A
Acceptance Criteria	RNS removal forces between (b) (4)	Safety feature actuates after injection	Able to remove syringe cap by hand	Less than or equal to (b) (4)	No leakage observed
Acceptance Criteria Met (Pass/Fail)	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

Diluent Needle performance

The RNS Removal test was performed at a rate of 10 mm/min. The highest recorded force was 7.18 N and the lowest force value was 4.31 N, meeting the acceptance criteria of RNS removal forces being between (b) (4)

The Safety Device Actuation test was performed at a rate of 150 mm/min. The safety device actuated after every injection; meeting the acceptance criteria of the safety feature actuating after injection.

Assembled Diluent Syringe and Needle performance

The Injection Force test was performed at a rate of 150 mm/min which is faster than ISO 7886-1:1993 standard rate of 100 mm/min ± 5 mm/min. Performing the test at a rate of 150 mm/min is a more conservative method to determine injection force because the higher injection rate produces a greater break loose force which is the highest force observed during injection.

The highest injection force value observed was 10.4 N. All samples achieved the acceptance criteria of injection forces being less than or equal to (b) (4)

All samples achieved the acceptance criteria of no leakage observed between the assembled Diluent Syringe and Needle.

Conclusion
The results verify the Diluent Syringe and Diluent Needle meet applicable design input requirements.
Diluent Needle
22 samples passed RNS removal testing to meet 90/90 confidence and reliability.
59 samples passed safety device actuation testing to meet 95/95 confidence and reliability.
Diluent Syringe
22 samples passed syringe cap removal testing to meet 90/90 confidence and reliability.
Assembled Diluent Syringe and Needle
22 samples passed injection force testing to meet 90/90 confidence and reliability. IR sent, see Reviewer comment below and Section 6.2
22 samples passed luer compatibility testing to meet 90/90 confidence and reliability.
Number: DVTR-240004 Version: 1.0 Status: Approved Date: 12 Jun 2020 dvtr-240004.pdf - Page 17

Administration Syringe Design Verification testing of after distribution cycle 13 per ASTM D4169-16:

Table 6.1: Tested Performance Requirements

Requirement	Source of Requirement	Report Section
Rigid Needle Shield (RNS) removal force	DVVP-240000	9.2
The dose indicator text to be readable 40.64 cm (16 inches) from aided eye (per HE75:2009/(R)2018)	DIR	9.3
Injection force not to exceed (b) (4)	DIR	9.3
Safety feature actuation	DIR	9.3

7.3 The sample sizes were determined using a risk base approach to determine the confidence and reliability levels. **Table 7.1** indicates the minimum sample size to achieve the confidence and reliability levels for attribute data, per ISO 16269-6.

Table 7.1: Administration Syringe Sample Size

Study Description	Sample Size	Confidence	Reliability
RNS Removal Force	22	90%	90
Dose Text Legibility	22	90%	90
Injection Force	22	90%	90
Safety Device Actuation	59	95%	95

10 Results and Discussion

The testing was performed by [redacted] (b) (6) on April 28, 2020 in lab [redacted] (b) (4) Digital Dr., Novato, CA 94949 following good laboratory practices (GLP).

The procedure established per approved protocol was followed during the execution of this testing. Data was recorded in attached documents SPDC-247892, BMN111 Admin Syringe Inj Force Verification Data 04282020 and BMN111 Admin RNS Removal Verification Data 04282020 and summarized in **Table 10.1** below.

Table 10.1: Functional Performance Results

Attribute	Sample Size	Maximum Value (N)	Minimum Value (N)	Acceptance Criteria	Acceptance Criteria Met (Pass/Fail)
RNS Removal Force	22	9.9	5.58	RNS removal forces between [redacted] (b) (4)	**Pass**
Dose Text Legibility	22	N/A	N/A	Dose indicator text readable [redacted] (b) (4)	**Pass**
Injection Force	22	5.8	2.8	Less than or equal to [redacted] (b) (4)	**Pass**
Safety Device Actuation	59	N/A	N/A	Safety feature actuates after injection	**Pass**

Administration Syringe RNS Removal Performance
The RNS Removal test was performed at a rate of 10 mm/min. The highest recorded force was 9.9 N and the lowest force value was 5.58N, meeting acceptance criteria of RNS removal forces being between [redacted] (b) (4)

Administration Syringe Injection, Safety Actuation Performance, and Dose Indicator Text Legibility

The Injection Force and Safety Actuation Force test was performed at a rate of 150 mm/min which is faster than ISO 7886-1:1993 standard rate of 100 mm/min ± 5 mm/min. Performing the test at a rate of 150 mm/min is a more conservative method to determine maximum injection force because the higher injection rate produces a greater break loose force which is the highest observed force.
The highest injection force value observed was 5.8 N. All samples achieved the acceptance criteria of injection forces being less than or equal to (b) (4)

The safety device actuated after every injection; meeting acceptance criteria of safety feature actuates after injection.
The dose indicator text was readable 40.64 cm from naked eye which meets acceptable text design per human factors guidance, HE75:2009/(R)2018.

Conclusion
The results verify the Administration Syringe meets applicable design input requirements.

22 samples passed RNS removal testing to meet 90/90 confidence and reliability.
22 samples passed injection force testing to meet 90/90 confidence and reliability. IR sent, see Reviewer comment below and Section 6.2
22 samples passed dose text legibility verification to meet 90/90 confidence and reliability.
59 samples passed safety device actuation testing to meet 95/95 confidence and reliability.

Materials
5.1 BMN 111 vials
- *Qty: 16*
- *2 year real-time aged*
  - *The vials and stoppers have been real-time aged for 2 years 7 months. This is considered worst case for the elastomeric stoppers. Elastomeric materials become more brittle as they age. The shelf life of the drug product (DP) is labelled for 2 years, testing vial stoppers that are aged greater than 2 years ensures the needle is compatible with the stopper throughout the life of the DP.*
- *Material Number:* (b) (4)
- *Lot Number: BOQI02A1*
- *Manufacture Date: October 2nd, 2017*

5.2 Administration Syringes and Diluent needle

- *Qty: 48*

Table 8.1: Vial Fragmentation Results

Samples	Particles observed (Yes/No)	Number of fragments observed per sample	Total number of fragments observed	Acceptance Criteria Met - [redacted] visible fragments (Pass/Fail)
1	No	0	0	Pass
2	No	0	0	Pass
3	No	0	0	Pass
4	No	0	0	Pass
5	No	0	0	Pass
6	No	0	0	Pass
7	No	0	0	Pass
8	No	0	0	Pass
9	No	0	0	Pass
10	No	0	0	Pass
11	No	0	0	Pass
12	No	0	0	Pass
13	No	0	0	Pass
14	No	0	0	Pass
15	No	0	0	Pass
16	Yes	0	0	Pass

All needles were able to fully pierce through the vial stoppers and no needles were observed to be blunted during testing.

No fragments were observed which meets acceptance criteria of less than [redacted] fragments observed with the naked eye for 48 piercings.

Table 8.1: Vial Fragmentation Results

Samples	Particles observed (Yes/No)	Number of fragments observed per sample	Total number of fragments observed	Acceptance Criteria Met - [redacted] visible fragments (Pass/Fail)
1	No	0	0	Pass
2	No	0	0	Pass
3	No	0	0	Pass
4	No	0	0	Pass
5	No	0	0	Pass
6	No	0	0	Pass
7	No	0	0	Pass
8	No	0	0	Pass
9	No	0	0	Pass
10	No	0	0	Pass
11	No	0	0	Pass
12	No	0	0	Pass
13	No	0	0	Pass
14	No	0	0	Pass
15	No	0	0	Pass
16	Yes	2	2	Pass

All needles were able to fully pierce through the vial stoppers and no needles were observed to be blunted during testing.

Two dark fragments were observed for Sample #16. These 2 fragments were the only visible particles for all 16 vials, which met acceptance criteria of less than [redacted] fragments observed with the naked eye for 48 piercings.

Table 3.2.P.5.4.4: Results of Release Testing BioMarin's sWFI pre-filled syringes [redacted] fill volume each in 1.5 mL syringe format) used as diluent for lyophilized vosoritide DP

Batch No.			VOTD18A[5]	VOTD18B[5]	VOSI35	VOSJ43
Syringe Format			1.5 mL	1.5 mL	1.5 mL	1.5 mL
Fill Volume			[redacted]			
Test	Results	Specification	Results	Results	Results	Results
Extractable Volume/ Volume in Container	Ph. Eur. 2.9.17 USP-NF <697> JP 6.05	[redacted] (1.5 ml presentation) (1.5 ml presentation) (1.5 ml presentation)	0.50 mL		0.594 mL	0.705 mL

CCIT (Blue Dye)[6]	[redacted] SOP	pass	conforms		N/A[7]	N/A[7]
Break Loose and Glide Force[6]	[redacted] SOP, ISO 11608-3:2000(E)	max. break-loose force [redacted] mean glide force [redacted]	4.35 N 1.08 N	3.84 N 1.49 N	N/A[7]	N/A[7]

1 Equivalent to the Ph. Eur.
2 According to monograph for ´Sterile Water for Injection`
3 According to monograph `Sterilized water for injections'
4 According to monograph for `Sterile Water for Injection in Containers`
5 Validation batch conducted for extension of the sWFI pre-filled syringe bracketing approach by introducing a BMRN-specific filling volume
6 CCIT and Break Loose and Glide Force testing were performed for release testing of the validation batch only. They are not part of the regular release testing of sWFI pre-filled syringes
7 N/A = Not Applicable as these tests are not part of regular release testing.
8 Acceptance criteria wa [redacted] mL at the time of validation. Commercial lots will be tested to the acceptance criteria of [redacted] mL.

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy – sWFI – (extractable volume/volume in container) - 0.4 mg / 0.5 mL - 0.56 mg / 0.7 mL - 1.2 mg / 0.6 mL - [redacted]	[redacted]	Ph. Eur. 2.9.17 USP-NF <697> JP 6.05 [redacted] SOP	Y The target extractable volume (TEV) or reconstitution volume for 0.56 mg/vial 1.2 mg/vial [redacted] DP strengths are 0.70 mL, 0.60 mL, [redacted] respectively; these volumes are within [redacted] bracketed platform ranges.	Y	Y
Break loose Force (sWFI)		[redacted] SOP	[redacted]	Y	Y
Glide Force (sWFI)		[redacted] SOP	[redacted]	Y	Y
Seal integrity test to assess dye ingress (container closure integrity)		[redacted] Procedure (Blue dye test)	[redacted]	Y	Y

Piston seal blow back for the sWFI PFS	(b) (4)	ISO 11040-4 6.5.3.3 Annex G.2 + H	(b) (4)	Y	Y
Device Sections Overview					
	Specification	**Method Acceptable (Y/N)**	**Results/ Deviations**	Adequate	
				Yes	No
Dose Accuracy (Administration Syringe) n=22 (variable testing analysis)	(b) (4)	DVTR-240003	No deviation	X	
Injection force (Administration Syringe) post transport n=59 (attribute testing for the reconstituted DP) n=22 (variable testing analysis with sWFI only)		DVTR-240004(sWFI) DVTR-240005(DP)	No deviation	X	
Rigid Needle Shield (RNS) removal force)		DVVP-240000	No deviation	X	
Safety Device Actuation N=59		(b) (4) (n=500) (b) (4) Certificate of Analysis provided for both clearance DVTR-240004(sWFI) – diluent needle DVTR-240005(DP) – administration syringe	No deviation	X	
Luer compatibility		DIR ISO 80369-7	No deviation	X	
Fragmentation test		Y ISO 8871-5	No deviation	X	
Cap Removal Force of diluent syringe		Y DVTR-240004(sWFI)	PASS No deviation	X	

Reviewer Comment

The Sponsor used a bracketing approach for sWFI PFS. The manufacturer's (b) (4) experience with sWFI and the validation data available for 1.5 mL (b) (4) syringe format (note that the 1.5 mL is the only validation data used for the DP) were utilized by the Sponsor. The Sponsor's specification for the sWFI PFS fill volumes of (b) (4) mL and (b) (4) mL fall within (b) (4) validation data. However, the fill volume of (b) (4) mL is a little lower than (b) (4) mL validated range. Therefore, the Sponsor provided supplemental validation batch (VOTD18) with a target fill volume of (b) (4) mL. Although the Sponsor added a supplemental validation batch for the lower fill volume, it is still acceptable for the Sponsor to leverage (b) (4) mL fill volume because of its history. Since the minimum extractable volume of the Sponsor (b) (4) mL diluent is slightly lower ((b) (4) mL difference), it was therefore concluded that (b) (4). With (b) (4) validation and supplemental validation performed by the Sponsor the results demonstrated that the extractable volume met the pre-defined acceptance criteria for the 2 DP concentration of either 0.8 mg/mL or 2 mg/mL post-reconstitution that are applicable to the (b) (4) dosages/strength presentation of the DP (0.4 mg/vial, 0.56 mg/vial, 1.2 mg/vial (b) (4)). Despite (b) (4) validation data for the sWFI, in order to fulfill the Design Control requirements per 21 CFR 820.30, the Sponsor performed verification testing to ensure that (b) (4) WFI PFS functions adequately with the components in the co-package combination product such as compatibility with luer connections (e.g., sWFI PFS with the diluent needle). The design verification is in Table 3.2.R.2.5.1 above.
It is noted:

- extractable volume/volume in container is part of regular release testing and stability
- container closure integrity test (Dye Leak Test), is not part of regular release testing, but part of stability and release testing was done in the validation batches only
- BL/GF are not part of regular release testing and release testing was done in the validation batches only
- The Sponsor also performed other functional performance test (e.g., luer compatibility [sWFI + diluent needle]) with 90% confidence and 90% confidence in which the methodologies are FDA recognized.
- The focused of this review is to ensure that the essential performance requirements (dose accuracy, BL/GF, injection force, needle safety feature) meet a 95% confidence and 95% reliability.

Dose Accuracy: acceptable

- The Sponsor provided validation testing for the fill volume for the sWFI PFS to ensure that an appropriate amount is extruded in the DP vial for reconstitution. In addition to the above testing, a withdrawal volume assessment was also performed to evaluate that the fill volumes (per USP <697>) are adequate to withdraw the label claim volumes (3.2.P.2.2.1.6)
- *The test method is performed according to the current Ph. Eur., the current USP-NF and the current JP as described in the ICH Q4B Annex 2 harmonized Tripartite Guideline 'Test for Extractable Volume of Parenteral Preparations General Chapter'.*
- A Dose accuracy verification with the 510(k) cleared syringe (b) (4) was also performed, please note that the administration syringe is a 1 mL (b) (4) syringe with graduation appropriate for the various weight base dosing of the reconstituted DP. It is noted that the Sponsor only performed attribute testing with a sample size of n=22. This is not acceptable. An IR is sent to the Sponsor on 11/16/2020.
- On 12/17/2020, the Sponsor provided a response, in which the Sponsor analyzed the data as variable with the appropriate graphical summary and sample size justification. Please see section 6.2 for the complete response information.
- the provided data is acceptable

Break loose / Glide Force (BL/GF) for the sWFI: acceptable

- sWFI per (b) (4)

- the Sponsor provided a comparison of BL/GF with an empty syringe and PFS with sWFI, the results are comparable and met specifications of max. breakloose forc (b) (4) and mean glide force (b) (4)
- the provided data is acceptable

Injection Force with the reconstituted drug product (DP) (not to exceed (b) (4): acceptable

- Design input Requirement (DIR) that demonstrate that when reconstituted DP is administered to the patient that it does not exceed (b) (4) The defined specification of (b) (4) is acceptable
- N=22 not acceptable, the sample size is not adequate for attribute testing because, the Agency typically requires a 95% confidence and 95% reliability with PFS. An IR will be sent to the Sponsor for Mid-Cycle.
- The IR response was received on 12/17/2020, in the response, the Sponsor performed an attribute testing with n=59. All samples met the acceptable criteria. Therefore, the response if acceptable.

Needle Safety feature: acceptable

- n=59 is acceptable, for needle Safety feature per the FDA Guidance, " Supplementary Guidance on Premarket Notifications for Medical Devices with Sharps Injury Prevention Features", https://www.fda.gov/media/71142/download
- it is noted that MAUDE search was also performed to cross reference any device issues with the 510(k) cleared devices used in this application
- (b) (4) clearance provided a simulated use study for the safety feature with 500 sample size. The sponsor performed attribute testing with a sample size of n=59 (DVTR-240004 report) and the 510(k) clearance simulated use testing is adequate to support the needle safety feature of the diluent needle. Therefore, it is acceptable.
- (b) (4) clearance predates the simulated used testing for the needle safety feature, therefore, this syringe did not have any simulated use testing for the safety feature with 500 sample size. However, a MAUDE search was performed to ensure that the syringe in this application is safe and effective.
  - Based on the search criteria below (Product Code: (b) (4) Report date: 11/1/2010 – 1/4/2021), there are only 6 reports related to the specific syringe ((b) (4)) being used in this application. The focus of the MAUDE search is if there are needles being left in the patient's tissue. It is noted that none of the reports pertains to needle being left in the patient.
  - The Sponsor also performed Safety Actuation Performance with the reconstituted DP and the syringe and there are no deviation reported in the n=59 sample size per DVTR-240005 report
  - Therefore, since there are no major issues with this model, I do not have any issues with the syringe not having the simulated use testing for the safety feature from its clearance.
- There are no recalls found with the 510(k) cleared devices included in this application

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(b) (4)

Reviewer Comments

The stability data for the sWFI performed by (b) (4) for up to (b) (4) months are leveraged by the Sponsor for the lots in the table above (Table 3.2.P.8.3.1). With (b) (4) platform and its history of providing sWFI with other approved drug, the provided data from is adequate to demonstrate that the sWFI extractable volume needed to dilute the DP at the end of shelf life meets the specified volume.
The dose accuracy and injection force evaluation is adequate per DVTR-240003, DVTR-240004, DVTR-240005

6.1.4. Biocompatibility Evaluation

☐ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]
☑ Biocompatibility was not evaluated **because**: the sWFI is under the purview of CDER and the 510(k) cleared device's biocompatibility has been evaluated with its clearance. In addition, the 510(k) cleared devices are being used as intended.

6.1.5. Sterility Evaluation

☑ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)
☐ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

☑ The Syringe is 510(k) Cleared
☐ The Syringe **is NOT 510(k) Cleared**

510(k) Number: (b) (4) (diluent needle), (b) (4) (administration syringe)			
	Yes	No	N/A
Contact classification of proposed device consistent with cleared 510(k) [if not, please evaluate the following]:	X		
If device is sterilized with EO, review acceptability of EO and ECH **residuals** (gamma for both 510(k) device)			X
Ensure endotoxin limits are consistent with proposed administration route	X		

Reviewer Comments

The diluent needle and administration syringe are 510(k) cleared devices that are co-package with the combination product. The co-package is not being re-sterilized and the intended use is the same. Therefore, the provided information in the 510(k) is adequate.

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The validation and verification testing provided are adequate, however, the sample size use for the attribute testing is not adequate. Information Request is requested.		
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 11/16/2020	**Date/Sequence Received:** 12/11/2020
Information Request #1	You provided verification testing for the functional performance for dose accuracy (DVTR-240003) and injection force for the assembled diluent needle and sWFI PFS (DVTR-240004) and reconstituted administration syringe (DVTR-240005), You performed attribute testing with the sample size n=22 for the dose accuracy and injection force. The functions tested are critical elements of the devices in the co-package combination product. The Agency typically accepts 95% confidence and 95% reliability to ensure that these essential performance function as intended. Therefore, the provided attribute testing with n=22 is not acceptable. Provide the following: • Dose Accuracy – provide attribute testing with a 95% confidence and 95% reliability (e.g. sample size, n=59) • Injection force – provide attribute testing for assembled (a)diluent syringe and sWFI PFS and (b)administration syringe (with the reconstituted drug product or representative fluid) with a 95% confidence and 95% reliability for each (a and b) • Alternatively, analyze your data as variable with graphical summary with sample size justification	
Sponsor Response	*In this response, additional administration syringe injection force testing data (n=59) are provided. Further, as suggested by the Agency, for administration syringe dose accuracy and assembled diluent needle and sWFI PFS injection force, data has been analyzed as variable with graphical summary with sample size justification. K-factor analyses performed per the appropriate ISO standards (ISO-16269-6, Statistical interpretation of data- Part 6: Determination of the Statistical Tolerance Intervals) demonstrate 95% confidence and 95% reliability.* ***Injection Force - Administration Syringe*** *As requested by the Agency, BioMarin is providing additional data in accordance with 95% confidence and 95% reliability for the administration syringe injection force attribute testing. The additional data demonstrate that the administration syringe achieved the injection force requirement with a 95% confidence and 95% reliability.* *In administration syringe design verification report (DVTR-240005), injection force and needle safety feature actuation were tested in conjunction since the syringe's plunger must be completely depressed to activate the safety mechanism. The needle retraction safety mechanism was tested at 95/95% confidence/reliability due to higher risk to patients per the*	

internal risk assessment. Testing was done with 59 reconstituted drug product samples for both injection force and needle retraction safety mechanism. However, only results for the first 22 samples were provided as required for the 90/90% confidence/reliability as specified in ISO-16269-6, Statistical interpretation of data- Part 6: Determination of the Statistical
Tolerance Intervals.
Table 1 summarizes the complete data set of all 59 samples testing the administration syringe injection force. The injection force for all 59 samples measured well below the N acceptance criteria with an average of 3.9 N and a standard deviation of 0.65. The administration syringe achieved the injection force requirement with 95/95% confidence/reliability. (b) (4)

Table 1: Administration Syringe Injection Force for 59 Samples

Sample #	Injection Force (N) (b) (4)	Acceptance Criteria (b) (4) (Pass/Fail)	Sample #	Injection Force (N) (b) (4)	Acceptance Criteria (b) (4) (Pass/Fail)
1		Pass	31		Pass
2		Pass	32		Pass
3		Pass	33		Pass
4		Pass	34		Pass
5		Pass	35		Pass
6		Pass	36		Pass
7		Pass	37		Pass
8		Pass	38		Pass
9		Pass	39		Pass
10		Pass	40		Pass
11		Pass	41		Pass
12		Pass	42		Pass
13		Pass	43		Pass
14		Pass	44		Pass
15		Pass	45		Pass
16		Pass	46		Pass
17		Pass	47		Pass
18		Pass	48		Pass
19		Pass	49		Pass
20		Pass	50		Pass
21		Pass	51		Pass
22		Pass	52		Pass

Sample #	Injection Force (N) (b) (4)	Acceptance Criteria (b) (4) (Pass/Fail)	Sample #	Injection Force (N) (b) (4)	Acceptance Criteria (b) (4) (Pass/Fail)
23		Pass	53		Pass
24		Pass	54		Pass
25		Pass	55		Pass
26		Pass	56		Pass
27		Pass	57		Pass
28		Pass	58		Pass
29		Pass	59		Pass
30		Pass			
Average (n=59)	3.9				
Standard Deviation (std)	0.65				

Administration Syringe Dose Accuracy – k-factor Analysis

(b) (4)

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(b) (4)

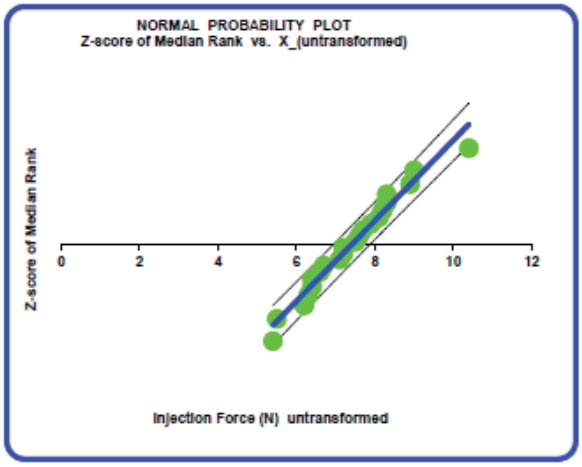
Assembled Diluent Needle and sWFI PFS Injection Force – k-factor Analysis
To demonstrate acceptable injection force for the assembled diluent syringe, BioMarin analyzed the data as variable with a graphical summary and sample size justification, as

requested by the Agency. BioMarin performed k-factor analysis and demonstrated that the assembled diluent needle and sWFI PFS achieved the 95/95% confidence/reliability tolerance interval for injection force acceptance criteria (b) (4)
The data measured for injection force were considered variable and tested for normality. The data set was proven to be normal by Anderson-Darling's A2 Test for Normality with results provided in Table 5 below. The injection force data set plotted suggest normality is provided in Figure 5.

Table 5: Results for Diluent Syringe Injection Force Test for Normality

Attribute	Test Result	Approximate p-value
Injection Force	NOT statistically significant from Normality	0.8694

Figure 5: Normal Distribution Testing for Assembled Diluent Syringe Injection Force



Twenty-two (22) assembled diluent needle and sWFI PFS were tested to measure injection force and their results are summarized in Table 6 below.

Table 6: Assembled Diluent Needle and sWFI PFS Injection Force Testing Results

Sample #	Injection Force (N) (b) (4)	Acceptance Criteria (Pass/Fail) (b) (4)
1		Pass
2		Pass
3		Pass
4		Pass
5		Pass
6		Pass
7		Pass
8		Pass
9		Pass
10		Pass
11		Pass
12		Pass
13		Pass
14		Pass
15		Pass
16		Pass
17		Pass
18		Pass
19		Pass
20		Pass
21		Pass
22		Pass
Average (x)	7.40	
Standard Deviation (std)	1.205	
k-factor[1]	2.349	
Upper 95/95 Tolerance Limit x+k*std	10.24	
Acceptance Criteria	(b) (4)	

[1] k-factor for one-side tolerance interval per ISO 16269-6.

The calculated tolerance interval by k-factor analysis is 10.24 N and less than the injection force acceptance criteria of (b) (4) *Therefore, the assembled diluent needle and sWFI PFS achieves 95/95% confidence/reliability for injection force as demonstrated in Figure 6.*

Figure 6: Assembled Diluent Syringe Injection Force Results

(b) (4)

Reviewer Comments	The Sponsor provided the following: • Injection force: o (a) of the diluent sWFI, the Sponsor re-analyzed the data (n=22) as variable and tested for normality (see Table 5 and Figure 5 above) o (b) of the administration syringe testing with a sample size of n=59 which met the 95% confidence and 95% reliability. There is no deviation reported. (b) (4) The provided response is adequate.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

7. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

(b) (4)

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	sWFI PFS: Minimum extractable volume (MEV) (b) (4) mL [5] mL [6] mL [7] [5] Acceptance criteria for the sWFI pre-filled syringe with (b) (4) mL filling volume [6] Acceptance criteria for the sWFI pre-filled syringe with mL filling volume [7] Acceptance criteria for the sWFI pre-filled syringe with mL filling volume • Ph. Eur. 2.9.17 • USP-NF <697> • (b) (4) SOP	Y
	Administration Syringe: (b) (4) target volume is (b) (4) mL (b) (4) target volume is (b) (4) mL. • DVTR-240003 • The 510(k) cleared (b) (4) syringe are graduated, hence, this graduation is able to control the dose accuracy	
Break loose Force	(b) (4) N • (b) (4) SOP	Y
Glide Force	glide force (b) (4) N • (b) (4) SOP	Y
Injection Force	(b) (4) N DVTR-240004(sWFI) – injection force during reconstitution • DVTR-240005(DP) – injection force for administration	Y
Cap Removal Force	DVTR-240004(sWFI)	Y
Safety Device Actuation	(b) (4) (n=500) simulated use testing for safety feature • DVTR-240004(sWFI) with diluent needle (b) (4) (pre-guidance) • DVTR-240005 with administration syringe • MAUDE search performed did not yield significant issues with safety feature and there are no recalls	Y

Reviewer Comments
The provided control strategy is adequate to ensure that the combination product meets its EPRs.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

7.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The provided control strategy is adequate to ensure that the combination product meets its EPRs.		
CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

8.2. Mid-Cycle Information Requests

8.3. Interactive Information Requests

8.3.1. Interactive Information Requests sent on 11/16/2020

9. APPENDIX B: FACILITIES & QUALITY SYSTEMS REVIEW

N/A

10. APPENDIX C (CONSULTANT MEMOS)

N/A

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.

/s/

HAMET M TOURE
01/08/2021 04:01:43 PM