CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214938Orig1s002

Trade Name:	VOXZOGO
Generic or Proper Name:	(vosoritide)
Sponsor:	BioMarin Pharmaceutical Inc.
Approval Date:	October 20, 2023
Indication:	VOXZOGO is a C type natriuretic peptide (CNP) analog indicated to increase linear growth in pediatric patients with achondroplasia with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s)

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 214938/S-002

ACCELERATED APPROVAL

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

Dear Tabitha Santoso:

Please refer to your supplemental new drug application (sNDA) dated and received December 21, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Voxzogo (vosoritide) for injection.

This "Prior Approval" sNDA provides for expansion of the patient population from pediatric patients who are 5 years of age and older to include all pediatric patients for the use of Voxzogo (vosoritide) for injection to increase linear growth in pediatric patients with achondroplasia with open epiphyses.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, text for Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2] The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RELEASE FROM POSTMARKETING REQUIREMENT

We have received your submission dated October 6, 2023, requesting release from the following postmarketing requirement listed in our November 19, 2021, approval letter:

4134-1 Conduct an open-label, external-controlled trial in subjects with achondroplasia (ACH) 5 years of age and older with open epiphyses to measure the effect of vosoritide on final adult height. The trial should also evaluate disproportionality and bone age as secondary endpoints. The safety endpoints related to the drug (e.g., blood pressure) or to the disease itself that may improve or worsen with long-term treatment (e.g., neurological complications, bone deformities, sleep apnea) should also be included. The total exposure to vosoritide for each patient should be sufficient to meet the study's stated objectives. The vosoritide-treated trial population should include subjects who are already enrolled and treated with vosoritide in Studies 111-202[3]/205[4], and 111-301[5]/302[6] and/or treatment-naïve subjects with a genetically confirmed ACH diagnosis.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] A Phase 2, Open Label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia
[4] A Phase 2, Open-Label, Extension Study to Evaluate the Long-Term safety, Tolerability, and Efficacy of BMN 111 in Children with Achondroplasia
[5] A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with Achondroplasia
[6] A Phase 3, Open-Label Lon-Term Extension Study to Evaluate the Safety and Efficacy of BMN 111 in Children with Achondroplasia

The original timetable you submitted on September 14, 2021, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	March 2022
Final Protocol Submission:	September 2022
Trial Completion:	November 2024
Final Report Submission:	August 2025

We have reviewed your submission and have determined that you are released from the above postmarketing requirement (PMR) for the following reason: modifications to the above PMR are necessary to include additional subjects with ACH 5 years of age and younger with open epiphyses to verify and describe clinical benefit of vosoritide in all age groups of patients with ACH and open epiphyses.

The above postmarketing requirement will be replaced by the new postmarketing requirement as described below.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510 you are required to conduct further adequate and well-controlled clinical trial(s) intended to verify and describe clinical benefit. You are required to conduct such clinical trial(s) with due diligence. If required postmarketing clinical trial(s) fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement(s) specified in your submission dated October 6, 2023. This requirement is listed below.

4134-2 Conduct an open-label, external-controlled trial in pediatric subjects with achondroplasia (ACH), whose epiphyses are not closed, to measure the effect of vosoritide on final adult height. The trial should also evaluate disproportionality and bone age as secondary endpoints. The safety endpoints related to the drug (e.g., blood pressure) or to the disease itself that may improve or worsen with long-term treatment (e.g., neurological complications, bone deformities, sleep apnea) should also be included.

The timetable you submitted on October 6, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	April 2024
Final Protocol Submission:	October 2024
Trial Completion:	November 2025
Final Report Submission:	August 2026

Submit clinical protocols to your IND 111299 for this product. FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this NDA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). One report will be a standalone submission and the other report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval of the original NDA (with a 60-day grace period). Submit the other 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[7] Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[8]

180-day reports must be clearly designated "**NDA 214938/S-002 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval of the original NDA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

[7] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

[8] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[9]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[9] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[10]

If you have any questions, call Linda Galgay, Regulatory Project Manager, at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Naomi Lowy, M.D.
Deputy Director
Division of General Endocrinology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
- Prescribing Information
- Patient Package Insert
- Instructions for Use (Approved November 19, 2021)

[10] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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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/

NAOMI N LOWY
10/20/2023 01:42:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214938Orig1s002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VOXZOGO safely and effectively. See full prescribing information for VOXZOGO.

VOXZOGO (vosoritide) for injection, for subcutaneous use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------

Indication and Usage (1)	10/2023
Dosage and Administration (2.2)	10/2023
Dosage and Administration (2.4)	10/2023

----------INDICATIONS AND USAGE----------
VOXZOGO is a C type natriuretic peptide (CNP) analog indicated to increase linear growth in pediatric patients with achondroplasia with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1)

----------DOSAGE AND ADMINISTRATION----------
- Ensure adequate food and fluid intake prior to administration. (2.1)
- Recommended dosage is based on patient's actual body weight. Administer VOXZOGO subcutaneously once daily. (2.2)
- Reconstitute prior to use. Injection volume is based on both patient's weight and concentration of reconstituted VOXZOGO. (2.2)
- Monitor growth and adjust dosage according to actual body weight. Permanently discontinue upon closure of epiphyses. (2.3)
- See full prescribing information for reconstitution, dilution, and administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 0.4 mg, 0.56 mg, or 1.2 mg of vosoritide as a lyophilized powder in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Risk of Low Blood Pressure: Transient decreases in blood pressure have been reported. Instruct patients to be well-hydrated and have adequate food intake prior to administration of VOXZOGO (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>10%) are injection site erythema, injection site swelling, rash, vomiting, injection site urticaria, arthralgia, decreased blood pressure, and gastroenteritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment: Not recommended in patients with eGFR < 60 mL/min/1.73 m^2. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VOXZOGO is indicated to increase linear growth in pediatric patients with achondroplasia with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Important Instructions Prior to Administration of VOXZOGO

To reduce the risk of low blood pressure and its associated signs and symptoms, instruct the caregiver and patient that the patient should *[see Warnings and Precautions (5.1)]*:

- Have adequate food intake prior to VOXZOGO administration.
- Drink approximately 240 to 300 mL of fluid in the hour prior to VOXZOGO administration.

2.2 Recommended Dosage and Administration

The recommended dosage of VOXZOGO is based on the patient's actual body weight (see Table 1). VOXZOGO is administered by subcutaneous injection once daily *[see Dosage and Administration (2.4)]*.

Inject VOXZOGO at approximately the same time each day, if possible. The volume of VOXZOGO to be administered (injection volume) is based on the patient's actual body weight and the concentration of reconstituted VOXZOGO (0.8 mg/mL or 2 mg/mL) (see Table 1). VOXZOGO must be reconstituted prior to use *[see Dosage and Administration (2.4)]*.

Table 1: Recommended VOXZOGO Daily Dosage and Injection Volume

Actual Body Weight*	Dose	Injection Volume	Vial Strength for Reconstitution**
3 kg	0.096 mg	0.12 mL	0.4 mg
4 kg	0.12 mg	0.15 mL	0.4 mg
5 kg	0.16 mg	0.2 mL	0.4 mg
6 to 7 kg	0.2 mg	0.25 mL	0.4 mg
8 to 11 kg	0.24 mg	0.3 mL	0.4 mg
12 to 16 kg	0.28 mg	0.35 mL	0.56 mg
17 to 21 kg	0.32 mg	0.4 mL	0.56 mg
22 to 32 kg	0.4 mg	0.5 mL	0.56 mg
33 to 43 kg	0.5 mg	0.25 mL	1.2 mg
44 to 59 kg	0.6 mg	0.3 mL	1.2 mg
60 to 89 kg	0.7 mg	0.35 mL	1.2 mg
≥ 90 kg	0.8 mg	0.4 mL	1.2 mg

* Intermediate body weights that fall within these weight bands should be rounded to the nearest whole number.
**The concentration of vosoritide in reconstituted 0.4 mg vial and 0.56 mg vial is 0.8 mg/mL. The concentration of vosoritide in reconstituted 1.2 mg vial is 2 mg/mL.

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, skip the missed dose and administer the next daily dose according to the usual dosing schedule.

2.3 Growth Monitoring

Monitor and assess patient body weight, growth, and physical development regularly every 3 to 6 months. Adjust the dosage according to the patient's actual body weight *[see Dosage and Administration (2.2)]*.

Permanently discontinue VOXZOGO upon confirmation of no further growth potential, indicated by closure of epiphyses.

2.4 Preparation and Administration

Reconstitute VOXZOGO before administration using the provided diluent syringe containing Sterile Water for Injection, USP (see Reconstitution Instructions below).

Caregivers may inject VOXZOGO subcutaneously after proper training by a healthcare professional on the preparation and administration of VOXZOGO *[see Instructions for Use]*.

Reconstitution Instructions

- Select the correct VOXZOGO vial strength (co-packaged with prefilled syringe with Sterile Water for Injection diluent) based on the patient's actual body weight *[see Dosage and Administration (2.2)]*.
- Remove VOXZOGO vial and prefilled diluent syringe from the refrigerator and allow the vial and prefilled diluent syringe to reach room temperature before reconstituting VOXZOGO.
- Attach the diluent needle provided with ancillary supplies to the diluent prefilled syringe.
- Inject the entire diluent prefilled syringe volume into the vial (see Table 2).
- Gently swirl the diluent in the vial until the white powder is completely dissolved. Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Once reconstituted VOXZOGO is a clear, colorless to yellow liquid. The solution should not be used if discolored or cloudy, or if particles are present. The concentration of reconstituted solution is 0.8 mg/mL or 2.0 mg/mL (see Table 2).
- After reconstitution, VOXZOGO can be held in the vial at a room temperature 20°C to 25°C (68°F to 77°F) for a maximum of 3 hours.
- For administration, extract the required dose volume from the vial using the supplied administration syringe *[see Dosage and Administration (2.2)]*.

Table 2: Dilution Requirements for VOXZOGO Prior to Administration

Vial Strength	Reconstitution Volume	Reconstituted Concentration
0.4 mg	0.5 mL	0.8 mg/mL
0.56 mg	0.7 mL	0.8 mg/mL
1.2 mg	0.6 mL	2 mg/mL

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than 1 dose from a vial. Do not mix with other medications.

Instructions for Subcutaneous Administration

See the Instructions for Use document for detailed, illustrated instructions.

- Ensure patients have had adequate food and fluid intake prior to VOXZOGO administration *[see Dosage and Administration (2.1)]*. Slowly withdraw the dosing volume of the reconstituted VOXZOGO solution from the single-dose vial into a syringe.
- Rotate sites for subcutaneous injections.
- The recommended injection sites for VOXZOGO are: the front middle of the thighs, the lower part of the abdomen at least 2 inches (5 centimeters) away from the navel, top of the buttocks or the back of the upper arms. The same injection area should not be used on two consecutive days. Do not inject VOXZOGO into sites that are red, swollen, or tender.

3 DOSAGE FORMS AND STRENGTHS

For injection: 0.4 mg, 0.56 mg, or 1.2 mg of vosoritide as a white to yellow lyophilized powder in a single-dose vial for reconsistitution.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Low Blood Pressure

Transient decreases in blood pressure were observed in clinical studies of VOXZOGO. Subjects with significant cardiac or vascular disease and patients on anti-hypertensive medicinal products were excluded from participation in VOXZOGO clinical trials. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, fatigue and/or nausea), instruct patients to be well hydrated and have adequate food intake prior to administration of VOXZOGO *[see Dosage and Administration (2.1) and Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risk of Low Blood Pressure *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pediatric Patients 5 Years of Age and Older
VOXZOGO was studied in a 52-week, randomized, double-blind, placebo-controlled trial in 121 subjects with achondroplasia (Study 1) *[see Clinical Studies (14)]*.

The subjects' ages ranged from 5.1 to 14.9 years with a mean of 8.7 years. Sixty four (53%) subjects were male and 57 (47%) were female. Overall, 86 (71%) subjects were White, 23 (19%) were Asian, 5 (4%) were Black or African American, and 7 (6%) were classified as "multiple" race. The demographic and baseline characteristics were balanced between treatment groups. The subjects received either VOXZOGO 15 mcg/kg, or placebo administered subcutaneously once daily.

Table 3 shows adverse reactions that occurred in ≥5% of patients treated with VOXZOGO and at a percentage greater than placebo.

Table 3: Adverse Reactions that Occurred in ≥5% of Patients Treated with VOXZOGO and at a Percentage Greater than Placebo in Study 1*

Adverse Reaction	**Placebo** (N=61) **n (%)**	**VOXZOGO** (N=60) **n (%)**
Injection site erythema	42 (69%)	45 (75%)
Injection site swelling	22 (36%)	37 (62%)
Vomiting	12 (20%)	16 (27%)
Injection site urticaria	6 (10%)	15 (25%)
Arthralgia	4 (7%)	9 (15%)
Decreased blood pressure	3 (5%)	8 (13%)
Gastroenteritis[a]	5 (8%)	8 (13%)
Diarrhea	2 (3%)	6 (10%)
Dizziness[b]	2 (3%)	6 (10%)
Ear pain	3 (5%)	6 (10%)
Influenza	3 (5%)	6 (10%)
Fatigue[c]	2 (3%)	5 (8%)
Seasonal allergy	1 (2%)	4 (7%)
Dry skin	0	3 (5%)

Abreviations: N, total number of subjects in the treatment arm; n, number of subjects with the adverse reaction; %, percent of subjects with the adverse reaction.
* Includes adverse reactions occurring more frequently in the vosoritide arm and with a risk difference of ≥5% (i.e., difference of >2 subjects) between treatment arms
[a] Includes the preferred terms: gastroenteritis and gastroenteritis, viral
[b] Includes the preferred terms: dizziness, presyncope, procedural dizziness, vertigo
[c] Includes the preferred terms: fatigue, lethargy, malaise

Laboratory Abnormalities

Increase in Alkaline Phosphatase
More VOXZOGO-treated patients had an increase in alkaline phosphatase levels during the study compared to placebo (17% vs 7%).

Discussion of Selected Adverse Reactions

Decreased blood pressure
Eight (13%) of 60 subjects treated with VOXZOGO had a total of 11 events of transient decrease in blood pressure compared to 3 (5%) of 61 subjects on placebo, identified predominantly during periods of frequent monitoring at clinical visits after dosing over a 52-week treatment period. The median time to onset from injection was 31 (18 to 120) minutes with resolution within 31 (5 to 90) minutes in VOXZOGO-treated subjects. Two out of 60 (3%) VOXZOGO-treated subjects each had one symptomatic episode of decreased blood pressure with vomiting and/or dizziness compared to 0 of 61 (0%) subjects on placebo.

Injection site reactions
Injection site reactions occurred in 51 (85%) subjects receiving VOXZOGO and 50 (82%) subjects receiving placebo over a 52 week period of treatment. Injection site reactions included the preferred terms injection site erythema, injection site reaction, injection site swelling, injection site urticaria, injection site pain, injection site bruising, injection site pruritus, injection site hemorrhage, injection site discoloration, and injection site induration. Over a 52 week period, 51 (85%) of 60 subjects receiving VOXZOGO experienced a total of 6983 events of injection site reactions, while 50 (82%) of 61 subjects receiving placebo experienced a total of 1776 events of injections site reactions, representing 120.4 events per person/year exposure and 29.2 per person/year exposure, respectively. One injection site reaction event could have been associated with one or more injection site reaction symptoms (e.g., injection site swelling, injection site erythema, injection site urticaria, etc.). Two subjects in the VOXZOGO arm discontinued treatment due to adverse reactions of pain and anxiety with injections.

Pediatric Patients <5 Years
The safety of VOXZOGO in pediatric patients <5 years with achondroplasia was evaluated in a 52-week randomized, double blind, placebo-controlled study (Study 2). In this study, 64 patients from 4.4 months to <5 years of age were randomized to receive either a daily vosoritide dose with similar exposure to that characterized to be safe and effective in children with ACH aged ≥5 years old, or placebo. An additional 11 patients received open-label treatment as part of this study. Subjects received 30 mcg/kg while they were <2 years of age. The daily dose for subjects was adjusted to 15 mcg/kg immediately following their 2 year birthday. The most common adverse reactions (>10%) reported in pediatric patients <5 years were injection site reactions (86%) and rash (28%).

The overall safety profile of VOXZOGO in pediatric patients <5 years was similar to that seen in older pediatric patients.

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. In animal reproduction studies, there was no evidence of embryo-fetal toxicity or congenital malformations when pregnant rats and rabbits were administered vosoritide subcutaneously at doses equivalent to 14-times and 200-times, respectively, the exposure at the maximum recommended human dose (MRHD) *(see Data)*.

The estimated background risk of major birth defects for the indicated population is higher than the general population. 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
In an embryofetal developmental toxicity study in rats, vosoritide was administered at 90, 270, 540 mcg/kg once daily by subcutaneous injection during the period of major organogenesis from gestation day (GD) 6 – 17. There were no effects on maternal animals or on embryofetal development at the highest dose administered (14-times the exposure at the MRHD).

In an embryofetal developmental toxicity study in rabbits, vosoritide was administered at 45, 135, 240 mcg/kg once daily by subcutaneous injection during the period of major organogenesis (GD 7 – 19). No effects were observed in maternal animals or on embryofetal development at the highest dose administered (200-times the exposure at the MRHD).

In a pre- and postnatal toxicity study in rats, vosoritide was administered at 90, 270, and 540 mcg/kg once daily by subcutaneous injection during the period of major organogenesis and continuing to weaning (GD 6 through postpartum day 20). There were no effects on maternal animals, including maintenance of pregnancy, parturition, or care of offspring, and no effects were noted on offspring growth and development or ability to reproduce at the highest dose (14-times the exposure at the MRHD).

8.2 Lactation

Risk Summary

There is no information regarding the presence of vosoritide in human milk, the effects on the breastfed infant, 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.

8.4 Pediatric Use

The safety and effectiveness of VOXZOGO have been established in pediatric patients for the improvement in linear growth in patients with achondroplasia with open epiphyses.

Use of VOXZOGO for this indication is supported by evidence from an adequate and well-controlled study in 121 pediatric patients aged 5 to 15 years with achondroplasia, pharmacokinetic data in pediatric patients aged 4.5 months to 15 years, and additional safety data in pediatric patients aged 4.4 months to <5 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.6 Renal Impairment

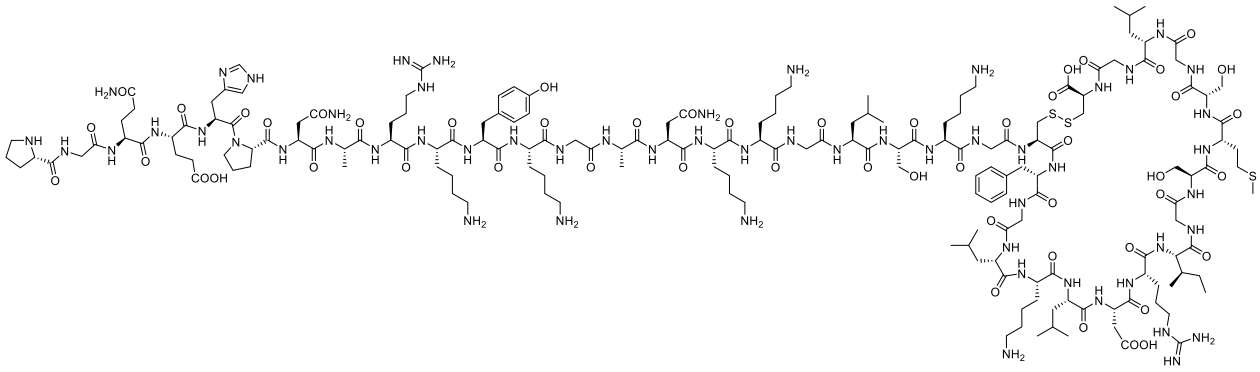
The effect of renal impairment on the pharmacokinetics of VOXZOGO has not been evaluated. No dosage adjustment is needed for patients with eGFR ≥ 60 mL/min/1.73 m^2. VOXZOGO is not recommended for patients with eGFR < 60 mL/min/1.73 m^2.

11 DESCRIPTION

VOXZOGO contains vosoritide, a human C type natriuretic peptide (CNP) analog. Vosoritide is a 39 amino acid peptide. Its amino acid sequence includes the 37 C terminal amino acids of the human CNP53 sequence plus Pro Gly on the N terminus to convey resistance to neutral endopeptidase (NEP) degradation. Vosoritide is manufactured from *Escherichia coli* using recombinant DNA technology. Vosoritide has a chemical formula of $C_{176}H_{290}N_{56}O_{51}S_3$ with a molecular weight of 4.1 kDa.

Vosoritide has the structural formula shown in Figure 1.

Figure 1



VOXZOGO (vosoritide) for injection, is a sterile, preservative-free white-to-yellow lyophilized powder, for subcutaneous administration after reconstitution with Sterile Water for Injection, USP.

VOXZOGO is provided as a single-dose vial containing 0.4 mg, 0.56 mg, or 1.2 mg of vosoritide per vial. A pre-filled syringe containing Sterile Water for Injection, USP for use as a diluent is also provided. The contents of each single dose vial are summarized by strength in Table 4. The product contains no preservative.

Table 4: Contents of VOXZOGO

Strength	Inactive Ingredients per Vial
VOXZOGO 0.4 mg	Citric acid monohydrate (0.14 mg), mannitol (7.5 mg), methionine (0.36 mg), polysorbate 80 (0.025 mg), sodium citrate dihydrate (0.54 mg) and trehalose dihydrate (29.01 mg). After reconstitution with 0.5 mL Sterile Water for Injection USP, the resulting concentration is 0.4 mg/0.5 mL of vosoritide and the nominal deliverable volume is 0.4 mL.
VOXZOGO 0.56 mg	Citric acid monohydrate (0.20 mg), mannitol (10.50 mg), methionine (0.51 mg), polysorbate 80 (0.035 mg), sodium citrate dihydrate (0.76 mg) and trehalose dihydrate (40.61 mg). After reconstitution with 0.7 mL Sterile Water for Injection USP, the resulting concentration is 0.56 mg/0.7 mL of vosoritide and the nominal deliverable volume is 0.6 mL.
VOXZOGO 1.2 mg	Citric acid monohydrate (0.17 mg), mannitol (9 mg), methionine (0.44 mg), polysorbate 80 (0.030 mg), sodium citrate dihydrate (0.65 mg) and trehalose dihydrate (34.81 mg). After reconstitution with 0.6 mL Sterile Water for Injection USP, the resulting concentration is 1.2 mg/0.6 mL of vosoritide and the nominal deliverable volume is 0.5 mL.

Trehalose dihydrate and D-Mannitol are used as isotonic agent. Citric acid monohydrate and sodium citrate dihydrate are used as buffering agent.

12 CLINICAL PHARMACOLOGY

12.1 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.

In animal models with open growth plates, vosoritide administration resulted in the promotion of chondrocyte proliferation and differentiation that led to a widening of the growth plate and subsequent increase in skeletal growth. In the mouse models of FGFR3-related chondrodysplasia, a partial or complete normalization of the dwarfism phenotype was observed.

12.2 Pharmacodynamics

NPR-B Binding Activity Biomarker and Bone Metabolism Biomarker

An increase in urinary cyclic guanosine monophosphate (cGMP) concentrations from pre-dose baseline were observed within the first four hours post-dose, with a maximum level at 2 hours post-dose, after VOXZOGO administration to pediatric patients with achondroplasia.

Daily administration of VOXZOGO also led to the increase from baseline in serum collagen type X marker (CXM), an endochondral ossification biomarker and remains elevated beyond 24 months. In subjects aged 5 - 14 years old at screening, exposure-response analyses showed that vosoritide activity measured by urinary cGMP was near saturation at the dose of 15 mcg/kg once daily, while maximal increase in growth plate activity indicated by CXM was achieved at this dose.

Cardiac Electrophysiology

At the maximum approved recommended dose, VOXZOGO does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The area under the concentration-time curve (AUC) and peak concentration (C_{max}) of vosoritide increased greater than proportionally following subcutaneous administration to pediatric subjects with achondroplasia in the dose range of 7.5 to 30.0 mcg/kg. The pharmacokinetics of vosoritide were evaluated in 58 subjects aged 5 to 13 years with achondroplasia who received subcutaneous injections of vosoritide 15 mcg/kg once daily for 52 weeks. The mean (± SD) C_{max} and area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) observed across 52 weeks of treatment ranged from 4.71 (± 2.32) to 7.18 (± 9.65) ng/mL, and 161 (± 98.1) to 290 (± 235) ng-min/mL, respectively. No drug accumulation was observed following 15 mcg/kg once daily dosing. The exposure of vosoritide increased with the duration of treatment. The mean AUC_{0-t} at week 52 increased approximately 20% compared to that at day 1.

Absorption

Absolute bioavailability for vosoritide following subcutaneous injection was not determined. Vosoritide was absorbed with a median T_{max} of 15 minutes after dosing.

Distribution

The mean (± SD) apparent volume of distribution of vosoritide across 52 weeks of subcutaneous administration of VOXZOGO 15 mcg/kg once daily ranged from 2880 (± 2450) to 3020 (± 1980) mL/kg

Elimination

The mean (± SD) apparent clearance of vosoritide across 52 weeks of subcutaneous administration of VOXZOGO 15 mcg/kg once daily ranged from 79.4 (± 53.0) to 104 (± 98.8) mL/min/kg. The mean (± SD) half-life ranged from 21.0 (± 4.7) to 27.9 (± 9.9) minutes.

Metabolism
The metabolism of vosoritide is expected to occur via catabolic pathways with degradation into small peptide fragments and amino acids.

Specific Populations

No clinically significant differences in the vosoritide pharmacokinetics were observed based on age (0.4 to 15 years), sex or race. The effect of hepatic or renal impairment on the pharmacokinetics of vosoritide is unknown.

Body weight
Population pharmacokinetic analyses indicated that body weight is a significant covariate for vosoritide clearance and volume of distribution. The apparent clearance and volume of distribution of vosoritide increased with increasing body weight in patients with achondroplasia (5 to 74.5 kg).

Drug Interaction Studies

In vitro assessment of drug-drug interactions
In vitro studies showed that vosoritide, at therapeutic concentrations, does not inhibit or induce Cytochrome P450 enzymes. Based on *in vitro* studies, vosoritide is considered unlikely to inhibit the human drug uptake or efflux transporters such as OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP at clinically relevant concentrations and therefore, no effect of vosoritide is anticipated on concomitantly administered drugs that are substrates of these transporters.

In vivo assessment of drug-drug interactions
No clinical studies evaluating the drug-drug interaction potential of vosoritide have been conducted.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of vosoritide.

Of 131 subjects aged 5 years and older who were treated with VOXZOGO 15 mcg/kg/day and evaluable for the presence of anti-drug antibodies (ADA) for up to 240 weeks, ADA were detected in 35% (46/131). The earliest time to ADA development was day 85. All ADA-positive subjects tested negative for

anti-vosoritide neutralizing antibodies. There was no correlation between the number, duration, or severity of hypersensitivity adverse reactions or injection site reactions and ADA positivity or mean ADA titer. There was no association between ADA positivity or mean ADA titer and change from baseline in annual growth velocity (AGV) or height Z-score at month 12. There was no impact of serum ADA detected on the plasma PK measurements of vosoritide.

In subjects under 5 years of age, 33% (20/61) of vosoritide-treated subjects tested positive for ADA and all placebo-treated subjects tested negative for ADA for up to 44 months. The earliest time to ADA development was week 26. All of the ADA-positive subjects tested negative for neutralizing antibodies at all time points. There was no impact of ADA development on safety, efficacy or PK of vosoritide up to Month 12.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term carcinogenicity studies and genotoxicity studies with vosoritide have not been performed.

In a fertility and reproductive study in male and female rats at doses up to 540 mcg/kg/day (15-times the exposure at the MRHD), vosoritide had no effect on mating performance, fertility, or litter characteristics.

14 CLINICAL STUDIES

14.1 Pediatric Patients 5 Years of Age and Older

The safety and effectiveness of VOXZOGO in patients with achondroplasia were assessed in one 52-week, multi-center, randomized, double-blind, placebo-controlled, phase 3 study - Study 1 (NCT03197766).

Study 1 was conducted in 121 subjects with genetically-confirmed achondroplasia, who were randomized to either VOXZOGO (N=60) or placebo (N=61). The dosage of VOXZOGO was 15 mcg/kg administered subcutaneously once daily. Baseline standing height, weight Z-score, body mass index (BMI) Z-score, and upper to lower body ratio were collected for at least 6 months prior to randomization. Subjects with limb-lengthening surgery in the prior 18 months or who planned to have limb-lengthening surgery during the study period were excluded. The study included a 52-week placebo-controlled treatment phase followed by an open-label treatment extension study period in which all subjects received VOXZOGO. The primary efficacy endpoint was the change from baseline in annualized growth velocity (AGV) at Week 52 compared with placebo.

The subjects' ages ranged from 5.1 to 14.9 years with a mean of 8.7 years. Sixty four (53%) subjects were male and 57 (47%) were female. Overall, 86 (71%) subjects were White, 23 (19%) were Asian, 5 (4%) were Black or African American, and 7 (6%) were classified as "multiple" race. The subjects had a mean baseline height standard deviation score (SDS) of -5.13.

Treatment with VOXZOGO for 52 weeks resulted in a treatment difference in the change from baseline in AGV of 1.57 cm/year after 52 weeks of treatment (Table 5).

Table 5: Annualized Growth Velocity (cm/year) at Week 52 in Subjects 5 Years of Age and Older with Achondroplasia - Study 1

	Placebo (N=61[a])	**VOXZOGO 15 mcg/kg Daily** (N=60[a])
Baseline mean (SD)[b]	4.06 (1.20)	4.26 (1.53)
Change from baseline[c]	-0.17	1.40
Difference in change of VOXZOGO – Placebo[c] (95% CI)	1.57 (1.22, 1.93)[d]	

Abbreviations: AGV, annualized growth velocity; 95% CI, 95% confidence interval; LS, least-square; SD, standard deviation
[a] All randomized subjects. Two patients in the VOXZOGO group discontinued from the study before Week 52. The values for these 2 patients were imputed assuming baseline growth rate for the period with missing data.
[b] Baseline AGV was based on standing height at least 6 months prior to enrollment into the study.
[c] LS means were estimated from the ANCOVA (analysis of covariance) model, which included treatment, stratum defined by sex and Tanner stage, baseline age, baseline AGV and baseline height Z-score.
[d] 2-sided p-value <0.0001 for superiority.

The improvement in AGV in favor of VOXZOGO was consistent across all predefined subgroups analyzed including sex, age group, Tanner stage, baseline height Z-score, and baseline AGV.

Height Standard Deviation Score (SDS)
The LS mean change from baseline to Week 52 in height SDS was -0.02 in the placebo group and 0.26 in the VOXZOGO group. The difference in LS mean change from baseline was 0.28 (95% CI 0.17, 0.39; p<0.0001) in favor of VOXZOGO. The LS mean change from baseline to Week 52 in upper to lower body segment ratio was -0.02 in the placebo group and -0.03 in the VOXZOGO group. The difference in LS mean change from baseline was -0.01 (95% CI -0.05, 0.02; p=0.5).

Open-label extension
After the 52 week double blind, placebo-controlled, phase 3 study, Study 1, 58 subjects initially randomized to VOXZOGO enrolled into an open-label extension. Among the subjects who had 2 years of follow-up since randomization, the improvement in AGV was maintained.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VOXZOGO for injection is a white to yellow lyophilized powder for reconstitution and is provided as a co-pack which includes ten:

- Sterile, single-dose 2 mL glass vials containing VOXZOGO
- Diluent (Sterile Water for Injection, USP) in a single-dose prefilled syringe
- Diluent transfer needles (23 gauge)
- Single-dose administration syringes (30 gauge) both with needle retraction safety devices

Strength (mg)	**Diluent (mL)**	**Co-pack NDC Number**	**Flip Cap Color**
0.4	0.5	NDC 68135-082-36	White
0.56	0.7	NDC 68135-119-66	Magenta
1.2	0.6	NDC 68135-181-93	Grey

The following items to be obtained separately; alcohol aseptic wipes, gauze, bandages and sharps container.

Storage

Refrigerate VOXZOGO vials and prefilled diluent syringes at 2°C to 8°C (36°F to 46°F). Do not freeze.

VOXZOGO can be stored at room temperature 20°C to 25°C (68°F to 77°F); 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.

After reconstitution, VOXZOGO can be held in the vial at room temperature 20°C to 25°C (68°F to 77°F) for a maximum of 3 hours *[see Dosage and Administration (2.4)]*.

Record the starting date of room-temperature storage clearly on the unopened product carton.

Do not use beyond expiration date on the label.

Store in the original package to protect from light.

Handling

Reconstituted VOXZOGO must be administered within 3 hours of reconstitution *[see Dosage and Administration (2.4)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient and caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Preparation and Administration

Instruct caregivers on proper preparation and administration of VOXZOGO. Ensure caregivers have demonstrated the ability to perform a subcutaneous injection *[see Dosage and Administration (2.4)]*.

Instruct caregivers in the technique of proper syringe and needle disposal, and advise them not to reuse these items. Instruct caregivers to dispose needles and syringes in a puncture-resistant container.

Risk of Low Blood Pressure

Inform caregivers and patients that VOXZOGO may lower blood pressure after administration. Instruct caregivers and patients that prior to VOXZOGO administration, the patient should have adequate food intake and within the hour prior to administration, the patient should drink approximately 8-10 ounces (240-300 mL) of fluid *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

Manufactured for:
BioMarin Pharmaceutical Inc.
105 Digital Drive, Novato, CA 94949

PATIENT INFORMATION
VOXZOGO (vox zoe' goe)
(vosoritide)
for injection, for subcutaneous use

What is VOXZOGO?

VOXZOGO is a prescription medicine used to increase linear growth in children with achondroplasia with open bone growth plates (epiphyses).

Before you give your child VOXZOGO, tell your child's healthcare provider about all your child's medical conditions, including if they:

- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if VOXZOGO will harm your child's unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VOXZOGO passes into your child's breast milk. Talk to your child's healthcare provider about the best way to feed your child's baby if your child takes VOXZOGO.

Tell your child's healthcare provider about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines your child takes. Keep a list of them to show your child's healthcare provider and pharmacist when your child gets a new medicine.

How should I give VOXZOGO?

- See the detailed **Instructions for Use** that comes with this Patient Information leaflet for instructions about the right way to store, prepare, and give VOXZOGO injections at home.
- VOXZOGO is given as an injection under the skin (subcutaneous or SC). Inject VOXZOGO 1 time every day, at about the same time each day.
- If your child's healthcare provider decides a caregiver can give the injections of VOXZOGO at home, your child's caregiver should receive training on the right way to prepare and inject VOXZOGO. Do not try to inject VOXZOGO until you have been shown the right way by your child's healthcare provider or nurse.
- Your child's healthcare provider will tell you how often you should give VOXZOGO. If your child misses a dose of VOXZOGO, it can be given within 12 hours of the scheduled time of injection. If more than 12 hours have passed, do not give the missed dose. Give the next daily dose according to your child's usual schedule.
- Your child should eat a meal and drink about 8 to 10 ounces of fluid within 1 hour before injection.
- In case you are not sure when to inject VOXZOGO, call your child's healthcare provider or pharmacist. Do not give VOXZOGO more often than as directed by your child's healthcare provider.
- Your child's dose of VOXZOGO depends on his or her body weight. Your child's healthcare provider will tell you which strength of VOXZOGO to use and how much to give your child.
- Your child's healthcare provider will monitor your child's growth and instruct you on when your child should stop VOXZOGO if they determine that your child is no longer able to grow. Stop giving VOXZOGO to your child if instructed by your child's healthcare provider.

What are the possible side effects of VOXZOGO?

VOXZOGO may cause serious side effects, including:

- **risk of low blood pressure.** VOXZOGO may temporarily lower blood pressure in some people. To help reduce the risk of low blood pressure and its symptoms (dizziness, feeling tired, or nausea), your child should eat a meal and drink about 8 to 10 ounces of fluid within 1 hour before receiving VOXZOGO.

The most common side effects of VOXZOGO include:

- injection site reactions (redness, itching, swelling, bruising, rash, hives, pain)
- high levels of blood alkaline phosphatase (shown in blood tests)
- vomiting
- joint pain
- decreased blood pressure

- stomach ache

These are not all the possible side effects of VOXZOGO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VOXZOGO?

- Store the VOXZOGO vial and prefilled diluent syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store VOXZOGO (before mixing) at room temperature between 68°F to 77°F (20°C to 25°C) for 90 days.
- Record the date you started storing VOXZOGO at room temperature on the carton to keep track of the 90 days.
- **Do not** return VOXZOGO to the refrigerator after it has been stored at room temperature. Throw VOXZOGO away if unused within 90 days of storing at room temperature.
- Do not use VOXZOGO past the expiration date.
- Do not freeze VOXZOGO.
- Store VOXZOGO out of direct sunlight.

Keep VOXZOGO and all medicines out of the reach of children.

General information about the safe and effective use of VOXZOGO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VOXZOGO for a condition for which it was not prescribed.

Do not give VOXZOGO to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about VOXZOGO that is written for health professionals.

What are the ingredients in VOXZOGO?

Active ingredient: vosoritide

Inactive ingredients: trehalose dihydrate, mannitol, sodium citrate dihydrate, methionine, citric acid monohydrate, and polysorbate 80

BIOMARIN®

BioMarin Pharmaceutical Inc.
Novato, CA 94949

For more information, go to www.VOXZOGO.com or call 1-877-695-8826.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: mm/yyyy

INSTRUCTIONS FOR USE

VOXZOGO™ [Vox zoe' goe]
(vosoritide)

for injection, for subcutaneous use
Single-Use

This Instructions for Use contains information for caregivers on how to inject VOXZOGO.
Read this Instructions for Use before you start using VOXZOGO and each time you get a refill. There may be new information. This information does not take the place of talking to your child's healthcare provider about your child's medical condition and their treatment. Before you use VOXZOGO for the first time, make sure your child's healthcare provider shows you the right way to use it. Contact your child's healthcare provider if you or your child have any questions.

Important Information You Need to Know Before Injecting VOXZOGO

- **Wash your hands** with soap and water.
- **Do not** drop VOXZOGO or put opened items down on surfaces that are not clean.
- VOXZOGO is available in more than 1 strength. **Make sure the strength matches your prescription strength. Do not** open packaging until ready to use.
- Take the VOXZOGO vial and prefilled diluent syringe out of the refrigerator and allow them to reach room temperature before mixing.
- **Inspect the vial and supplies for any signs of damage or contamination. Do not** use if damaged or contaminated.
- **Check the expiration date.** The expiration date can be found on the carton, vial and prefilled diluent syringe. **Do not** use if expired.
- **Your child should eat a meal and drink a glass (about 8 to 10 ounces) of fluid (such as water, milk, or juice) within 1 hour before injection.**
- **VOXZOGO should be given at about the same time every day.**
- Do not mix VOXZOGO with other medicines.
- **After mixing the VOXZOGO, use it right away. Do not** use the mixed VOXZOGO if it has been sitting at room temperature for more than 3 hours. Throw it away (dispose of) in a sharps container. **See** step 18 and **"How to Throw Away (Dispose of) VOXZOGO"** for more information.
- **Do not reuse any of the supplies. After the injection, throw away (dispose of) the used vial even if there is VOXZOGO remaining. See** step 18 and **"How to Throw Away (Dispose of) VOXZOGO"** for more information.

How to Store VOXZOGO

- Store the VOXZOGO vial and prefilled diluent syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store VOXZOGO (before mixing) at room temperature between 68°F to 77°F (20°C to 25°C) for 90 days. Record the date you started storing VOXZOGO at room temperature on the carton to keep track of the 90 days. **Do not** return VOXZOGO to the refrigerator after it has been stored at room temperature. Throw VOXZOGO away if unused within 90 days of storing at room temperature.
- **Do not** freeze VOXZOGO.
- Store VOXZOGO out of direct sunlight.

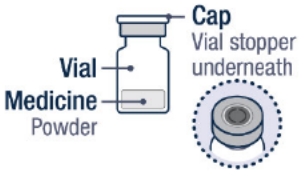
Keep VOXZOGO and all other medicines out of the reach of children.

Supplies Needed to Inject VOXZOGO

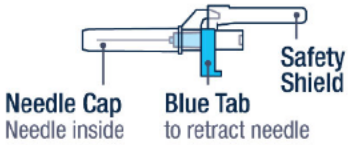
Gather all of these supplies on a clean, flat surface before injecting.

Items supplied

VOXZOGO



Diluent Needle



Prefilled Diluent Syringe

Injection Syringe

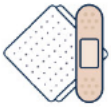
Items not supplied

If you do not have these items, ask your pharmacist.

Alcohol Pads

Sharps Container

Gauze or Bandage



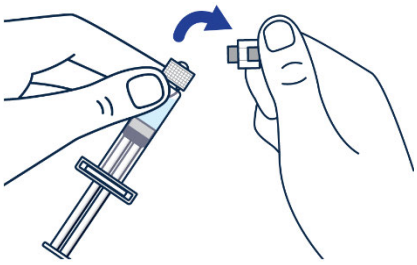
Preparing VOXZOGO for Injection

► Step 1

On a clean flat surface, flip off the vial cap **and wipe** the top with an alcohol pad.

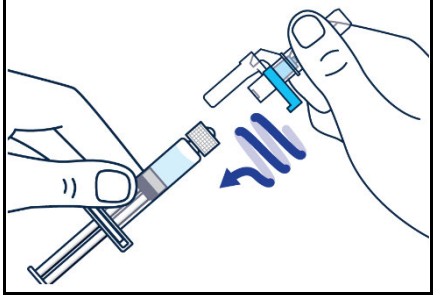
► Step 2

Gently bend to **snap off** the cap from the prefilled diluent syringe.



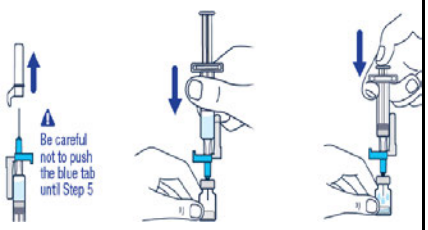
► Step 3

Twist the diluent needle **onto** the prefilled diluent syringe until you can no longer twist it. **Do not** use the prefilled diluent syringe to give the injection.



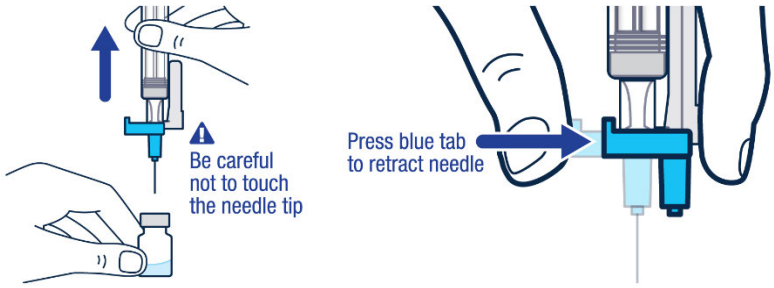
► Step 4

Pull off the needle cap **and insert the needle** through the **middle** of the vial stopper. **Slowly push** the plunger rod down to inject **all of the liquid.**



► Step 5

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 prefilled diluent syringe to give the injection.



► Step 6

Gently swirl the vial until the powder has completely dissolved and the solution is clear. **Do not shake.**

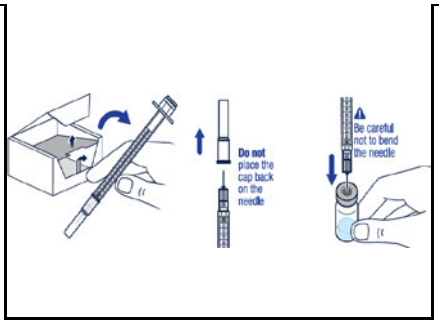
Make sure medicine is clear to yellow, not cloudy and does not have particles.

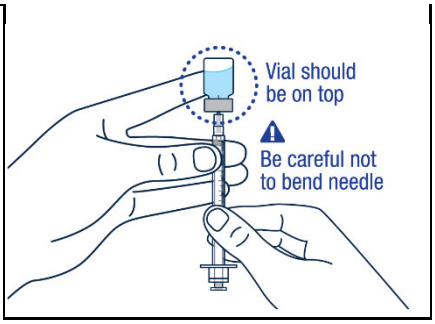
► Step 7

Take the injection syringe out of the carton. **Pull off** the needle cap from the injection syringe **and insert the needle straight** through the **middle** of the vial stopper. Be careful not to bend the needle.

► Step 8

Carefully hold the vial and syringe and turn the vial upside down with the needle still inserted. The vial should be on top. Be careful not to bend the needle.

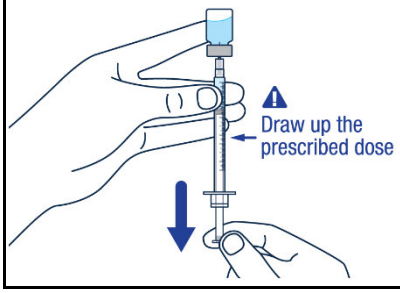




Preparing VOXZOGO for Injection (continued)

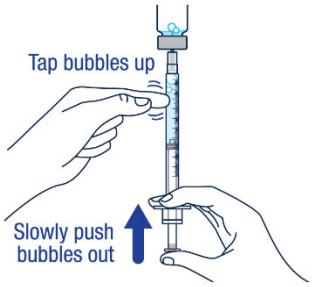
► Step 9

Keep the needle tip in the medicine and slowly pull the plunger rod back to draw up the prescribed dose in the syringe. **Check the prescription label for how much to draw up.**



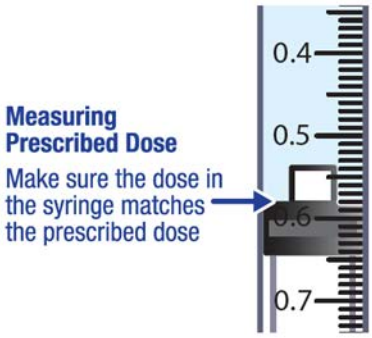
► Step 10

Remove large air bubbles in the syringe by gently tapping the syringe. Then push the bubbles back into the vial.



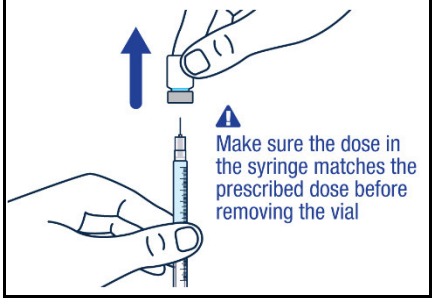
► Step 11

Repeat steps 9 and 10 until you have the correct prescribed dose in the syringe and no large bubbles.



► Step 12

Make sure you have the prescribed dose in the syringe, then remove the vial and prepare to give the dose.



Select and Prepare Injection Site

► Step **13**

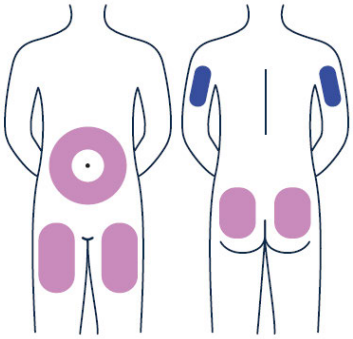
VOXZOGO should be injected into the fatty layer under the skin (subcutaneous) only.
Do not inject into the same site 2 times in a row.

⚠ **Do not** inject through clothes.

Do not inject into skin that is swollen, sore, bruised, red, hard, or scarred.

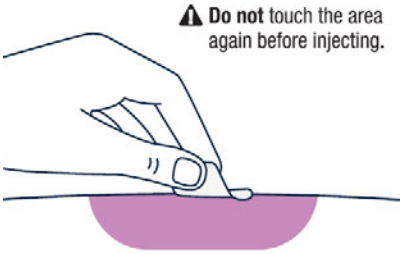
The following sites are recommended for injection:

- **Thighs** or
- **Abdomen** (2 inches from belly button) or
- **Buttocks**
- Healthcare providers and caregivers may also inject VOXZOGO into the **back of the upper arms.**



► Step **14**

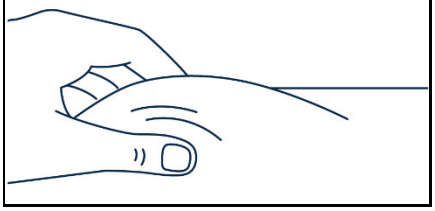
Wipe the injection site with an alcohol pad and let the skin air dry.



Giving VOXZOGO Injection

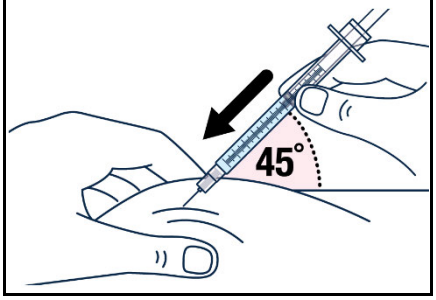
► Step **15**

After wiping the site with an alcohol pad, **pinch** the skin up around the selected injection site.



► Step **16**

Quickly insert the needle all the way into the skin **at a 45-degree angle.**

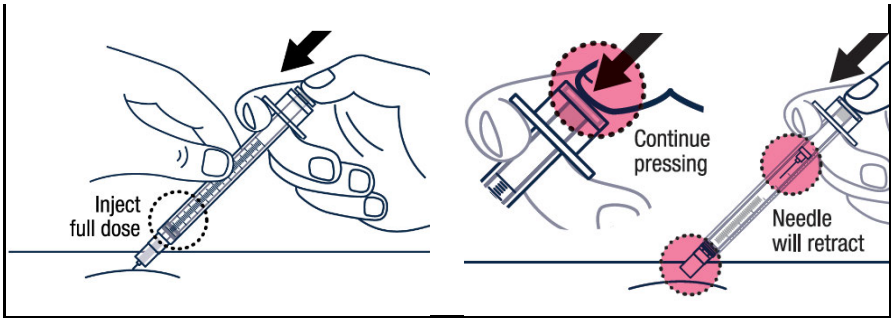


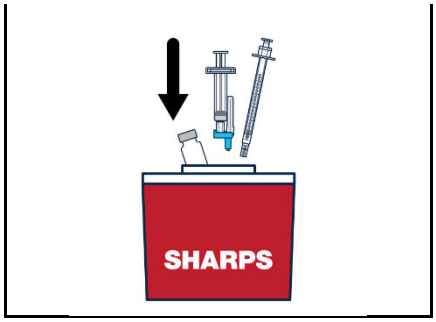
► Step **17**

Release the pinch and slowly push the plunger rod all the way down. → **Continue pressing the plunger rod until the needle retracts into the syringe.**

► Step **18**

Throw away the used vial, syringes and needles in a sharps container. **See "How to Throw Away (Dispose of) VOXZOGO"** for more information.





How to Throw Away (Dispose of) VOXZOGO

Put your used or expired vials, needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) the vials, loose needles and syringes in your household trash.**

If you do not have a FDA-cleared sharps disposal container, you may use a household container that:

- is made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid without sharps being able to come out,
- is upright and stable during use,
- is leak-resistant, and
- is properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

After the Injection

- Inspect the injection site. If a small amount of bleeding occurs from the injection site, gently press a gauze pad on it for a few seconds or apply a bandage. **Do not** rub the injection site.
- Monitor for signs of low blood pressure, such as dizziness, tiredness, and nausea. If your child experiences these symptoms you should call your child's healthcare provider, then get your child to lay back with legs raised.

For Help or More Information

- Call your healthcare provider
- Call BioMarin at 1-800-123-4567
- Visit www.VOXZOGO.com

Manufactured for:
BioMarin Pharmaceutical Inc.,
Novato, CA 94949

REP-5233-C10

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Approved: November 2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214938Orig1s002

INTEGRATED REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Integrated Review

Table 1. Application Information

Application type	NDA
Application number	214938/S-002
Priority or standard	Standard
Submit date	12/21/2022
Received date	12/21/2022
PDUFA goal date	10/21/2023
Action date	10/20/2023
Division/office	Division of General Endocrinology (DGE)
Review completion date	8/21/2023
Established/proper name	Vosoritide
(Proposed) proprietary name	VOXZOGO
Pharmacologic class	C-type natriuretic peptide (CNP) analog
Other product name(s)	Click or tap to enter name.
Applicant	Biomarin Pharmaceutical, Inc.
Dosage form(s)/formulation(s)	15µg/kg (2 years and older); 30µg/kg (<2 years of age)
Dosing regimen	Daily subcutaneous injection
Applicant-proposed indication(s)/ population(s)	To increase linear growth in children with achondroplasia whose epiphyses are not closed
SNOMED CT code for proposed indication disease term(s)[1]	86268005 Achondroplasia (disorder)
Regulatory action	Accelerated approval
Approved dosage (if applicable)	Weight based dosing
Approved indication(s)/ population(s) (if applicable)	To increase linear growth in children with achondroplasia whose epiphyses are not closed
SNOMED CT code for approved indication disease term(s)[1]	86268005 Achondroplasia (disorder)

[1] For internal tracking purposes only.
Abbreviations: CNP, C-type natriuretic peptide; DGE, Division of General Endocrinology; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AC	advisory committee
ACH	achondroplasia
AchNH	Achondrolpasia Natural History
AE	adverse event
AGV	annualized growth velocity
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	antero-posterior
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CMC	cervicomedullary compression
CNP	C-type natriuretic peptide
CSR	clinical study report
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DBP	diastolic blood pressure
DMC	data monitoring committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
FAS	full analysis set;
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities Query
HR	heart rate
HRQoL	Health-Related Quality of Life
IC_{50}	half maximal inhibitory concentration
IND	investigational new drug
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute–Common Terminology Criteria for Adverse Event
NDA	new drug application
NH	natural history
NOAEL	no observed adverse effect level
NPR-B	natriuretic peptide receptor-B
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
PD	pharmacodynamic
PI	Prescribing Information
PK	pharmacokinetic
PMR	postmarketing requirement
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure

SDS	standard deviation score
SMD	standardized mean difference
SOC	system organ class
T_{max}	time to maximum concentration
TQT	thorough QT
ULN	upper limit of normal

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I. Executive Summary

1. Summary of Regulatory Action

Vosoritide was approved in 2021, under the accelerated approval pathway, to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. The Applicant is required to conduct a post-marketing study to assess final adult height. With this supplemental new drug application (sNDA) for vosoritide, the Applicant is seeking to expand the indication to include patients under the age of 5.

This sNDA was reviewed by the multidisciplinary review team. Each discipline recommends approval, and I, the signatory authority for this application, concur with those recommendations. Based on the data submitted, vosoritide will be approved under the accelerated approval pathway with the following indication: Voxzogo is indicated to increase linear growth in pediatric patients with achondroplasia with open epiphyses. Consistent with the requirements following the original approval, the Applicant will be required to conduct a post-approval trial to verify the clinical benefit of improved final adult height based on the intermediate clinical endpoint of improved annualized growth velocity.

In the original review and approval, there were scant data for subjects below age 5. Extrapolation from older children could not be applied in this disease which--although generally similar across ages—has growth patterns, disproportionality, and comorbid conditions that are age-dependent. The team concluded that neither efficacy nor safety could be extrapolated to children under 5 years of age. Therefore, vosoritide was approved for children 5 and above.

In this sNDA, the Applicant provides growth and disproportionality data from a phase 2 study which show similarity between the two age groups and therefore provides assurance that extrapolation of efficacy to the younger group is appropriate. Furthermore, the Applicant has provided pharmacokinetic data—which shows that vosoritide exposure with the proposed doses in the younger age group are within the range of exposures observed in the Phase 3 Study (111-301) in > 5 years old children with ACH--as well as reassuring safety data that both allow for extrapolation. Therefore, substantial evidence of effectiveness is based on the previous findings of effectiveness of the drug in the older age group (> 5 years old), together with scientific evidence that justifies such reliance.

In 2018, a Pediatric Advisory Committee /Endocrinologic and Metabolic Drugs Advisory Committee meeting was held to identify therapeutic goals of the achondroplasia community and to discuss the appropriate elements of the clinical development program of vosoritide for treatment of achondroplasia. The committee agreed that the sub-population of children younger than 2 years of age should be the priority for study. The committee suggested that the greatest benefit for patients may be through improvement in early growth parameters. The committee noted that, for example, the cardiorespiratory and neurologic complications of ACH are a function of the size of the chest and foramen magnum, respectively, and these may be mitigated through early treatment.

Unfortunately, in this sNDA, there is no evidence of vosoritide benefit on other disease manifestations (i.e., foramen magnum area) beyond height in children with achondroplasia <5 years of age.

The safety data in this supplement show that vosoritide is safe for its intended use in the expanded population. I concur that identified risks can be mitigated through labeling. The overall benefit-risk is favorable as described in the Benefit-Risk Framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Integrated Assessment document and the Product Quality Review.

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2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Achondroplasia (ACH) is a rare disease of skeletal dysplasia caused by a gain-of-function mutation in the FGFR3 gene, which leads to disruption in chondrocyte proliferation and differentiation in the growth plate with resulting inhibition of linear bone growth. • ACH manifests by disproportional growth and severe short stature as well as serious complications (i.e., increased mortality, particulary in infants, spinal cord compression and associated neurological complications, sleep disorders, chronic otitis media, hearing loss, kyphoscoliosis, spinal stenosis). • The combination of impairments in body structure and function presents significant social challenges and difficulty in performance of activities of daily living. • A 2018 Pediatric Advisory Committee /Endocrinologic and Metabolic Drugs Advisory Committee agreed that the sub-population of children less than 2 years of age should be the priority for study. The committee suggested that the greatest benefit for patients may be through improvement in early growth parameters. The committee noted that, for example, the cardiorespiratory and neurologic complications of ACH are a function of the size of the chest and foramen magnum, respectively, and these may be mitigated through early treatment.	ACH is a serious medical condition that is associated with disproportional and delayed growth, leading to severely short final adult height, multiple neurological, respiratory, and skeletal comorbidities, as well as impaired functional and social performance. Targeting of certain disease manifestations, sush as foramen magnum diameter, in the youngest children with achonroplasia, particularly those below 2, is critically important to try to modify or prevent serious complications.
Current treatment options	• Vosoritide is approved to increase linear growth in children with achondroplasia with open epiphyses 5 years of age and older, but there is no approved pharmacologic	Achondroplasia is a condition with an unmet medical need; currently, there is no cure or specific treatment for achondroplasia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment in US in children with achondroplasia younger than 5 years of age. • Recombinant human growth hormone has been used off-label to improve linear growth. However, no clear long-term benefit on final height has been established. • Surgical limb lengthening has been used to increase stature, in adolescent children with achondroplasia. However, the procedure is controversial as it often requires repeat procedures, long-term use of orthopedic appliances, and is associated with surgical complications. – Other supportive treatments are intended to prevent or treat complications of the disease (i.e., limb deformity, spinal stenosis, sleep apnea)	Vosoritide is the only approved medical therapy to increase linear growth in children with achondroplasia 5 years of age and older, while there is no approved pharmacologic treatment in US in children with achondroplasia younger than 5 years of age. The available supportive treatments aim to prevent or treat complications of the disease. Medical treatment that induces linear growth has a potential to improve final adult height, potentially leading to improved functional performance and decreased social stigma associated with severe short stature.
Benefit	• The efficacy of vosoritide in children with achondroplasia <5 years of age relies on pediatric extrapolation, specifically on FDA's previous findings of effectiveness of vosoritide in children with achondroplasia 5 years of age and older. Extrapolation is appropriate because growth and disproportionality data from the phase 2 trial (111-206) show similarity between the below 5 and the 5 and above age groups. Pharmacokinetic and safety data now allow for extrapolation to the proposed younger age group. • The effect of vosoritide on other important clinical endpoints, such as changes in the MRI parameters of skull and brain morphology (i.e., foramen magnum area) and sleep study indices, was not different from placebo after one year of treatment in Trial 111-206.	The substantial evidence of effectiveness of vosoritide in children with achondroplasia <5 years of age relies on extrapolation of efficacy from the older pediatric population. The new data provided in the supplement, including pharmacokinetic data and assuring growth data from Trial 111-206, as well as no apparent worsening of disproportionality, allow for extrapolation of FDA's previous findings of effectiveness of vosoritide in children with achondroplasia 5 years of age and older. Verification of the clinical benefit of vosoritide on final adult height in children with achondroplasia <5 years of age is needed. There is no evidence of drug benefit on other disease manifestations, including foramen magnum area, beyond height in children with achondroplasia <5 years of age.
Risk and risk management	• The most common adverse events associated with vosoritide in the randomized, placebo-controlled Phase 2 study (111-206) were injection site reaction (79%), injection site erythema (77%), rash (28%), injection site swelling (19%), viral infection (19%), fall (16%), injection site urticaria (14%), injection site induration (12%). • Injection site reactions were nonserious, mild, resolved within short period of time, and did not lead to treatment discontinuation.	The safety profile of vosoritide has been sufficiently characterized in the clinical program in children with achondroplasia <5 years of age. The safety profile of vosoritide in children <5 years of age is similar to the safety profile described in the approved label for older children (ages 5 to 18 years). No new safety signals were detected in the studied population of children <5 years of age. The label adequately describes the known risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Vosoritide has the potential to induce abnormal bone growth, while the increase in drug-induced linear growth carries a potential risk of worsening skeletal deformities and disproportionality. – No adverse events that may potentially be associated with vosoritide-induced abnormal bone growth, or accelerated growth, such as worsening or new bone deformities, arthralgia, fractures, and other ACH-related comorbidities were noted in the phase 2 study 111-206. – No new or worsening skeletal deformities (spine and lower extremities) were detected on x-ray during the first year of treatment with vosoritide in 111-206 or its extension study. • Because vosoritide induces vascular muscle relaxation. it carries a potential risk of hypotension, which is a labeled risk. – Changes in blood pressure with vosoritide were small and transient. – During Trials 111-206 and the extension 111-208, two subjects had AEs of hypotension or blood pressure decreased that were mild, transient, and did not require medical treatment. – No serious adverse events of hypotension were reported. • The immunogenicity data in Trials 111-206 and 111-208 did not raise any concerns. No severe allergic reactions were reported.	APPEARS THIS WAY ON ORIGINAL

Abbreviations: ACH, achondroplasia; AE, adverse event; AGV, annualized growth velocity; CI, confidence interval; FDA, Food and Drug Administration; FGFR3, fibroblast growth factor receptor 3; MRI, magnetic resonance imaging; US, United States

2.2. Conclusions Regarding Benefit-Risk

Achondroplasia (ACH) is a rare (1 in 25,000 births) and serious condition characterized by severe short stature and disproportionate growth (normal size torso and short limbs). Abnormal bone growth in ACH is associated with serious comorbidities, including neurological, musculoskeletal, and cardiorespiratory disorders. The primary deficit in ACH is a mutated, constitutively active Fibroblast Growth Factor Receptor 3 (FGFR3) that negatively affects skeletal growth and development through inhibition of mitosis and cellular differentiation of chondrocytes, as well as matrix deposition in active growth plates.

Vosoritide is approved to increase linear growth in children with achondroplasia with open epiphyses, 5 years of age and older. There are no approved treatments in children under 5 years of age. Vosoritide is a modified recombinant human C-type natriuretic peptide (CNP) that inhibits the FGFR3 signaling pathway and consequently stimulates chondrocyte proliferation and differentiation, which promotes linear growth. Other therapies that address short stature in ACH pre-epiphyseal closure include off-label use of human growth hormone and surgical limb lengthening. The benefit of growth hormone therapy on final adult height has not been established. Surgical limb lengthening of the lower extremities is associated with significant surgical complications and requires repeated procedures and long-term use of orthopedic appliances.

The efficacy of vosoritide on short-term linear growth in children with achondroplasia <5 year of age relies on extrapolation, specifically FDA's previous findings of effectiveness of vosoritide in children with achondroplasia 5 years of age and older. In the two age groups, there is shared general pathophysiology and in this sNDA there are data that show that growth and disproportionality in the 2 groups is similar, findings that provide assurance that extrapolation of efficacy to the younger group is appropriate. Furthermore, the Applicant has provided pharmacokinetic data and safety data that allow for extrapolation. The benefit of vosoritide on final adult height will be confirmed postmarketing.

The safety profile of vosoritide has been adequately characterized in the clinical program in children with achondroplasia <5 years of age. Overall, vosoritide had a favorable safety profile in the studied patient population and is similar to the safety profile described in the approved label. The most frequent adverse reactions were injection site reactions, which were nonserious, mild, resolved within short period of time, and did not lead to treatment discontinuation. Similar to children 5 years of age and older, vosoritide-induced blood pressure changes (hypotension) were asymptomatic, transient, and did not have obvious clinical significance. There were no new safety signals identified in the studied population of children <5 years of age.

In conclusion, the benefits of vosoritide outweigh the risks for treatment of short stature in pediatric patients with ACH <5 years of age. The safety and efficacy data support expansion of the indication for vosoritide to increase linear growth in pediatric patients with ACH <5 years of age, under accelerated approval pathway.

II. Interdisciplinary Assessment

3. Introduction

The Applicant, BioMarin, submitted this supplemental new drug application (sNDA) for vosoritide, to expand the indication to increase linear growth in pediatric population with achondroplasia <5 years of age, while the indication granted with original new drug application (NDA) approval was limited to children with achondroplasia 5 years of age and older, whose epiphyses are not closed.

Achondroplasia (ACH) is a rare (1 in 25,000 births) but serious condition characterized by severe short stature (average adult height: 131 cm/4 feet 3 inches [men] and 124 cm/4 feet [women], or approximately a -6 standard deviation score [SDS] below average stature) and disproportionate growth (normal size torso and short limbs) that is associated with frequent comorbidities (e.g., neurological, musculoskeletal, cardiorespiratory, and ear, nose and throat system-related) due to abnormal skeletal architecture. The primary deficit in ACH is a constitutively active mutated fibroblast growth factor receptor 3 (FGFR3) that negatively affects skeletal growth and development through inhibition of mitosis and cellular differentiation of chondrocytes, as well as matrix deposition in active growth plates. Vosoritide is the only medical therapy approved by FDA to increase linear growth in children with achondroplasia 5 years of age and older with open epiphyses (NDA 214938, November 19, 2021). The drug was approved under accelerated approval pathway, with evaluation of clinical benefit (i.e., improvement in final adult height) to be performed in postmarketing confirmatory trials. There is no approved pharmacological therapy in United States in children with achondroplasia <5 years of age. Other therapies that address short stature in ACH children include human growth hormone and surgical limb lengthening. The benefit of growth hormone therapy on final adult height has not been established and most experts do not recommend growth hormone therapy for ACH (Horton et al. 2007). Surgical limb lengthening of the lower extremities may confer up to 15 to 30 cm of added standing height. However, it is associated with significant surgical complications (e.g., wound complications and complications related to stretching of non-skeletal tissue such as nerves and blood vessels) and requires repeated procedures and long-term use of orthopedic appliances.

Vosoritide is a modified recombinant human C-type natriuretic peptide (CNP) that promotes linear growth by inhibition of the FGFR3 signaling pathway and consequent stimulation of chondrocyte proliferation and differentiation. The proposed dose of vosoritide is 15 mg/kg administered subcutaneously daily in children 2 to <5 years of age, and 30µg/kg administered subcutaneously daily in children <2 years of age.

The Applicant submitted a sNDA for vosoritide to improve growth velocity in pediatric patients with achondroplasia <5 years of age on December 21, 2022. The Applicant included data from 3 clinical studies in the intended population and from natural history (NH) studies to support the efficacy and safety of the drug in the intended patient population. Trial 111-206 was a phase 2, randomized, placebo-controlled, 12-month study evaluating the safety and efficacy of the drug compared to placebo in children <5 years of age, which was followed by the open-label extension Trial 111-208, evaluating the long-term safety and efficacy of the drug. Trial 111-209

is a phase 2, randomized, placebo-controlled, open-label, 24-month study to evaluate the safety of vosoritide in infants and young children (0 – ≤12 months) with ACH at risk of requiring cervicomedullary decompression surgery. The Applicant also included data from natural history studies to be used as an external control group to evaluate the vosoritide-attributable effect on growth in Trial 111-208, which was uncontrolled (long-term treatment with placebo in pediatric subjects with ACH was considered not feasible).

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

The review team identified 5 key review issues that had a significant impact on the overall determination of the approvability of vosoritide in children with ACH <5 years of age. Some of these issues were identified prior to submission of the sNDA, whereas others emerged during the sNDA review. In depths analyses of the benefit and risk issues can be found in Section 6.3 and 7.7, respectively.

3.1.1.1. Sources of Substantial Evidence of Effectiveness

3.1.1.2. Apparent Smaller Effect of Vosoritide on Growth Velocity in Children With Achondroplasia <5 Years Compared to Children ≥5 Years of Age

3.1.2. Key Safety Review Issues

3.1.2.1. Blood Pressure Decrease/Hypotension

3.1.2.2. Abnormal Skeletal Growth

3.2. Approach to the Clinical Review

Table 3 provides an overview of the clinical trials reviewed to evaluate the risk and additional evidence of benefit of vosoritide in children with achondroplasia <5 years old.

Trial 111-206, conducted in children <5 years old with ACH, was not adequately powered to evaluate the effect of the drug on linear growth and did not achieve statistical significance in the primary endpoint among the randomized subjects, and as such, it is not considered to be an adequate and well-controlled study to demonstrate substantial evidence of efficacy. During the review of the original NDA application, data in children below the age of 5 were scant, and the FDA team determined that extrapolation of efficacy data from older (≥ 5 years of age) to younger (<5 years of age) children was not appropriate at because of differences in growth

patterns, disproportionality, and comorbid conditions between the 2 age groups. There were also concerns with inadequate safety data in the youngest children, particularly what effect vosoritide would have on the growth of cranial and axial endochondral bones in the youngest kids. After review of data submitted with the current application, including pharmacokinetic data that are similar to those in the older kids, disproportionality, and safety data in the younger population, the review team now believes that such extrapolation of efficacy is acceptable (Section 6.3.1). Data from the Phase 2 trial provide assurance that the disease is similar in the two age groups, and the pharmacokinetic and safety data in the younger age population allow for extrapolation.

Trials 111-206 and 111-208 provide safety data and evidence of vosoritide-induced growth in children with achondroplasia <5 years of age.

Trial 111-206 was a Phase 2, 52-week, placebo-controlled study conducted in children between 3 months to less than 5 years of age. Efficacy endpoints included height Z-score and AGV. AGV is considered by FDA to be an intermediate efficacy endpoint of growth in short stature conditions characterized by disproportionate growth. AGV was used as the primary efficacy endpoint in Trial 111-301 in children with ACH 5 years of age and older. Growth velocity (i.e., AGV) is highly variable in infants and children up to 2 years of age, therefore, evaluation of height Z-score, which represents height conversion to age-and sex-appropriate standard score (SDS) by comparison with reference data of average stature children, can some of the observed variability. In addition, height Z-score is one of the growth parameters typically evaluated in pediatric clinical trials for short stature. Overall, height Z-score provides supportive evidence of growth in addition to AGV. Additionally, Trial 111-206 evaluated the skull and brain morphology using MRI assessments as secondary efficacy endpoints, since many of the comorbidities affecting children with ACH during early life arise from abnormal cranial development and premature closure of the synchondroses within the first years of life.

Trial 111-208 is an uncontrolled study, which follows subjects previously enrolled in Trial 111-206. In the absence of a control group, it is challenging to distinguish the effect of vosoritide on growth from natural growth. As such, external control data originating from two sources [Achondroplasia Natural History Study (AchNH) and Study 111-901)] were used to evaluate the effect of vosoritide on long-term growth in this population, since long-term treatment with placebo in pediatric subjects with vosoritide is not feasible (refer to Section 6.2.3 for details).

Trial 111-209 is a phase 2, controlled study, of 104 weeks duration on randomized treatment, followed by 156 weeks open-label extension period, conducted in children 0 to ≤12 months, who are at risk of requiring cervicomedullary cord decompression surgery. The primary endpoint is evaluation of safety, while secondary efficacy endpoints include evaluation of the frequency of surgical cervicomedullary decompression over the course of the study, the change in clinical signs and symptoms (including, but not limited to, neurological assessment) every 6 months, and the change in various cranial and brain MRI measurements, including area of foramen magnum, every 6 months. This is an ongoing trial, with limited data (i.e., 9 subjects exposed to vosoritide for approximately 25 weeks) available at the time of the sNDA submission. At the Agency's request, additional safety data were submitted by the Applicant during the review cycle in order to verify the safety profile of the drug in the studied patient population (refer to Section 7.6.8).

Two external control datasets were used as comparators:

- The AchNH study was an investigator-initiated, observational, retrospective study that aimed to characterize growth in patients with a molecular or clinical diagnosis of ACH at

four specialized skeletal dysplasia centers[1] in the United States. Growth was extracted from medical records of the clinical visits in 1,374 eligible patients aged 75 years or younger. The AchNH control included 10,444 anthropometric measurements derived from medical records of 1,142 unique patients aged <8 years.

- Study 111-901 was a prospective cohort study, aiming to collect baseline growth measurements on pediatric subjects with ACH for up to 7 years. If eligible, subjects from Study 111-901 may join the vosoritide clinical studies, including Trials 111-202, 111-206 and 111-301. The placebo arms provided an extension of vosoritide-untreated longitudinal data for one year. Growth data in Study 111-901 were collected every 3 months for at least 6 months (or 3 months for Cohort 3 in Trial 111-206) prior to enrolment into clinical trials. The observational/placebo control encompasses 2,286 anthropometric measurements from 314 subjects aged <8 years in the observational Study 111-901 and the placebo arms of two clinical trials, 111-206 and 111-301.

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[1] The four centers are Johns Hopkins University, Al DuPont Hospital for Children, University of Texas, and University of Wisconsin-Madison.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations1 for Vosoritide in Children With Achondroplasia Age <5 Years

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[2]	No. of Centers and Countries
111-206	Children from birth to <60 months old with achondroplasia	Control type: Placebo, concurrent Randomization: Randomized 1:1 Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: Sentinel population treated prior to randomized population of subjects.	Drug: Vosoritide Dose: 15 µg/kg (age ≥24 months) 30 µg/kg (age <24 months) Number treated: 43 Duration: 52 weeks, 1 dose/day	Primary: Safety/tolerability Change from baseline in height Z-score at Week 52. Key secondary: Change from baseline in height at Week 52 Change from baseline in AGV at Week 52 Change from baseline in upper to lower body segment ratio at Week 52	Planned: 70 Actual: 75	Centers: 16 Countries: 4
111-208	Children with achondroplasia who have completed one year of vosoritide or placebo treatment in Trial 111-206	Open-label, long-term extension study Blinding: During dosing, investigators and subjects blinded to subject's treatment allocation in 111-206	Drug: Vosoritide Dose: 15 µg/kg (age ≥24 months) 30 µg/kg (age <24 months) Number treated: 73 Duration: Until subjects attain near-final adult height (evidence of growth plate closure and <1.5 cm/year annualized growth velocity), 1 dose/day	Primary: Safety/tolerability Change from baseline in height Z-score at Week 52. Key secondary: Change from baseline in height at Week 52 Change from baseline in AGV at Week 52 Change from baseline in upper to lower body segment ratio at Week 52	Planned: N/A Actual: 73	Centers: 16 Countries: 4

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[2]	No. of Centers and Countries
111-209	Pediatric subjects with achondroplasia aged 0 to ≤12 months, at risk of requiring cervicomedullary cord decompression surgery	Control type: Standard-of-care Randomization: Stratified randomization Blinding: Open-label	Drug: Vosoritide Dose: 30 µg/kg Number treated: 11 vosoritide, 9 placebo Duration: Up to 268 weeks, 1 dose/day	Primary: Safety Secondary: Frequency of surgical cervicomedullary decompression over the course of the study Change in clinical signs and symptoms (including, but not limited to, neurological assessment) every 6 months Change in MRI measurement of area of foramen magnum and antero-posterior (AP) diameter, brain stem and spinal cord volume and ratio of area of spinal cord to foramen magnum every 6 months	Actual: 20	Centers: 3 Countries: 2
111-301	Pediatric subjects ages 5 to <18 years with achondroplasia	Control type: Placebo concurrent Randomization: Stratified randomization Blinding: Double-blind	Drug: Vosoritide Dose: 15µg/kg daily subcutaneous injection Number treated: 60 vosoritide, 61 placebo Duration: 52 weeks, 1 dose/day	Primary: Change from baseline in annualized growth velocity at Week 52 Secondary: Change from baseline in height Z-score at Week 52 Change from baseline in upper to lower body segment ratio at Week 52	Planned: 110 Actual: 121 – (60 vosoritide, 61 placebo)	Centers: 24 Countries: 7

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[2]	No. of Centers and Countries
111-302	Pediatric subjects with achondroplasia who completed Study 111-301	Control type: No treatment concurrent (single arm) Randomization: No randomization (single arm) Blinding: Open-label	Drug: Vosoritide Dose: 15µg/kg daily SC injection Number treated: 119 vosoritide Duration: 5 years, or until subject attains NFAH (evidence of growth plate closure and 6-month interval AGV <1.5 cm/year), whichever comes later	Primary: Change from baseline in AGV Key secondary: Change from baseline in height Z-score Change from baseline in upper to lower body segment ratio	Actual: 119	Centers: 24 Countries: 7
111-202	Pediatric subjects ages 5 to 14 years with achondroplasia	Control type: No treatment concurrent (single-arm) Randomization: No randomization (single-arm) Blinding: Open-label	Drug: Vosoritide Dose: 2.5, 7.5, 15, or 30µg/kg daily SC injection with escalation after 6 months in 2.5 and 7.5µg/kg groups Number treated: 35 (Initial dosage: 8 on 2.5µg/kg, 8 on 7.5µg/kg, 10 on 15µg/kg, and 9 on 30µg/kg) Duration: Up to 24 months	Primary: Safety/tolerability Key secondary: Change from baseline in AGV, growth measures, and body proportions	Actual: 35	Centers: 9 Countries: 4

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[2]	No. of Centers and Countries
111-205	Pediatric subjects with ACH achondroplasia who completed 2 years of vosoritide treatment in Study 111-202	Control type: No treatment concurrent (single-arm) Randomization: No randomization (single-arm) Blinding: Open-label	Drug: Vosoritide Dose: 15 or 30µg/kg daily SC injection Number treated: 30 (6 on dose of 2.5 to 7.5 to 15µg/kg in Study 111-202, then 15µg/kg in 205; 6 on dose of 7.5 to 15µg/kg in Study 111-202, then 15µg/kg in 205; 10 on 15µg/kg; 8 on 30µg/kg) Duration: 5 years, or until subject attains NFAH) (evidence of growth plate closure and 6-month interval AGV <1.5 cm/year), whichever comes later	Primary: Safety/tolerability Key secondary: Change from baseline in AGV, growth measures and body proportions	Actual: 30	Centers: 9 Countries: 4
AchNH	All prior or current subjects of all ages with a diagnosis of achondroplasia at participating study sites	Observational, retrospective	Drug: not applicable	Anthropometry data collection (height, height velocity, weight, BMI, head circumference)	Actual: 1374	Centers: 4
111-901	Pediatric subjects with achondroplasia from birth to age ≤17 years	Observational, prospective	Drug: not applicable Duration: up to 7 years	Growth measurements on subjects being considered for subsequent enrollment in Studies 111-202, 111-301, and 111-206	Actual: 363	Centers: 27

Source: Generated by the Clinical Review Team based on Clinical Study Reports and adsl.xpt
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled."
Abbreviations: AchNH, achondroplasia Natural History; AGV, annualized growth velocity; AP, antero-posterior; BMI, body mass index; MRI, magnetic resonance imaging; N/A, not applicable; NFAH, near final adult height; SC, subcutaneous

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☒	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☒	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

No additional nonclinical data were submitted to support the expanded indication in younger patients. The nonclinical data supporting clinical investigation in younger patients and the overall effectiveness were summarized in the original review of the NDA. Refer to Integrated review dated November 18, 2021, in DARRTS (FDA 2021), for details.

5.2. Clinical Pharmacology/Pharmacokinetics

The Clinical Pharmacology and Pharmacokinetics of vosoritide was summarized in the original review of the NDA. Refer to original NDA for details. The pediatric efficacy supplement

included pharmacokinetic data in pediatric patients aged 4.5 months to < 5 years old. The vosoritide exposure after the proposed doses were within the range of exposures observed in the Phase 3 (Study 111-301) in > 5 years old children with ACH. In subjects under 5 years of age, 33% (20/61) of vosoritide-treated subjects tested positive for anti-drug antibody (ADA) and all placebo-treated subjects tested negative for ADA for up to 43 months. All of the ADA-positive subjects tested negative for neutralizing antibodies at all time points. No obvious impact of ADA on PK parameters (C_{max} and AUC_{0-t}) or efficacy (change from baseline in Height Z-Score to Week 52) was observed. This supplement also included in vitro studies indicating that vosoritide was not an inhibitor of the human uptake (OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3) and efflux (MATE1, MATE2-K, BCRP, P-gp, and BSEP) transporters at clinically relevant concentrations.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Is the Proposed Weight-Band Dosing Regimen Of Vosoritide Appropriate for Patients Aged Less Than Five Years?

Yes, the proposed weight-band dosing regimen is appropriate for patients <5 years old. Under the original NDA review cycle, the weight-band dosing for vosoritide was approved in patients weighing ≥10 kg (Table 5). As per the original exposure-response analysis in pediatric patients with achondroplasia (ACH) aged ≥5 years (Studies 111-202 and 111-205), the change in annualized growth velocity (AGV) at Month 6 plateaued at an exposure of 15µg/kg and there was no obvious improvement in AGV for subjects receiving vosoritide 30 µg/kg compared to 15 µg/kg at Month 48. The population pharmacokinetic (PK) analyses in the original submission had also shown that the body weight-normalized apparent clearance of vosoritide decreased with increasing body weight in patients with ACH. Hence, the original approved weight band dosing recommended doses [redacted] (b) (4)

Table 5. Dosing Regimen for Vosoritide Approved in the United States for ACH Patients Weighing 10 kg and Above

Actual Body Weight (kg)	Dose	Vial Strength for Reconstitution*	Injection Volume
10-11	0.24 mg	0.4 mg	0.3 mL
12-16	0.28 mg	0.56 mg	0.35 mL
17-21	0.32 mg	0.56 mg	0.4 mL
22-32	0.4 mg	0.56 mg	0.5 mL
33-43	0.5 mg	1.2 mg	0.25 mL
44-59	0.6 mg	1.2 mg	0.3 mL

Actual Body Weight (kg)	Dose	Vial Strength for Reconstitution*	Injection Volume
60-89	0.7 mg	1.2 mg	0.35 mL
≥90	0.8 mg	1.2 mg	0.4 mL

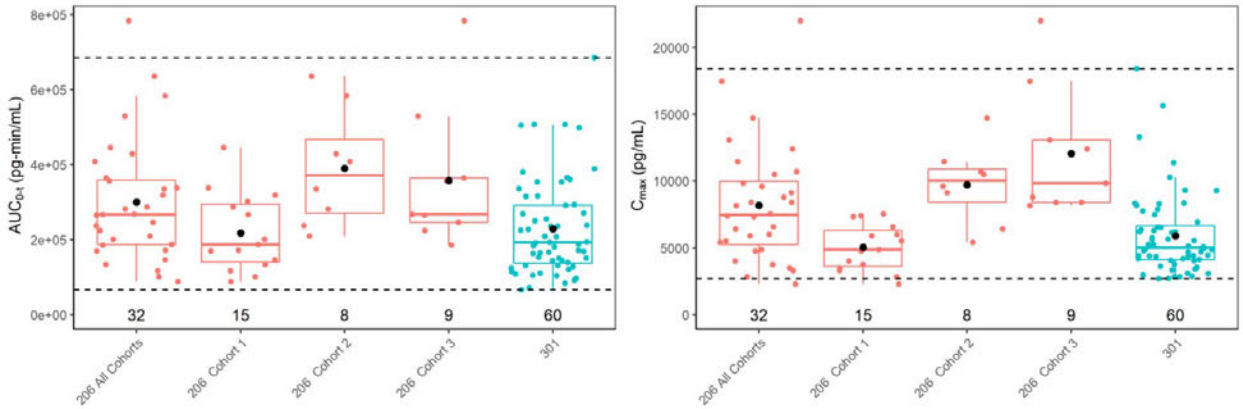
Source: U.S. Prescriber Information for Voxzogo
*The concentration of vosoritide in reconstituted 0.4 mg vial and 0.56 mg vial is 0.8 mg/mL. The concentration of vosoritide in reconstituted 1.2 mg vial is 2 mg/mL.
Abbreviations: ACH, achondroplasia; US, United States

In the current efficacy supplement, the Applicant has proposed to add the weight-band dosing regimen for children weighing < 10 kg (Table 6) and maintain the same dosing recommendation for children weighing ≥ 10 kg, based on results of Trial 111-206.

Dose Selection for Trial 111-206

Trial 111-206 was a randomized, double-blind, placebo-controlled study to test the efficacy and safety of vosoritide in children with ACH <5 years old. In this study, the dose selection for ACH patients <5 years old was based on targeting the exposures after the reference dose of 15 µg/kg/day in ≥ 5 years old patients (Study 111-202). Based on the exposures observed in a sentinel cohort of subjects (AUC_{0-t} for 4 hours) in Trial 111-206, patients ≥ 2 years old received daily vosoritide dose of 15µg/kg and patients <2 years old received daily vosoritide dose of 30µg/kg. When subjects turn 2 years old, the dose was reduced to 15µg/kg/day. Consistent with the higher doses received, the median exposures in cohorts 2 (children aged ≥ 6 to < 24 months) and 3 (children aged 0 to < 6 months) were higher than in cohort 1 (children aged ≥ 24 to < 60 months) but the overall exposure values for both AUC_{0-t} and C_{max} were within the range of exposures observed in the Phase 3 (Study 111-301) in > 5 years old children with ACH, as shown in Figure 1.

Figure 1. Comparison of Vosoritide AUC_{0-t} and C_{max} Across Studies 111-206 and 111-301



Source: Module 5.3.4.2, Comparative Pharmacokinetics and Biomarker Analysis Report for 111-206 and 111-301, Figure 5.2.1.1
The line inside the box represents the median, the box represents the limits of the middle half of the data. The range of the box, from the first quartile (Q1) to the third quartile (Q3), defines the interquartile range (IQR). Each circle represents individual mean exposure (AUC_{0-t} and C_{max}) across visit. The mean exposure of all the subjects at that visit is shown as a black circle. The numbers at the bottom of each plot indicate the number of subjects with PK data available for that visit. Dashed lines represent minimum and maximum limits from 111-301 study.
Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from 0 to the time of last measurable concentration; C_{max}, maximum observed plasma concentration

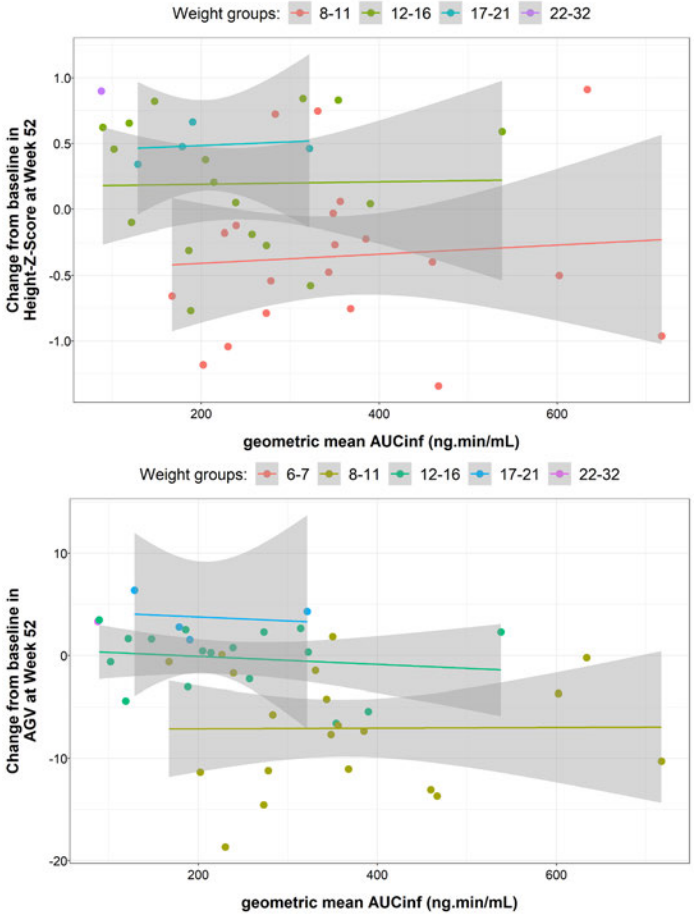
Exposure-Response on pharmacodynamic markers and efficacy endpoints

There was an increase in exploratory pharmacodynamic (PD) biomarkers (urinary cyclic GMP and serum collagen X marker) in response to vosoritide treatment in comparison to placebo.

Across all the cohorts, a significant correlation was observed between the maximum change from baseline in urine cGMP/Cr and C_{max} and AUC_{0-t} of vosoritide ($p<0.05$). However, no apparent correlation was observed between individual mean vosoritide exposure and mean CXM (from Week 6 to Week 39). See Section 13.2 for additional information. In general, the cGMP response was comparable or even higher across the cohorts of Trial 111-206 compared to Study 111-301 while the serum CXM response compared to placebo was decreased especially in cohorts 2 and 3 of Trial 111-206 in comparison to Study 111-301.

The primary efficacy endpoint in study 111-206 was the change in height Z-score from baseline to Week 52. The endpoint of annualized growth velocity (AGV) was not used as primary endpoint due to the rapidly declining growth velocity in children younger than 3 years and this may result in high variability between the children of different age groups in Trial 111-206. The exposure-response (ER) analyses for efficacy endpoints (Change in height Z-score and AGV from baseline to Week 52) were evaluated by Applicant for all the subjects together as well as subjects separated by cohorts. Within each cohort, there was no apparent correlation between individual vosoritide exposure and the change in height-Z score or AGV from baseline. The reviewer's independent ER analysis adjusting for either cohorts (not shown) or body weight groups (Figure 2) did not find a significant relationship between the change from baseline in height-Z score or AGV at Week 52 and the mean AUC_{inf} estimated by NCA for either the observed data (Figure 2) or the model-predicted data (not shown). The ER analysis results conform to the expected pattern considering the exposures were associated with the narrow range of doses that were used in the Trial 111-206.

Figure 2. Exposure-Response Analysis for Changes in Height Z Score and AGV From Baseline at Week 52 by Mean AUC_{inf} in Trial 111-206



Source: FDA Reviewer.
Note: Solid lines are the fits through the data and the shaded regions are the 95% CI. The data were fit using a linear regression with body weight groups (kg) as an interaction term. At Week 52, the data contained only one subject with body weight 6-7 kg and 22-32 kg and no data for subject with 5 kg.
Abbreviations: AGV, annualized growth velocity; AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinite time; CI, confidence interval

Switch from age-based dosing to weight-band dosing

Despite age-base dosing was used in Trial 111-206 (i.e., 15 µg/kg for patients 2-5 years old and 30 µg/kg for patients <2 years old), the proposed weight-band dosing for ACH patients < 10 kg was supported by population PK modeling and simulation.

In cohort 1, the mean body weight across PK visits ranged between 13 to 15 kg (received dose of 15 µg/kg) and in cohorts 2/3 the mean body weight across PK visits ranged between 5 to 11 kg (received 30 µg/kg), respectively. The actual dosing in Trial 111-206 and proposed weight-band doses for ACH patients weighing < 10 kg is shown in Table 6. The proposed doses range between 27 to 33 µg/kg compared to the randomized doses of 30 to 34 µg/kg (due to rounding off the volume) in the clinical study, which will presumably not lead to clinically significant differences in exposure or response. Specifically, the simulated median AUCs in subjects ≤ 9 kg were similar or lower than the median area under the concentration-time curve (AUC) observed in Study 111-301. However, the lower median AUCs were still within the lower range of the AUCs that were simulated for the subjects >10 kg (Figure 3). The simulated median C_{max} in

subjects ≤ 9 kg were similar or higher than the median C_{max} observed in Study 111-301, but the higher C_{max} were still within the upper range of the simulated C_{max} in heavier subjects (Figure 3). Though the 95th percentile for the simulated C_{max} in the 5 kg to 8 kg patients were slightly exceeding the corresponding interval for the heavier subjects, there was no apparent increase in heart rate based on the analysis of the exposure-response data for heart rate and no adverse clinical outcome was reported in clinical study (See Section 14.5 for additional information). Overall, given the lack of exposure-response relationship for efficacy or safety that were observed within the range of observed and simulated exposures using the weight-based dosing, the proposed doses for ACH patients from 5 kg to 9 kg seems acceptable.

Extrapolation of dosing to infants weighing <5 kg

Trial 111-206 did not include ACH patients with a body weight less than 5 kg. To extend the dosing that can include newborns (at birth), the Applicant has proposed the doses of 96 µg and 120 µg for subjects with body weight of 3 kg and 4 kg, respectively using pharmacokinetic (PK) modeling and simulation. The PK model was used to simulate the expected concentration time profiles with dense sampling over the first 5 hours and the predicted concentrations were further used to derive exposure metrics ($AUC_{[0-5h]}$ and C_{max}). In subjects who weigh 3 and 4 kg and will receive a dose of 30µg/kg, the range of model-predicted $AUC_{[0-5h]}$ and C_{max} are within the range of observed (study 301 dose of 15µg/kg) and predicted exposure metrics (from the approved weight-band dosing) in subjects weighing 5 kg and above. However, the median values of predicted $AUC_{[0-5h]}$ in subjects 3 and 4 kg are within the lower range of the median $AUC_{[0-5h]}$ that was predicted in heavier subjects (Figure 3). See Section 6.1.1 and Section 14.5 for additional information. In general, given the lack of exposure-efficacy relationship that was observed at the exposure range of 200ng.min/mL ($AUC_{[0-5h]}$) in the reference population of patients weighing greater than 5 kg or older than 2 years, and given that no novel safety issues with vosoritide are anticipated, the proposed extrapolation of dosing to infants weighing 3 or 4 kg is considered acceptable. Of note, the extent of elimination of vosoritide by glomerular filtration has not been studied and is unknown, and the Applicant's PK model used for dose extrapolation did not include a renal maturation function to describe the maturation of renal filtration in younger patients < 2 years. A sensitivity analysis was performed to account for the maturation in renal filtration with age in the PK model and to predict vosoritide exposure in infants weighing 3 or 4 kg, with the assumption that vosoritide is completely eliminated by kidneys. The simulation was performed using demographic data from the CDC growth chart to account for the physiological correlation between age and body weight. The sensitivity analysis showed that the proposed dose is expected to remain acceptable, with a predicted $AUC_{[0-5h]}$ and C_{max} in subjects weighing 3 and 4 kg within the range of those values observed and predicted in heavier and older subjects (see Section 14.5). The sensitivity analysis evaluated the highest expected exposure in case the vosoritide is eliminated by kidneys.

Additionally, the currently marketed commercial device will support the lower proposed doses and Applicant has provided the accuracy of the lowest dosing volumes (0.1 mL) using a design verification study.

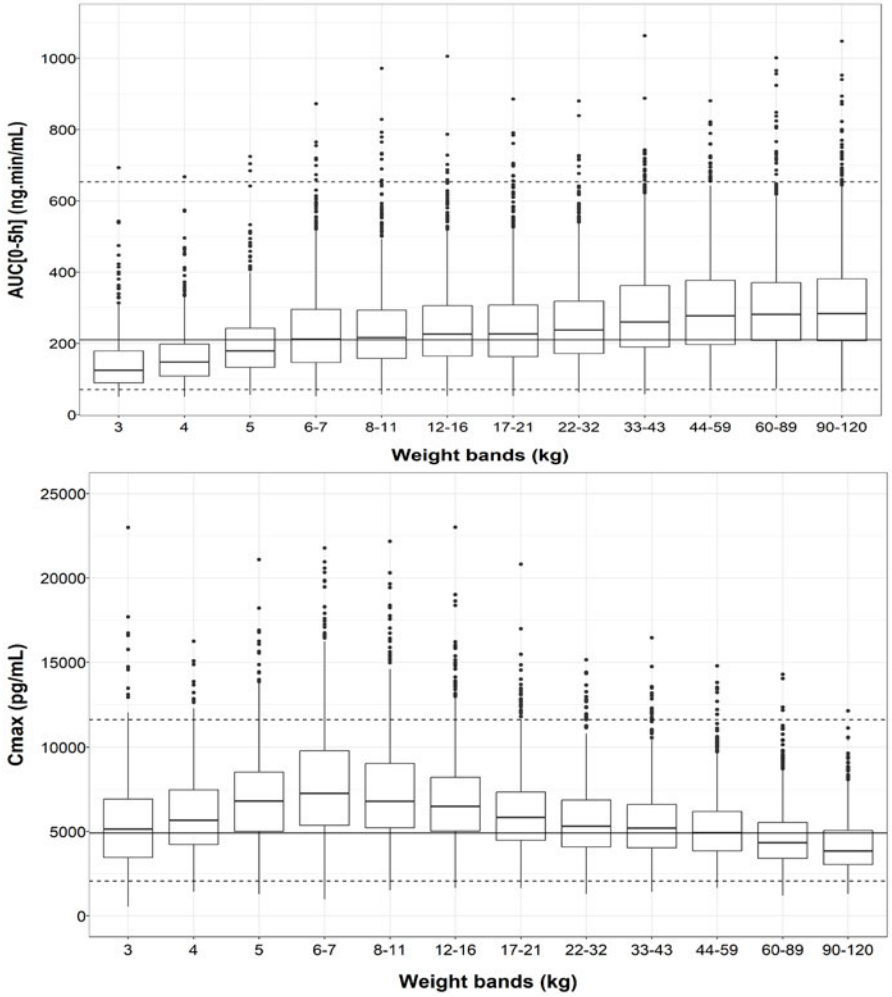
In conclusion, the proposed weight-band dosing regimen of vosoritide is appropriate for patients aged less than 5 years.

Table 6. Proposed Doses vs. Randomized Doses in Trial 111-206 for ACH Subjects Weighing <10 kg

Body Weight (kg)	Randomized Dose (mg)	Proposed Dose (mg)	Proposed Dose (µg/kg)
3	NA	0.096	32
4	NA	0.12	30
5	0.16	0.16	32
6	0.20	0.20	33
7	0.24	0.20	29
8	0.24	0.24	30
9	0.30	0.24	27

Source: Table 2.7.2.3.1.4.3 in Summary of Clinical Pharmacology
NA: There were no subjects weighing 3 or 4 kg in 111-206.
Abbreviations: ACH, achondroplasia

Figure 3. Simulated Vosoritide AUC and C_{max} Based on Weight-Band Dosing Using the Reviewer's Updated PK Model



Source: FDA Reviewer.
Note: the horizontal dashed and solid lines are 5th percentile, median and 95th percentile of the observed $AUC_{(0-t)}$ and C_{max} under a dose of 15µg/kg in study 111-301 of 70500, 210000 and 653000 pg.min/mL and 2060, 4910 and 11600 pg/mL, respectively.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic

6.2. Clinical Trials Intended To Demonstrate Efficacy

6.2.1. Trial 111-206

6.2.1.1. Design, Trial 111-206

Trial 111-206 was designed as a 52-week, randomized, double-blind, placebo-controlled, multicenter trial intended to evaluate the safety and efficacy of vosoritide in subjects with ACH age ≥ 3 months to < 60 months old. The study enrolled the sentinel subjects treated with open-label vosoritide and additional subjects randomized in a 1:1 ratio to receive vosoritide or placebo. The sample size of this study was not based on calculation to achieve certain power to demonstrate efficacy with statistical significance.

The subjects were enrolled into three age cohorts based on their age at study screening, using a staggered, age-descending recruitment approach, as follows: Cohort 1 – children aged ≥ 24 to < 60 months; Cohort 2 - children aged ≥ 6 to < 24 months; Cohort 3 - children aged 0 to < 6 months (treatment began at ≥ 3 months to < 6 months after 3 months of observation period, see below). The subjects in Cohorts 1 and 2 were required to have at least 6 months of baseline growth data collected in the observational Study 111-901. The subjects in Cohort 3 (0 to < 3 months old) could be enrolled directly into Trial 111-206 and have a minimum of 3 months of pretreatment observation (baseline growth data) prior to starting treatment with vosoritide or could be enrolled in Study 111-901 for the 3-month observational period.

Each cohort included at least three sentinel subjects receiving vosoritide to evaluate the short-term safety and PK of the drug before opening the rest of the cohort for randomized subjects.

Endpoints

The primary objective of the study was to evaluate the safety and tolerability of the drug in this age group. The Applicant assessed the following efficacy endpoints:

Change from baseline to Week 52 in height Z-score

Height Z-score itself is not a validated endpoint of clinical benefit, however, it is also one of growth parameters typically evaluated in pediatric clinical trials for short stature and provides additional evidence of growth (together with the improvement in AGV). It is expected that height Z-scores will correlate with improvement in AGV. In addition, growth velocity is highly variable in infants and children up to 2 years of age, therefore, evaluation of height Z-score, which represents height conversion to age-and sex-appropriate SDS by comparison with reference data of average stature children, may attenuate some of the observed variability. As such, evaluation of height Z-score as primary efficacy endpoint in the intended population was found acceptable by the review team.

Other efficacy endpoints included change from baseline to Week 52 in height, change from baseline to Week 52 in AGV, and change from baseline to Week 52 in upper to lower body segment ratio. Upper to lower body segment ratio is a measure of disproportionality, which is of particular importance in this condition where the upper to lower body segment ratio is higher

than in children without ACH. A potential decrease in the ratio as an effect of the drug would be a benefit, while an increase in the ratio as a result of treatment may be associated with increased risk (i.e., decreased mobility). Other efficacy endpoints included evaluation of various skull and brain morphology parameters (i.e., foramen magnum, facial sinus, ventricular and brain parenchymal dimensions), evaluation of sleep study indices, weight, and quality of life. Refer to Section 15.1 for a full list of efficacy endpoints.

For anthropometric measurements, standing height/sitting height were used for subjects age ≥ 24 months at baseline and body length/crown to rump were used for subject age < 24 months at baseline. At Week 52, the like-to-like rule was used based on their measurements available for their age at baseline to ensure the same parameters were compared (e.g., if body length was used at baseline for a subject aged 18 months, body length would be preferred at Week 52 even if the subject became > 24 months, at which time standing height likely became available). However, if body length/crown to rump were not measured, standing/sitting height were used.

6.2.1.2. Eligibility Criteria, Trial 111-206

The inclusion and exclusion criteria were consistent with the indication sought in this application (i.e., to extend the indication of increase linear growth in pediatric patients with ACH to children <5 years of age). The study included subjects ages 3 months to <5 years of age with a confirmed diagnosis of ACH by genetic testing. The Applicant adequately excluded subjects with various medical conditions or medical therapy that might influence growth and hence efficacy assessment, as well as safety assessments (e.g., medications that might affect hemodynamic status). Refer to the Section 15.1 for a detailed list of inclusion and exclusion criteria.

6.2.1.3. Statistical Analysis Plan, Trial 111-206

The efficacy endpoints were analyzed using two analysis population set - full analysis set (FAS), as defined by the Applicant, contained all enrolled sentinel and randomized subjects, and FAS (randomized) which included only the randomized subjects. The Applicant prespecified primary analysis population was the FAS population despite the Agency recommended the randomized subjects be the primary analysis population. Analysis of covariance (ANCOVA) models were used for change from baseline at Week 52 in standing height/body length Z-Score, standing height/body length, AGV, and upper to lower body ratio for individual cohorts and for overall, as appropriate. All ANCOVA models included the following baseline covariates: randomization age stratum, age at baseline, baseline AGV, and sex. Analyses of standing height/body length Z-Score, standing height/body length, and upper to lower body ratio included their baseline as additional covariate. Missing assessments at Week 52 were handled in two different ways as follows:

- if assessments were available before and after Week 52, a linear interpolation using the measurements closest to the before and after Week 52 was used, otherwise
- for the subjects with no assessment after Week 52, multiple imputation by using placebo data from subjects in the same cohort was implemented to impute the missing values for standing height/body length and upper to lower body segment ratio at Week 52.

6.2.1.4. Results of Analyses, Trial 111-206

6.2.1.4.1. Disposition, Baseline Demographics and Baseline Clinical Characteristics

All 75 screened subjects were enrolled in the study and received at least one dose of the study drug (Table 7). Of these, 64 subjects were randomized to receive vosoritide (n = 32, here in referred to as "randomized vosoritide" arm) or placebo (n = 32), while 11 subjects were enrolled as sentinel subjects. All 75 subjects (randomized + sentinel, herein referred to as "all vosoritide") were included in the FAS.

The study completion rate was high, with 73/75 (97%) subjects completing the study (Table 8). Of the two subjects who discontinued the study, one was because of death in the randomized vosoritide arm (Cohort 3) (refer to Section 7.6.2), while the other subject in placebo arm discontinued with the reason of "withdrawal by subject."

Table 7. Subject Screening and Enrollment, Trial 111-206

Disposition	Trial A
Subjects screened	75
Screening failures	0 (0%)
Subjects enrolled	75 (100%)
Sentinel	11 (14.67%)
Subjects randomized	64 (85.33%)

Source: ADSL, ADGM dataset for study 111-206, Statistical Reviewer's analysis

Table 8. Subject Disposition, Trial 111-206

Disposition	Sentinel (N=11)	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)
Subjects enrolled in trial, n (%)[a]	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
Cohort 1	4 (100.0)	15 (100.0)	16 (100.0)	19 (100.0)
Cohort 2	4 (100.0)	8 (100.0)	8 (100.0)	12 (100.0)
Cohort 3	3 (100.0)	9 (100.0)	8 (100.0)	12 (100.0)
Subject's treatment/trial status, n (%)[a]				
Treated	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
Completed treatment	11 (100.0)	31 (96.9)	31 (96.9)	42 (97.7)
Discontinued from treatment	0	1 (3.1)	1 (3.1)	1 (2.3)
Subject's trial status, n (%)[a]				
Completed trial	11 (100.0)	31 (96.9)	31 (96.9)	42 (97.7)
Discontinued from trial	0	1 (3.1)	1 (3.1)	1 (2.3)

Source: ADSL dataset for study 111-206, Statistical Reviewer's analysis.
[a] Percentages were calculated using the total number of participants in the full analysis set of each column as the denominator.
Cohort 1 included participants aged ≥24 to <60 months, Cohort 2 included participants aged ≥6 to <24 months and Cohort 3 included participants aged 0 to <6 months.
Abbreviation: N, number of subjects

All 73 subjects were enrolled into the extension Trial 111-208 and were treated with vosoritide.

The compliance rate with the treatment regimen was high in all treatment arms (98.7% randomized vosoritide versus 98.8% randomized placebo), with ≥ 80% of the subjects reporting a 100% compliance rate in all treatment arms. (Table 47, Section 16.1).

Baseline demographic characteristics were generally balanced between treatment arms (randomized vosoritide/all-vosoritide versus placebo (Table 9) in the study. Subjects in randomized vosoritide arm were slightly younger than those in placebo arm (mean [SD] age: 23.0 [16.9] randomized vosoritide versus 26.5 [19.3] randomized placebo). The age range of the subjects on Day 1 of study treatment ranged from 4.4 months to 59.8 months in all subjects enrolled. Males and females were both well-balanced in the study. The majority of subjects were White (66% randomized vosoritide versus 78% randomized placebo), followed by Asian (31% randomized vosoritide versus 19% randomized placebo).

The baseline demographic characteristics were also well-balanced in each age Cohort (Table 48).

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Table 9. Baseline Demographic Characteristics, Trial 111-206, FAS

Demographic Characteristic	Sentinel (N=11)	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)
Age at Screening, months				
Mean (SD)	23.4 (21.0)	23.0 (16.9)	26.5 (19.3)	23.1 (17.8)
Median	15.0	22.0	25.5	20.0
Min, max	3, 59	3, 54	2, 58	3, 59
Age on Day 1, months				
Mean (SD)	24.71 (20.79)	24.39 (16.83)	27.82 (19.25)	24.47 (17.66)
Median	16.03	23.29	26.43	21.82
Min, Max	4.5, 59.8	4.8, 55.3	4.4, 59.8	4.5, 59.8
Sex, n (%)[a]				
Male	8 (72.7)	17 (53.1)	13 (40.6)	25 (58.1)
Female	3 (27.3)	15 (46.9)	19 (59.4)	18 (41.9)
Race, n (%)[a]				
White	8 (72.7)	21 (65.6)	25 (78.1)	29 (67.4)
Asian	1 (9.1)	10 (31.3)	6 (18.8)	11 (25.6)
Other	1 (9.1)	6 (18.8)	2 (6.3)	7 (16.3)
Japanese	0	4 (12.5)	4 (12.5)	4 (9.3)
Multiple	2 (18.2)	1 (3.1)	0	3 (7.0)
Native Hawaiian or Other Pacific Islander	0	0	1 (3.1)	0
Ethnicity, n (%) [a]				
Not Hispanic or Latino	11 (100.0)	29 (90.6)	29 (90.6)	40 (93.0)
Hispanic or Latino	0	3 (9.4)	3 (9.4)	3 (7.0)

Source: ADSL dataset for study 111-206, Statistical Reviewer's analysis
[a] Percentages were calculated using the total number of participants in the full analysis set of each column as the denominator. Max, maximum; Min, minimum; SD, standard deviation.
Abbreviations: FAS, full analysis set; max, maximum; min, minimum; N, number of subjects; n, number of subjects within specific demographic; SD, standard deviation

Disease characteristics

At baseline, the mean height Z-score and annualized growth velocity were slightly higher in the randomized vosoritide (and all vosoritide) arm compared to randomized placebo arm. The higher annualized growth velocity could be explained, at least in part, by the slightly younger age of the vosoritide treatment arm cohort.

Table 10. Baseline Growth Characteristics (Mean[SD]), Trial 111-206, FAS

Growth Measure (Mean[SD])	Sentinel (N=11)	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)
Height Z-score	-4.15 (0.65)	-3.79 (0.97)	-4.28 (1.48)	-3.88 (0.90)
Height (cm)	69.76 (12.16)	70.90 (10.42)	70.84 (10.88)	70.61 (10.75)
Annualized growth velocity (AGV) (cm/year)	13.39 (8.64)	11.06 (7.57)	9.60 (7.74)	11.66 (7.82)
Upper to lower body segment ratio	2.60 (0.46)	2.60 (0.41)	2.52 (0.36)	2.60 (0.42)
Head circumference (cm)	50.44 (5.08)	50.68 (4.53)	50.96 (4.41)	50.62 (4.62)

Source: ADSL dataset for study 111-206, Statistical Reviewer's analysis
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.
Abbreviations: AGV, annualized growth velocity; N, number of subjects; n, number of subjects with specific growth characteristic; SD, standard deviation

The treatment arms were overall well-balanced in terms of ACH comorbidities, except for the system organ class (SOC) Nervous System Disorders where subjects in vosoritide arm had a higher rate of comorbidities (40%) compared to placebo arm (22%) [i.e., hypotonia (16% versus 3%), hydrocephalus (12% versus 3%), spinal cord compression (12% versus 0), cervical cord compression (7% versus 3%)] (Table 49).

6.2.1.4.2. Efficacy Results

6.2.1.4.2.1. Primary Analysis

The change in height Z-score from baseline to Week 52 in the vosoritide and placebo groups is summarized in Table 11. Although the sample size was not based on achieving certain power to demonstrate efficacy, the results of the Applicant's primary analysis were significant in the FAS with treatment effect 0.30 and 95% CI (0.07, 0.54) based on the prespecified analysis method. However, this endpoint did not achieve statistical significance at level 0.05 in the Agency-recommended randomized population. The ANCOVA analysis showed a positive treatment difference at Week 52 of 0.24 SDS in the vosoritide group compared with placebo among the randomized subjects.

Table 11. Analysis of Covariance of Height Z-Score at Week 52

Height Z-Score	Placebo	Vosoritide
Randomized		
N	32	32
Baseline, mean (SD)	-4.28 (0.26)	-3.79 (0.17)
LSM change from baseline (95% CI)	-0.31 (-0.48, -0.13)	-0.06 (-0.26, 0.15)
Difference in LSM (95% CI)[a]	0.24 (-0.02, 0.53)	
p-value[b]	0.065	

Height Z-Score	Placebo	Vosoritide
FAS		
N	32	43
Baseline, mean (SD)	-4.28 (0.26)	-3.88 (0.14)
LSM change from baseline (95% CI)	-0.30 (-0.47, -0.13)	0.01 (-0.15, 0.17)
Difference in LSM (95% CI)[a] p-value[b]	0.30 (0.07, 0.54) 0.014	

Source: Statistical Reviewer's analysis
[a] Difference is vosoritide minus placebo.
[b] Two-sided p-value. Least square means (LSM) were obtained from an analysis of covariance model with 10 multiple imputation.
Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least square mean; SD, standard deviation

Overall, the amount (2.6%) of missing data were minimal. Two out of 75 subjects had missing assessment at Week 52. One placebo subject withdrew from the study and the Week 52 Height Z-score was imputed by linear interpolation. The other subject treated with vosoritide died and the Week 52 Heigh Z score was multiply imputed using placebo data from the same cohort (Cohort 3) in the Applicant's prespecified analysis. This analysis imputed what the height at Week 52 would likely have been had the subject been alive, which is counterfactual and hypothetical. We performed an alternative analysis using the height at death as the last height given the height would not change after death for calculating the Z-score at Week 52, acknowledging this analysis might provide a relative conservative estimation of the treatment effect. Based on this alternative analysis, the treatment difference failed to achieve significance in FAS. The point estimate was 0.25 with 95% C.I. being (-0.02, 0.52) and p-value of 0.064.

6.2.1.4.2.2. Secondary Analysis

Other Efficacy Endpoints Related to Linear Growth

The Analysis of covariance (ANCOVA) results of the three efficacy endpoints - change in AGV from baseline to Week 52, change in upper to lower body ratio from baseline to Week 52 and, change in standing height (cm) from baseline to Week 52 are summarized in Table 12 and Table 13, respectively. All these parameters demonstrated positive changes trends as expected with the improvement in height Z-scores. However, these changes are small and of unknown clinical significance.

AGV achieved nominal significance at level 0.05 in both the randomized population and FAS. The treatment effect for AGV was 0.78 cm/year with 95% CI being (0.02, 1.54) in the randomized population.

Table 12. Analysis of Covariance of Annualized Growth Velocity (cm/year) at Week 52

Annualized Growth Velocity (cm/year)	Placebo	Vosoritide
Randomized		
N	32	32
Baseline, mean (SD)	9.60 (1.37)	11.06 (1.34)
LSM change from baseline	-2.95	-2.17
Difference in LSM (95% CI)[a] p-value[b]	0.78 (0.02, 1.54) 0.0452	

Annualized Growth Velocity (cm/year)	Placebo	Vosoritide
FAS		
N	32	43
Baseline, mean (SD)	9.60 (1.37)	11.66 (1.19)
LSM change from baseline	-3.32	-2.41
Difference in LSM (95% CI)[a] p-value[b]	0.92 (0.24, 1.59) 0.0075	

Source: Statistical Reviewer's Analysis.
[a] Difference is vosoritide minus placebo.
[b] Two-sided p-value. Least square mean (LSM) were obtained from an analysis of covariance model with 10 multiple imputation
Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least square mean; SD, standard deviation

Change in upper to lower body ratio from baseline to Week 52 was not statistically significant in both the analysis populations, with negative treatment differences.

Table 13. Analysis of Covariance of Upper to Lower Body Proportions Ratio at Week 52

Analysis of Covariance	Placebo	Vosoritide
Randomized		
N	32	32
Baseline, mean (SD)	2.52 (0.06)	2.60 (0.07)
LSM change from baseline	-0.13	-0.20
Difference in LSM (95% CI)[a] p-value[b]	-0.07 (-0.17, 0.04) 0.2163	
FAS		
N	32	43
Baseline, mean (SD)	2.52 (0.06)	2.60 (0.06)
LSM change from baseline	-0.13	-0.19
Difference in LSM (95% CI)[a] p-value[b]	-0.06 (-0.15, 0.03) 0.2050	

Source: Statistical Reviewer's Analysis.
[a] Difference is vosoritide minus placebo.
[b] Two-sided p-value. Least square means (LSM) were obtained from an analysis of covariance model with 10 multiple imputation.
Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least square mean; SD, standard deviation

The ANCOVA analysis of height at Week 52 in vosoritide compared with placebo is presented in Table 14. Results in the randomized population showed a positive change in standing height (LS mean difference of 0.77 cm), but the treatment difference was not significant. However, in the FAS, statistical significance was achieved which is aligned with the observed change in height Z-score.

Table 14. Analysis of Covariance of Change in Standing Height (cm) at Week 52

Analysis of Covariance	Placebo	Vosoritide
Randomized		
N	32	32
Baseline, mean (SD)	70.84 (1.92)	70.90 (1.84)
LSM change from baseline (95% CI)	7.38 (6.87, 7.89)	8.15 (7.55, 8.75)
Difference in LSM (95% CI)[a] p-value[b]	0.77 (-0.02, 1.56) 0.0570	

Analysis of Covariance	Placebo	Vosoritide
FAS		
N	32	43
Baseline, mean (SD)	70.84 (1.92)	70.61 (1.64)
LSM change from baseline (95% CI)	7.45 (6.95, 7.95)	8.41 (7.93, 8.89)
Difference in LSM (95% CI)[a]	0.96 (0.26, 1.66)	
p-value[b]	0.0072	

Source: Statistical Reviewer's Analysis
[a] Difference is vosoritide minus placebo.
[b] Two-sided p-value. Least square means (LSM) were obtained from an analysis of covariance model with 10 multiple imputation.
Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least square mean; SD, standard deviation

Other Efficacy Endpoints (Unrelated to Linear Growth)

Skull and Brain Parameters Evaluated by MRI

Significant comorbidities affecting children with achondroplasia during early life arise from abnormal cranial development due to decreased growth of cartilaginous bone, abnormal ossification, and premature closure of synchondroses (ranging between 1 to 4 years of age (Hecht et al. 1989; Calandrelli et al. 2017)), which result in foramen magnum stenosis, cranio-cervical junction stenosis, and mid-facial hypoplasia, among others. These skeletal abnormalities underly many of the most serious complications seen early in life in children with achondroplasia, such as severe brainstem compression leading to apnea, sudden death, jugular foramen stenosis or hydrocephalus, sleep-disordered breathing (SDB), hypotonia, chronic otitis media, and hearing loss. As such, the ability to promote bone tissue growth by maintaining patency of the cranial synchondroses may disappear as early as age 1 (Horton et al. 2007; Calandrelli et al. 2017).

The effect of vosoritide on the skull and brain morphology, to include foramen magnum, as well as ventricular and brain parenchymal dimensions, was evaluated by MRI of the head and neck, at baseline and Week 52 (Table 15). The data were analyzed using descriptive summary statistics.

There were no numerical differences between vosoritide and placebo arms in any of these measures in Cohorts 1 and 2. In Cohort 3 (age 0 to < 6 months), numerical changes of higher magnitude were noted with vosoritide treatment compared to placebo for sinus volume, facial volume, and area of foramen magnum.

Table 15. Change in MRI Parameters (Area of Foramen Magnum, Sinus Volume, Face Volume) From Baseline to Week 52 by Cohort (Safety Population)

	Cohort 1 (≥24 to <60 months)		Cohort 2 (≥6 to <24 months)		Cohort 3 (0 to <6 months)	
Measure (unit)	**All Vosoritide (N=19)**	**Placebo (N=16)**	**All-Vosoritide (N=12)**	**Placebo (N=8)**	**All-Vosoritide (N=12)**	**Placebo (N=8)**
Volume of face (cm^3)						
Baseline, n	16	13	12	8	11	8
Mean (SD)	582.407 (88.151)	573.834 (91.019)	451.478 (61.453)	450.791 (71.198)	340.366 (38.678)	357.529 (51.159)
Week 52, n	14	8	7	7	9	6
Change from baseline at Week 52	34.953 (39.151)	61.454 (23.214)	89.583 (42.331)	68.800 (24.630)	144.378 (24.110)	111.170 (33.088)
% Change at Week 52	6.32 (7.82)	11.85 (4.96)	20.56 (10.48)	15.08 (5.66)	43.49 (10.33)	33.74 (12.66)
Volume of sinus (cm^3)						
Baseline, n	19	16	12	8	12	8
Mean (SD)	9.481 (4.201)	8.899 (3.905)	4.351 (3.458)	5.376 (4.482)	2.334 (1.621)	2.781 (2.200)
Week 52, n	17	11	8	7	10	6
Change from baseline at Week 52	12.754 (5.511)	11.086 (3.086)	1.110 (3.729)	0.079 (3.428)	1.862 (2.388)	-1.010 (3.395)
% Change at Week 52	52.01 (82.95)	100.90 (177.15)	44.91 (78.80)	80.91 (160.39)	128.81 (128.18)	48.49 (191.74)
Area of foramen magnum (cm^2)						
Baseline, n	19	16	12	8	12	8
Mean (SD)	0.139 (0.021)	0.136 (0.022)	0.140 (0.032)	0.130 (0.031)	0.091 (0.033)	0.094 (0.026)
Week 52, n	17	12	8	7	10	6
Change from baseline at Week 52	-0.012 (0.034)	0.000 (0.022)	-0.001 (0.022)	0.006 (0.018)	0.029 (0.029)	0.018 (0.018)
% Change at Week 52	-7.26 (21.86)	0.93 (16.07)	0.76 (14.82)	4.00 (11.99)	43.89 (74.44)	24.74 (26.07)

Source: Source: Statistical Reviewer's Analysis based on ADCE dataset.
Change from baseline and percent change from baseline was based on the participants with available measurements at both time points
Abbreviations: max, maximum; min, minimum; N, number of subjects; n, number of subjects at baseline; SD, standard deviation

To further evaluate the observed treatment difference on area of foramen magnum, volume of sinus, and volume of face, the Applicant conducted exploratory post-hoc ANCOVA analyses, with subjects being stratified by age into the following cohorts: <6 Months, <12 Months, ≥12 Months, and ≥24 Months (Table 16).

In subjects aged < 6 months and <12 months, the LS mean difference between vosoritide and placebo was positive for volume of face [31.51 mL (3.66, 59.36) and 36.32 mL (11.30, 61.33), respectively], volume of sinus [2.33 mL (0.06, 4.60) and 2.38 mL (0.56, 4.19), respectively], while no difference was noted for the area of foramen magnum [0.01 cm2 (-0.02, 0.04) and 0.01 cm2 (-0.01, 0.04), respectively]. No difference between vosoritide and placebo was noted in any of the 3 MRI parameters in subjects ≥12 months and ≥ 24 months, respectively.

Table 16. Analysis of Covariance of MRI Parameters (Area of Foramen Magnum, Sinus Volume, Face Volume) at Week 52, Trial 111-206, Safety Analysis Population

	Age Group							
	<6 Months		<12 Months		≥12 Months		≥24 Months	
Assessment	**Placebo**	**Vosoritide**	**Placebo**	**Vosoritide**	**Placebo**	**Vosoritide**	**Placebo**	**Vosoritide**
Area of foramen magnum (cm^2)								
N	6	10	8	12	17	23	12	17
LS mean at Week 52 (95% CI)	0.11 (0.09, 0.13)	0.12 (0.11, 0.14)	0.11 (0.10, 0.13)	0.13 (0.11, 0.14)	0.14 (0.12, 0.15)	0.13 (0.12, 0.14)	0.13 (0.11, 0.15)	0.13 (0.11, 0.14)
LS mean difference in vosoritide vs. placebo (95% CI)	0.01 (-0.02, 0.04)		0.01 (-0.01, 0.04)		-0.01 (-0.02, 0.01)		-0.00 (-0.02, 0.02)	
p-value[a]	0.3696		0.2509		0.3850		0.8433	
Sinus volume (cm^3)								
N	6	10	8	12	16	23	11	17
LS mean at Week 52 (95% CI)	1.93 (0.14, 3.72)	4.27 (2.88, 5.65)	2.66 (1.16, 4.15)	5.03 (3.67, 6.40)	10.07 (8.14, 12.00)	10.83 (9.27, 12.39)	12.08 (9.55, 14.60)	12.39 (10.51, 14.28)
LS mean difference in vosoritide vs. placebo (95% CI)	2.33 (0.06, 4.60)		2.38 (0.56, 4.19)		0.76 (-1.68, 3.20)		0.32 (-2.80, 3.43)	
p-value[a]	0.0450		0.0136		0.5325		0.8350	
Face volume (cm^3)								
N	6	9	8	11	13	19	8	14
LS mean at Week 52 (95% CI)	452.11 (430.5, 473.67)	483.61 (466.02, 501.21)	451.54 (429.67, 473.41)	487.86 (468.57, 507.15)	593.91 (572.96, 614.86)	576.95 (559.87, 594.04)	616.98 (588.65, 645.30)	589.60 (568.81, 610.40)
LS mean difference in vosoritide vs. placebo (95% CI)	31.51 (3.66, 59.36)		36.32 (11.30, 61.33)		-16.96 (-44.42, 10.51)		-27.37 (-63.46, 8.71)	
p-value[a]	0.0298		0.0074		0.2160		0.1284	

Source: Adapted from Tables 4.1.1.1., 14.1.1.2.1 and 4.1.1.3.1, 111-206 MRI Report
Abbreviations: CI, confidence interval; LS, least square; MRI, magnetic resonance imaging; N, number of subjects

In summary, for the majority of the MRI parameters (i.e., area of foramen magnum, volume of calvarium, whole brain total volume, ventricles total volume), no notable differences were observed between vosoritide and placebo arms in any of the age cohorts at Week 52. A nominally significant change from baseline to Week 52 in the volume of sinus and volume of face in favor of vosoritide compared to placebo was noted in subjects < 12 months, when evaluated the changes using post-hoc ANCOVA analyses. However, the clinical significance of the magnitude of changes in these parameters remains unknown. Also, these results should be interpreted with caution, given the nature of the analyses (i.e., post-hoc) and the risk of positive findings due to chance while conducting multiple testing.

Sleep Study Indices

Sleep apnea is a common comorbidity in children with achondroplasia, particularly during early life, with at least 10% of patients being diagnosed with sleep apnea by age of 4 (Horton et al. 2007). The causes of sleep apnea are multifactorial, to include: 1) mid-facial hypoplasia resulting in relative adenoid and tonsil hypertrophy (obstructive sleep apnea); 2) jugular foramen stenosis causing jugular venous hypertension and progressive hydrocephalus with subsequent central nervous system and muscular upper airway compromised (central sleep apnea); 3) hypoglossal canal (foramen magnum) stenosis resulting in muscular upper airway obstruction (central and obstructive sleep apnea).

Sleep study at baseline and Week 52 was performed during Trial 111-206, to assess the presence and severity of sleep-disordered breathing by evaluating the following parameters: Apnea Index (i.e., number of episodes of apnea per hour), Hypopnea Index (i.e., number of episodes of hypopnea per hour), Apnea Hypopnea Index (i.e., number of episodes of obstructive apnea hypopneas per hour), Obstructive Apnea Index (i.e., number of episodes of obstructive apneas per hour), Central Apnea Index (i.e., number of episodes of central apneas per hour), number of desaturations per hour ≥ 3%.

A numerical reduction in all polysomnography parameters, except one (central apnea index in Cohort 3) was observed at Week 52 in the vosoritide group, while the results for subjects in placebo arm were variable (Table 51, Appendix). While directional positive change in all but one polysomnography parameters were seen with vosoritide in all cohorts, the changes are small and clinical meaningfulness of the observed changes remain unknown.

Health-Related Quality of Life (HRQoL)

The Applicant utilized the following Clinical Outcome Assessments (COAs) as exploratory efficacy endpoints to assess HRQoL:

- The Infant Toddler Quality of Life (ITQoL), an observer-reported outcome (ObsRO) assessment developed for use in children aged from 2 months to 5 years that attempts to capture physical, mental, and social well-being.
- Functional Independence Measure (Wee-FIM®-II), a clinician-rated outcome (ClinRO) assessment designed to measure the functional independence of children between the ages of 6 months and 18 years who have physical or general developmental limitations. The WeeFIM-II is comprised of 3 domains that are rated by clinicians based on information obtained from parents/caregivers related to self-care, mobility, and cognition.

- The Bayley Scales of Infant and Toddler Development, Third Edition (BSIDIII), a performance-based clinician-reported outcome assessment, which was used to evaluate the following domains: cognitive, language, and motor.

The Applicant did not include sufficient information to evaluate the adequacy of the selected COAs and to support their use in the intended population. In the absence of sufficient information to support the validity and fitness-for-use of the proposed instruments in the intended population, no conclusion can be drawn based on the endpoints derived from the above instruments. Nevertheless, there were no clinically significant observed differences in change from baseline to Week 52 between the vosoritide and placebo arms in any of the above COAs.

6.2.1.4.2.3. Subgroup Analysis of the Linear Growth-related Efficacy Endpoint by Age Cohort

The height Z-scores and AGV were analyzed by age cohort in the randomized analysis population (see Table 17). In all cohorts, there was a decline in height Z-score in the placebo group, as indicated by the negative LS mean change from baseline at Week 52. The treatment difference was not significant at significance level of 0.05 across all cohorts. However, the LS mean difference between the treatment groups was consistent across the cohorts with point estimates in favor of vosoritide.

Table 17. Analysis of Covariance of Height Z Score and AGV (cm/year) by Age Cohort (Analysis Population: Randomized)

	Cohort 1		Cohort 2		Cohort 3	
Analysis of Covariance	**Placebo**	**Vosoritide**	**Placebo**	**Vosoritide**	**Placebo**	**Vosoritide**
Height Z score						
N	16	15	8	8	8	9
LSM change from baseline	-0.06	0.27	-0.19	0.02	-0.91	-0.68
Difference in LSM (95% CI)[a] p-value[b]	0.33 (0.00, 0.67) 0.051		0.21 (-0.37, 0.79) 0.443		0.23 (-0.45, 0.91) 0.508	
AGV						
LSM change from baseline	0.89	1.99	-3.00	-2.36	-10.19	-9.34
Difference in LSM (95% CI)[a] p-value[b]	1.10 (0.13, 2.07) 0.028		0.63 (-0.60, 1.87) 0.280		0.79 (-1.08, 2.67) 0.407	

Source: Statistical Reviewer's Analysis.
[a] Difference is vosoritide minus placebo.
[b] Two-sided nominal p-value without multiplicity adjustment. Least square means (LSM) were obtained from an analysis of covariance model with 10 multiple imputation.
Abbreviations: AGV, annualized growth velocity; CI, confidence interval; LSM, least square mean; N, number of subjects

For AGV, in Cohort 1 the treatment difference was nominally significant. Placebo showed an increase in LS mean at Week 52, with a marked increase seen in the vosoritide group. Cohorts 2 and 3 showed a marked decline in AGV with placebo, with the most pronounced decline seen in Cohort 3, consistent with a rapidly declining growth velocity in these younger children. Cohort 2 and 3 showed less pronounced decline in AGV on vosoritide treatment. The LS mean difference between the treatment groups was consistent across the Cohort 2 and 3 with point estimates in favor of vosoritide and 95% CIs increasing in size from Cohort 1 to Cohort 3. Additional subgroup analyses of the height Z-scores by Sex and Race and using Bayesian shrinkage prior methodology are provided in Section 16.1.

6.2.2. Trial 111-208

Trial 111-208 is an ongoing, Phase 2, open-label, multicenter, long-term extension study to evaluate the safety and efficacy of vosoritide in children who had completed 52 weeks of vosoritide or placebo treatment in Trial 111-206. Participation continues until subjects reach near final adult height. (refer to Section 14.2 for further details regarding study design). The eligibility criteria were similar to that of Trial 111-206. As of the data cut-off on January 26, 2022, all 73 subjects who had completed Trial 111-206 had enrolled in Trial 111-208 and received vosoritide. Of these 73 subjects, 31 had previously received placebo and 42 had previously received vosoritide in Trial 111-206.

6.2.2.1. Results of Analyses, Studies 111-206/111-208

Two-year Comparative Analyses Between Randomized Groups in Trial 111-206/111-208

As requested by the FDA, to examine the benefit of vosoritide treatment beyond 1 year, the Applicant conducted 2-year comparative analyses in the randomized FAS of Trial 111-206/111-208 by age subgroup and in the overall population. These analyses examined the change in growth parameters from the baseline to Week 104 (Week 52 in Trial 111-208). The subjects who were randomized to vosoritide in Trial 111-206 received 2 years of vosoritide (Vos/Vos), whereas the subjects who were randomized to placebo in 111-206 received 1 year of placebo followed by 1 year of vosoritide (Pbo/Vos). Only observed data (after linear interpolation) were included in these analyses. The like-to-like rule was applied selecting the same height parameter (i.e., body length versus standing height) at Week 104 as taken at baseline, whenever possible.

The two-year comparative analyses from Trial 111-206/111-208 provided supportive evidence to the sustained benefit of vosoritide treatment beyond 1 year. The treatment difference for change in height Z-score, height, and cumulative AGV from baseline to year 2 was presented in Table 18. The point estimates were positive in Cohorts 1 and 3 and the all-age group, suggesting better growth when starting vosoritide treatment 1 year earlier. The negative point estimates in Cohort 2 could be related to the imbalance of body length and standing height measures between treatment groups. Some Cohort 2 subjects did not have body length measurement available at Year 2 due to their age, despite the preference for body length under the like-to-like rule. The Vos/Vos group in Cohort 2 had 4 subjects with standing height at Year 2, whereas the Pbo/Vos group only had 1 such subject. This could potentially negatively impact the treatment estimate in Cohort 2, given that standing height measurement yielded smaller values than body length measurement, in general (refer to Section 16.2.4.4 for details).

Table 18. Key Efficacy Endpoints by Age Subgroup and in the Overall Population at Year 2, Trials 111-206/111-208 Randomized Full Analysis Set[1]

Age Group	N (Vos/Vos, Pbo/Vos)	Treatment Difference Vos/Vos – Pbo/Vos (95% CI)[2]		
		Height Z-Score	Height (cm)	AGV (cm/year)
≥24 to <60 months (Cohort 1)	15, 16	0.25 (-0.19, 0.69)	1.12 (-0.51, 2.74)	0.76 (-0.01, 1.53)
≥ 6 to <24 months (Cohort 2)	8, 7	-0.28 (-1.14, 0.57)	-1.07 (-4.22, 2.08)	-0.50 (-1.90, 0.89)
3 to < 6 months (Cohort 3)	8, 7	0.28 (-0.08, 0.64)	0.98 (-0.13, 2.09)	0.49 (-0.05, 1.03)

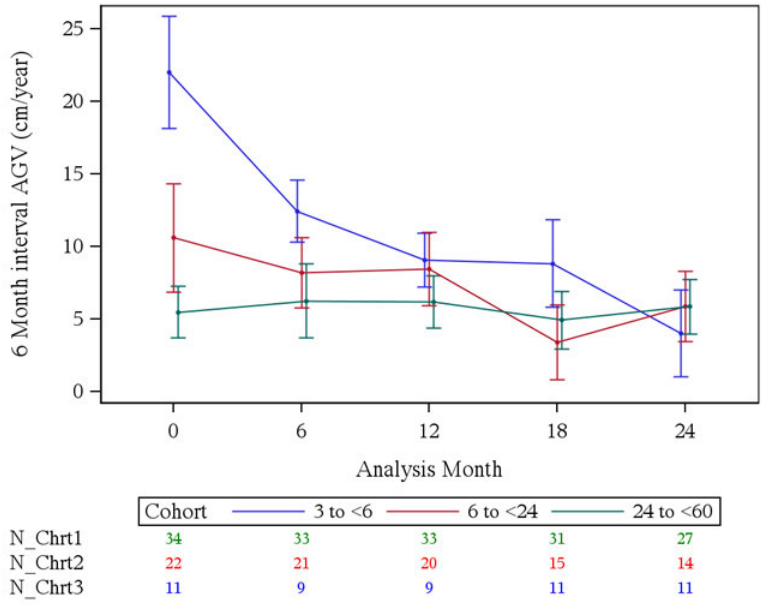
Age Group	N (Vos/Vos, Pbo/Vos)	Treatment Difference Vos/Vos – Pbo/Vos (95% CI)[2]		
		Height Z-Score	Height (cm)	AGV (cm/year)
All	31, 30	0.09 (-0.20, 0.38)	0.43 (-0.71, 1.58)	0.70 (0.01, 1.39)

Source: Applicant's June 23, 2023, response to FDA's May 26, 2023, information request, verified by statistical reviewer
[1] The analysis population included all randomized subjects from Trial 111-206 with no missing values at week 104 visit.
[2] ANCOVA model included treatment, matching ID, baseline age strata, baseline AGV and baseline height Z-score or height if the endpoint was height Z-score or height.
Abbreviations: AGV, annualized growth velocity; CI, confidence interval; N, number of subjects

Six-Month Interval AGV Over Time

Figure 4 shows the 6-month interval AGV over time in vosoritide-treated subjects by age subgroup: ≥24 to < 60 months (Cohort 1), ≥ 6 to < 24 months (Cohort 2), and < 6 months (Cohort 3), at the start of treatment. There was a sharp decrease in average AGV from baseline to year 2 (22.03 to 4.04 cm/year) in Cohort 3, and a smaller decrease in average AGV from baseline to year 2 (10.61 to 5.88 cm/year) in Cohort 2. AGV was relatively stable in Cohort 1. The decline in AGV in the younger age cohorts (i.e., Cohorts 2 and 3) reflect the natural decline in growth velocity seen in the first 2 years of life of pediatric population, including children with ACH. The larger than expected decrease in AGV from month 12 to 18 in Cohort 2 and from month 18 to 24 in Cohort 3 (to a level smaller than the AGV observed in older Cohort 1) may be due to the switching of height measurement methodology from body length to standing height in these cohorts, when the like-to-like rule was no longer applied after Year 1 and the subjects reached 2 years of age (refer to Section 16.2.4.4 for details).

Figure 4. Six-Month Interval AGV in Vosoritide-Treated Subjects by Age Subgroup (Mean±SD), Trial 111-206/111-208 Full Analysis Set



Source: Statistical reviewer, based on Applicant's integrated summary of efficacy
Analysis Month 0 refers to the start of treatment, which is Week 0 in Trial 111-206 for subjects randomized to Vosoritide in Trial 111-206 and Week 0 in Trial 111-208 for subjects randomized to placebo in Trial 111-206.
Abbreviations: AGV, annualized growth velocity; Chrt, cohort; SD, standard deviation

6.2.3. Comparative Analyses of Growth Parameters Between Vosoritide-Treated Subjects and External Controls

6.2.3.1. Design, Studies With External Controls

Results from the extension Trial 111-208 were submitted to demonstrate long-term efficacy (beyond 1 year) of vosoritide in subjects aged <5 years. Because Trial 111-208 lacked a parallel control arm (since all subjects received vosoritide treatment in the extension phase), the Applicant proposed and used two external control datasets as comparators: the Achondroplasia Natural History (AchNH) control and the observational/placebo control (from observational Study 111-901 and clinical Trials 111-206 and 111-301).

The AchNH study was an investigator-initiated, observational, retrospective study that aimed to characterize growth in patients with a molecular or clinical diagnosis of ACH at four specialized skeletal dysplasia centers[2] in the United States. Growth was extracted from medical records of the clinical visits in 1,374 eligible patients aged 75 years or younger. The AchNH control included 10,444 anthropometric measurements derived from medical records of 1,142 unique patients aged <8 years. In the review of the original NDA submission (FDA 2021) the Division of Epidemiology -I and Division of Biometrics II reviewers concluded that data from AchNH study were deemed fit-for-purpose as an external control for efficacy determination on growth for ACH subjects aged > 5 years. Study 111-901 was a prospective cohort study, aiming to collect baseline growth measurements on pediatric subjects with ACH for up to 7 years. If eligible, subjects from Study 111-901 may join the vosoritide clinical studies, including Studies 111-202, 111-206 and 111-301. The placebo arms provided an extension of vosoritide-untreated longitudinal data for one year. Growth data in Study 111-901 were collected every 3 months for at least 6 months (or 3 months for Cohort 3 in Trial 111-206) prior to enrolment into clinical trials. The study inclusion and exclusion criteria and anthropometric data collection of Study 111-901 were consistent with Trial 111-206 and Study 111-301. The observational/placebo control encompasses 2,286 anthropometric measurements from 314 subjects aged <8 years in the observational Study 111-901 and the placebo arms of two clinical trials, 111-206 and 111-301.

The treated groups consisted of vosoritide-treated subjects from Trial 111-206 and 111-208. The baseline (index date) was the start of vosoritide treatment. The three age cohorts examined were ≥24 to <60 months (Cohort 1), ≥ 6 to <24 months (Cohort 2) and <6 months (Cohort 3) at baseline. Trial 111-208 is ongoing and following subjects until subjects achieve near-final adult height. Treatment effect of vosoritide at 1, 2 and 3 years (according to data availability) was evaluated in separate comparisons with the two external controls. Change in height Z-score and change in height from baseline were evaluated as primary and secondary endpoints respectively. Refer to Sections 16.2.1 and 16.2.2 for details about the inclusion exclusion criteria and statistical analysis plan.

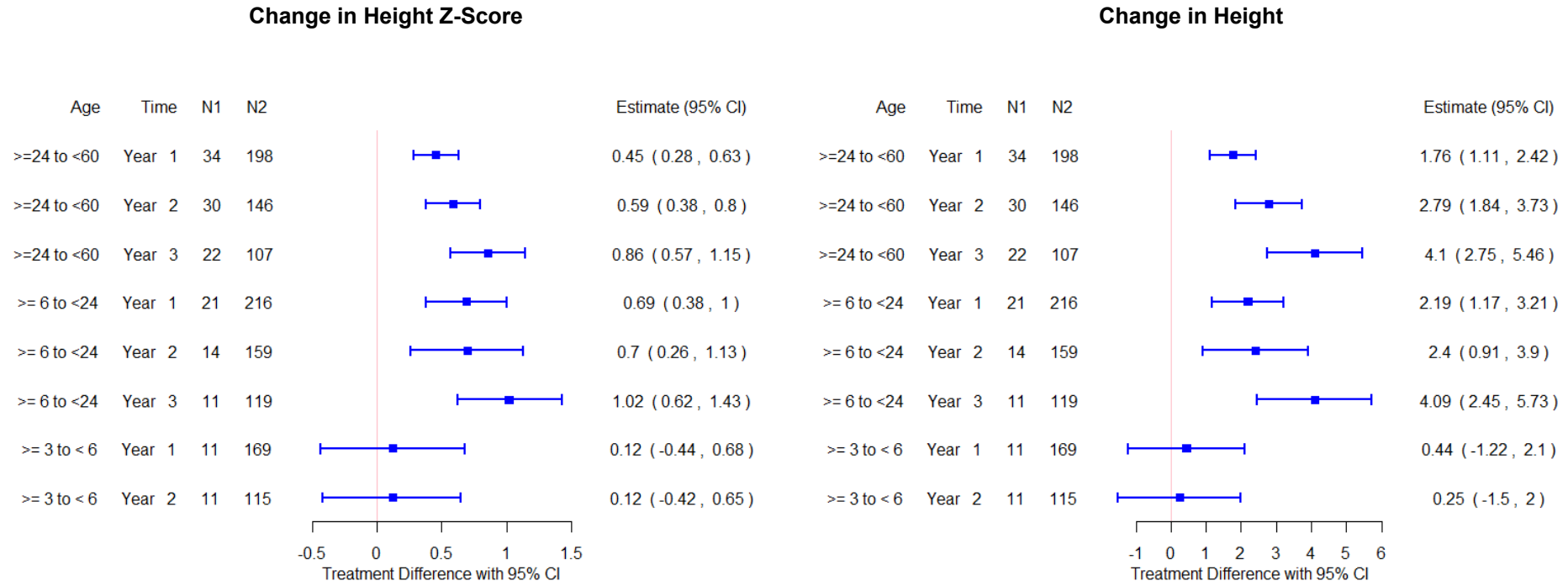
6.2.3.2. Results of Analyses, Studies With External Controls

In the analyses using the AchNH control (by the data cut-off on December 19, 2022), effectiveness was evaluated up to 3 years of follow-up from baseline in the ≥24 to <60 months (Cohort 1) and ≥ 6 to < 24 months (Cohort 2) age cohorts, and up to 2 years from baseline in the < 6 months age cohort (Cohort 3). In the analyses using the observational/placebo control, results from subjects with at least 2 years of follow-up from baseline were presented.

The results from the two external controls were largely consistent (Figure 5 and Figure 6).

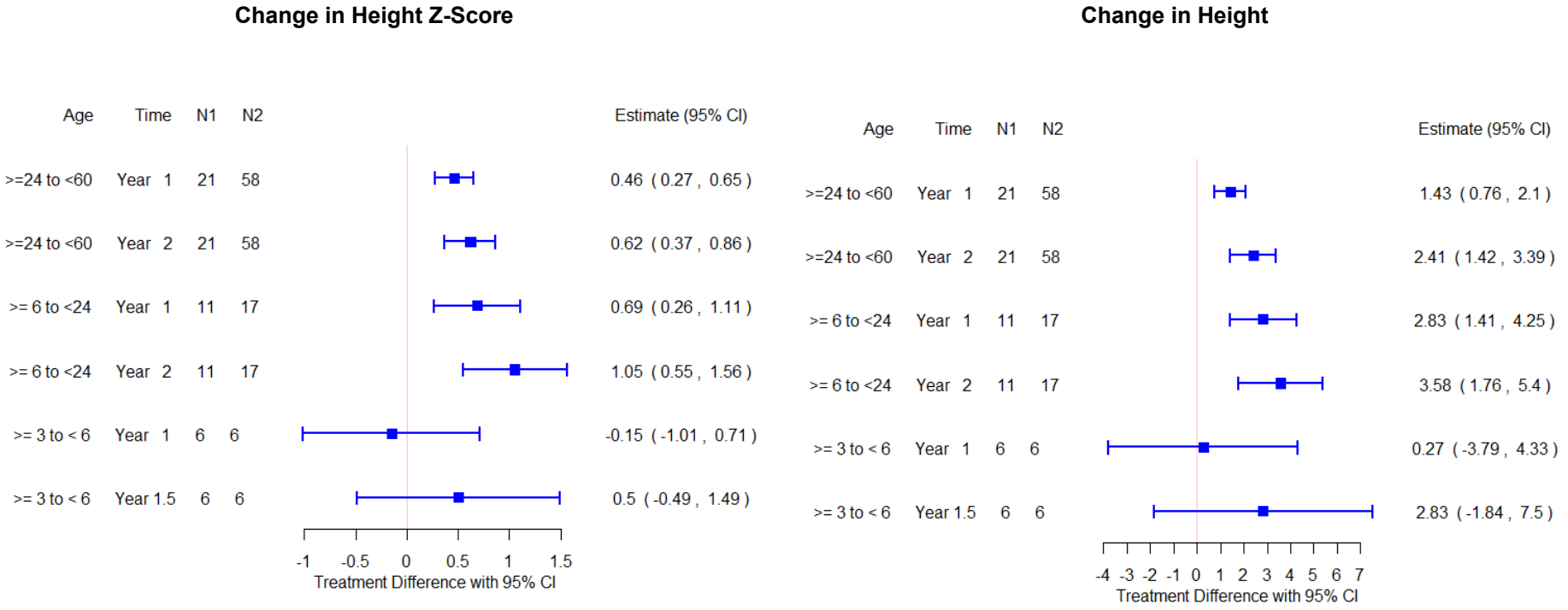
- In the analyses using the AchNH control, the treatment difference between vosoritide-treated subjects and the AchNH controls in change in height Z-score and height incremented from Year 1 to Year 3 in Cohort 1 (0.45 to 0.86 in height Z-score difference and 1.76 cm to 4.1 cm in height difference, respectively). In Cohort 2, change in treatment difference was similar at Year 1 and Year 2, but there was a noticeable increase from Year 2 to Year 3 (0.7 to 1.02 in height Z-score difference; 2.4 cm to 4.09 cm in height difference, respectively). In Cohort 3, there was little treatment difference at both Year 1 and Year 2. The lack of increase in treatment difference from Year 1 to Year 2 in Cohorts 2 and 3 may be due to the switch in height measurement from body length to standing height in the treated group after 1 year of treatment when the like-to-like rule was no longer applied (the standing height noted to be shorter than body length for same subject at a given time; refer to Figure 41 in Section 16.2.4.4 for details).
- In analyses with the observational/placebo control, which applied the same like-to-like rule as the treated arm, there was an increase in treatment difference from Year 1 to Year 2 (Figure 6). Overall, these results suggest an incremental improvement in height Z-score and height in vosoritide-treated subjects through 3 years of treatment in Cohorts 1 and 2. For Cohort 3, a longer follow-up time is required to better evaluate long-term efficacy. Growth trajectories from individual treated subjects further support these conclusions (Figure 39, Section 16.2.3).

Figure 5. Forest Plot of Treatment Difference in Change in Height Z-Score and Height (at Years 1, 2 and 3), Vosoritide-Treated Subjects in Trials 111-206/111-208 Versus AchNH[1]



Source: Summarized from applicant's efficacy update report for 111-208 with data cut-off December 19, 2022, verified by statistical reviewer
[1] ANCOVA model included treatment, matching ID, baseline age strata, baseline AGV, and baseline height Z-score or height.
Abbreviation: AchNH, Achondroplasia Natural History Study; CI, confidence interval; N1, number of treated subjects; N2, number of controls

Figure 6. Forest Plot of Treatment Difference in Change in Height Z-Score and Height (at Years 1 and 2), Vosoritide-Treated Subjects in Trials 111-206/111-208 Versus Placebo/Observational[1]



Source: Summarized from Applicant's integrated summary of efficacy, verified by statistical reviewer
[1] The same subjects from both arms were used for year 1 and year 2 analyses. ANCOVA model included treatment, baseline age strata, and baseline height Z-score or height
Abbreviation: CI, confidence interval; N1, number of treated subjects; N2, number of controls

To assess the impact of using external controls instead of a randomized control, the Applicant conducted comparative analyses of the vosoritide-treated arm in Trial 111-206 versus the AchNH control or the observational/placebo control, replacing the randomized placebo arm in Trial 111-206. The treatment difference in change in height Z-score or height appeared to be considerably larger in the analyses with external controls compared to the analyses of the randomized study. For example, the treatment difference in change in height Z-score at Year 1 was 0.25 in Trial 111-206 versus 0.51 with the AchNH control and 0.46 with the observational/placebo control (Table 54, Section 16.2.3). Discrepancies in results between the analyses using the AchNH control and the analyses using the randomized placebo control were also observed in age subgroup analyses, with the largest discrepancy in the 6 to < 24 months cohort (Table 55, Section 16.2.3). In addition, comparative analyses of the randomized placebo arm in Trial 111-206 versus the AchNH control yielded considerable differences in height Z-score, height and AGV at Year 1 (Table 56, Section 16.2.3), suggesting better growth in the placebo arm compared to the AchNH control, despite the fact that the two groups achieved good balance in important covariates at baseline (Table 57, Section 16.2.3). To explore possible sources of bias that may account for these discrepancies, we have evaluated each of the following issues related to the use of external controls:

- Contemporaneousness of height data in AchNH
- Confounding
- Selection bias
- Discrepancy between body length and standing height

Our analyses suggest that using historic data from AchNH in the external control did not introduce substantial bias into the comparative analyses results. Matching had adequately balanced the observed potential confounders although unmeasured or residual confounding was possible. The discrepancy in the treatment difference at Year 1 from analyses using the AchNH control versus those from Trial 111-206 may be partially due to the inconsistent height measurement methods (body length versus standing height) at baseline and Year 1 in the AchNH control. Such an impact is expected to be less pronounced at Year 3 and beyond.

The reviewers consider that the studies with external controls are supportive for vosoritide efficacy assessment on growth in patients with ACH. However, the small sample size and short follow-up time limited its use for evaluating long-term efficacy. Without matching and adjusting for baseline AGV, the analyses results using the observational/placebo control were likely subject to confounding. Results from sensitivity analyses suggest that the estimates from these analyses were sensitive to the choice of baseline visits.

In general, potential selection bias due to subjects transfer from Study 111-901 to Trial 111-206 is less of a concern, given that subjects transferring into Trial 111-206 were randomized when entering Trial 111-206 and those who were randomized to the placebo group were combined with the subjects remaining in Study 111-901 as external control. Sensitivity analyses appeared to provide consistent findings, and descriptive analysis results did not suggest potential selection bias would overestimate the treatment effect on height increase. In summary, although the impact of potential selection bias from differential loss to follow-up cannot be readily assessed, it does not constitute a major concern in this study scenario based on study design characteristics and potential direction of bias.

In conclusion, our assessment did not find major concerns in contemporaneousness of height data in AchNH, confounding, selection bias, and discrepancy between body length and standing height except that results from the analyses with the observational/placebo control appeared to be affected by residual confounding. Refer to Section 16.2.4 for detailed assessments.

Overall, the comparative analyses results using two external controls suggest the treatment effect of vosoritide sustained beyond 1 year. The treatment difference (between vosoritide-treated subjects and controls) in change in height Z-score and height from baseline was shown to increase from Year 1 to Year 3 in subjects aged ≥24 to <60 months and 6 to <24 months. However, longer follow-up time is required to better evaluate long-term efficacy in subjects aged <6 months.

6.3. Key Efficacy Review Issues

6.3.1. Sources of Substantial Evidence of Effectiveness

Issue

Trial 111-206, the primary trial conducted by the Applicant to support efficacy in the population under 5 years of age, was not powered to demonstrate efficacy with statistical significance. Therefore, whether the data submitted provides substantial evidence for the treatment of patients with achondroplasia under the age or 5 years old is a central issue in this review.

Background

Vosoritide was approved under the accelerated approval pathway to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. For that approval, substantial evidence of effectiveness was established based on a phase 3 adequate and well-controlled trial (111-301) and confirmatory evidence from the long-term open-label trials (111-302 and 111-202/205**).** Continued approval for this indication is contingent upon verification and description of clinical benefit in confirmatory trial(s).

During the review of the original application, the team concluded that extrapolation of efficacy and safety data from older children to younger children was not appropriate at that time because the growth patterns, disproportionality, and comorbid conditions may be different in these age groups. There was concern that the safety profile in this younger age group could be different, given that cranial and axial endochondral bones ossification is still active in these youngest patients.

Trial 111-206 was not powered to demonstrate efficacy of vosoritide with statistical significance in this youngest age group. However, in order to meet the substantial evidence standard for a new population, FDA can rely, in some cases, on its previous finding of effectiveness of the approved drug together with scientific evidence that justifies such reliance (December 2019).

Assessment

Although generally similar pathophysiology and manifestations are shared across age groups among children with achondroplasia, growth patterns can vary across ages. In addition,

ossification of the cranial and axial endochondral bones is only active in children under 2. The data from the phase 2 Trial 206 provide assurance that the disease, particularly growth and disproportionality, are similar in those below 5 and those 5 and above. The magnitude of the improvement in height Z-scores observed in Trial 111-206 was consistent with the improvement in height Z-scores observed in children > 5 years old in Study 111-301.

As discussed below (Section 6.3.2), AGV also improved in children <5 years old with ACH during the first year of treatment compared to placebo and external controls. The smaller effect on AGV in children <5 years old compared to children > 5 years old can be explained by the high variability in this parameter in the younger age group (compared to less variability in height Z-scores) and the small sample size. However, there appears to be a drug-induced effect on the growth parameters (height, height Z-score and AGV) during the first year and beyond one year of treatment. No worsening in disproportionality was noted during Trials 111-206 and 111-208. Lastly, while there was no notable difference in favor of vosoritide in any of the age subgroups on the growth of the cranial and brain morphology, including foramen magnum stenosis after 52 weeks of treatment, a slight increase in the sinus volume and volume of the face in subjects < 12 months treated with vosoritide was observed. The clinical significance of the observed change is unknown. Nevertheless, there were no emerging safety concerns related to the abnormal cranial and axial growth in the children < 5 years of age. Thus, the review team determined that the effect of the drug on various growth parameters (i.e., linear growth, disproportionality, cranial endochondral bones) is overall similar between the older (≥ 5 years of age) and the younger (< 5 years of age) children with achondroplasia.

Similar to the older age group of children with ACH (i.e., > 5 years of age and older), data on final adult height is needed to confirm the treatment benefit in the intended patient population.

Therefore, substantial evidence of effectiveness of vosoritide in children with achondroplasia <5 years of age can rely on the FDA's previous findings of effectiveness of vosoritide in children with achondroplasia 5 years of age and older. Data can then be extrapolated to the younger age group with pharmacokinetic data submitted in the supplement, which show that vosoritide exposures in all age groups in Study 111-206 (<5 years old) were similar or higher than those observed in the Phase 3 (Study 111-301) in > 5 years old children with ACH." In addition, safety data assures of a similar safety profile between the 2 age groups.

Although the lowest age of the subjects enrolled in Trial 111-206 (and vosoritide clinical program) was 4.4 months (as subjects in the age cohort 0 to < 6 months were required to participate in an observational study for at least 3 months), approval of the drug for the proposed indication in children with achondroplasia down to birth is acceptable. The decision is supported by the growth data from Trial 111-206, while the safety data in the vosoritide clinical development program is reassuring. As such, vosoritide is expected to be safe and effective in children 0 to 4.4 months.

Conclusion

The clinical team concluded that substantial evidence of effectiveness of vosoritide on linear growth in children with achondroplasia <5 years of age can be based on FDA's previous findings of effectiveness in children with achondroplasia 5 years of age and older. Once the data provided assurance that the disease is similar in the 2 relevant age groups, pharmacokinetic data and and safety data allow for this extrapolation approach. Continued approval for this indication is

contingent upon verification and description of clinical benefit (i.e., final adult height) in confirmatory trial(s).

6.3.2. Apparent Smaller Effect of Vosoritide on Growth Velocity in Children With Achondroplasia <5 Years Compared to Children ≥ 5 Years of Age

Issue

Growth data derived from vosoritide-treated subjects <5 years of age showed a smaller effect on AGV compared to 5 years and older, raising concerns whether efficacy derived from studies in subjects <5 years of age is supportive of the benefit of vosoritide on growth demonstrated in children 5 years of age and older.

Background

Similar to children of normal stature, growth velocity in children with achondroplasia is characterized by a steep decline during the first 2 years of life, from a value of 20 cm/year during the first year of life (compared to 44 cm/year in children of average stature), to approximately 10 cm/year during the 2nd year (compared to 14 cm/year children of average stature), followed by an average of approximately 4-5 cm/year after 2 years of age (compared to 6-8 cm/year in children of average stature), which remains relatively stable thereafter (Hoover-Fong et al. 2008). As noted, most of the height deficit of children with achondroplasia compared to children of average stature occurs during the first 2 years of life, which is reflected in the height standard deviation scores (SDS, or Z-scores) trends of children with achondroplasia, which decline from a value of -3 SDS at birth, to -4 SDS at year 1, -5 SDS at year 2, and remains relatively stable until teenage years (Merker et al. 2018).

The benefit of vosoritide on short-term linear growth was demonstrated in children with achondroplasia 5 years of age and older, in whom AGV and height Z-score are relatively stable overtime (Hoover-Fong et al. 2008; Merker et al. 2018), based on data derived from one adequate and well-controlled trial (Study 111-301) and confirmatory evidence from long-term extension trials (Studies 111-302, 111-202/205) (refer to Integrated review, dated November 18, 2021, in DARRTS). Although, the results of Trials 111-206/208 demonstrated an improvement in growth in children <5 years old with ACH treated with vosoritide compared to placebo, the growth rate (i.e., AGV) in this age group was lower compared to the growth rate in children > 5 years old in Study 111-301, particularly for the age cohort 3- to < 6 months

Assessment

The Applicant evaluated the effect of vosoritide on short term growth in children with achondroplasia 3 months to <5 years of age in Trial 111-206, which was followed by its long-term extension study (111-208). Of note, Trial 111-206 was designed primarily as a safety study; therefore, it was not powered to detect statistically significant changes for the efficacy parameters.

Height Z-score

The effect of vosoritide on height Z-score after 1 year of treatment (i.e., the primary efficacy endpoint) was numerically similar in children with ACH <5 years of age in Trial 111-206, compared to children > 5 years of age in Study 111-301 [0.24 SDS (95% CI, -0.02, 0.53) versus 0.28 (95% CI, 0.17, 0.39), respectively], but did not reach statistical significance (p-value 0.06) (Section 6.2.1.4.2.1). The treatment difference on height Z-score between treatment arms was consistent across the 3 age cohorts [Cohort 1 (≥24 to <60 months), Cohort 2 (≥ 6 to < 24 months) and Cohort 3 (3 months to < 6 months)], with point estimates in favor of vosoritide (Section 6.2.1.4.2.3).

Because of variability in the growth parameters in the young pediatric ACH population, interpretation of drug-induced effect on growth is challenging. The high variability in AGV during the first 2 years of life may affect interpretation of treatment-induced effect on growth, however, such variability is potentially attenuated when growth is evaluated by the height Z-score. Height Z-scores are calculated by conversion of height to age-and sex-appropriate (SDS) in comparison with reference data of average stature children, thus eliminating potential confounders related to age and gender. Overall, evaluation of height Z-score may represent a better parameter for evaluation of treatment effect on growth in younger children. Therefore, comparable findings in the improvement in height Z-scores between older and younger age groups is reassuring and indicates that there is a comparable effect of the drug on growth in all age groups. The study's small sample size may explain the lack of statistical significance of the observed treatment effect.

AGV

The effect of vosoritide on AGV after 1 year of treatment showed a numerical improvement in children with ACH <5 years of age in Trial 111-206 [0.78 cm/year (95% CI 0.02, 1.54, p -value 0.04)]. Similar to the effect observed on heigh Z-score, the treatment difference on AGV between treatment arms was consistent across the 3 age cohorts, with point estimates in favor of vosoritide (Section 6.2.1.4.2.3). However, the overall effect on AGV was smaller when compared to children 5 years of age and older in Study 111-301 [1.57 cm/year (95% CI 1.22, 1.93), p-value < 0.0001] (Section 6.2.1.4.2.2). While a definite explanation for the observed treatment difference on AGV after 1 year of treatment between subjects <5 years of age compared to subjects 5 years of age and older could not be found, the observed difference in the AGV responses between older and younger age groups may be due to the small sample size, high variability in growth velocity during the first 2 years of life (see above), and differences in the methodology used to measure height (i.e., body length, which is more prone to measurement errors, was measured during first 2 years, and standing height was measured after 2 years).

The drug effect on growth in children <5 years of age appeared also to be sustained over time as demonstrated by positive numerical changes in height Z-score and AGV after one additional year of treatment in Trial 111-208, when comparing subjects randomized to vosoritide in Trial 111-206 (vos/vos) (i.e., after 2 years of treatment with vosoritide) to subjects randomized to placebo in Trial 111-206 (pbo/vos) (i.e., after 1 year of treatment with vosoritide). The treatment difference (95% CI) from baseline to Week 104 (Year 2) for height Z-score and AGV were 0.09 (-0.20, 0.38) and 0.70 cm/year (0.01, 1.39) (Section 6.2.2.1). The smaller treatment difference in height Z-score was driven by a negative change in the treatment estimate for subjects in Cohort 2 (≥ 6 to <24 months). The negative treatment difference in this age cohort could be explained by

the high proportion of subjects in the vos/vos arm (4 out of 8 in vos/vos arm compared to 1 out of 7 in pbo/vos arm) who had standing height measured at Week 104 as opposed to body length, which underestimated treatment difference (Section 16.2.4.4). Otherwise, the treatment estimates at Year 2 for height Z-score in Cohorts 1 and 3 between vos/vos and pbo/vos arms were consistent with the treatment effect in height Z-score observed at Year 1 in Trial 111-206, suggesting a sustained effect of vosoritide on growth after 2 years of treatment.

The drug-induced improvement in growth observed in Studies 111-206 and 111-208 is further supported by comparative analyses with two external controls (AchNH and placebo/observational) (Section 6.2.3). The results of these analyses showed the treatment difference between vosoritide-treated subjects and AchNH in change from baseline in height Z-score incremented in Cohorts 1 and 2 from 0.45 and 0.69, respectively at Year 1 to 0.86 and 1.02, respectively at Year 3 (Section 6.2.3). The treatment difference between vosoritide-treated subjects and placebo/observational subjects also increased in Cohorts 1 and 2 from Year 1 to Year 2. In Cohort 3, there was little treatment difference from baseline at both Year 1 and Year 2 when compared against AchNH, while no data were available at Year 2 for comparison against placebo/observational (Section 6.2.3).The lack of increase in treatment difference from Year 1 to Year 2 in Cohort 3 may be due to the switch in height measurement from body length to standing height in the treated group after 1 year of treatment (refer to Section 16.2.4.4 for details).

No worsening in disproportionality that may affect vosoritide-induced growth was noted during Studies 111-206 and 111-208.

Conclusion

The substantial evidence of efficacy of the drug in children <5 years of age is based on extrapolation from efficacy in children > 5 years of age. Although the disease has generally similar pathogenesis across age groups and manifests with similar signs and symptoms (short stature, bone-related complications), differences exist. The drug mechanism of action is also similar in all age groups. In addition, the growth data in children <5 years of age obtained in Trials 111-206/208 show an effect on the growth parameters (height, height Z-score and AGV). The smaller effect on AGV can be explained by the high variability of this parameter in the younger age group and small sample size. Because AGV is an intermediate surrogate of clinical benefit, data on final adult height in all age groups is needed to confirm the treatment benefit in the intended patient population.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Vosoritide (identified as BMN111 in all nonclinical study summaries) has been characterized in a complete series of nonclinical studies supporting the original marketing application. The primary effects noted in the nonclinical studies were related to the pharmacologic activity of the compound on vascular and skeletal tissues, with adverse effects related to exaggerated pharmacology only being seen in 'normal' animals. No significant off-target liability (e.g., >50%

inhibition at concentrations <1μM) was detected in an in vitro receptor-binding screen (radioligand binding assays).

Natriuretic peptide receptor-B (NPR-B), the receptor to which CNP binds, is expressed on vascular smooth muscle (where it induces muscle relaxation) and cardiac fibroblasts. Therefore, multiple cardiovascular safety pharmacology studies were performed. Across species, dose-related reductions in blood pressure were observed with compensatory increases in heart rate. In monkeys, reductions in blood pressure (maximum decrease of 16%) were observed at doses (50μg/kg) with exposures equivalent to the clinical C_{max} that was associated with a compensatory 37% increase in heart rate, with the effects becoming more pronounced at higher doses. These effects on heart rate were associated with time dependent shortening of the PR interval (maximum -15%), QT interval (maximum -23%), and heart rate-corrected QT interval (QTcB; maximum -8%) at 11x the clinical C_{max}. The maximum effects were generally reached within 15 to 30 mins of dose administration and persisted for up to 8 hours before returning to baseline. Upon repeated dosing, the magnitude of the blood pressure effects, but not heart rate, appeared to attenuate. In mice, slight changes in blood pressure (-17%) and heart rate (+11%) were observed at >12x the clinical C_{max} at the maximum recommended human dose.

The primary drug-related observations in the repeat-dose toxicity studies in both the rat and non-human primate (NHP) were related to the pharmacologic activity of the drug on the skeletal system and were similar in both juvenile and adult animals. In 'normal' animals, BMN-111 induced dose- and time-dependent skeletal changes associated with bone growth, particularly at the growth plates. The pharmacologic effects on bone often resulted in bone overgrowth (e.g., kinking of the tail/hunched posture, valgus deformity, swollen limbs, degeneration, and dysfunction of joints) that impeded movement. These effects, and the associated microscopic changes to skeletal tissues/growth plates, that were not reversible were the basis for the identification of the no observed adverse effect level (NOAEL) in the various nonclinical studies. In general, the NOAEL decreased with increasing study duration. These effects were also evident at lower dosages/exposures in juvenile rat as compared to that reported in adult rats, but a similar pattern was not noted in NHPs. Regardless, the observed effects were considered to reflect exaggerated pharmacologic activity and are not considered to be a safety concern in the targeted population where enhanced bone growth is the desired outcome.

A full series of reproductive and developmental toxicity studies were performed with BMN-111. In a rat fertility study, reductions in testicular spermatid count/density (but within the historical range) and slight increases in the time to mating were observed, but there were no effects on the fertility rates or any other endpoints evaluated. No effects were noted on embryofetal development in rats or rabbits, nor were there any effects seen on parental female animals or offspring in the pre- and postnatal toxicity study in rats. In these studies, the highest doses administered were considered the NOAEL.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Not applicable.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

The safety profile of vosoritide has been characterized in the clinical development program of the drug in children ≥ 5 years of age with open epiphyses. include Injection site reactions (i.e., erythema, swelling and urticaria), vomiting, arthralgia, and decreased blood pressure are the most common. Decreased blood pressure, which is associated with the drug's pharmacologic action causing vascular muscle relaxation and vasodilatation, is also a labeled adverse reaction.

No new safety signals have been identified in the postmarket setting.

7.3.1. Adverse Events Identified in Postmarket Experiences

Postmarket safety data include those from ongoing clinical trials in children 5 years of age and older (Study 111-302 and 111-205) that were not reviewed with the original NDA (data after June 30, 2020, until August 25, 2022), as well as data from spontaneous reports (non-clinical trial experience) included in the Periodic Benefit Risk Evaluation Reports. Data generated from these sources are consistent with t data that supported the original approval, without any new safety signals. There is no increased incidence of serious adverse events (SAEs), and the ones reported were consistent with complications of achondroplasia. From the post-approval clinical trial experience, there were 10 subjects who had 12 SAEs reported as follows: genu valgus, torticollis, cervicothoracic kyphoscoliosios, spinal stenosis, foramen magnum stenosis, femur fracture (4 subjects), genu varum, myasthenia gravis, COVID-19. After reviewing the narratives of all cases, the clinical team concluded that a causal relationship between the study drug and the event could not be excluded in three cases-- spinal stenosis, one event of Grade 3 femur fracture (refer to Clinical review in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) under investigational new drug (IND) 111299, dated 8/2/2022, 10/4/2022 and 7/12/2023) and cervicothoracic kyphoscoliosis (refer to Clinical review in DARRTS under IND 111299, dated 5/3/2022). Spinal stenosis and cervicothoracic kyphoscoliosis are common in the achondroplasia pediatric population. In addition, one SAE of hypotension requiring fluid administration was reported from the non-clinical trial experience. Decreased blood pressure is a labeled risk associated with vosoritide.

Fracture is not labeled in the vosoritide label. Four SAEs of femoral fractures were reported during the post-marketing experience from clinical trials, while none were reported in the original submission. Therefore, the Agency requested the Applicant to conduct an extensive analysis of all events of fractures reported in the vosoritide development program (refer to Supporting Documents 172 and 173, respectively, under IND 111299, in DARRTS).

Ten out of 241 (4.1%) subjects experienced a total of 11 events of fractures (annual event rate 0.015) while receiving vosoritide (one subject prior to drug approval and 9 subjects during post-approval period). Two events were reported during the 12-month placebo-controlled period of Study 111-301 (one in vosoritide and one in placebo arm). No fractures were reported in spontaneous reports. The incidence rate of fractures was consistent with the rate from epidemiologic data in both the general and ACH pediatric population. In the vosoritide-treated population, the most common type of fracture was femur [1.7%; annual event rate 0.005)

followed by hand (1.2%; annual event rate 0.003), and radius (0.8%; annual event rate 0.002), while epidemiologic data report that the most common sites of fractures in general pediatric population are 'radius and/or ulna' (20%), 'patella, tibia or fibula or ankle' (19%) and 'hand [wrist and other distal part]'(13%), while femur fractures accounted for 6%. A higher incidence rate of femoral fractures was noted in vosoritide development program compared to general pediatric population and ACH pediatric population, respectively [incidence rate per 100,000 (95% CI): 511 (192-1361) versus 109 (85-139) versus 205 (83-423), respectively]. Fracture incidence did not appear to depend on total drug exposure, as they were reported at similar frequencies throughout the duration of the development program. The sex, age and mechanism of injury leading to fractures in vosoritide development program were consistent with epidemiologic data reporting boys having a higher risk than girls and falls and sports-related accidents as being the most common causes of fractures (including femoral fractures) in children aged between 4 and 12 years. All fractures healed, or are healing, while on study drug, except 1 subject who was discontinued shortly before the event of femoral fracture.

Vitamin D deficiency was a confounder in 60% of cases of fractures, however, the distribution of vitamin D values in subjects who sustained fractures was consistent with the overall findings in the vosoritide clinical development program and with National Health and Nutrition Examination Survey (NHANES 2001-2004) data that indicate an epidemic of low vitamin D in the general population, with ACH children being affected to a similar degree as their average stature peers. As such, the clinical review team concurred with the Applicant's assessment that there was no evidence that Vitamin D levels correlated with occurrence of fracture in the vosoritide program.

The clinical review team also evaluated the individual bone mineral density/ bone mineral content (BMD/BMC) data by dual energy x-ray absorptiometry (DXA) in all subjects who experienced fractures in the vosoritide clinical development program and concluded that there was no consistent and meaningful decline observed in BMD/BMC over time. In addition, evaluation of BMD/BMC data of all subjects enrolled in vosoritide development program was reviewed and there was no evidence of a negative impact of vosoritide on BMD/BMC in children treated with vosoritide to suggest a predisposition to increased risk of fracture.

Moreover, the Applicant presented the fractures data in vosoritide clinical development program to an independent Data Monitoring Committee (DMC), a Steering Committee (SC) and Key opinion leaders (KOLs) in the field of Achondroplasia and Pediatric orthopedics. DMC concluded that while multiple contributing factors were implicated in the occurrence of the femoral fractures, including primary driver events of trauma in all four cases, femoral fracture should be monitored closely. The SC acknowledged the higher rate of femur fractures observed but given the small number of cases (n = 4), they concluded that the imbalance appeared to be a statistical aberration with no compelling evidence that vosoritide caused this. The KOLs (Dr. (b) (4) and Dr. (b) (4), pediatric orthopedic surgeon specializing in skeletal dysplasia) noted that the nature of the femoral fractures in all four cases were not of concern as they were assessed as "short midshaft displaced oblique fractures," and not spiral, and they did not involve the growth plate, suggesting that the fractures were due to a change in bone biomechanics rather than a change in bone quality.

In conclusion, the clinical review team found the Applicant's analysis of femoral fractures adequate and comprehensive. The clinical review team considers that while a causal relationship between the event of femoral fracture and vosoritide cannot be excluded, given the relatively

small number of femoral fracture cases reported to date, the presence of alternative etiology (i.e., trauma), and the nature of the fractures suggestive of altered biomechanics rather than a change in bone quality, no further action is indicated at this time. The fracture events overall, and femoral fractures in particular, should continue to be closely monitored in the clinical development program and postmarketing setting.

The incidence and exposure adjusted rates of the AEs commonly reported in clinical trials (i.e., injection site reactions, vomiting, arthralgia, decreased blood pressure, diarrhea, dizziness, headache, knee deformity, pain in extremity) were similar or lower in the subsequent years of drug exposure in the ongoing clinical trials. Also, there was no increase in the incidence, or exposure adjusted event rates of the AEs related to skeletal abnormalities and related neurological complications (i.e., spinal kyphosis, spinal lordosis, spinal stenosis, scoliosis, knee deformities) with long-term exposure to vosoritide in the interventional trials, while the overall incidence of these events was lower than reported in the achondroplasia pediatric population.

In summary, there were no new safety signals identified from the post-marketing experience of vosoritide in children 5 years of age and older that would warrant safety labeling updates. Vosoritide safety profile will continue to be closely monitored during the ongoing clinical trials and in the post-marketing setting.

7.4. FDA Approach to the Safety Review

7.4.1. Sources of Data for Clinical Assessment

The safety data for vosoritide in subjects <5 years of age are primarily derived from a completed phase 2 trial (Trial 111-206) and its ongoing open-label single arm long-term extension trial (Trial 111-208). Additional safety data in subjects <5 years of age is provided from the ongoing open-label phase 2 trial (Trial 111-209) conducted in ACH subjects ≤ 12 months who are at risk of requiring cervicomedullary decompression surgery (refer to Section 15 for study design details).

The safety profile of vosoritide was characterized during the review of data included in the original NDA, which included data for vosoritide in subjects ages ≥ 5 years from a completed phase 3 trial (Study 111-301) and its ongoing open-label single arm long-term extension trial (Study 111-302), and one completed phase 2 open-label single arm trial (Study 111-202) and its ongoing long-term extension trial (Study 111-205) (refer to Integrated Review in DARRTS dated November 18, 2021). These data are not addressed in detail in this supplement review.

Long-term safety data in subjects ≥ 5 years of age from the ongoing open-label single arm extension trials 111- 302 and 111-205 that were not reviewed with the original NDA submission (data after June 30, 2020) are discussed in Section 7.3.1 above.

The cut-off dates for the safety data review for the ongoing Trials 111-208 and 111-209 in subjects <5 years of age are January 26, 2022, and February 25, 2022, respectively. The cut-off date for the safety data review for the ongoing Studies 111-302 and 111-205 in subjects ≥ 5 years of age is February 25, 2022.

Safety data for studies 111-208 and 111-209, included in the 120-safety update (cutoff date August 25, 2022) were reviewed as well.

7.4.2. Safety Analysis Plan and Definitions

The prespecified safety analysis plan and definitions were reviewed during the clinical development program and were acceptable.

The Safety Population was defined as all subjects with ACH who were enrolled in the studies and treated with at least 1 dose of study drug. Use of descriptive statistics was predefined in the study protocols for summarizing the safety outcomes. The review team agreed with the proposed approach.

Treatment-emergent AEs were protocol-defined as any adverse event (AE) with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.

As specified in the protocol, the severity of AEs was assessed by the Investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4 ranging from Grade 1 to Grade 5.

No major issues were identified with respect to recoding, coding, and categorizing AEs. The Applicant translated verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for the events reported in the trials. The translations were reviewed and found overall acceptable, unless specifically noted in this review.

The Applicant's strategy for injection site reaction (ISR) reporting included the following algorithm: if an ISR was associated with a single sign or symptom (e.g., erythema) the sign or symptom was reported as an event on the AE page (ADAE) (e.g., injection site erythema); if the ISR was associated with multiple signs or symptoms (e.g., injection site swelling and erythema) the event was reported as ''Injection Site Reaction" on the AE page, while each associated sign and symptom was reported on a separate ISR symptom page (ADCE). A summary of individual ISR signs and symptoms was created and reported, by combining data from the ISR symptom page and AE page, referred to as ISR symptoms. This approach was found acceptable.

Lastly, the FDA review team conducted a separate analysis of adverse reactions (ARs) occurring during Studies 111-206 and 111-208 using Food and Drug Administration Medical Dictionary for Regulatory Activities queries (FMQs), or Grouped Queries (GQs). FMQs were developed by FDA to improve the capture of synonymous adverse event terms and to improve overall safety signal detection.

7.4.3. Reviewer's Approach to Safety Evaluation

Safety data from Trial 111-206 is the primary source of safety assessment in subjects <5 years of age, as it was the only completed trial with a double-blind design that included a placebo arm. Supportive safety data for subjects <5 years of age were also obtained from Studies 111-208 and 111-209 (Refer to Section 15 for details regarding study design and objectives). Trial 111-208 also provided long-term safety data. Considering the significant differences in trial designs, including use of blinding, use of control arms, duration, doses, and age groups studied, the clinical reviewer analyzed and presented the safety data separately for each individual trial.

Clinical trial data were independently analyzed by clinical review team using R software. All safety assessments and conclusions are those of the clinical review team unless otherwise

specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for a comprehensive safety assessment of vosoritide for the proposed indication, patient population, and dosage regimen. While the level of exposure to the study drug during the clinical development program does not satisfy the International Conference on Harmonization E1 guidelines for safety assessment for chronically administered medications, the level of exposure is adequate for a chronically administered drug in the orphan population of patients with ACH and similar or larger to the level of exposure used for the approval of other drugs for pediatric orphan indications. To date, 223 subjects were exposed to vosoritide for at least 6 months, and 215 subjects were exposed for at least 1 year (Table 66, Section 17.1).

The mean (SD) exposure to vosoritide in Trial 111-206 was 51.9 weeks. Table 19 summarizes the exposure for Trial 111-206.

Table 19. Duration of Exposure, Safety Population, Trial 111-206

Parameter	Placebo N=32 n (%)	Vosoritide N=43 n (%)
Duration of treatment, weeks		
Mean (SD)	52.2 (1.5)	51.9 (3.6)
Median (min, max)	52.2 (45.9, 55.1)	52.1 (29.6, 55)
Total exposure (person years)	32	43
Subjects treated, by duration, n (%)		
<26 weeks	0	0
≥26 to <39 weeks	0	1 (2.3)
≥39 to <52 weeks	5 (15.6)	14 (32.6)
≥52 to <65 weeks	27 (84.4)	28 (65.1)
≥65 weeks	0	0

Source: adex.xpt and adsl.xpt; Software: R
Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

The mean (SD) duration of exposure to vosoritide in all subjects enrolled in Studies 111-206 and 111-208 was 23.81 (10.79) months (Table 26, Section 17.1).

In Trial 111-209, the mean (SD) duration of treatment is much shorter, with 179.0 [150.3] days in standard of care (SoC) + vosoritide group and 279.3 [163.7] days in the comparator arm (SoC only).This is an ongoing study, with final data to include a total exposure of 104 weeks (24 months) in the randomized period and an additional 156 weeks (36 months) in the extension period.

7.6. Safety Results

7.6.1. Overall Safety Results Summary

Vosoritide was well-tolerated and had an acceptable safety profile in the pediatric population enrolled ages 3 months to <5 years with ACH at the proposed dosing regimen. There was one death in the clinical development program, a case of sudden infant death syndrome, that is likely unrelated to vosoritide. There were no discontinuations due to AEs, the incidence of SAEs was low and similar between study drug and placebo. Most AEs reported in the clinical program were nonserious and mild or moderate in severity.

In Trial 111-206, the most frequent AEs were injection site reactions, which are expected with injectable products. Other AEs with a higher incidence in vosoritide arm compared to placebo were respiratory infections, fall, constipation and sleep apnea. Respiratory infections and falls are common in this age group and even more common in children with achondroplasia. Sleep apnea is also common condition in children with achondroplasia. All cases were mild and likely unrelated to vosoritide.

The potential of vosoritide to induce abnormal bone growth at growth plates and subsequent clinical manifestations (i.e., bone deformity, dysfunctional joints), or contribute to worsening of skeletal deformities and associated ACH-related comorbidities due to accelerated bone growth were evaluated in the clinical studies in children <5 years of age. There was no evidence of increase incidence of sign and/or symptoms potentially related to abnormal skeletal growth (i.e., genu valgus/varum deformity, swollen limbs, joint pain), worsening of skeletal deformities (genu varum, spinal kyphosis/lordosis), or bone morphology as evaluated by radiographic assessments with vosoritide use. Also, there was no increase in frequency or severity of achondroplasia-related conditions (i.e., ear infections, lower extremities/spinal deformities, back pain, sleep apnea) with vosoritide use compared to placebo.

Diastolic blood pressure decrease, an expected pharmacologic effect of vosoritide, was noted in a slightly higher percentage of children in vosoritide group compared to placebo, but events were mostly asymptomatic, transient, and self-limiting.

Lastly, the safety profile of vosoritide was similar among the age sub-groups. The safety profile of vosoritide with long-term exposure in Trial 111-208 was similar to safety data reported in Trial 111-206, without any new safety signals detected.

In summary, the demonstrated safety profile of vosoritide in pediatric population age 3 months to <5 years with ACH is similar to the safety profile described in the approved label for older children (ages 5 to 18 years).

7.6.2. Overview of Treatment-Emergent Adverse Events Summary

Trial 111-206

Not unexpected in this patient population, all subjects had at least one AE reported during the study (Table 20). One subject randomized to vosoritide had a fatal respiratory event, due to sudden infant death syndrome (see below).

No subject discontinued study drug due to AE, while SAEs were reported in three (7%) subjects in vosoritide arm and 6 (19%) subjects in placebo arm (Table 20). Table 20. Overview of Treatment-Emergent Adverse Events, Safety Population, Trial 111-206

Event Category	Randomized Vosoritide N=32 n (%)	Randomized Placebo N=32 n (%)	Sentinel Vosoritide N=11 n (%)	All Patients Vosoritide N=43 n (%)	All Patients Vosoritide vs. Randomized Placebo Risk Difference (%)
SAE	3 (9.4)	6 (18.8)	0	3 (7.0)	-11.8
SAEs with fatal outcome	1 (3.1)	0	0	1 (2.3)	2.3
Life-threatening SAEs	0	0	0	0	-
AE leading to permanent discontinuation of study drug	0	0	0	0	-
AE leading to dose modification of study drug	11 (34.4)	15 (46.9)	3 (27.3)	14 (32.6)	-14.3
AE leading to interruption of study drug	11 (34.4)	15 (46.9)	3 (27.3)	14 (32.6)	-14.3
Any AE	32 (100)	32 (100)	11 (100)	43 (100)	-
Severe and worse	2 (6.2)	3 (9.4)	0	2 (4.7)	-4.7
Moderate	15 (46.9)	22 (68.8)	6 (54.5)	21 (48.8)	-19.9)
Mild	15 (46.9)	7 (21.9)	5 (45.5)	20 (46.5)	24.6

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.
Duration is 1 year treatment period.
Risk difference is shown between total treatment and comparator.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

Trial 111-208

The overall safety profile of vosoritide in Trial 111-208 was similar between subjects previously randomized to vosoritide in Trial 111-206 and subjects previously exposed to placebo. The incidence of SAEs was low, with majority of AEs being of mild, or moderate intensity (Table 21).

Table 21. Overview of Adverse Events, Safety Population, Trial 111-208

Event Category	Vosoritide to Vosoritide N=42 n (%)	Placebo to Vosoritide N=31 n (%)	All Subjects Vosoritide N=73 n (%)
SAE	3 (7.1)	3 (9.7)	6 (8.2)
SAEs with fatal outcome	0	0	0
Life-threatening SAEs	0	0	0
AE leading to permanent discontinuation of study drug	0	0	0
AE leading to dose modification of study drug	9 (21.4)	8 (25.8)	17 (23.3)
AE leading to interruption of study drug	9 (21.4)	8 (25.8)	17 (23.3)

Event Category	Vosoritide to Vosoritide N=42 n (%)	Placebo to Vosoritide N=31 n (%)	All Subjects Vosoritide N=73 n (%)
Any AE	42 (100)	29 (93.5)	71 (97.3)
Severe and worse	1 (2.4)	3 (9.7)	4 (5.5)
Moderate	22 (52.4)	16 (51.6)	38 (52.1)
Mild	19 (45.2)	10 (32.3)	29 (39.7)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.
Duration is from Day 1 of vosoritide treatment in Trial 111-208 to the end of Trial 111-208.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

Deaths Trial 111-206

There was one death due to sudden infant death syndrome (SIDS) reported in Trial 111-206.

Subject [redacted] (b) (6), randomized to vosoritide 30 µg/kg/day. [redacted] (b) (6) diagnosed with obstructive sleep apnea syndrome (OSA) requiring supplemental oxygen, chondrodystrophy, mild pharyngeal dysphagia, mild gastroesophageal reflux, poor head control without other neurologic findings, foramen magnum stenosis noted as "not severe" and cervical medullary cord compression with diffuse effacement of cerebro-spinal fluid (CSF) flow around the cord noted on screening magnetic resonance imaging (MRI). On study Day 99, the subject was started on Continuous Positive Airway Pressure (CPAP) for unspecified reason. On study Day 106, the subject was hospitalized for grade 3 Respiratory Syncytial Virus bronchiolitis with oxygen saturation of 70-80% despite use of CPAP that was treated with ibuprofen and salbutamol. Vosoritide was continued. On study Day 116 the event was reported as resolved and the participant was discharged home on oxygen therapy and CPAP.

On study Day 207 at age [redacted] (b) (6), the subject was diagnosed with SIDS after being noted not breathing after 20 minutes of unobserved time. According to the report, the subject was fine prior to the event. An autopsy was not performed. According to the mother, she observed no behaviors or occurrences on that day that would indicate an unusual reaction to the drug. The Investigator and the Applicant classified the event as related to underlying disease (i.e., achondroplasia) and not related to study drug. After reviewing the unblinded case, the DMC agreed with Sponsor's assessment of causality.

This clinical team agrees with the Investigator and DMC assessments of the SIDS as unlikely to be related to study drug. While a causal relationship between vosoritide and the event of SIDS cannot be completely ruled out, the presence of several risk factors known to be associated with SIDS makes a causal relationship between the study drug and event unlikely. Confounding factors include history of obstructive sleep apnea which was severe enough to require both CPAP and supplemental oxygen therapy, radiographic evidence of cervical medullary cord compression with marked stenosis and foramen magnum stenosis, as well as clinical evidence of poor head control, likely a manifestation of abnormal cranial and neurological development associated with achondroplasia. These conditions are known risk factors for SIDS. According to literature (Hecht et al. 1987; Pauli 2019), SIDS occurs in infants with achondroplasia with an estimated incidence ranging from 2 to 7.5%, which is higher than the CDC reported annual incidence (CDC 2023) of SIDS of 33.3 in 100,000 live births in the general population and is likely due to the bony

abnormalities associated with achondroplasia (i.e., foramen magnum stenosis and spinal canal stenosis) resulting in brain-stem/medullary cord compression leading to respiratory insufficiency/central sleep apnea and potential death.

Trial 111-208

No deaths occurred during Studies 111-208 and 111-209, up to the data cut-off date of the sNDA submission.

Serious Treatment-Emergent Adverse Events

The incidence of SAEs in the clinical program in children with achondroplasia younger than 5 years of age was low; all events occurred in 1 subject each. The narratives of all SAEs were reviewed in detail by FDA; most events are unlikely to be related to study drug but represent expected comorbidities associated with achondroplasia (i.e., spinal cord compression, intracranial pressure increased, adenoidal hypertrophy, obstructive/central sleep apnea), or common events seen in young pediatric population (i.e., upper, and lower respiratory tract infections, fractures). The events were deemed serious in majority of cases due to need for surgery and/or hospitalization The data do not suggest an increase incidence or worsening of severity of these events with vosoritide. The SAEs that are unlikely to be related to study drug are not discussed further in this review. Trial 111-206

Three (7%) subjects in the all-vosoritide group and 6 (18.8%) subjects in the placebo group reported 4 SAEs and 8 SAEs, respectively. The SAEs in the vosoritide arm (one subject each) were: oxygen saturation decreased, respiratory syncytial virus bronchiolitis and sudden infant death syndrome, and pneumonia (Table 22). The case of the child with both respiratory syncytial virus bronchiolitis and sudden infant death syndrome was reviewed above. The clinical review team considered the events of oxygen saturation decreased and pneumonia as unlikely to be related to study drug.

Table 22. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial 111-206

System Organ Class Preferred Term	Randomized Vosoritide N=32 n (%)	Randomized Placebo N=32 n (%)	Sentinel Vosoritide N=11 n (%)	All Patients Vosoritide N=43 n (%)	All Patients Vosoritide vs. Randomized Placebo Risk Difference (%)
Any SAE	3 (9.4)	6 (18.8)	0	3 (7.0)	-11.8
Gastrointestinal disorders (SOC)	0	1 (3.1)	0	0	-3.1
Vomiting	0	1 (3.1)	0	0	-3.1
General disorders and administration site conditions (SOC)	1 (3.1)	0	0	1 (2.3)	2.3
Sudden infant death syndrome	1 (3.1)	0	0	1 (2.3)	2.3
Infections and infestations (SOC)	2 (6.2)	3 (9.4)	0	2 (4.7)	-4.7
Pneumonia	1 (3.1)	0	0	1 (2.3)	2.3
Respiratory syncytial virus bronchiolitis	1 (3.1)	0	0	1 (2.3)	2.3
Gastroenteritis	0	1 (3.1)	0	0	-3.1
Otitis media	0	1 (3.1)	0	0	-3.1
Parainfluenza virus infection	0	1 (3.1)	0	0	-3.1
Injury, poisoning and procedural complications (SOC)	0	1 (3.1)	0	0	-3.1
Skull fracture	0	1 (3.1)	0	0	-3.1
Investigations (SOC)	1 (3.1)	0	0	1 (2.3)	2.3
Oxygen saturation decreased	1 (3.1)	0	0	1 (2.3)	2.3
Nervous system disorders (SOC)	0	1 (3.1)	0	0	-3.1
Petit mal epilepsy	0	1 (3.1)	0	0	-3.1
Psychiatric disorders (SOC)	0	1 (3.1)	0	0	-3.1
Autism spectrum disorder	0	1 (3.1)	0	0	-3.1
Respiratory, thoracic, and mediastinal disorders (SOC)	0	1 (3.1)	0	0	-3.1
Respiratory distress	0	1 (3.1)	0	0	-3.1

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 1 year treatment period.
Risk difference is shown between total treatment and comparator.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Trial 111-208

Eleven subjects experienced 13 SAEs (Table 23). Except for the event of subdural hygroma, the SAEs were unlikely related to study drug but represent comorbidities related to ACH. The SAE of adenoidal hypertrophy requiring surgery was reported in 3 subjects, while the SAEs of respiratory syncytial virus infection and sleep apnea syndrome were reported in 2 subjects each. The SAEs of cervical cord compression, intracranial pressure increased, subdural hygroma, foramen magnum stenosis, otitis media and vomiting were reported in single subjects.

Table 23. Patients With Serious Adverse Events by Preferred Term, Safety Population, Trial 111-208

Subject ID (Treatment Arm)	Age (Months)/ Sex	Adverse Event (PT)	Onset Day	Duration (Days)	Outcome
(b) (6) (Plc/vos)	(b) (6)	Cervical cord compression	39	5	Recovered/resolved
		Sleep apnea syndrome	220	3	Recovered/resolved
(b) (6) (Plc/vos)		Intracranial pressure increased	65	320	Recovered/resolved
(b) (6) (Vos/vos)		Adenoidal hypertrophy	548	89	Recovered/resolved
(b) (6) (Vos/vos)		Sleep apnea syndrome	445	1	Recovered/resolved
(b) (6) (Vos/vos)		Subdural hygroma	387	Ongoing	Not recovered/not resolved
		Adenoidal hypertrophy[a]	501	140	Recovered/resolved
(b) (6) a (Plc/vos)		Foramen magnum stenosis	94	2	Recovered/resolved
(b) (6) a (Vos/vos)		Pneumonia respiratory syncytial viral	813	9	Recovered/resolved
(b) (6) a (Vos/vos)		Otitis media	546	1	Recovered/resolved
(b) (6) a (Vos/vos)		Vomiting	905	4	Recovered/resolved
(b) (6) a (Vos/vos)		Adenoidal hypertrophy	678	135	Recovered/resolved

Source: adae.xpt; Software: R
[a] SAE reported with 120-day safety update addendum after sNDA submission
Abbreviations: F, female; M, male; plc/vos, placebo/vosoritide; PT, preferred term; vos/vos, vosoritide/vosoritide.

Trial 111-209

Fourteen SAEs were reported in 10 subjects; 2 (22.2%) subjects experienced 3 SAEs in Standard of Care (SoC) alone group and 8 (72.7%) subjects experienced 7 SAEs in the SoC + vosoritide group (this data also includes SAEs that were reported with the 120-safety update report with a cutoff date of August 25, 2022). The SAEs were as follows: SoC alone group: foramen magnum stenosis, bronchiolitis, pneumonia; SoC + vosoritide group: lower respiratory tract infection, worsening cervical cord compression (2 subjects), fractured skull, urosepsis, head injury from fall, hydrocephalus, dehydration, pneumonia, foramen magnum stenosis, milk allergy (Table 24). After reviewing the cases narrative, the clinical reviewer deemed all SAEs as unlikely to be related to vosoritide. It is important to note that the patient population enrolled in this study consisted of subjects with severe foramen magnum stenosis causing medullary cord compression, as the primary objectives of the study were to assess the safety of vosoritide in this high surgical risk population, as well as drug effect on the need for surgical cervicomedullary

decompression, among others. As such, the relatively higher incidence of SAEs compared to studies 111-206/208, particularly with regards to the neurological SAEs (i.e., worsening cervical cord compression, foramen magnum stenosis, hydrocephalus in vosoritide arm) are likely explained by the underlying disease characteristics of the patient population. Additionally, during the review cycle, the Agency requested an update regarding the SAEs data from the ongoing study. According to the Applicant's response to the information request, during the period August 22, 2022, until August 21, 2023, no additional subjects exposed to vosoritide experienced SAEs of worsening cervical cord compression, or foramen magnum stenosis. During the reporting period, a total of 18 SAEs were reported in 9 subjects with majority of the events being infectious in etiology and similarly distributed between treatment arms.

Table 24. Summary of Serious Adverse Events, Safety Population, Trial 111-209

Subject ID (Treatment Arm)	Age(Months)/ Sex	Adverse Event (PT)	Onset Day	Duration (Days)	Outcome
(b) (6) (SoC+vos)	(b) (6)	Lower Respiratory Tract Infection	344	6	Recovered/resolved
(b) (6) (SoC+vos)		Worsening cervical cord compression	273	1	Recovered/resolved
(b) (6) (SoC+vos)		Fractured skull depressed	49	3	Recovered/resolved
		Worsening cervical cord compression	169	3	Recovered/resolved
(b) (6) (SoC+vos)		Urosepsis	128	3	Recovered/resolved
(b) (6) [a] (SoC+vos)		Head injury	273	1	Recovered/resolved
(b) (6) [a] (SoC+vos)		Hydrocephalus	269	4	Recovered/resolved
(b) (6) [a] (SoC+vos)		Dehydration	378	3	Recovered/resolved
(b) (6) [a] (SoC+vos)		Pneumonia	84	3	Recovered/resolved
(b) (6) [a] (SoC+vos)		Foramen magnum stenosis	180	28	Recovered/resolved
(b) (6) [a] (SoC+vos)		Milk allergy	-16	5	Recovered/resolved
(b) (6) [a] (SoC alone)		Pneumonia	327	6	Recovered/resolved
(b) (6) [a] (SoC alone)		Bronchiolitis	69	17	Recovered/resolved
		Foramen magnum stenosis	71	14	Recovered/resolved

Source: Excerpted from Table 12.3.1.2.2, Interim CSR, Trial 111-209 and Appendix 1, 120-day-safety report
[a] SAE reported with 120-day safety update addendum after sNDA submission
Abbreviations: F, female; M, male; PT, preferred term; SoC, standard of care; vos, vosoritide

7.6.3. Adverse Events Leading to Treatment Discontinuation

Except for the AE of death attributed to SIDS in one subject exposed to vosoritide during Trial 111-206 (refer to Section 7.6.2 above), there were no other AEs leading to study drug discontinuation in Trials 111-206, 111-208, and 111-209.

7.6.4. Treatment-Emergent Adverse Events

Although only data from the placebo- controlled Trial 111-206 will be included in labeling, Trial 111-208 provided supportive and/or long-term safety data that is important for chronic use.

Trial 111-206

Nearly all subjects in vosoritide and placebo arms experienced at least one AE during this study.

AEs that occurred with an incidence of ≥5% in all vosoritide group and higher incidence than placebo are listed in Table 25. Reporting incidence of AEs with a risk difference < 2% between vosoritide and placebo would elicit AEs occurring with a difference of one subject or less, which is not considered clinically meaningful.

Table 25. Treatment-Emergent Adverse Events Reported With ≥5% Incidence in All-Vosoritide Group and Higher Incidence Compared to Placebo, Safety Population, Trial 111-206

Preferred Term	Randomized Vosoritide N=32 n (%)	Randomized Placebo N=32 n (%)	Sentinel Vosoritide N=11 n (%)	All Subjects Vosoritide N=43 n (%)	All Subjects Vosoritide vs. Randomized Placebo Risk Difference (%)
Any AE	32 (100)	32 (100)	11 (100)	43 (100)	
Injection site reaction[a]	26 (81.2)	13 (40.6)	8 (72.7)	34 (79.1)	38.4
Injection site erythema	25 (78.1)	13 (40.6)	8 (72.7)	33 (76.7)	36.1
Injection site swelling	7 (21.9)	2 (6.2)	1 (9.1)	8 (18.6)	12.4
Injection site induration	5 (15.6)	0	0	5 (11.6)	11.6
Injection site urticaria	4 (12.5)	1 (3.1)	2 (18.2)	6 (14.0)	10.8
Rhinitis	3 (9.4)	0	1 (9.1)	4 (9.3)	9.3
Arthropod bite	6 (18.8)	2 (6.2)	0	6 (14.0)	7.7
Epistaxis	2 (6.2)	0	1 (9.1)	3 (7.0)	7.0
Sleep apnea syndrome	2 (6.2)	0	1 (9.1)	3 (7.0)	7.0
Viral upper respiratory tract infection	2 (6.2)	0	1 (9.1)	3 (7.0)	7.0
Fall	3 (9.4)	3 (9.4)	4 (36.4)	7 (16.3)	6.9
Dermatitis diaper	2 (6.2)	1 (3.1)	2 (18.2)	4 (9.3)	6.2
Lower respiratory tract infection	3 (9.4)	1 (3.1)	1 (9.1)	4 (9.3)	6.2
Viral infection	5 (15.6)	4 (12.5)	3 (27.3)	8 (18.6)	6.1
Constipation	2 (6.2)	2 (6.2)	3 (27.3)	5 (11.6)	5.4
Impetigo	2 (6.2)	0	0	2 (4.7)	4.7
Procedural pain	0	0	2 (18.2)	2 (4.7)	4.7
Pain in extremity	3 (9.4)	1 (3.1)	0	3 (7.0)	3.9
Rash	4 (12.5)	4 (12.5)	3 (27.3)	7 (16.3)	3.8
Hand-foot-and-mouth disease	3 (9.4)	2 (6.2)	1 (9.1)	4 (9.3)	3.1
Injection site hemorrhage	3 (9.4)	2 (6.2)	1 (9.1)	4 (9.3)	3.1
Injection site mass	3 (9.4)	2 (6.2)	1 (9.1)	4 (9.3)	3.1
Upper respiratory tract infection	12 (37.5)	11 (34.4)	4 (36.4)	16 (37.2)	2.8

Source: adae.xpt; Software: R
[a] Injection site reactions that were associated with multiple signs or symptoms (refer to section 7.4.3 for details)
Risk difference is shown between total treatment and comparator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

The most common AEs in vosoritide arm were injection site reactions and respiratory tract infections (i.e., rhinitis, upper/lower respiratory tract infections). Injection site reactions are expected AEs of the study drug and are reviewed further below. Respiratory tract infections and

other viral infections are common conditions in children and particularly in children with achondroplasia due to cranial and thoracic skeletal deformities. In addition, while the events of rhinitis, lower respiratory tract infection, viral upper respiratory tract infection and upper respiratory tract infections were higher in vosoritide arm compared to placebo, the overall incidence of events in SOC Infections and infestations was lower in the vosoritide arm compared to placebo (Table 67, Section 17, Appendix). Sleep apnea syndrome is a common comorbidity in children with achondroplasia. The narratives of the 3 events of sleep apnea syndrome were reviewed in detail by the clinical team. All events were non-serious and mild to moderate in severity. Vosoritide was continued in all subjects after the event occurrence. The event was reported as resolved in one subject while on vosoritide therapy and as ongoing for the other 2 subjects. Two of the events were reported following completion of the protocol mandated 52-week sleep study, that showed the sleep study indices improving at Week 52 in 2 subjects and stable in one subject when compared to baseline. The other AEs of epistaxis, fall, dermatitis diaper and constipation are common pediatric conditions. Pain in extremities is common in children with achondroplasia due to skeletal deformities, although the AE was reported with low incidence [3 (7%) subjects in all vosoritide versus one subject (3.1%) in placebo].

There was no apparent difference in the incidence of treatment-emergent adverse events in randomized vosoritide subjects for each age cohort (Table 68, Section 17.1).

Table 26 summarizes the FMQ analysis that shows AEs with a higher incidence in vosoritide arm and with a risk difference ≥5%.

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Table 26. Treatment-Emergent Adverse Events by Narrow FDA Medical Query and Preferred Term Occurring With Higher Incidence in Vosoritide Arm and With a Risk Difference ≥5%, Safety Population, Trial 111-206

FMQ (Narrow) Preferred Term	Randomized Vosoritide N=32 n (%)	Randomized Placebo N=32 n (%)	Sentinel Vosoritide N=11 n (%)	All Subjects Vosoritide N=43 n (%)	All Subjects Vosoritid vs. Randomize Placeb Risk Difference (%
Viral Infection (FMQ)	15 (46.9)	12 (37.5)	6 (54.5)	21 (48.8)	11.
Viral upper respiratory tract infection	2 (6.2)	0	1 (9.1)	3 (7.0)	7.
Viral infection	5 (15.6)	4 (12.5)	3 (27.3)	8 (18.6)	6.
Hand-foot-and-mouth disease	3 (9.4)	2 (6.2)	1 (9.1)	4 (9.3)	3.
Erythema infectiosum	1 (3.1)	0	0	1 (2.3)	2.
Molluscum contagiosum	0	0	1 (9.1)	1 (2.3)	2.
Respiratory syncytial virus bronchiolitis	1 (3.1)	0	0	1 (2.3)	2.
Respiratory syncytial virus infection	1 (3.1)	0	0	1 (2.3)	2.
Respiratory syncytial virus test positive	1 (3.1)	0	0	1 (2.3)	2.
Varicella	1 (3.1)	0	0	1 (2.3)	2.
Varicella virus test positive	1 (3.1)	0	0	1 (2.3)	2.
Viral rash	1 (3.1)	0	0	1 (2.3)	2.
Gastroenteritis viral	1 (3.1)	2 (6.2)	2 (18.2)	3 (7.0)	0.
Parainfluenzae virus infection	0	1 (3.1)	1 (9.1)	1 (2.3)	-0.8
Influenza	3 (9.4)	3 (9.4)	0	3 (7.0)	-2.
Asymptomatic COVID-19	0	1 (3.1)	0	0	-3.
Bronchiolitis	0	1 (3.1)	0	0	-3.
COVID-19	0	1 (3.1)	0	0	-3.
Rhinovirus infection	0	2 (6.2)	0	0	-6.2
Pharyngitis	0	1 (3.1)	0	0	-3.
Respiratory Failure (FMQ)	3 (9.4)	0	1 (9.1)	4 (9.3)	9.
Sleep apnea syndrome	2 (6.2)	0	1 (9.1)	3 (7.0)	7.
Oxygen saturation decreased	1 (3.1)	0	0	1 (2.3)	2.
Erythema (FMQ)	26 (81.2)	13 (40.6)	8 (72.7)	34 (79.1)	38.
Injection site erythema	25 (78.1)	13 (40.6)	8 (72.7)	33 (76.7)	36.
Erythema	1 (3.1)	1 (3.1)	0	1 (2.3)	-0.

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FMQ (Narrow) Preferred Term	Randomized Vosoritide N=32 n (%)	Randomized Placebo N=32 n (%)	Sentinel Vosoritide N=11 n (%)	All Subjects Vosoritide N=43 n (%)	All Subjects Vosoritid vs. Randomize Placeb Risk Differenc (%
Rash (FMQ)	7 (21.9)	5 (15.6)	5 (45.5)	12 (27.9)	12.
Rash	4 (12.5)	4 (12.5)	3 (27.3)	7 (16.3)	3.
Dermatitis	0	0	1 (9.1)	1 (2.3)	2.
Dermatitis allergic	1 (3.1)	0	0	1 (2.3)	2.
Dermatitis contact	1 (3.1)	0	0	1 (2.3)	2.
Injection site rash	1 (3.1)	0	0	1 (2.3)	2.
Rash macular	1 (3.1)	0	0	1 (2.3)	2.
Viral rash	1 (3.1)	0	0	1 (2.3)	2.
Urticaria	0	1 (3.1)	1 (9.1)	1 (2.3)	-0.
Urticaria (FMQ)	5 (15.6)	2 (6.2)	2 (18.2)	7 (16.3)	10.
Injection site urticaria	4 (12.5)	1 (3.1)	2 (18.2)	6 (14.0)	10.
Mechanical urticaria	1 (3.1)	0	0	1 (2.3)	2.
Urticaria	0	1 (3.1)	1 (9.1)	1 (2.3)	-0.

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Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.
Duration is 1 year treatment period.
Risk difference is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: COVID-19, coronavirus disease 2019; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

AEs that were seen more frequently in vosoritide group are briefly summarized below.

The FMQ "Viral infections" was reported in 21 (50%) subjects in vosoritide arm compared to 12 (38%) subjects in placebo arm. The high incidence is consistent with the high prevalence of these conditions in the studied patient population and age groups. The incidence of individual PTs of viral infections was small (i.e., 1 to 3 subjects per event), the viral infections were of different location or etiology, and as such the clinical review team considers there was no safety signal identified to warrant labeling.

Most of the PTs in the FMQs "erythema" and "urticaria" were related to ISRs, which were reviewed separately below. The FMQ of "rash" included single events of "dermatitis allergic", "dermatitis contact", "injection site rash", "rash macular", 'viral rash" and "urticaria", as well as the PT of "rash" that occurred in several subjects in both arms, with relatively similar incidence [7 (16%) all vosoritide versus 4 (13%) placebo]. The risk difference between all-vosoritide [12 (28%)] and placebo [5 (16%)] for the FMQ "rash" was 12%. Since the events represent relatively synonymous terms, the clinical review team recommends inclusion of the term "rash" reflecting the incidence under the FMQ "rash" in the adverse reactions section of the label.

Injection Site Reactions (ISRs) are expected local AEs with vosoritide and were evaluated as adverse events of special interest. There were no identified safety concerns related to immunogenicity in children with achondroplasia 5 years of age and older. Refer to Section 7.4.2 regarding the algorithm used by the Applicant for ISR reporting that FDA considered acceptable.

The incidence of each ISR sign or symptom (regardless of their occurrence as a single type of reaction or associated with other signs or symptoms) are presented in Table 27, and the exposure-adjusted event rates are presented in Table 28. Overall, the incidence of ISRs was higher with vosoritide (86%) than placebo (53%). Most common were injection site erythema, injection site swelling injection site induration, and injection site urticaria. ISRs were mild and transient, and no subjects discontinued from the study due to ISRs. The mean (SD) time from first dose to first event onset was 2.0 (1.8) days (median: 1.0 day; range: 1 to 9 days) and 12.6 (23.6) days (median: 4.0 days; range: 1 to 77 days) for the all-vosoritide and placebo groups, respectively.

Table 27. Injection Site Reactions (Local Administration Reaction, Narrow FDA Medical Query), Trial 111-206, Safety Population

Local Administration Reaction Assessment	Randomized Vosoritide N=32 n (%)	Randomized Placebo N=32 n (%)	Sentinel Vosoritide N=11 n (%)	All Subjects Vosoritide N=43 n (%)	All Subjects Vosoritide vs. Randomized Placebo Risk Difference (%)
Local administration reaction (nFMQ)	29 (90.6)	17 (53.1)	8 (72.7)	37 (86.0)	32.9
Injection site reaction[a]	26 (81.2)	13 (40.6)	8 (72.7)	34 (79.1)	38.4
Injection site erythema	25 (78.1)	13 (40.6)	8 (72.7)	33 (76.7)	36.1
Injection site swelling	7 (21.9)	2 (6.2)	1 (9.1)	8 (18.6)	12.4
Injection site induration	5 (15.6)	0	0	5 (11.6)	11.6
Injection site urticaria	4 (12.5)	1 (3.1)	2 (18.2)	6 (14.0)	10.8
Injection site hemorrhage	3 (9.4)	2 (6.2)	1 (9.1)	4 (9.3)	3.1
Injection site mass	3 (9.4)	2 (6.2)	1 (9.1)	4 (9.3)	3.1
Injection site pain	1 (3.1)	0	0	1 (2.3)	2.3
Injection site rash	1 (3.1)	0	0	1 (2.3)	2.3
Vaccination site pain	1 (3.1)	0	0	1 (2.3)	2.3
Infusion site extravasation	0	1 (3.1)	0	0	-3.1
Injection site bruising	4 (12.5)	6 (18.8)	1 (9.1)	5 (11.6)	-7.1
Maximum severity					
Death	0	0	0	0	
Life-threatening	0	0	0	0	
Severe	0	0	0	0	
Moderate	0	0	0	0	
Mild	29 (90.6)	17 (53.1)	8 (72.7)	37 (86.0)	32.9
Serious	0	0	0	0	
Deaths	0	0	0	0	
Resulting in discontinuation	0	0	0	0	

Source: adae.xpt; Software: R
*if more than one injection site symptom occurred
Duration is 1 year treatment period.
Risk difference is shown between total treatment and comparator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Table 28. Exposure-Adjusted Event Rates[a] of Injection Site Reactions by PT

Event Rates	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)
Any injection site reaction	6305 (196.2)	1928 (60.2)	8232 (197.7)
Injection site erythema	3849 (121.7)	1738 (54.3)	5100 (119.4)
Injection site swelling	30 (0.9)	3 (0.1)	36 (0.8)
Injection site urticaria	13 (0.4)	1 (0)	22 (0.5)
Injection site bruising	16 (0.5)	39 (1.2)	26 (0.6)
Injection site induration	14 (0.4)	0	14 (0.3)
Injection site hemorrhage	3 (0.1)	2 (0.1)	4 (0.1)
Injection site pain[b]	2 (0.1)	0	2 (0)
Injection site mass	14 (0.4)	2 (0.1)	17 (0.4)
Injection site rash	2 (0.1)	0	2 (0)

Source: adapted by clinical reviewer based on table generated using adae.xpt; Software: R and Table 11.3.1.4.1.1
[a] Event rate = total number of events divided by total treatment exposure
[b] Injection site pain includes PTs of Injection site pain and Vaccination site pain
Abbreviations: N, number of events; PT, preferred term

The incidences and event rates for ISR were relatively similar among age cohorts as follows: Cohort 1 (≥ 24 to < 60 months): 84.2% (event rate 166.1) in the all-vosoritide group and 43.8%

(event rate 21.1) in the placebo group; Cohort 2 (≥ 6 to < 24 months): 83.3% (event rate 199.9) in the all-vosoritide group and 50.0% (event rate 81.8) in the placebo group; Cohort 3 (≥ 3 to < 6 months): 91.7% (event rate 232.8) in the all-vosoritide group and 75.0% (event rate 118.1) in the placebo group.

Labeling recommendations

The clinical review team recommends labeling AEs occurring with a risk difference of ≥ 5% between vosoritide and placebo arms. Given the small sample size of Trial 111-206, a risk difference of <5% would reflect small numerical differences between events in vosoritide and placebo arms (i.e., 2 subjects or less), which would not be considered clinically meaningful. These small observed differences could be a result of chance in small cohorts. The clinical review team also recommends inclusion in the label of the FMQ "rash", which captures synonymous adverse event terms and therefore reflects occurrence of all similar events.

Trial 111-208

The safety data for Trial 111-208 is presented separately for subjects originally randomized to vosoritide in Trial 111-206 as vosoritide/vosoritide group, and for subjects originally randomized to placebo in Trial 111-206 as placebo/vosoritide group, in order to assess whether the safety profile of vosoritide changes with prolonged drug exposure.

The incidence and types of AEs in Trial 111-208 was similar between the treatment arms (vosoritide/vosoritide and placebo/vosoritide), with the most common (> 10%) AEs of being those of infectious etiology, which are commonly encountered in the young pediatric population (Table 29). There was no evidence of increased incidence in AEs with prolonged exposure to vosoritide beyond one year, compared to first year of exposure to treatment. While some AEs were reported with higher frequency in vosoritide/vosoritide arm compared to placebo/vosoritide arm [i.e., gastroenteritis (19% versus 3%), otitis media (17% versus 3%), conjunctivitis (12% versus 0), viral infection (26% versus 16%)], other AEs of infectious etiology were less frequently reported in vosoritide/vosoritide arm compared to placebo/vosoritide arm [i.e., rhinitis (7% versus 10%), sinusitis (5% versus 10%), cough (14% versus 20%), ear pain (5% versus 16%), ear infection 14% versus 26%]. There were no new safety signals identified during Trial 111-208. Since Trial 111-208 was uncontrolled and no new safety signal were identified with prolonged drug exposure, the safety results from this study will not be included in the label.

Table 29. Subjects With Common Adverse Events Occurring at ≥5% Frequency in at Least One Treatment Arm, Safety Population, Trial 111-208

Preferred Term	Vosoritide to Vosoritide N=42 n (%)	Placebo to Vosoritide N=31 n (%)	Vosoritide to Vosoritide vs. Placebo to Vosoritide Risk Difference (%)
Any AE	42 (100)	29 (93.5)	6.5
Gastroenteritis	8 (19.0)	1 (3.2)	15.8
Otitis media	7 (16.7)	1 (3.2)	13.4
Conjunctivitis	5 (11.9)	0	11.9
Viral infection	11 (26.2)	5 (16.1)	10.1
COVID-19	6 (14.3)	2 (6.5)	7.8
Pain in extremity	6 (14.3)	2 (6.5)	7.8

Preferred Term	Vosoritide to Vosoritide N=42 n (%)	Placebo to Vosoritide N=31 n (%)	Vosoritide to Vosoritide vs. Placebo to Vosoritide Risk Difference (%)
Lower respiratory tract infection	3 (7.1)	0	7.1
Procedural pain	3 (7.1)	0	7.1
Seasonal allergy	4 (9.5)	1 (3.2)	6.3
Teething	4 (9.5)	1 (3.2)	6.3
Skin laceration	5 (11.9)	3 (9.7)	2.2
Upper respiratory tract infection	13 (31.0)	9 (29.0)	1.9
Fall	6 (14.3)	4 (12.9)	1.4
Arthralgia	3 (7.1)	2 (6.5)	0.7
Constipation	4 (9.5)	3 (9.7)	-0.2
Respiratory syncytial virus infection	4 (9.5)	3 (9.7)	-0.2
Vomiting	8 (19.0)	6 (19.4)	-0.3
Nasopharyngitis	9 (21.4)	7 (22.6)	-1.2
Eczema	2 (4.8)	2 (6.5)	-1.7
Headache	2 (4.8)	2 (6.5)	-1.7
Lip injury	2 (4.8)	2 (6.5)	-1.7
Rhinitis	3 (7.1)	3 (9.7)	-2.5
Arthropod bite	1 (2.4)	2 (6.5)	-4.1
Contusion	1 (2.4)	2 (6.5)	-4.1
Head injury	1 (2.4)	2 (6.5)	-4.1
Skin abrasion	1 (2.4)	2 (6.5)	-4.1
Sleep apnea syndrome	1 (2.4)	2 (6.5)	-4.1
Vitamin D decreased	1 (2.4)	2 (6.5)	-4.1
Oropharyngeal pain	2 (4.8)	3 (9.7)	-4.9
Rash	2 (4.8)	3 (9.7)	-4.9
Sinusitis	2 (4.8)	3 (9.7)	-4.9
Cough	6 (14.3)	6 (19.4)	-5.1
Diarrhea	3 (7.1)	4 (12.9)	-5.8
Asymptomatic COVID-19	0	2 (6.5)	-6.5
Hematoma	0	2 (6.5)	-6.5
Otitis externa	1 (2.4)	3 (9.7)	-7.3
Tympanic membrane perforation	1 (2.4)	3 (9.7)	-7.3
Nasal congestion	2 (4.8)	4 (12.9)	-8.1
Hand-foot-and-mouth disease	0	3 (9.7)	-9.7
Rhinorrhea	5 (11.9)	7 (22.6)	-10.7
Ear pain	2 (4.8)	5 (16.1)	-11.4
Ear infection	6 (14.3)	8 (25.8)	-11.5
Pyrexia	10 (23.8)	11 (35.5)	-11.7

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.
Duration is from Day 1 of vosoritide treatment in Trial 111-208 to the end of Trial 111-208.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients with adverse event

Trial 111-209

Although the safety profile of the drug in the youngest age group (< 12 months) appears to be consistent with that of the drug in older children, this is based on few subjects per cohort.

The incidence of AEs reported in more than one subject per treatment arm is presented in Table 30. The most commonly (>30%) reported AEs by PT in the SoC alone and SoC +

vosoritide groups were vomiting (28.6% and 66.7%), viral infection (71.4% and 44.4%), teething (57.1% and 33.3%), rash (28.6% and 33.3%), abdominal pain (0% and 33.3%), pyrexia (57.1% and 22.2%), nasopharyngitis (28.6% and 22.2%), which are common manifestations in the general infant population.

Table 30. Subjects With Common Adverse Events Occurring at ≥20% Frequency in At Least One Treatment Arm, Safety Population, Trial 111-209

	SoC Alone N=7 n (%)	SoC+Vosoritide N=9 n (%)
Preferred Term	**Incidence n (%)**	**Incidence n (%)**
Any AE	6 (85.7)	8 (88.9)
Vomiting	2 (28.6)	6 (66.7)
Viral infection	5 (71.4)	4 (44.4)
Teething	4 (57.1)	3 (33.3)
Rash	2 (28.6)	3 (33.3)
Abdominal pain	0	3 (33.3)
Pyrexia	4 (57.1)	2 (22.2)
Nasopharyngitis	2 (28.6)	2 (22.2)
Fall	1 (14.3)	2 (22.2)
Gastroenteritis	1 (14.3)	2 (22.2)
Rhinorrhea	1 (14.3)	2 (22.2)
Cervical cord compression	0	2 (22.2)
Diarrhea	0	2 (22.2)
Discomfort	0	2 (22.2)
Vaccination complication	2 (28.6)	1 (11.1)
Constipation	2 (28.6)	1 (11.1)
Cough	2 (28.6)	1 (11.1)

Source: Excerpted from Table 14.3.1.2.2.1, Interim CSR, Trial 111-209
Abbreviations: AE, adverse event; N, number of subjects; n, number of subjects with specific events

Most subjects experienced Grade 1 AEs [6 (86%) subjects in the SoC alone group and 8 (89%) in SoC + vosoritide group, respectively]. Four (44.4%) subjects in SoC + vosoritide group experienced a total of 5 Grade 3/SAEs: 2 events of cervical cord compression and 1 event each of lower respiratory tract infection, urosepsis, and fractured skull depressed (refer to Section 7.6.2). No Grade ≥3 events were reported in the SoC alone group.

Hypersensitivity events were reported in 4 (57.1%) subjects in the SoC alone group and 3 (33.3%) subjects in the SoC + vosoritide group. There were no AEs of ISR, hypotension, or heart rate change. It is important to note that while ISRs are commonly encountered with vosoritide use, the absence of ISR reporting as an AE in Trial 111-209 could have been due to different reporting criteria used in this study compared to Trial 111-206, namely only ISRs of NCI-CTCAE Grade ≥2 severity, or ISR events considered clinically significant by Investigator were reported as AEs.

7.6.5. Laboratory Findings

Trial 111-206

The laboratory abnormalities that occurred more often the vosoritide arm compared to placebo are summarized in Table 69, Section 17, Appendix. The reported shifts in laboratory values were small, most were a shift from normal to Grade 1 (NCI-CTCAE), transient, and not associated with any symptoms. No SAEs associated with laboratory abnormalities were reported. One subject in all-vosoritide and 2 subjects in placebo arms had a normal (baseline) to Grade 3 increase in alkaline phosphatase. The increase was transient (one instance/measurement only), with laboratory value returning to normal with subsequent monitoring, while vosoritide was continued. Increase in alkaline phosphatase, a bone formation marker, is expected with vosoritide treatment because of the effect of CNP on bone.

Trial 111-208

Similar to Trial 111-206, there were no clinically meaningful changes in any laboratory parameter in the Trial 111-208. Four subjects were noted to have a shift from normal to Grade 3/4 hyperkalemia. The case narratives were reviewed in detail by the clinical review team. In all cases the event of hyperkalemia was isolated, transient, and asymptomatic, with documented normokalaemia before and after the event. No other associated abnormalities in serum chemistries (i.e., renal function and other metabolic indicators) and EKG were noted. Additionally, no trends related to serum potassium were observed with extended exposure to vosoritide in the clinical program. Therefore, the clinical review team concluded that the etiology for the isolated episodes of hyperkalemia was most likely due to the laboratory artifact of hemolysis of blood sample and subsequent potassium movement outside the cells, with resultant pseudo hyperkalemia. Hemolysis of blood sample is particularly common in the young pediatric population, due to difficulty with blood drawing process.

Trial 111-209

No clinically meaningful changes in hematology and chemistry laboratory parameters were noted during the study.

In conclusion, similarly to data from children with achondroplasia ≥ 5 years of age, no clinically meaningful changes in laboratory parameters were noted in the clinical program of vosoritide in children <5 years of age.

7.6.6. Immunogenicity

Trial 111-206

The incidence of ADA was consistent with that observed in children 5 years of age and older. Antidrug antibodies (ADA) were detected in 8 out of 43 (19%) subjects exposed to vosoritide and no subjects in placebo arm. ADA were detected in 5/19 (26%) subjects in Cohort 1, 1/12 (8%) subjects in Cohort 2 and 2/12 (17%) subjects in Cohort 3. No subject developed neutralizing antibodies (NAbs) during Trial 111-206.

Consistent with the findings in children 5 years of age and older, there was no evidence of impact of immunogenicity on safety, and/or efficacy of vosoritide in the younger population <5 years of age during Studies 111-206 and 111028.

Refer to Section 5.1 for the discussion of the antidrug antibody incidence and the potential effect of immunogenicity on efficacy. This section will focus on evaluation of the immunogenicity-related safety issues only.

Hypersensitivity Adverse Reactions

Hypersensitivity reactions are not uncommon in children.

The overall incidence of hypersensitivity reactions was similar between vosoritide and placebo (Table 31). The most common adverse reactions were rash (16% all vosoritide versus 12.5% placebo) and injection site urticaria (14% all vosoritide versus 3.1% placebo).

All hypersensitivity events were non-serious, mild (Grade 1, or Grade 2) and did not result in drug interruption-discontinuation. No grade 3 or hyper severity of hypersensitivity reaction, or anaphylaxis were reported in the study.

The frequency and nature of hypersensitivity events was similar across the three age subgroups (for vosoritide subjects the incidence of hypersensitivity reactions was 36.8% in Cohort 1, 37.5% in Cohort 2 and 41.7% in Cohort 3).

Table 31. Hypersensitivity Reactions, Any Grade, Safety Population, Trial 111-206

Standard MedDRA Query (SMQ) Preferred Term (PT) n (%)	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)	All Vosoritide vs. Placebo Risk Difference
Hypersensitivity	11 (34.4)	11 (34.4)	17 (39.5)	5.1
Rash	4 (12.5)	4 (12.5)	7 (16.3)	3.8
Injection site urticaria	4 (12.5)	1 (3.1)	6 (14)	10.8
Eczema	1 (3.1)	3 (9.4)	2 (4.7)	-4.7
Dermatitis	0	0	1 (2.3)	2.3
Dermatitis allergic	1 (3.1)	0	1 (2.3)	2.3
Dermatitis contact	1 (3.1)	0	1 (2.3)	2.3
Hypersensitivity	1 (3.1)	0	1 (2.3)	2.3
Injection site rash	1 (3.1)	0	1 (2.3)	2.3
Rash macular	1 (3.1)	0	1 (2.3)	2.3
Rhinitis allergic	1 (3.1)	0	1 (2.3)	2.3
Urticaria	0	1 (3.1)	1 (2.3)	-0.8
Allergic edema	0	1 (3.1)	0	-3.1
Perioral dermatitis	0	1 (3.1)	0	-3.1

Source: Excepted from Table 14.3.1.8.4.1, CSR 111-206
Abbreviations: N, number of subjects assessed; n, number of subjects with event; PT, Preferred Term; SMQ, Standard MedDRA Query

The incidence of hypersensitivity reactions was relatively similar between ADA positive (3 out of 8 [37.5%]) and ADA negative group (9 out of 25 [25.7%]). Also, no association was observed between the ADA titer and the incidence, or severity of hypersensitivity reactions in ADA positive subjects. Similarly, there was no association between the ADA positivity and incidence of injection site reactions (ISRs) (Figure 42, Section 17.1) during Trial 111-206.

In summary, there were no immunogenicity-related safety concerns with vosoritide use during Trial 111-206.

Trial 111-208

ADA were detected in 20 out of 61 (33%) subjects exposed to vosoritide during Trial 111-208, of whom 8 subjects had seroconverted to positive status while on vosoritide treatment in Trial 111-206. All of the remaining 12 (out of 20) subjects who had positive ADA during Trial 111-208 were on placebo in Trial 111-206. No new subjects exposed to vosoritide in Trial 111-206 seroconverted to positive status in Trial 111-208. All ADA-positive subjects tested negative for NAbs during Trial 111-208.

7.6.7. There was no change in the frequency and nature of hypersensitivity events observed in Trial 111-208 compared to Trial 111-206, or between subjects originally exposed to vosoritide versus placebo in Trial 111-206.

Electrocardiograms

FDA has waived the thorough QT study requirement because vosoritide is a large biologic peptide, such that an effect on cardiac ion channels is very unlikely and because the nonclinical program confirmed that vosoritide has a low QT prolongation potential (refer to Integrated Review in DARRTS, dated November 18, 2021).

During Trial 111-206, electrocardiogram (ECG) was performed at baseline (pre-dose) and at the following study visits (at around C_{max}, approximately 30 minutes post-dose): Day 1, Day 8, Week 6, Week 13, Week 26, Week 39, and Week 52. There were no observed meaningful changes in ECG findings and there no differences in the various ECG parameters between vosoritide and placebo arm. No subject had an abnormal QTc prolongation (i.e., > 450 msec) at any assessment time point.

During Trial 111-208, ECG was also assessed at baseline (pre-dose) and at selected study visits post-injection. Similarly, no abnormalities in the QTc prolongation (i.e., > 450 msec) were noted at any assessment time point.

No AEs related to ECG abnormalities were reported in the clinical program.

7.6.8. Imaging Results

Because of the potential safety concerns associated with disproportional growth, as well as underlying bone deformities and potential for abnormal bone growth, imaging studies were performed during the development program (skeletal X-Rays of lower limbs and lumbar spine, DXA scans, evaluation of bone age, and MRI of the cranial bone and brain). The results of skeletal X-Rays findings of lower limbs and lumbar spine, as well as DXA scans are discussed in Section 7.7.2.

While delay in bone maturation (i.e., bone age) is a known phenomenon in children with achondroplasia (Lee et al. 2009), there is a potential risk of acceleration in bone age with all growth-promoting products. There was no evidence of acceleration in bone age relative to chronological age in the clinical studies of vosoritide up to 5 years of exposure to study drug. To

evaluate the effect of the drug on bone age in younger children with achondroplasia, bone age was assessed in Trial 111-208 using Greulich and Pyle Atlas on X-rays of the left hand, a widely accepted method for bone age evaluation. Bone age was not assessed in Trial 111-206 due to the very young age of the subjects. The potential clinical value of the information from Trial 111-206 would have been of limited value, while the subjects would have been exposed to unnecessary additional radiation risk from the X-Rays. The results of the bone age assessed during Trial 111-208 are discussed below.

Lastly, MRI was conducted to assess cranial and brain morphology. The MRI findings were considered as efficacy endpoints in Trial 111-206 and are discussed in Section 6.2.1.4.2.2. MRI findings in Trial 111-209 were also considered as efficacy endpoints, however, given the ongoing status of the study and limited data available by the time of the current submission, the Applicant reported the results of these assessments as part of safety evaluation for the current submission. Therefore, the MRI findings from Study 111-209 are discussed below.

Bone Age

In Trial 111-208, bone age assessments were conducted at baseline, Week 52, and Week 104 (in only 3 subjects). The mean (SD) bone age at baseline was below the chronological age (Table 32), which is consistent with epidemiological data (Lee et al. 2009). The change in mean (SD) bone age from baseline after 1 year of treatment was smaller than the chronological age progression [0.36 (0.39) in males and 0.65 (0.47) in females], suggesting a delay in bone maturation.

Table 32. Bone Age and Chronological Age, Safety Population, Trial 111-208

Parameter	Male	Female	Overall
Bone age (years)			
Baseline	N=13	N=13	N=26
Mean (SD)	2.86 (1.41)	2.27 (0.81)	2.56 (1.17)
Week 52: change from baseline[a]	N=11	6	17
Mean (SD)	0.36 (0.39)	0.65 (0.47)	0.46 (0.43)
Week 104: change from baseline[a]	N=3	0	N=3
Mean (SD)	1.25 (0.43)	NA	1.25 (0.43)
Chronological age (years)			
Baseline	N=13	N=13	N=26
Mean (SD)	3.46 (1.29)	2.68 (1.62)	3.07 (1.49)
Week 52: change from baseline[a]	N=11	N=6	N=17
Mean (SD)	1.01 (0.02)	0.99 (0.01)	1.00 (0.02)
Week 104: change from baseline[a]	N=3	0	N=3
Mean (SD)	2.03 (0.05)	NA	2.03 (0.05)
Difference between bone age and chronological age (years)			
Baseline	N=13	N=13	N=26
Mean (SD)	-0.60 (1.00)	-0.41 (0.99)	-0.50 (0.98)
Week 52: change from baseline[a]	N=11	N=6	N=17
Mean (SD)	-0.65 (0.40)	-0.34 (0.47)	-0.54 (0.43)
Week 104: change from baseline[a]	N=3	0	N=3
Mean (SD)	-0.78 (0.40)	NA	2.03 (0.05)

Source: Table 11.2.3.6.1.1, CSR 111-208
[a] Change from baseline was calculated in subjects with available measurements at both time points.
Abbreviations: n, number of subjects with assessment; NA, not available; SD, standard deviation

Similarly, the change from baseline to Week 52 in the mean (SD) bone age Z-score was slightly negative in the overall population, as well as for both sexes (Table 33), also suggesting a delay in bone maturation compared to the general pediatric population.

Table 33. Bone Age Z-Score Over Time by Sex and Overall

Bone Age Z-score	Male	Female	Overall
Overall			
Baseline	N=13	N=13	N=26
Mean (SD)	-0.22 (2.14)	0.75 (2.33)	0.26 (2.24)
Week 52: change from baseline[a]	N=11	N = 6	N = 17
Mean (SD)	-0.76 (0.87)	-0.53 (1.37)	-0.68 (1.04)
Week 104: change from baseline[a]	3	0	3
Mean (SD)	-0.72 (0.75)	NA	-0.72 (0.75)
≥6 to <24 months			
Baseline	N=2	N=8	N=10
Mean (SD)	-0.37 (0.79)	2.12 (1.74)	1.62 (1.88)
Week 52: change from baseline[a]	N=1	N=1	N=2
Mean (SD)	-0.94 (NA)	-3.20 (NA)	-2.07 (1.60)
≥24 to <60 months			
Baseline	N=9	N=4	N=13
Mean (SD)	-0.11 (2.45)	-1.19 (1.06)	-0.44 (2.14)
Week 52: change from baseline[a]	N=8	N=4	N=12
Mean (SD)	-0.77 (1.03)	-0.05 (0.51)	-0.53 (0.94)
Week 104: change from baseline[a]	N=3	0	N=3
Mean (SD)	-0.72 (0.75)	NA	-0.72 (0.75)
≥60 months			
Baseline	N=2	N=1	N=3
Mean (SD)	-0.59 (2.33)	-2.46 (NA)	-1.22 (1.97)
Week 52: change from baseline[a]	N=2	N=1	N=3
Mean (SD)	-0.63 (0.05)	0.19 (NA)	-0.36 (0.48)

Source: Table 11.2.3.6.1.2, CSR 111-208
[a] Change from baseline was calculated in subjects with available measurements at both time points.
Abbreviations: n, number of subjects with assessment; NA, not available; SD, standard deviation

interpretation of vosoritide effect on bone maturation based on results from Trial 111-208 is challenging, because of absence of a control arm, small sample size, and heterogeneity in the baseline bone age, as reflected by the big standard deviation of baseline bone age Z-score of ± 2.24 (Table 33). In addition, the reliability and validity of bone age assessment in children with achondroplasia of such young age (i.e., <5 years of age) remains unknown. Given the limitations, there was no evidence of a vosoritide-associated delay in bone maturation in children ≥5 years of age during the randomized, placebo-controlled study of 1 year duration (Study 301) or the long-term extension study (Study 302) for an additional 2 years of follow up, as well as during the long-term uncontrolled study 111-205 (up to 7 years of follow up).

In conclusion, there was no evidence of acceleration in bone age after one year of treatment with vosoritide in children <5 years of age based on the data collected in a limited number of subjects during Trial 111-208.

Magnetic Resonance Imaging Assessments of Cranial and Brain Morphology in Trial 111-209

At the time of the sNDA submission (data cut off February 25, 2022), limited data from MRI assessments in Trial 111-209 were available (3 subjects in SoC alone arm and 4 subjects in SoC

+ vosoritide arm had data at Week 26 only). Those data indicated a decrease from baseline in the mean (SD) values for the area of foramen magnum and area of spinal cord at the foramen magnum level of -0.013 (0.026) cm^2 from baseline of 0.124 (0.024) cm^2, and -0.010 (0.008) cm^2 from baseline of 0.059 (0.010) cm^2, respectively in SoC+ vosoritide group, while slightly positive changes from baseline were observed in the SoC alone group for the same parameters [0.013 (0.029) cm^2 change from baseline of 0.113 (0.025 cm^2, and 0.007 (0.015) cm^2 change from baseline of 0.055 (0.014) cm^2, respectively]. The decreases from baseline correlated clinically with reported SAEs of worsening cervical cord compression (2 subjects) and foramen magnum stenosis (1 subject) in SoC + vosoritide arm, which were unlikely to be related to study drug (refer to Section 7.6.2 above). Otherwise, increases from baseline to Week 26 were noted in both treatment arms for other MRI parameters (i.e., facial volume, calvarium volume, whole brain total volume, and ventricles total). To better understand the significance of the foramen magnum findings in the setting of few subjects and a limited follow up period, the Agency requested additional data regarding the MRI assessments of the skull and brain morphology in the ongoing Trial 111-209. In their response, dated August 25, 2023, the Applicant included MRI data from 13 subjects (7 subjects in SoC alone arm and 6 subjects in SoC + vosoritide arm) who completed Week 52 and 7 subjects (5 subjects in SoC alone arm and 2 subjects in SoC + vosoritide arm) who completed Week 104 (Table 75, Section 17, Appendix). Since 4 subjects had cervicomedullary decompression surgery (3 in the vosoritide + SoC arm and 1 in the SoC arm) during the study due to worsening foramen magnum stenosis, the MRI data for the parameters impacted by the surgery (area of foramen magnum, and area of spinal cord at the foramen magnum level) in the 4 subjects who underwent FM decompression surgery were not included in the analysis. The clinical review team evaluated the 4 cases with worsening foramen magnum stenosis in detail and concluded that a drug-induced effect on the decrease in foramen magnum area was unlikely).

Increases of similar magnitude between treatment arms (excluding the 4 subjects had cervicomedullary decompression surgery) were observed in all MRI parameters, including foramen magnum and area of spinal cord at the foramen magnum level, from baseline to Weeks 52, and 104, respectively (Table 75, Section 17, Appendix). These results are consistent with the MRI findings in Trial 111-206 (Section 6.2.1.4.2.2). The longer-term results in more subjects from Trial 111-209 do not show the decrease in foramen magnum area observed in SoC + vosoritide arm compared to SoC alone after 26 weeks and indicate that vosoritide is unlikely to be associated with deleterious effects on cranial and brain morphology in children already at risk of needing decompression surgery. However, as this study is ongoing, these conclusions are preliminary and they will be updated when the final clinical study report will become available.

7.6.9. Subgroup Analyses

Trial 111-206

There was no difference in the incidence of AEs by various demographic characteristics during Trial 111-206 (Table 70, Section 17, Appendix). Evaluation of safety results based on the three age subgroups [Cohort 1 (≥24 to < 60 months), Cohort 2 (≥ 6 to < 24 months), and Cohort 3 (3 months to < 6 months)] during Trial 111-206 was reported in each subsection above, as deemed appropriate. There were no clinically meaningful differences in the safety profile among the three cohorts.

7.7. Key Safety Review Issues

7.7.1. Blood Pressure Decrease/Hypotension

Background

Vosoritide binds to the CNP receptor and induces vascular muscle relaxation. Dose-dependent asymptomatic hypotension and tachycardia were observed in nonclinical studies across all species. Transient decreases in blood pressure post vosoritide administration have been observed in clinical studies with vosoritide in children 5 years of age and older. Majority of the events were asymptomatic, with few cases [2/60 (3%)] experiencing transient mild symptomatic hypotension (e.g., dizziness). The effect of vosoritide on lowering blood pressure, including symptoms associated with low blood pressure, is a labeled adverse reaction in children 5 years of age and older.

Assessment

Blood pressure (BP) and heart rate (HR) were monitored in the clinical program in children <5 years of age with achondroplasia at prespecified time points after injections. The Applicant also included the evaluation of AEs of hypotension and AEs that may potentially be related to hypotension (e.g., dizziness, syncope, presyncope) as adverse events of special interest in all trials.

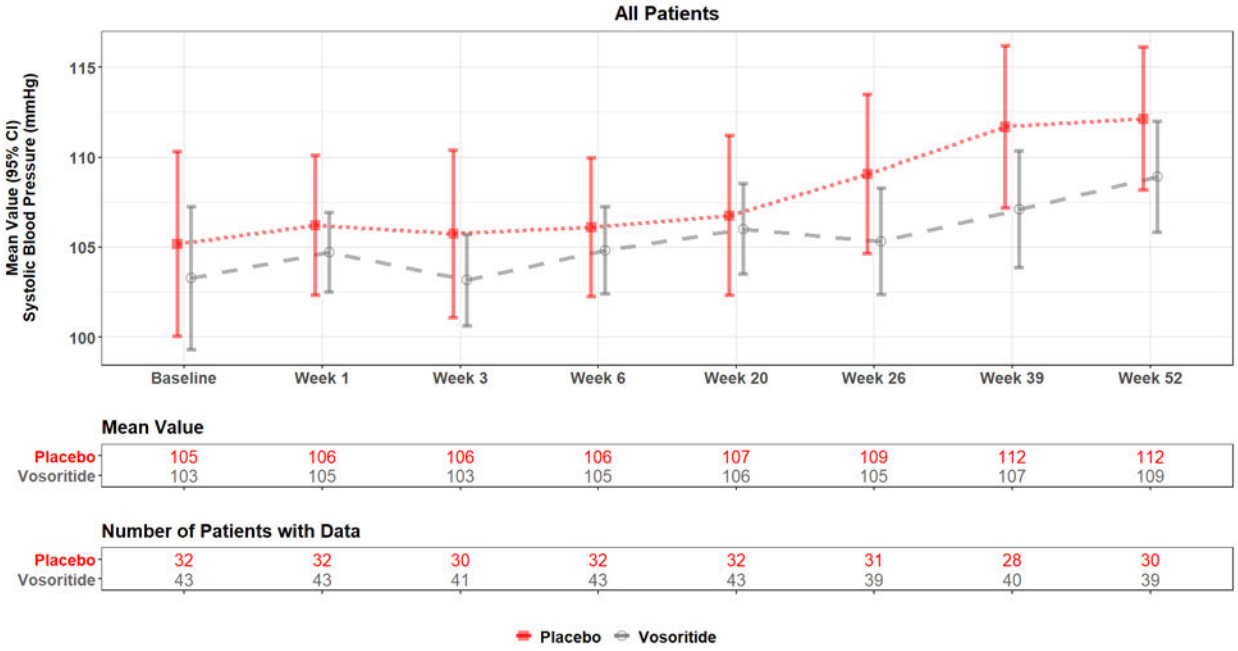
Trial 111-206

In Trial 111-206, BP and HR were monitored for 8 hours post-dose during the first 2 study visits (Day 1 and Day 2: every 15 mins for the first 2 hours, then every 30 mins for the 3rd hour; then hourly for the next 5 hours), for 4 hours post-dose during the next 2 visits (Day 3 and Day 8: every 15 mins for the first 2 hours, then every 30 mins for the 3rd hour; then hourly for the 4th hour) and for 1 hour (every 15 minutes) on the subsequent visits.

Changes in Mean BP and HR values

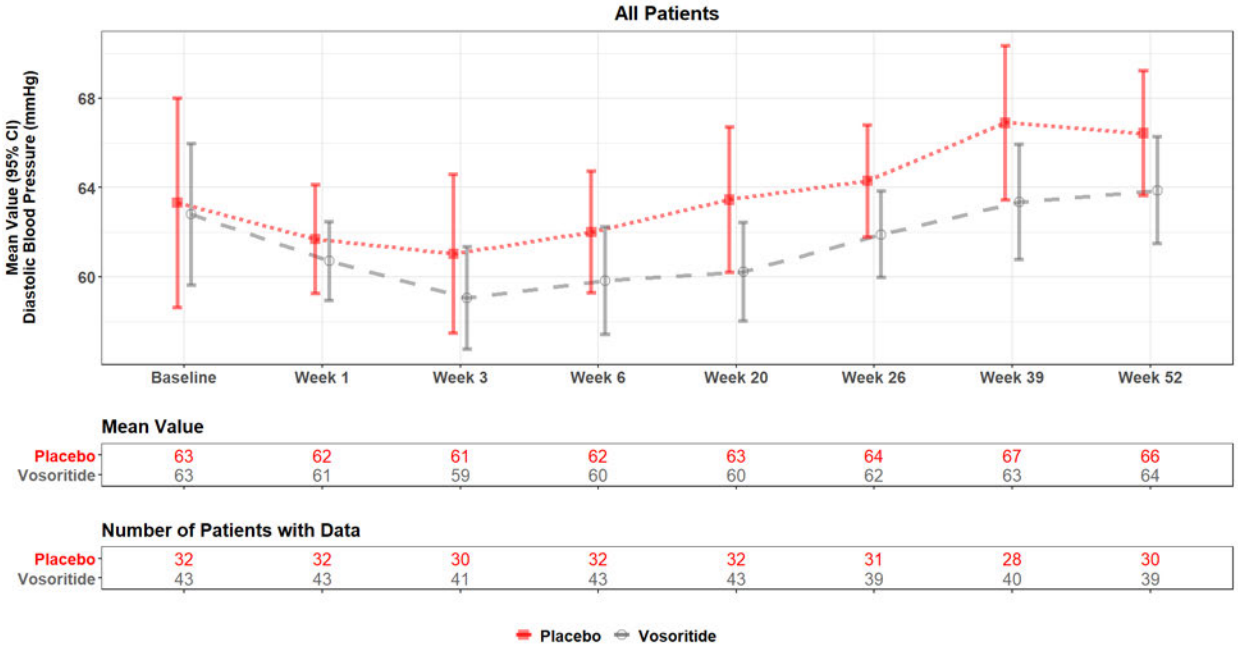
There were no meaningful changes for pre-dose systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR over the 52-week study (Figure 7, Figure 8, Figure 9).

Figure 7. Mean and 95% Confidence Interval of Systolic Blood Pressure Over Time by Treatment Arm, Safety Population, Trial 111-206



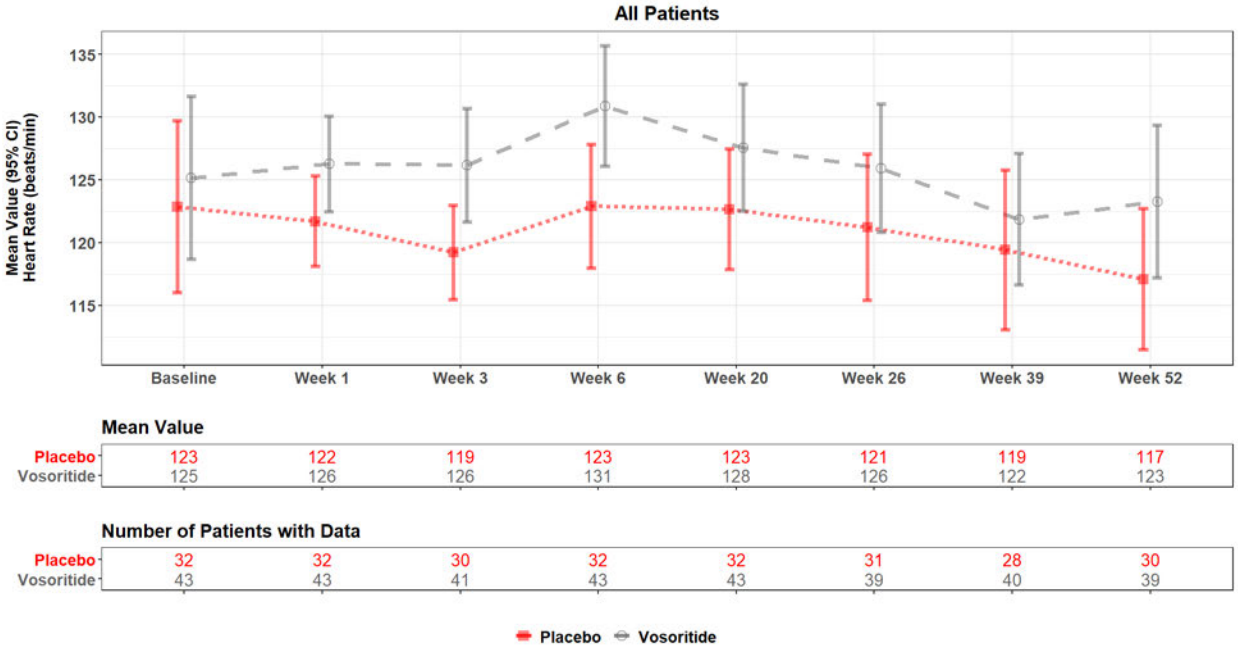
Source: advs.xpt; Software: R
Vertical bars show 95% confidence intervals.
Abbreviation: CI, confidence interval

Figure 8. Mean and 95% Confidence Interval of Diastolic Blood Pressure Over Time by Treatment Arm, Safety Population, Trial 111-206



Source: advs.xpt; Software: R
Vertical bars show 95% confidence intervals.
Abbreviations: CI, confidence interval

Figure 9. Mean and 95% Confidence Interval of Heart Rate Over Time by Treatment Arm, Safety Population, Trial 111-206



Source: advs.xpt; Software: R
Vertical bars show 95% confidence intervals.
Abbreviations: CI, confidence interval

Similarly, no meaningful changes were observed in the pre-dose vital signs overtime when they were evaluated by each cohort.

Evaluation of post-dose changes in mean SBP, mean DBP and mean HR also did not show meaningful differences between treatment arms (Table 71, Section 17.1). A transient decrease in mean DBP ranging from 4 to 8 mm Hg was noted between 30 to 90 minutes post-dose, which was accompanied by a transient increase in the mean HR ranging between 6 -13 beats/min at 15- and 30-minutes post vosoritide injection. This is an expected physiologic effect of CNP because of its vasodilatory properties. No AEs related to post-dose changes in HR were reported.

Evaluation of post-dose changes in mean SBP, mean DBP and mean HR by each age cohort did not reveal any consistent meaningful changes in any cohorts. A sporadic slight decline in mean DBP in Cohort 3 of approximately 10 mm Hg was noted during the first hour post-dose, with DBP returning to pre-dose values afterwards.

Trial 111-206

Analysis of BP-Related AEs

In total, 2 (4.7%) subjects in the all-vosoritide group and 2 (6.3%) subjects in placebo group had AEs of BP decreased or hypotension (i.e., defined as BP decreased that was symptomatic). The 2 subjects in all-vosoritide group experienced one event each, while the 2 subjects in the placebo group experienced 2 events each. The narratives of the subjects experiencing BP decreased/hypotension in all vosoritide group are summarized below.

Subject [redacted] (b) (6) randomized to vosoritide who had an event of hypotension on study Day 1. The event occurred 60 minutes post-dose and manifested

with symptoms of pallor and lethargy which lasted for 6 minutes. The BP value trends were as follows: 89/58 (pre-dose), 91/44 (60 minutes post-dose), 101/86 (75 minutes post-dose). The event resolved without any intervention.

Subject [redacted] (b) (6) randomized to vosoritide who had an event of decreased BP on study Day 2. The BP decreased from a pre-dose value of 122/67 mm Hg to 89/42 mm Hg 45 minutes post-injection. The subject did not report any symptoms, while BP improved to 128/65 mm Hg at next assessment (60 minutes post-injection).

No subject discontinued study treatment due to AEs of decreased blood pressure and symptomatic hypotension.

In addition, the clinical review team searched the safety database for AEs by PTs that could potentially be associated with blood pressure decreases (e.g., dizziness, presyncope, syncope, pallor, fatigue, lethargy, blurred vision). The results of this search identified only one subject [redacted] (b) (6) in all-vosoritide arm who experienced 2 AEs of dizziness on Study Days 72, and 81, respectively. The events were reported 23 minutes and 15 minutes post-vosoritide administration. The events occurred at home, and blood pressure was not recorded at the time of the events, however, the timing of the events suggest a potential effect of vosoritide on blood pressure lowering. The events were non-serious, transient and did not require any intervention. There were no other associated symptoms. Evaluation of blood pressure trends during the study visits for this subject revealed transient small changes post-vosoritide administration, with recovery of blood pressure readings to baseline with next assessment (i.e., within 15-30 minutes), consistent with known effect of vosoritide.

No other AEs suggestive of blood pressure decrease were reported during Trial 111-206.

In summary, there were no clinically meaningful changes in the blood pressure and heart rate parameters in subjects exposed to vosoritide during Trial 111-206. Mild and transient decrease in DBP and increase in HR post vosoritide injection (first 60 minutes) were noted, which are expected physiologic effects of CNP on cardiovascular system, with vasodilatory effects on blood vessels and reflex increase in heart rate. Only one subject experienced a symptomatic event of hypotension post-vosoritide injection, that was mild, transient and did not require medical intervention, while symptoms potentially associated with blood pressure decreases were reported in one subject only. These findings are consistent with the known effects of vosoritide on the hemodynamic status in children 5 years of age and older, and is a labeled risk associated with the study drug.

Trial 111-208

The observed changes in blood pressure and heart rate parameters were consistent with findings in Trial 111-206 and they were not clinically meaningful. No AEs of hypotension, or decreased blood pressure were reported during Trial 111-208**.**

Conclusion

Changes in the mean SBP, DBP, and HR observed in the clinical program over time, as well as from pre-dose to post-dose, were small and of no clinical significance. No difference between vosoritide and placebo arms was noted in decrease in post-dose SBP according to prespecified threshold criteria, while a slightly higher percentage of subjects in vosoritide arm compared to placebo had a decrease in DBP. All events were transient, the majority were asymptomatic, and

were of no clinical significance. Two subjects had reported AEs of hypotension or blood pressure decreased that were mild, transient, and did not require medical treatment. No SAEs related to hypotension were reported in the clinical program. No subjects discontinued studies due to hypotension-associated AEs. The potential risk of hypotension is adequately mitigated through the label in Section 5. Warning and Precautions and Section 6. Adverse Reactions.

7.7.2. Abnormal Skeletal Growth

Issue

Potential effect of vosoritide on abnormal bone growth and potential for accelerated growth on bone abnormalities/morphology

Background

There is a potential for vosoritide to induce abnormal bone growth at growth plate or alter bone morphology which may results in clinical manifestations such as new or worsening pre-existing bone deformity, dysfunctional joints, arthralgia, slipped capital femoral epiphysis, avascular necrosis and osteonecrosis, or bone fractures. Additionally, the vosoritide-induced accelerated bone growth may result in new or worsening of pre-existing skeletal deformities (i.e., genu varum, spinal kyphosis/lordosis), or other achondroplasia-related comorbidities (i.e., neurological, musculoskeletal, cardiorespiratory, or ear-nose and throat system-related conditions).,

No safety signals related to the abnormal or accelerated growth were identified in children > 5 years old during the review of the original NDA.

Spinal and lower extremities skeletal deformities are common in younger children with achondroplasia, with some mostly seen in infants. Thoracolumbar kyphosis (TLK) is one of the most common sagittal deformities in children with ACH, with highest incidence (as high as 94%) in infancy, when children are able to sit, while the TLK gradually improves once children become ambulatory (reported incidence of approx. 40% in children 2-5 years of age, and 10% in children 5-10 years of age) (Kopits 1988b; Abousamra et al. 2019). The TLK angle in a newborn with ACH ranges from 15-25 degrees and may increase to 60-70 degrees or more during the sitting phase (6-18 months). By the time the child is walking, the TLK angle improves in most children with ACH. In addition to TLK, lumbosacral hyperlordosis is another common (78%) spinal deformity of children with ACH (Kopits 1988a). Lumbosacral hyperlordosis results from an abnormal degree of anterior pelvic tilt (i.e., an increase in sacral slope, SS). Clinically, lumbosacral hyperlordosis results in a forward rotation of the pelvis, hip flexion contractures, and a prominent abdomen and buttocks. In children with ACH, the lumbar lordosis (LL) angle, increases in value when the infant stands, simultaneously with the decrease in TLK (Kopits 1988a).

Tibial bowing is another common feature in children with achondroplasia. While bowing of the legs is a normal feature in average stature children in the first 2 years of life, the bowleg deformity progresses rapidly throughout early childhood (between ages 3-4 years and 6-7 years) in most children with ACH and has become a hallmark of the condition, with about 25% of the children requiring surgical intervention related to symptomatic bowleg deformity (Pauli 2019). The most common related symptoms include pain with activity and self-limitation of walking.

Assessment

Changes in skeletal deformities were monitored in the clinical studies by X-Rays of the lower extremities and lumbar spine to evaluate for any potential drug-induced adverse effect on skeletal growth. In addition, if clinically significant abnormalities were noted (although the protocol did not define clinically significant skeletal changes), the investigators were required to assess whether the observed changes were appropriate to be reported as adverse events and if any additional clinical management was warranted. The Applicant also conducted evaluation of bone morphology by dual energy X-ray absorptiometry (DXA) scans. ACH-related AEs, as well as other AEs known to be related to acceleration of growth induced by growth-promoting therapies, such as slipped capital femoral epiphysis, avascular necrosis, and osteonecrosis, were evaluated. These assessments were found acceptable by the clinical review team and adequate to evaluate for potential drug-induced effect on abnormal bone growth, as well as potential adverse events related to drug-induced acceleration in bone growth. The clinical findings are discussed below.

X-Ray Findings

Lower limbs

The skeletal deformities assessments included evaluation of tibial bowing angle, femur to tibia length ratio, and tibia and fibula lengths.

Tibia bowing angle

Consistent with epidemiological data, subjects presented with some degree of tibial bowing at baseline (Table 34). A bigger bowing angle correlates with more severe bowing. A positive change from baseline in the bowing angle reflects worsening of tibial bowing. There was no evidence of worsening of the tibial bowing angle with vosoritide treatment, as reflected by a negative change from baseline to Week 52 of greater magnitude in vosoritide arm compared to placebo in all subjects, as well as each age cohort (Table 34).

Table 34. Tibia Bowing Angle by Cohort and Overall, in Trial 111-206 (Safety Population)

	Left Tibia Bowing Angle (Degree)		Right Tibia Bowing Angle (Degree)	
Parameter	**Placebo**	**Vosoritide**	**Placebo**	**Vosoritide**
All				
N	32	31	32	31
Baseline, mean (SD)	12.59 (7.98)	10.26 (7.04)	11.41 (7.44)	11.06 (6.72)
Change at Week 52, mean (SD)	1.07 (5.38)	-1.28 (5.55)	-0.93 (5.54)	-2.75 (5.73)
Cohort 1 (≥24 to <60m)				
N	16	15	16	15
Baseline, mean (SD)	10.56 (7.05)	8.67 (6.63)	8.88 (5.43)	7.67 (3.90)
Change at Week 52, mean (SD)	-0.54 (5.09)	-1.86 (6.29)	-0.23 (4.23)	-1.46 (4.77)
Cohort 2 (≥6 to <24m)				
N	8	8	8	8
Baseline, mean (SD)	15.50 (10.95)	9.38 (7.21)	18.13 (8.64)	13.63 (6.86)
Change at Week 52, mean (SD)	4.33 (5.72)	-0.25 (4.30)	-1.83 (6.79)	-3.75 (6.84)

Parameter	Left Tibia Bowing Angle (Degree)		Right Tibia Bowing Angle (Degree)	
	Placebo	Vosoritide	Placebo	Vosoritide
Cohort 3 (3 to <6m)				
N	8	8	8	8
Baseline, mean (SD)	13.75 (5.87)	14.13 (7.00)	9.75 (6.14)	14.88 (8.18)
Change at Week 52, mean (SD)	1.25 (5.06)	-1.29 (5.88)	-1.38 (6.97)	-4.00 (6.38)

Source, Table 3, Response to Agency's IR dated May 26, 2023
Change from baseline is based on the subjects with available measurements at both time points.
Abbreviations: N, number of subjects; SD, standard deviation

A greater numerical improvement in the length of the long bone of lower extremities in vosoritide arm compared to placebo was noted at Week 52, as expected, while the change from baseline to Week 52 in the femur to tibia ratio was similar between vosoritide and placebo arms (Table 71, Section 17).

Lumbar Spine

The skeletal deformities involving spine included evaluation of spinal sagittal deformities, such as spinal thoraco-lumbar kyphosis (TLK) angle, spinal lumbar lordosis (LL) angle and sacral tilt (or sacral slope, SS) angle. Additionally, the lumbar spine vertebral body height ratios, interpedicle distance and sagittal width were also measured.

A summary of mean (SD) baseline and change from baseline (SD) to Week 52 in TLK, SS, and LL angles during Trial 111-206 is presented by Cohort and Overall in 73, Section 17, Appendix, while a summary of the proportion of participants with a change in lumbar spine angle of ≥5 to < 10 and ≥10 degrees by Cohort and Overall is presented in Table 74, Section 17, Appendix.

Small positive changes from baseline to Week 52 were noted in the mean lumbar lordosis (15.2 degrees vosoritide versus 8.4 degrees placebo) and sacral tilt (13.4 degrees vosoritide versus 5.7 deg placebo) angles in both vosoritide and placebo arms (73, Section 17, Appendix), which is consistent with epidemiological data (Lee et al. 2009) suggesting worsening of these spinal deformity parameters in young children with achondroplasia. The numerical changes between treatment arms were small and not clinically meaningful. Small negative changes from baseline to Week 52 were noted in the mean thoracolumbar kyphosis angle in both vosoritide (- 5.1 degrees) and placebo (-2.1 degrees) arms. Negative changes from baseline over time in the thoracolumbar kyphosis angle are also expected, as the thoracolumbar kyphosis deformity improves with age, according to epidemiological data (Lee et al. 2009).The percent of subjects with an increase of ≥ 10 degrees from baseline to Week 52 was similar between treatment arms for lumbar lordosis (44% each) and thoracolumbar kyphosis (12.5% each) and slightly higher in the vosoritide arm than placebo for the sacral tilt angle (66% vosoritide versus 31% placebo) (Table 74, Section 17, Appendix).

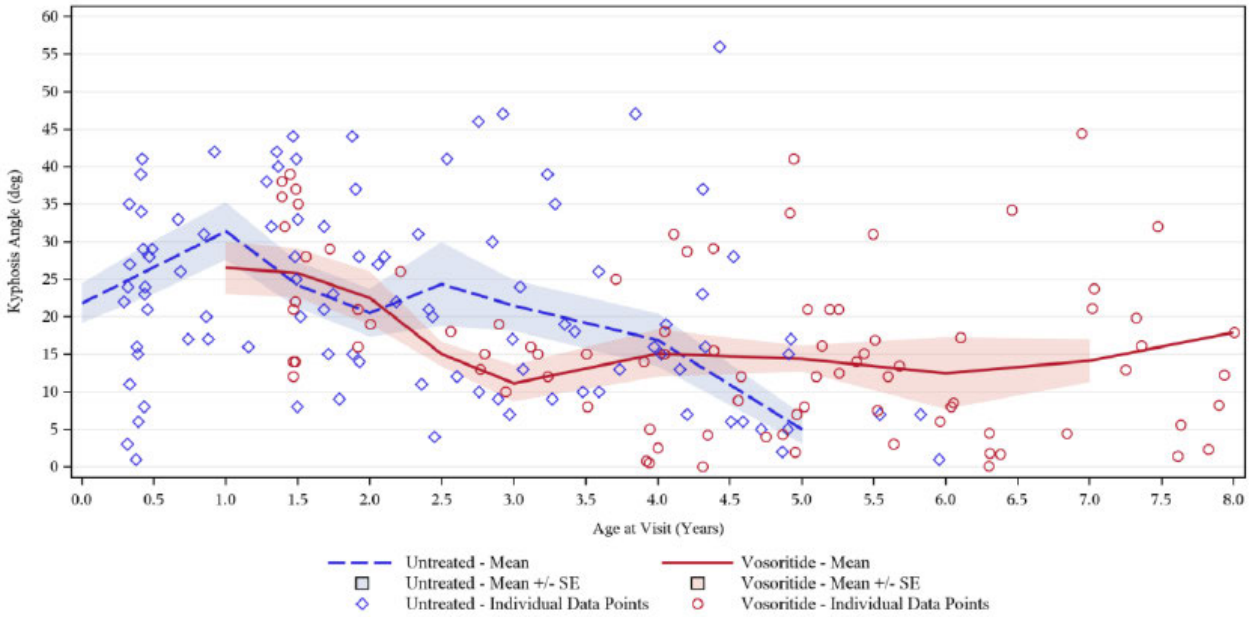
To further understand the pattern of change in each of the three spinal deformity parameters, the Applicant evaluated the scatter plots by age for each parameter using data from Studies 111-206 and 111-208 using all assessments up to data cut of December 19, 2022. Each plot include on-treatment (vosoritide) and untreated data (includes all placebo and pre-first dose from the vosoritide arm) assessments (Figure 10, Figure 11, and Figure 12).

The magnitude and pattern of change in TLK angle with age is consistent with the age-dependent change in TLK angle reported in the literature and they were similar between the placebo and

vosoritide groups. The decline in TLK was associated with an increase in lumbar lordosis (LL) and sacral tilt (SS) up to 2-2.5 years of age before plateauing, in both vosoritide and placebo groups, similar to literature reports. **Error! Bookmark not defined.,Error! Bookmark not defined.** The greatest numerical difference is noted in Cohort 2 (≥6 to <24m, 73, and Table 74, Section 17, Appendix), an age when the greatest change (and intra subject variability) is expected as each child begins to sit unaided and become mobile at different times.

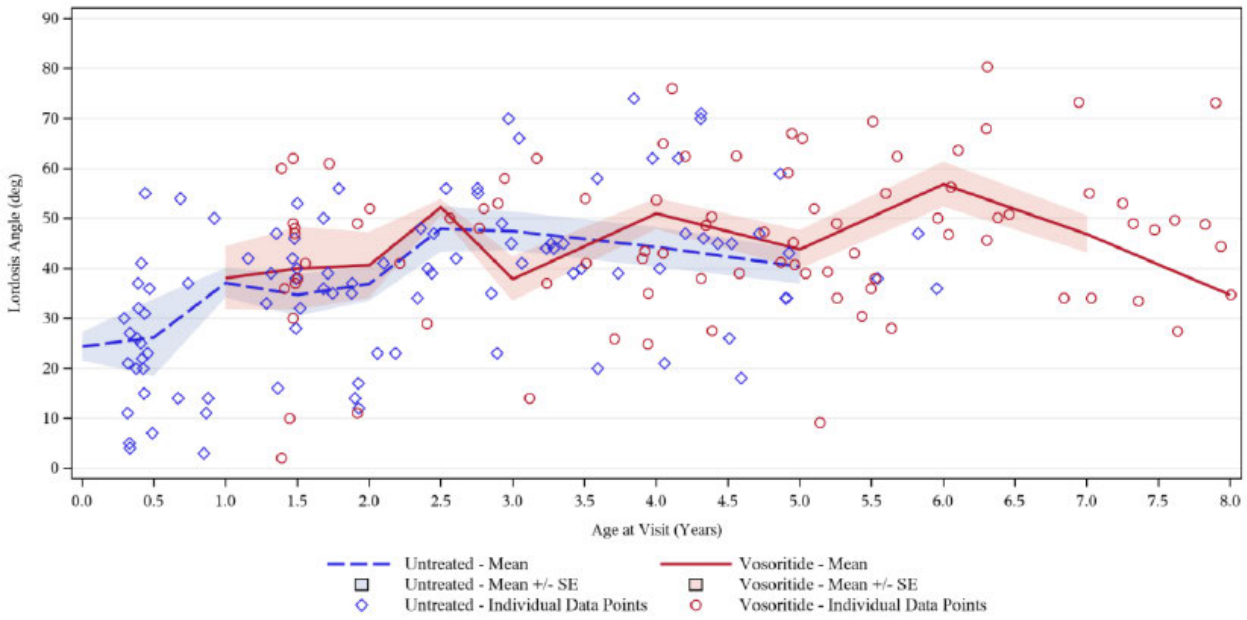
Overall, the numerical differences observed between vosoritide-treated subjects compared to placebo in the spine angle parameters were small and not clinically relevant.

Figure 10. Thoracolumbar Kyphosis Angle by Age in Trials 111-206/208



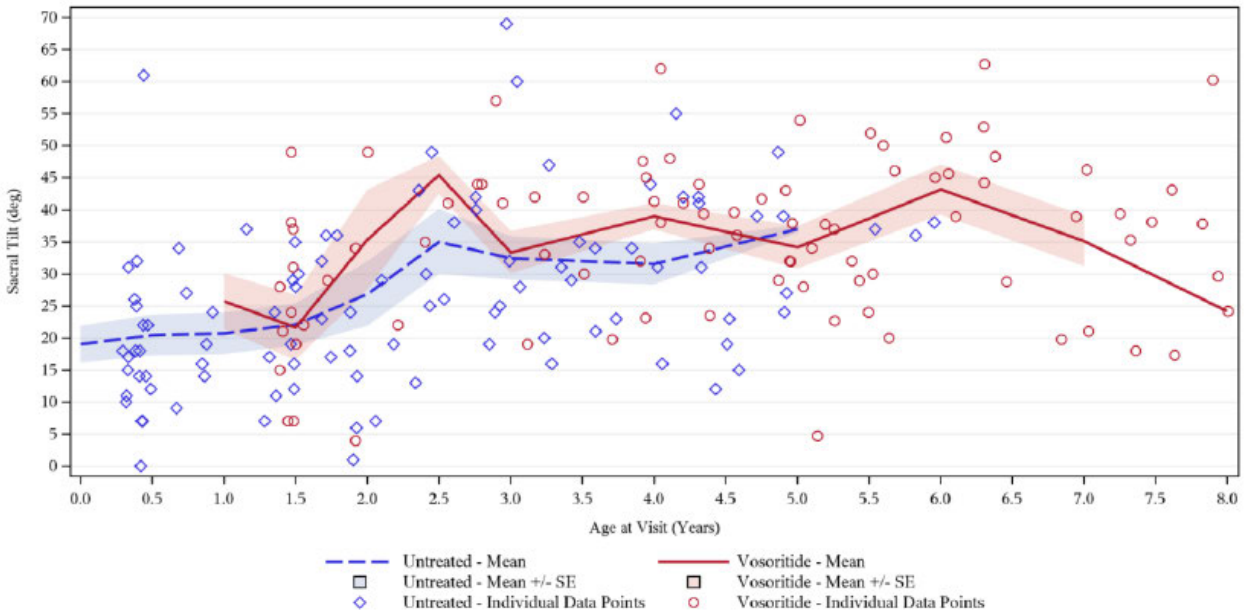
Source: Figure 2, Applicant's response to Agency's IR dated May 26, 2023
Abbreviations: SE, standard error

Figure 11. Lumbar Lordosis Angle by Age in Trials 111-206/208



Source: Figure 4, Applicant's response to Agency's IR dated May 26, 2023
Abbreviations: SE, standard error

Figure 12. Sacral Tilt Angle by Age in Trials 111-206/208



Source: Figure 3, Applicant's response to Agency's IR dated May 26, 2023
Abbreviations: SE, standard error

There were no concerning differences observed between vosoritide and placebo arms in the change from baseline to Week 52 in the vertebral height ratios, interpedicle distance or width of the spinal canal in Trial 111-206.

In summary, the magnitude and pattern of changes in spinal deformity angles (TLK, LL and SS) and tibial bowing observed in vosoritide arm were consistent with subjects in the placebo arm as well as published data, suggesting no effect of vosoritide on spinal deformity angles.

Dual Energy X-ray Absorptiometry (DXA)

DXA scans of the whole body, except head, and lumbar spine were performed in Trial 111-206. There were no notable changes in the bone mineral content (BMC) and bone mineral density (BMD) at any sites studied at Week 52 in either treatment arm.

AEs that May Potentially be Associated with Abnormal Bone Growth

Achondroplasia-related AEs

Achondroplasia-related AEs include conditions related to abnormal skeletal growth resulting in various comorbidities such as neurological, musculoskeletal, cardiorespiratory, and ear-nose and throat system-related.

The incidence of achondroplasia-related AEs by SOC and PT was evaluated by the Applicant during Trial 111-206, to assess whether vosoritide may potentially have a deleterious effect on these conditions (Table 35). Overall, the incidence of achondroplasia-related AEs by SOC was higher in placebo arm compared to vosoritide arm, as follows: SOC Ear and labyrinth disorders: 23.3% all vosoritide versus 34.4% placebo; SOC Musculoskeletal and connective tissue disorders: 18.6% all vosoritide versus 18.8% placebo, and SOC Respiratory, thoracic, and mediastinal disorders: 4.7% all vosoritide versus 15.6% placebo. There were no significant differences in any AEs by PT between treatment arms to suggest a vosoritide-induced worsening of achondroplasia-related condition.

The incidence and type of ACH-related events was similar between the three cohorts in all-vosoritide groups (63.2%, 66.7%, and 66.7% each in Cohorts 1, 2, and 3, respectively).

Table 35. Incidence of ACH-Related AE by SOC and PTs

SOC/PT	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)	All Vosoritide vs. Placebo Risk Difference
Any ACH-related AEs	19 (59.4)	23 (71.9)	28 (65.1)	-6.8
Ear-related disorders	18 (56.2)	24 (75)	26 (60.4)	-14.6
Ear infection	5 (15.6)	6 (18.8)	8 (18.6)	-0.2
Otitis media	2 (6.2	6 (18.8)	6 (14.0)	-4.8]
Otitis media acute	2 (6.2)	2 (6.2)	2 (4.7)	-1.6
Otitis media chronic	0	2 (6.2)	1 (2.3)	-3.9
Ear pain	2 (6.2)	4 (12.5)	4 (9.3)	-3.2
Deafness	1 (3.1)	1 (3.1)	2 (4.7)	1.5
Conductive deafness	1 (3.1)	0	1 (2.3)	2.3
Middle ear disorder	1 (3.1)	0	1 (2.3)	2.3
Middle ear effusion	1 (3.1)	1 (3.1)	1 (2.3)	-0.8
Middle ear inflammation	1 (3.1)	0	1 (2.3)	2.3
Otorrhea	1 (3.1)	2 (6.2)	1 (2.3)	-3.9
Tympanic membrane hyperemia	0	0	1 (2.3)	2.3
Tympanic membrane perforation	0	1 (3.1)	1 (2.3)	-0.8
Deafness unilateral	0	1 (3.1)	0	-3.1
Eustachian tube dysfunction	0	1 (3.1)	0	-3.1
Hypoacusis	0	1 (3.1)	0	-3.1
Tympanosclerosis	0	1 (3.1)	0	-3.1

SOC/PT	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)	All Vosoritide vs. Placebo Risk Difference
Musculoskeletal and connective tissue disorders	6 (18.8)	6 (18.8)	8 (18.6)	-0.2
Pain in extremity	3 (9.4)	1 (3.1)	3 (7.0)	3.9
Arthralgia	1 (3.1)	0	1 (2.3)	2.3
Knee deformity	1 (3.1)	0	1 (2.3)	2.3
Kyphosis	1 (3.1)	2 (6.2)	1 (2.3)	-3.9
Ligament pain	0	0	1 (2.3)	2.3
Lordosis	0	0	1 (2.3)	2.3
Musculoskeletal discomfort	1 (3.1)	0	1 (2.3)	2.3
Back pain	0	1 (3.1)	0	-3.1
Neck pain	0	1 (3.1)	0	-3.1
Scoliosis	0	1 (3.1)	0	-3.1
Respiratory, thoracic, and mediastinal disorders	2 (6.3)	1 (3.1)	4 (9.3)	6.2
Sleep apnea	2 (6.2)	0	3 (7.0)	7.0
Adenoidal hypertrophy	0	1 (3.1)	1 (2.3)	-0.8
Tonsillar hypertrophy	0	0	1	2.3

Source: Adapted by clinical reviewer from Table 11.2.3.6.1, Trial 111-206, CSR
Abbreviations: ACH, achondroplasia; AE, adverse event; N, number of subjects; PT, preferred term; SOC, system of organs

The musculoskeletal AEs related to spinal and lower extremities bone deformities in Trials 111-206 and 111-208, were further reviewed below:

Kyphosis

There were three events of kyphosis reported in Trial 111-206, one event in the vosoritide arm and two events in the placebo arm. All events occurred in Cohort 3 (3 to < 6 months), consistent with epidemiologic data showing progression of kyphosis angle during the first 1-2 years of life, when patients are in a sitting position. No AEs of kyphosis were reported during Trial 111-208.

Lordosis

There was one AE of lordosis reported in Trial 111-206 in vosoritide arm in Cohort 1 (≥24 to < 60 months) that occurred on study Day 282 and was reported as resolved on study Day 373. Review of individual plot of the spinal angle progression over time, shows an increase in lordosis angle up to 69 degrees around age 5, before declining. Also, one AE of lordosis was reported in Trial 111-208 in a subject in Cohort 1, originally randomized to placebo during Trial 111-206. The event occurred on study Day 646 and it was reported as mild/Grade 1.

Scoliosis

One AE of scoliosis was reported in a subject in placebo arm, while no AEs were reported in subjects exposed to vosoritide in Trial 111-206.

Knee deformity

One AE of knee deformity was reported in one subject in vosoritide arm in Cohort 3 (3 to < 6 months). The event was reported on study Day 95. However, the evolution of the leg bowing angles were as follows: left leg: 22 degrees (baseline) to 22 degrees (Week 52); right leg: 31

degrees (baseline) to 19 degrees (Week 52), suggesting no progression of tibial bowing over time.

Overall, the number of AEs of spinal and lower leg skeletal deformities were small, non-serious and comparable between vosoritide and placebo arms.

No events of avascular necrosis or slipped capital femoral epiphysis were reported in Studies 111-206 and 111-208.

Fractures

There were 2 AEs of fracture reported in Trial 111-206, one event of grade 2 metaphyseal corner fracture that occurred in a subject enrolled in vosoritide arm (Cohort 1) and one grade 3 skull fracture that occurred in a subject enrolled in placebo arm (Cohort 3).

The event of metaphyseal fracture was reviewed in detail and was deemed by the review team as unrelated to study drug, but rather due to a traumatic event. The event resolved with conservative management while treatment with vosoritide was not interrupted.

No AEs of fracture were reported in Trial 111-208.

Conclusion

There were no findings on X-ray suggestive of worsening of preexisting or appearance of new bone abnormalities, or changes in bone morphology with vosoritide. There was no meaningful difference between vosoritide-treated subjects and placebo in the frequency and types of ACH-related AEs, including skeletal axial deformities that would suggest worsening of achondroplasia-related conditions with vosoritide treatment. There were no AEs that could be related to accelerated bone growth. The long-term risk of AEs related to potential abnormal bone growth or accelerated growth remain unknown and they should be further monitored in the postmarketing setting. Therefore, the Agency will issue a postmarketing requirement (PMR) to further evaluate the AEs related to potential abnormal bone growth or accelerated growth with long-term exposure to vosoritide (refer to Section 24, Postmarketing Requirements and Commitments, for details).

8. Therapeutic Individualization

8.1. Intrinsic Factors

The current popPK model was updated based on the previously developed PK model (describing the PK of vosoritide in pediatric patients with ACH (1 to 15 years old)) using the data from study 111-206, which included younger patients (4.5 months to <5 years old).

Body Weight

The identified covariates and covariate effects on the PK were comparable to the previous model, with body weight as covariate on CL/F and V/F and an exponential increase in bioavailability with time. No other covariates including age were found to be predictive for CL/F, Vd/F, or F in popPK analyses.

8.2. Extrinsic Factors

Vosoritide as perpetrator

In this supplement, the Applicant conducted in vitro studies to assess the potential for vosoritide to inhibit the in vitro transport of substrates by human uptake (OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3) and efflux (MATE1, MATE2-K, BCRP, P-gp, and BSEP) transporters using a range of concentrations (0.006µM to 2µM). The study results indicated that the inhibitory concentration (IC_{50}) values for vosoritide were >290-fold higher than the mean C_{max} values for the 15 µg/kg dose in Phase 3 studies. Hence, vosoritide is unlikely to affect the pharmacokinetics of concomitantly used substrates of the above transporters. See Section 14.1 for additional information.

8.3. Plans for Pediatric Drug Development

No new nonclinical data submitted. The Applicant relies upon clinical information in children > 5 years old with ACH that was previously reviewed during the original NDA submission and on new clinical information from 2 clinical studies in children <5 years old with ACH discussed in this review to support the expanding the approved indication to children <5 years old with ACH. Division of Pediatric and Maternal Health labeling recommendations are incorporated into labeling. Specifically, section 8.4 of labeling describes the basis of approval in this new age group, specifically, a summary of the clinical studies performed in the affected population.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

No new data were submitted. The current label appropriately includes the potential risks associated with pregnancy and lactation (Sections 8.1 and 8.2).

9. Product Quality

Approval

The Office of Pharmaceutical Quality (OPQ) review team has assessed the original NDA and this new supplement with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this supplemental NDA from a quality perspective.

9.1. Device or Combination Product Considerations

No new data included

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The inspection for this sNDA consisted of two domestic clinical study sites. Based on the inspection of the two clinical sites, the Office of Scientific Investigation (OSI) concluded that the inspectional findings support validity of data as reported by the Applicant under this sNDA.

Financial disclosure documentation was reviewed. No issues were identified that could influence the outcome of the trials.

11. Advisory Committee Summary

The Advisory Committee (AC) meeting was not convened during this supplemental marketing application review cycle because the previous AC meeting adequately addressed the important elements of the clinical development program (held on July 30, 2018). Refer to the review of the original NDA.

III. Additional Analyses and Information

12. Summary of Regulatory History

Vosoritide for injection Summary of Regulatory History NDA 214938/S-002

Voxzogo (vosoritide) for injection is currently approved for the indication to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. Although the Applicant, BioMarin, included data proposing to support an indication for children less than 5 years of age in their original application, the Food and Drug Administration (FDA) determined that those data were insufficient to support approval in the younger patients. Refer to the Integrated Review dated November 18, 2021, for full details of the development program, aspects of which are pertinent to the current submission are summarized below. For the current submission, new drug application (NDA) 214938/S-002, Biomarin has submitted additional data and analyses proposing to support the expansion for their current indication to include patients less than 5 years of age.

- Investigational new drug (IND) 111299 for vosoritide (BMN 111) was submitted on November 30, 2011, with phase 1 first in human, single and multiple doses study in healthy adult volunteers (Study 111-101).
- Orphan drug designation was granted on January 17, 2013, for vosoritide for the treatment of achondroplasia (ACH).
- Type C meeting, January 26, 2017

FDA recommended that at least two randomized, placebo-controlled studies be conducted to establish the efficacy and safety of the drug in the different age groups (infants and toddlers and older patients). The Sponsor agreed with FDA recommendations and indicated the intent to initiate a new study 111-206 in infants and toddlers that would replace (b) (4)

FDA also commented on the ongoing observational natural history (NH) study (111-901) that was included in the meeting package. Of note, the protocol for this study had not been submitted to FDA. FDA concluded that the study was not optimally designed to provide the most useful data on growth in children with ACH. FDA recommended the development of a new dedicated historical study protocol with the primary objective to obtain valid, contemporary, retrospective, and prospective information on growth (including final height) and to submit the protocol for FDA's review.

- On March 7, 2018, the Sponsor submitted Trial 111-206, entitled, A Phase 2 Randomized, Double-Blind, Placebo- Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months
- On May 1, 2018, FDA issued an Advice/Information Request with comments on the Trial 111-206 protocol
- On May 11, 2018, FDA held a Joint Meeting of the Pediatric Advisory Committee (PAC) and the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) to further

discuss the appropriate drug development program for drugs for the ACH indication including therapeutic goals and the appropriate elements of a clinical development program for the treatment of children with achondroplasia. Advisory Committee (AC) conclusions and recommendations are briefly summarized below:

  - The AC Committee agreed that the primary endpoint can be growth velocity. However, they indicated that improving in final height remains an ultimate goal of treatment. The improvement in compilations should be evaluated as secondary endpoints
  - AC members agreed that randomized, placebo-controlled study design is an optimal design to provide efficacy and safety data in the intended population for the drug approval. AC members also noted that if use of placebo is not feasible, the other option is to use historical control data as a comparator. However, the Committee also concluded that the existing natural history data to date were not sufficient for use as a reliable comparator.
  - AC members recommended to include as young patients as possible in the development program, but after the efficacy and safety profile of the drug is characterized in older children.
  - AC members also indicated that study should be at least of 2 years duration.

- The AC recommendations and overall development program based on AC recommendations were further discussed between the Sponsor and FDA on July 30, 2018 (Advice/Information Request letter) and October 17, 2018 (teleconference).

  - FDA recommended at least 2 randomized placebo-controlled trials be conducted in two different age groups.
  - FDA also concluded that without a validated prediction model that may help to extrapolate to final height from short-term height changes, the study should be at least of 2-year duration and should include at least a subset of children in these studies followed prospectively to final height. In addition, FDA recommended that the evaluation of other clinically meaningful endpoints including effect of drug on complications be included.

The Sponsor agreed with the majority of FDA's recommendations and indicated that it plans to have at least 30 subjects from the phase 2 study with final height data at the planned time of the original NDA submission. The Applicant reiterated that a 2-year study would have significant challenges with enrolling and retaining patients.

Of note, FDA provided the same recommendations regarding the clinical development program including endpoints, number of studies and NH study design to the Applicant on multiple occasions (refer to FDA Advice Letters on July 25, 2019, on January 23, 2020).

- On January 9, 2019, BioMarin submitted the new Protocol for Trial 111-208, entitled, A Phase 2 Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of BMN 111 in Children with Achondroplasia (an extension study to the 111-206 study) to evaluate the long-term safety and efficacy of BMN 111 until subjects reach near-final adult height. The dosing regimen included an age-appropriate daily dose for subjects <5 years of age.
- During the pre-NDA meeting between the Sponsor and FDA on March 4, 2020, FDA raised a concern that the blinded data from the ongoing study 111-206 in patients aged 2

and older might not be sufficient to support the efficacy and safety of vosoritide in younger patients. FDA reiterated the importance of bridging the improvement in short term linear height to final adult height. The Sponsor indicated that there were no longer plans to use extrapolation models to determine the effect of treatment on Final Adult Height (FAH), but plan to collect FAH in the post-marketing settings.

- NDA 214938 for vosoritide (BMN 111) was submitted on August 20, 2020.
- At the Late Cycle Meeting, September 9, 2021, FDA stated that there were insufficient data included in the NDA submission to support the use of vosoritide in patients ages 2 to less than 5 years. Biomarin reported additional data (study 111-206) was available to demonstrate the efficacy and safety of vosoritide use in 2 to less than 5-year-olds. FDA indicated that they would not consider additional data in the current review cycle but encouraged BioMarin to continue collecting data in the younger population (less than 5 years of age).
- NDA 214938 for Voxzogo (vosoritide) for injection was approved under the accelerated approval regulations, 21 CFR 314.510, on November 19, 2021, to increase linear growth in pediatric patients with achondroplasia (ACH) who are 5 years of age and older with open epiphyses.
- The Protocol change to Trial 111-208 received August 17, 2022, included:
    - Treatment administration by a weight-band dosing instead of weight-based dosing
    - Provision to measure body length and crown to rump length, along with standing and sitting height for subjects <5 years of age and ≤ 104 cm
- Pre-Supplemental NDA meeting, September 20, 2022

The Applicant proposes to evaluate the safety and efficacy of vosoritide in patients with ACH less than 5 years of age, in studies 111-206, A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months, and 111-208, A Phase 2 Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of BMN 111 in Children with Achondroplasia.

- The supplemental new drug application (sNDA), S-002, received December 21, 2022, proposes the treatment of pediatric patients with achondroplasia less than 5 years of age with open epiphyses.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The nonclinical studies conducted in support of the original marketing application were designed to support use in children as young as newborn. As a result, there were no additional nonclinical studies necessary to support expansion of use into children younger than 5 years of age. Refer to Integrated review dated November 18, 2021, in DARRTS, for details.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable

14. Clinical Pharmacology

14.1. In Vitro Studies

In the current NDA supplement, Applicant had submitted one in vitro study report on the potential for vosoritide to inhibit 11 human drug transporters.

14.1.1. Assessment Of Vosoritide as an Inhibitor of Human Drug Transporters (BMN111-21-004)

Trial BMN111-21-004: Assessment of BMN 111 (vosoritide) as an Inhibitor of Human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP Mediated Transport

The purpose of this study was to determine whether vosoritide inhibits transport mediated by human uptake (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3) and efflux (MATE1, MATE2-K, BCRP, P-gp, and BSEP) drug transporters using appropriate in vitro test systems. Vosoritide was tested at concentrations ranging from 6nM to 2000nM (molecular weight of vosoritide is 4100 Da). The test system for the Solute carrier (SLC) family of transporters including OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2-K) was the polarized monolayer of Madin-Darby Canine Kidney cells (MDCK-II) grown on permeable supports. For BCRP, the polarized monolayer of MDCK-II cells grown on permeable supports were transfected to express BCRP. MDCK-MDR1 cells grown on permeable supports was used as the test system for P-gp transport. Sf9 vesicles were used as BSEP transport system. The incubation conditions including reference substrates and inhibitors are shown in Table 36.

Table 36. Summary of Substrates and Inhibitors Used in Transporter Assays

		Probe Substrate		Reference Inhibitor		Pre-Incubation Time (min)	Incubation Time (min)
Transporter	Cell Line	Substrate	Conc. (μM)	Substrate	Conc. (μM)		
OAT1	MDCK-II	[^{3}H]-p-aminohippurate	2	Probenecid	100	30	5
OAT3	MDCK-II	[^{3}H]-estrone-3-sulfate	0.1	Probenecid	100	30	5
OCT1	MDCK-II	[^{14}C]-metformin	10	Quinidine	1000	30	5
OCT2	MDCK-II	[^{14}C]-metformin	10	Quinidine	1000	30	5
OATP1B1	MDCK-II	[^{3}H]-estradiol-17β-D-glucuronide	2	Rifampicin	100	30	5
OATP1B3	MDCK-II	[^{3}H]-CCK-8	2	Rifampicin	100	30	5
MATE1	MDCK-II	[^{14}C]-metformin	10	Cimetidine	100	30	5
MATE2-K	MDCK-II	[^{14}C]-metformin	10	Cimetidine	100	30	5
BCRP	MDCK-II	[^{3}H]-prazosin	2	Ko143	1	30	90

Transporter	Cell Line	Probe Substrate: Substrate	Probe Substrate: Conc. (µM)	Reference Inhibitor: Substrate	Reference Inhibitor: Conc. (µM)	Pre-Incubation Time (min)	Incubation Time (min)
P-gp	MDCK- MDR1	[^{3}H]-quinidine	0.1	Elacridar	3	30	90
BSEP	Sf9 vesicles	[^{3}H]-taurocholate	1	Rifampicin	300	10	15

Source: Table 1 of Study report BMN111-21-004
Abbreviations: breast cancer resistance protein; BSEP, bile salt export pump; MATE, multidrug and toxin extrusion protein; MDCK, Madin-Darby Canine Kidney cells; OAT, organic anion transporter; P-gp, p-glycoprotein

Results showed that the half-maximal inhibitory concentration (IC_{50}) values were >2000nM due to insufficient inhibition that was seen across all tested transporters, except for P-gp where approximately 70% inhibition seen at highest concentration. The $IC_{50}$for P-gp could not be reliably determined yet estimated to be around 900nM (~3690 ng/mL). The estimated IC_{50}values are several folds higher than the mean maximum plasma concentration (C_{max}) value observed at 15µg/kg in the Phase 3 study, suggesting that vosoritide was not an inhibitor of the transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp or BSEP at the doses recommended in ACH patients.

14.2. In Vivo Studies

Trial 111-206: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months

Study Design

Trial 111-206 was a 52-week, Phase 2, randomized double-blind, placebo-controlled study in patients <5 years of age with a clinical diagnosis of ACH that was confirmed by genetic testing. Considering the differences in pattern of growth during the first 5 years, participants with ACH were randomized into three sequential age cohorts starting with the eldest group: Cohort 1 (age ≥ 24 to < 60 months), Cohort 2 (age ≥ 6 to < 24 months), and Cohort 3 (0 to < 6 months). Each cohort included at least 3 sentinel participants to evaluate the short-term safety and pharmacokinetics (PKs) of vosoritide before initiating the rest of the cohort of randomized participants. Eligible participants for Cohort 3 (0 to < 6 months old) could enroll directly into Trial 111-206 and have a minimum of 3 months of pretreatment observation (baseline growth data) prior to commencing treatment with investigational product or could enroll in Study 111-901 for a minimum of 3 months of pretreatment growth assessment immediately before roll-over to 111-206. A total of 75 participants were enrolled: 11 sentinel, 32 randomized to vosoritide and 32 randomized to placebo. The study was started in May 2018 and completed with last participant out date of (b) (4)

Plasma samples from all subjects were collected on Day 1 and at every 13 weeks on Weeks 13, 26, 39 and 52 at pre-dose and at 5, 15, 30, 45, 60, 90, and 120-minutes post-dose. On Day 1, additional PK samples were collected at 180 and 240 minutes.

Sentinel PK and dose adjustment

Following a 4-hour PK in 3 sentinel subjects, the dose for remaining subjects in the cohort was scheduled to be adjusted if the mean observed $AUC_{0\text{-}120min}$ from sentinel subjects was <the 25th percentile or > the 75th percentile for $AUC_{0\text{-}120min}$ of the reference dosing (15µg/kg in Study111-

202, a phase 2 study in ACH participants aged 5-14 years). The new adjusted dose (determined by population PK) was to target median $AUC_{0\text{-}120}$ observed at the 15µg/kg dose level of Trial 111-202.

Cohort 1 sentinel subjects received 15µg/kg/day vosoritide on Day 1, consistent with dosing in children > 5 years in Study 111-202. The mean $AUC_{0\text{-}4\ h}$ was 167000 pg-min/mL, which was within the exposure characterized in Trial 111-202 and so the rest of the Cohort 1 received a daily dose of 15µg/kg. The daily dose for participants in Cohort 2 was adjusted from 15µg/kg to 30µg/kg following the PK evaluations (the mean $AUC_{0\text{-}4\ h}$ was 65900 pg-min/mL in the sentinel subjects), and subsequently participants in Cohort 3 were initially dosed with 30µg/kg daily. Participants in Cohorts 2 and 3 received 30µg/kg while they were < 2 years of age. The daily dose for participants in Cohort 2 was adjusted to 15µg/kg during the visit immediately preceding the 2nd birthday.

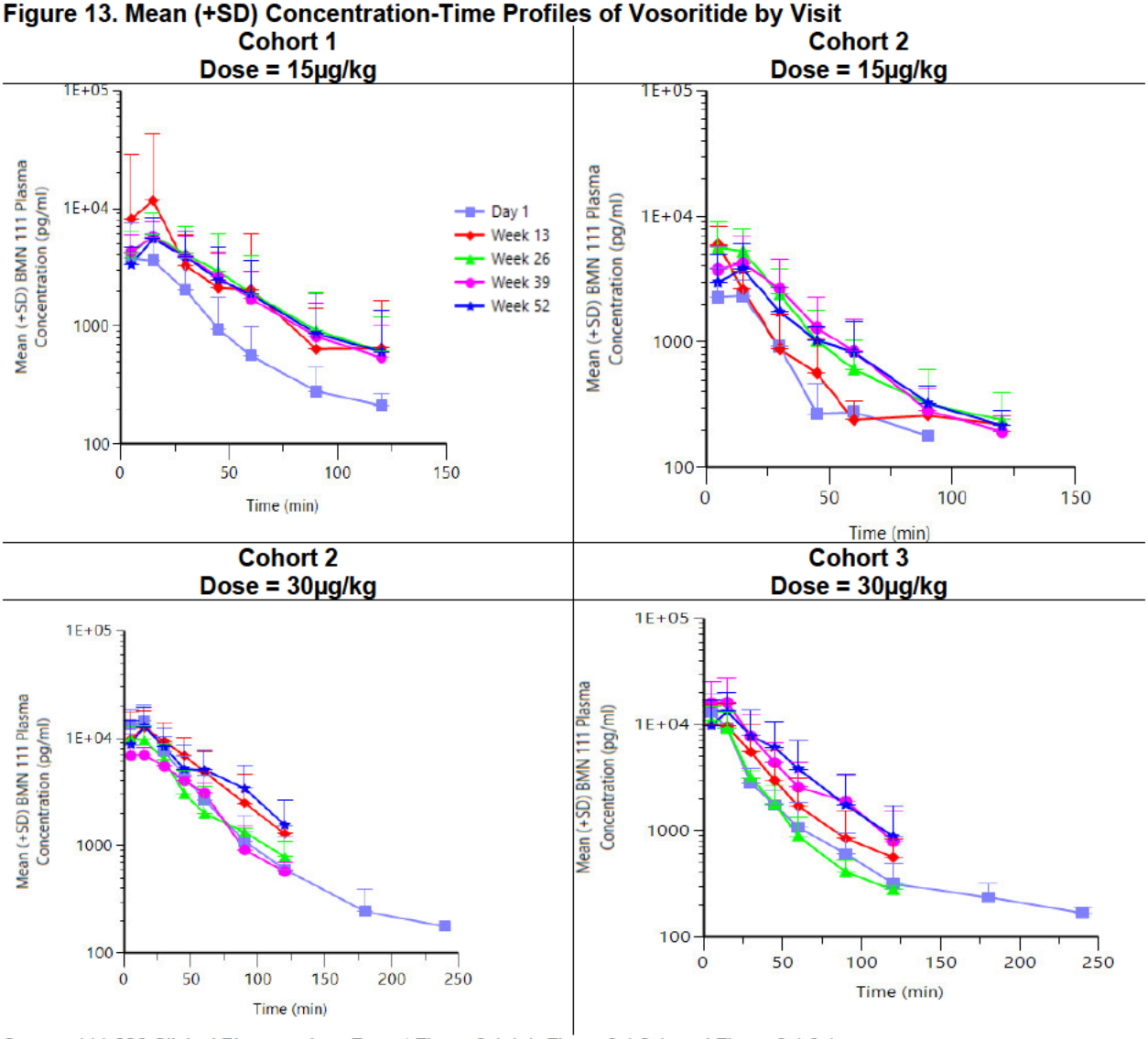
PK Results

Single and repeat dose PK during 12-month (52 weeks) of vosoritide treatment in ACH subjects aged 0 to <5 years were evaluated in Trial 111-206.

Over 52 weeks of treatment at 15µg/kg in Cohort 1, the mean C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}120min}$ and $AUC_{0\text{-}inf}$ ranged from 4350 to 5850 pg/mL, 132000 to 282000 pg-min/mL, 134000 to 283000 pg-min/mL, and 149000 to 306000 pg-min/mL respectively. Median time to maximum concentration (T_{max}) ranged from 15 to 16 mins, and mean $t_{1/2}$ ranged from 22 to 29 mins.

For subjects in Cohort 2 (PK parameters available at 30µg/kg), the mean C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}120min}$ and $AUC_{0\text{-}inf}$ ranged from 6980 to 14500 pg/mL, 365000 to 672000 pg/mL, 365000 to 670000 pg-min/mL, and 387000 to 768000 pg-min/mL respectively. Median T_{max} and mean $t_{1/2}$ ranged from 13 to 15 and 21 to 40 minutes, respectively.

Figure 13. Mean (+SD) Concentration-Time Profiles of Vosoritide by Visit



Source: 111-206 Clinical Pharmacology Report Figure 9.1.1.1, Figure 9.1.2.1, and Figure 9.1.3.1.
Each line represents the mean plasma vosoritide concentration across subjects for each visit. Error bars represent the standard deviation of the mean, and only the upper error bars are shown.
Abbreviation: SD, standard deviation

In Cohort 3, the mean C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}120min}$ and $AUC_{0\text{-}inf}$ ranged from 10500 to 18400 pg/mL, 297000 to 567000 pg-min/mL, 300000 to 591000 pg-min/mL, and 305000 to 622000 pg-min/mL respectively. Median T_{max} ranged from 5 to 16 mins, and mean $t_{1/2}$ ranged from 19 to 41 mins.

In general, subjects in age group with 30µg/kg dose (Cohorts 2 and 3) had higher exposure than 15µg/kg dose groups in Studies 206 and 301. Comparison of vosoritide PK across the clinical studies demonstrated that exposure was comparable between younger ACH participants in Trial 111-206 and ACH participants aged ≥ 5 years in Trial 111-301 (the pivotal phase 3 study supporting approval in original submission). Except for one participant in Trial 111-206 Cohort 3 (age group 0 to <6 month), the mean participant exposure reported in all three cohorts in 111-206 were within the range (max, min) of exposure reported in participants aged ≥ 5 years in 111-301.

Table 37. Comparison of Vosoritide AUC_{0-t} and C_{max} Across Trials 111-206 and 111-301

PK Parameters	Study	111-206				111-301
	Group	All Cohorts	Cohort 1	Cohort 2	Cohort 3	Vosoritide Arm
	Age	0 to 5 years	2 to 5 yr	6 to 24 mo	0 to 6 mo	5 to 18 yr
	n	32	15	8	9	60
	Dose (µg/kg)	15 or 30	15	15 or 30	30	15
AUC_{0-t} (pg-min/mL)	Mean (SD)	300000(161000)	218000(10300)	388000(156000)	358000(190000)	228000(128000)
	Median	267000	187000	371000	267000	192000
	Min, Max	88000,784000	88000,445000	209000,636000	185000,784000	66400,686000
C_{max} (pg/mL)	Mean (SD)	8180(4370)	5030(1740)	9730(2920)	12100(4840)	5910(3060)
	Median	7460	4860	10000	9820	5010
	Min, Max	2280,22000	2280,7540	5390,14700	8160,22000	2680,18400

Source: Table 5.2.1.1 Comparative Analysis Report for 111-206 and 111-301
The mean across all the visits for each randomized subject C_{max} and AUC_{0-t} are presented; Sentinel subjects were excluded and only the 32 randomized subjects were included for Trial 111-206.
Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from 0 to the time of last measurable concentration; C_{max}, maximum plasma concentration; max, maximum; min, minimum; PK, pharmacokinetic; SD, standard deviation; yr, year

Exploratory PD Biomarkers

Serum Collagen type X marker (CXM) and plasma/urine Cyclic guanosine monophosphate (cGMP) were measured following vosoritide treatment in ACH participants as exploratory biomarkers to assess growth plate activity and on-target vosoritide activity through the target receptor Natriuretic peptide receptor type B (NPR-B), respectively.

Mean change in serum CXM due to vosoritide treatment was higher in all three cohorts in study 111-206 compared to placebo group. However, magnitude of difference between vosoritide treated group and placebo group was highest in Cohort 1 (age group ≥2 y to <5 y) and lowest in Cohort 3 (age group 0 to <6 months).

Table 38. Comparison of Mean Change in Serum CXM Across Trials 111-206 and 110-301

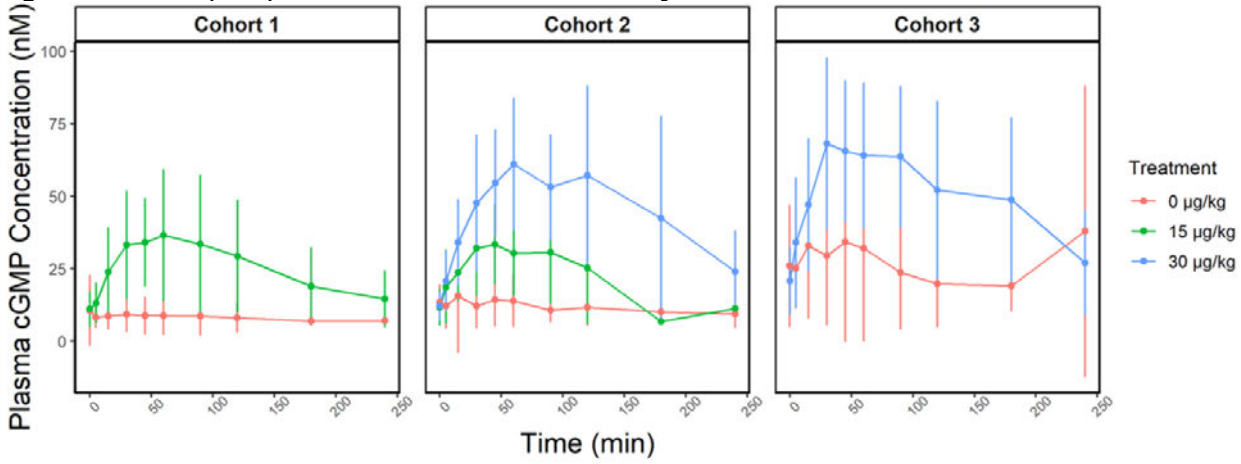
Change in Serum CXM (pg/mL)	Study	111-206				111-301
	Group	All Cohorts	Cohort 1	Cohort 2	Cohort 3	Vosoritide Arm
	Age	0 to 5 years	2 to 5 yr	6 to 24 mo	0 to 6 mo	5 to 18 yr
Vosoritide	n	32	15	8	9	56
	Mean (SD)	2610(3650)	3210(4580)	1650(3030)	2480(2310)	4980(4680)
	Median	2630	3830	1990	2610	4220
	Min, Max	-5030,11100	-5030,11100	-2580,5320	-893,5730	-4850,19300
Placebo	n	31	16	7	8	58
	Mean (SD)	977(3390)	1170(3940)	739(2540)	791(31900	170(3940)
	Median	1580	938	1580	1080	351
	Min, Max	-5660,9130	-5660,9130	-2800,3550	-4300,4150	-8700,13300

Source: Table 5.2.2.1 Comparative Analysis Report for Trials 111-206 and 111-301
The mean change in serum CXM from baseline in Trial 111-206 stratified by cohorts and Trial 111-301 from Week 6 to Week 52 are shown
Abbreviations: CXM, collagen type X marker; SD, standard deviation

In general, the magnitude of difference between vosoritide treated group and placebo group was highest in Trials111-301 and 111-206 Cohort 1, followed by Cohort 2 and Cohort 3 in Trial 111-206.

Mean plasma cGMP increased from predose and reached a maximum ~ 1-hour post-dose in treated group, whereas the mean plasma cGMP remained unchanged in placebo group. The magnitude of plasma cGMP response showed a dose dependent increase with participants receiving 30µg/kg having greater mean plasma cGMP levels than participants receiving 15µg/kg.

Figure 14. Mean (+SD) Plasma cGMP-Time Profiles by Cohort



Source: 111-206 Clinical Pharmacology Report Figure 9.2.2.1
Plasma cGMP over nominal time. Each line represents the mean cGMP of all subjects in the cohort. Error bars represent the standard deviation of the mean.
Abbreviations: cGMP, cyclic guanosine monophosphate; SD, standard deviation

Increase in urine cGMP normalized to creatinine was observed following vosoritide injection in ACH subjects. The increase in urine cGMP/Cr was greatest in subjects dosed with 30µg/kg (those <2 years of age in Trial 111-206 Cohort 2 and Cohort 3) compared to subjects dosed with 15µg/kg (those >2 years in Trials 111-206 Cohort 1 and 111-301).

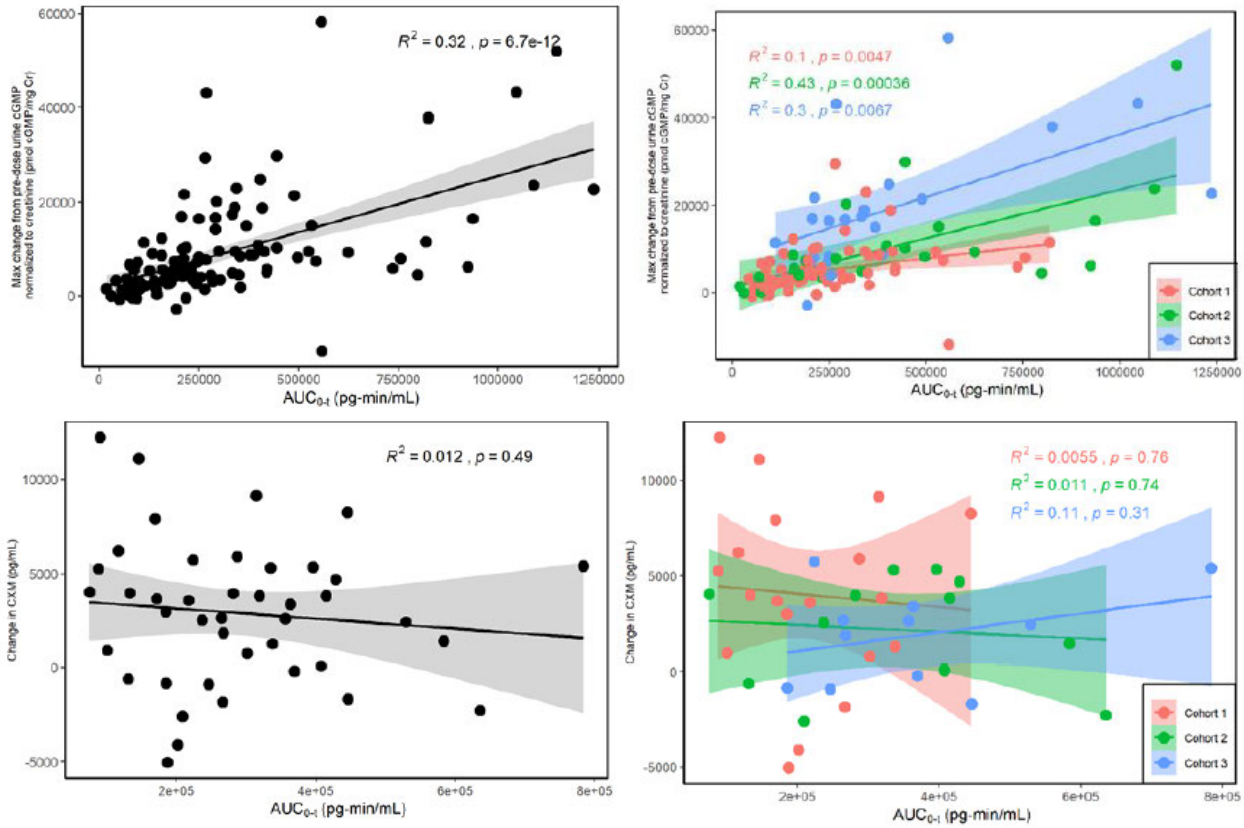
Table 39. Comparison of Urine cGMP Normalized to Creatinine Across Trials 111-206 and 111-301

Urine cGMP/Cr (pmol cGMP/mg Cr)	Study	111-206				111-301
	Group	All Cohorts	Cohort 1	Cohort 2	Cohort 3	Vosoritide Arm
	Age	0 to 5 years	2 to 5 yr	6 to 24 mo	0 to 6 mo	5 to 18 yr
Vosoritide	n	32	15	8	9	60
	Mean (SD)	10200(8110)	4380(2990)	12600(6680)	17700(8160)	6380(3370)
	Median	7130	3350	14400	15900	5490
	Min, Max	1760,38300	1760,13600	2670,21900	11500,38300	2210,17400
Placebo	n	32	16	8	8	61
	Mean (SD)	521(451)	322(207)	573(364)	865(669)	446(428)
	Median	400	322	492	503	348
	Min, Max	49.9,1960	49.9,717	208,1360	299,1960	51.9,3090

Source: Table 5.2.1.1 Comparative Analysis Report for 111-206 and 111-301
The mean maximum change in urine cGMP from pre-dose values in 111-206 stratified by cohorts and 111-301 are shown.
Abbreviations: cGMP, cyclic guanosine monophosphate; Cr, creatinine; SD, standard deviation

Overall, a significant correlation ($p < 0.05$) was observed between maximum change in plasma cGMP or urine cGMP/Cr (normalized to creatinine) from baseline and exposure (C_{max} and/or AUC_{0-t}) in all the subjects in Study111-206 as well as analyzing cohorts separately. No apparent correlation was observed between individual mean vosoritide exposure and mean CXM in all the subjects in study as well as analyzing cohorts separately.

Figure 15. Exposure-Response Analysis for Changes in Urine cGMP/Cr From Baseline and for CXM in Trial 111-206 (Left Panel: Pooled Data and Right Panel: by Cohort)



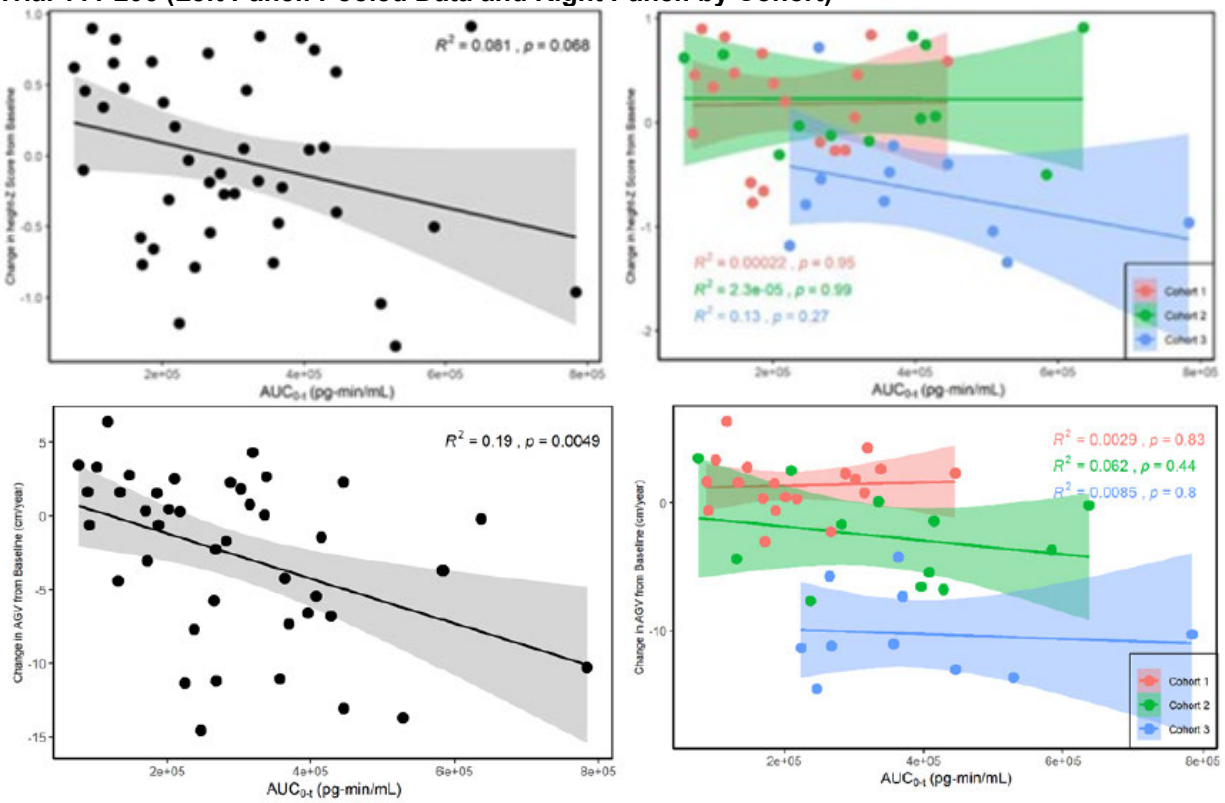
Source: 111-206 Clinical Pharmacology Report Figure 9.3.1.3-4 and Figure 9.3.1.5-6
Solid lines represent the fits through the data and the shaded regions, or the dashed lines represent the 95% confidence interval.
Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from 0 to the time of last measurable concentration; cGMP, cyclic guanosine monophosphate; Cr, creatinine; R, Pearson's correlation coefficient

Exposure-Response Analyses for Efficacy

The primary efficacy endpoint was the change in height-Z score from baseline to Week 52. Change in height-Z score or AGV was similar in Cohort 1 and Cohort 2 but was lower in Cohort 3. The exposure metric used in the analyses was the individual mean area under the plasma concentration-time curve from time 0 to last measurable vosoritide concentration area under the concentration-time curve ($AUC_{[0-t]}$), calculated for each subject on available PK data from all visit days. The mean $AUC_{[0-t]}$ value was used as representative measures of a subject's exposure during the entire study. The change in height-Z score and AGV from baseline to Week 52 by individual mean C_{max} and AUC_{0-t} of all the subjects in the study are shown in Figure 16. The negative correlations observed in the analyses not adjusted by Cohorts Figure 16 are likely due to the confounding effects of differences in the underlying change in growth by age as well as dose adjustment by age. In fact, Cohort 3 (the youngest cohort with age < 6-month-old) had a greater

change in height-Z score and AGV than the other cohorts, due to the underlying rapid decline in growth velocity in children during their early development, which makes the exposure analysis for changes in height-Z score and AGV challenging. In addition, Cohort 3 had a higher exposure due to the highest studied dose of 30µg/kg in all patients. To reduce these confounding effects, the Applicant analyzed the exposure-response by cohorts as shown in the right panel of Figure 16. No apparent and statistically significant correlation was observed between individual exposure and change from baseline in height-Z score or AGV at Week 52 within the different cohorts. See Section 14.5 for additional information.

Figure 16. Exposure-Response Analysis for Changes in Height-Z-Score and AGV From Baseline in Trial 111-206 (Left Panel: Pooled Data and Right Panel: by Cohort)

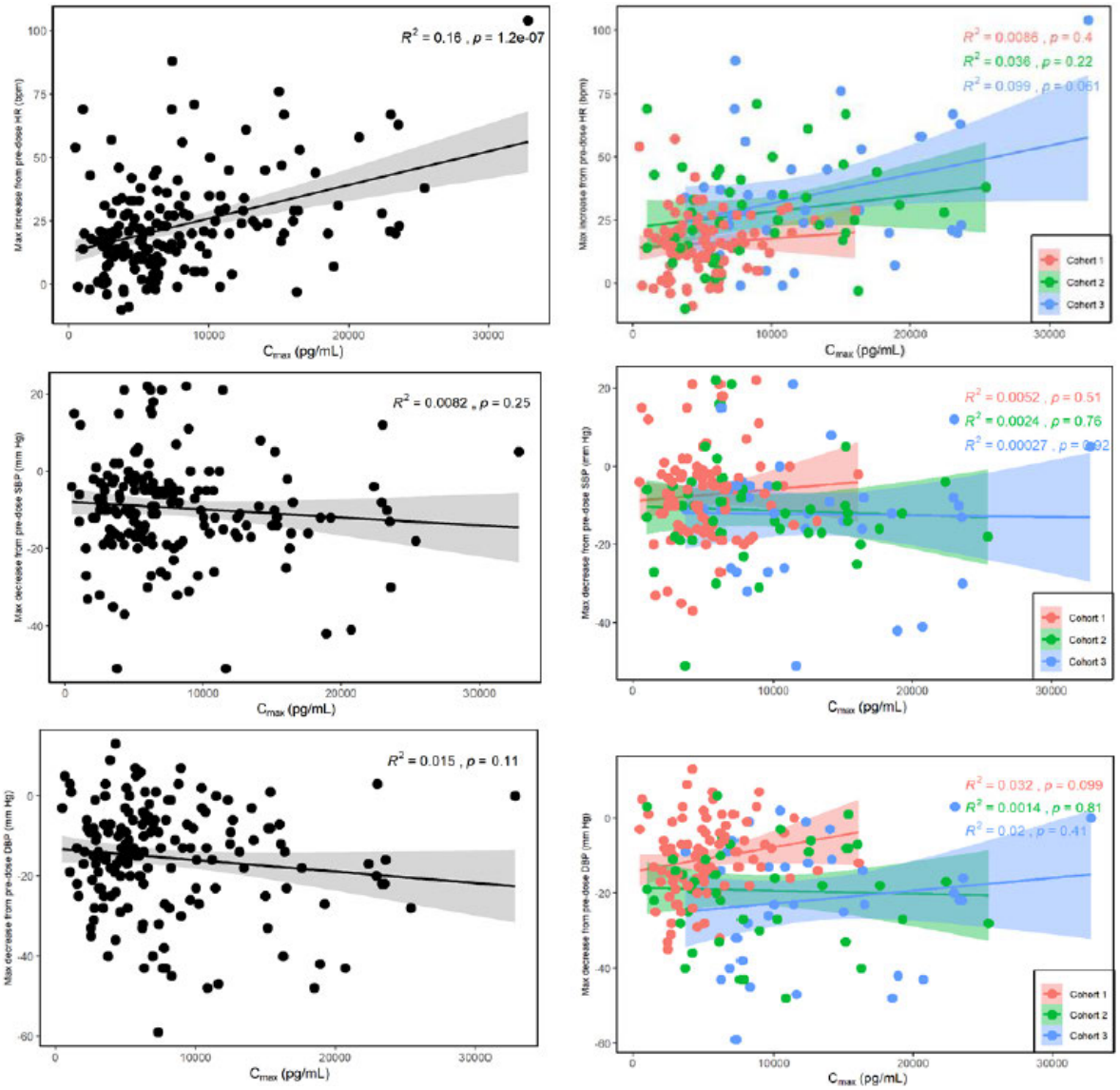


Source: 111-206 Clinical Pharmacology Report Figure 9.3.2.1 and 9.3.2.2 for Height Z-score and Figure 9.3.2.3-4 for AGV
Solid lines represent the fits through the data and the shaded regions, or the dashed lines represent the 95% confidence interval.
Abbreviations: AGV, annualized growth velocity; AUC_{0-t}, area under the plasma concentration-time curve from 0 to the time of last measurable concentration; R, Pearson's correlation coefficient

Exposure-Response Analyses for Safety

The Applicant conducted exposure-response analyses for safety endpoints such as changes in vital signs (Heart rate, Systolic blood pressure and Diastolic blood pressure) of ACH subjects treated with vosoritide in Trial 111-206. A weak positive correlation between the maximum increase from each pre-dose in heart rate (HR) and vosoritide C_{max}, was found statistically significant (p value= 0.061) in Cohort 3 only. However, the changes in HR were transient and self-limiting, not associated with an adverse clinical outcome. No adverse events of tachycardia or events related to change in HR were reported across all cohorts. Overall, there were no meaningful correlations between the plasma C_{max} of vosoritide and vital signs of the subjects treated with vosoritide in the study (Figure 17).

Figure 17. Visit-Matched Vosoritide C_{max} in Plasma and Maximum Change in Vital Signs in Trial 111-206



Source: 111-206 Clinical Pharmacology Report Figure 2.7.2.3.3.1.3.1
Solid lines represent the linear fits through the data and the shaded regions, or the dashed lines represent the 95% confidence interval.
Abbreviations: C_{max}, maximum plasma concentration; R, Pearson's correlation coefficient.

Reviewer's comment:

Across cohorts, the observed increase in exposures with time (Day 1 to Week 52), was unexplained, however, it may have possibly been confounded by the increase in body weight as well as the doses administered to the children during that time frame. Overall, the observed exposures of vosoritide in Trial 111-206 *were within the range of exposure reported in participants aged ≥ 5 years in 111-301. The observed lack of relationship in ER for efficacy in <5 y old ACH patients also seems to be related to the narrow range of dosing studied in Trial 111-206, as the dosing was targeted to achieve a narrow range of exposures that would be comparable to the 15µg/kg dose level in > 5 y old ACH patients of Trial 111-202.*

Trial 111-208: A Phase 2 Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of BMN 111 in Children with Achondroplasia

Study Design

Trial 111-208 is an ongoing, multicenter long-term extension study to evaluate the safety and efficacy of vosoritide in children with ACH who complete Trial 111-206. The study was started in June 2019 and interim clinical study report (CSR) was provided with cutoff date of 26 January 2022. All participants in Trial 111-208 were treated with vosoritide. A total of 73 of the 75 participants completed study 111-206 and were enrolled into Trial 111-208. All participants in Trial 111-208 were treated with vosoritide.

Of the 73 participants treated, 31 had previously received placebo in study 111-206 and 42 had previously received vosoritide (Table 40). At the time of the data-cut off, all participants remained in the study and were continuing treatment with vosoritide. The mean (SD) duration of treatment was 24.1 (10.7) months (range: 0.0 to 43.5 months). Participants received a daily dose of 30µg/kg while they were < 2 years of age. The daily dose was adjusted to 15µg/kg during the visit immediately preceding the 2-year birthday. Participants will continue to be evaluated in this study until they reach near final adult height (defined as evidence of growth plate closure and < 1.5 cm/year AGV).

Plasma samples collected at pre-dose and at, 15, 30-, 60-, 90-, and 120-minutes post-dose on Trial 111-206 Week 52/ Trial 111-208 Day 1 and at Weeks 26, 52, 78, 104, 130, 156, 182, 208, 234, 260 and 312.

PK Results

The PK parameters were estimated using non-compartmental analysis method. All the subjects included in the NCA analysis in Cohort 2 and Cohort 3 were aged >24 months, therefore all the subjects received a daily dose of 15µg/kg due to the dose adjustment (Figure 18).

Table 40. Available PK Data From Subjects in Trial 111-208

Cohort	Group	Visit (Week)						
		Week 26 (N)	Week 52 (N)	Week 78 (N)	Week 104 (N)	Week 130 (N)	Week 156 (N)	Week 182 (N)
Cohort 1	BMN 111/BMN 111	-	-	17	13	15	8	1
	Placebo/BMN 111	8	14	10	3	-	-	-
Cohort 2	BMN 111/BMN 111	-	-	7	9	4	-	-
	Placebo/BMN 111	5	4	1	-	-	-	-
Cohort 3	BMN 111/BMN 111	-	-	3	2	1	-	-
	Placebo/BMN 111	2	-	-	-	-	-	-

Note: This table only included subjects with at least one measuable post-dose PK data.
Source: Trial 111-208 Clinical Pharmacology Report Table 9.1.1
Abbreviations: BMN, vosoritide; N, number of subjects; PK, pharmacokinetic

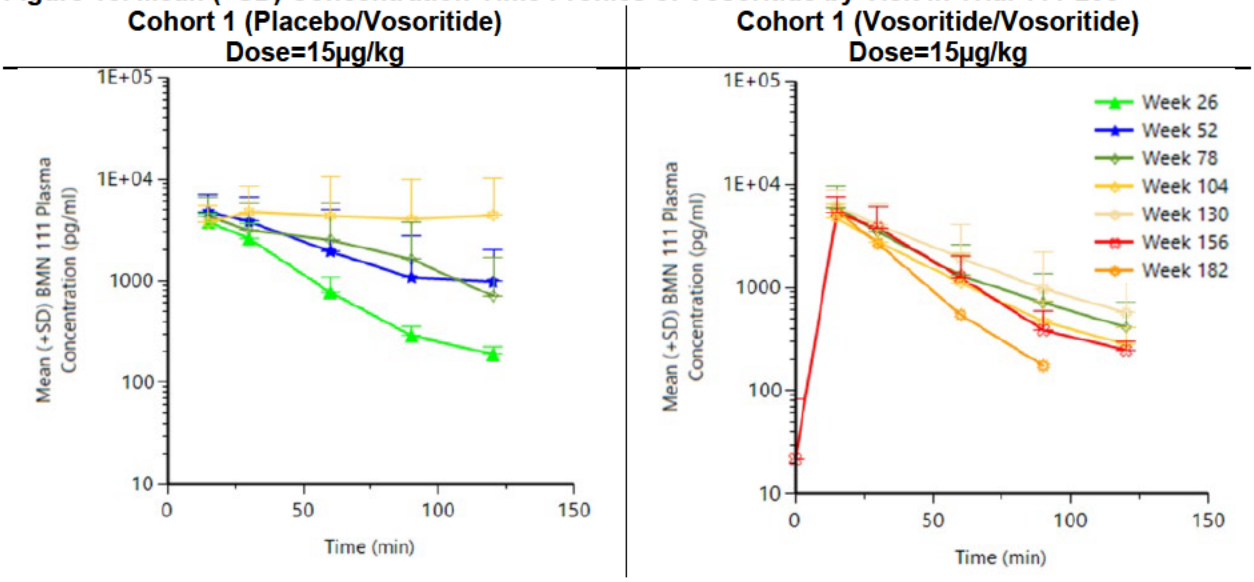
In Cohort 1, 19 subjects continued into vosoritide/vosoritide group, the mean C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}120min}$ and $AUC_{0\text{-}inf}$ ranged from 4750 to 6460 pg/mL, 158000 to 279000 pg-min/mL, 161000 to 278000 pg-min/mL, and 162000 to 290000 pgmin/ mL respectively, and 16 subjects

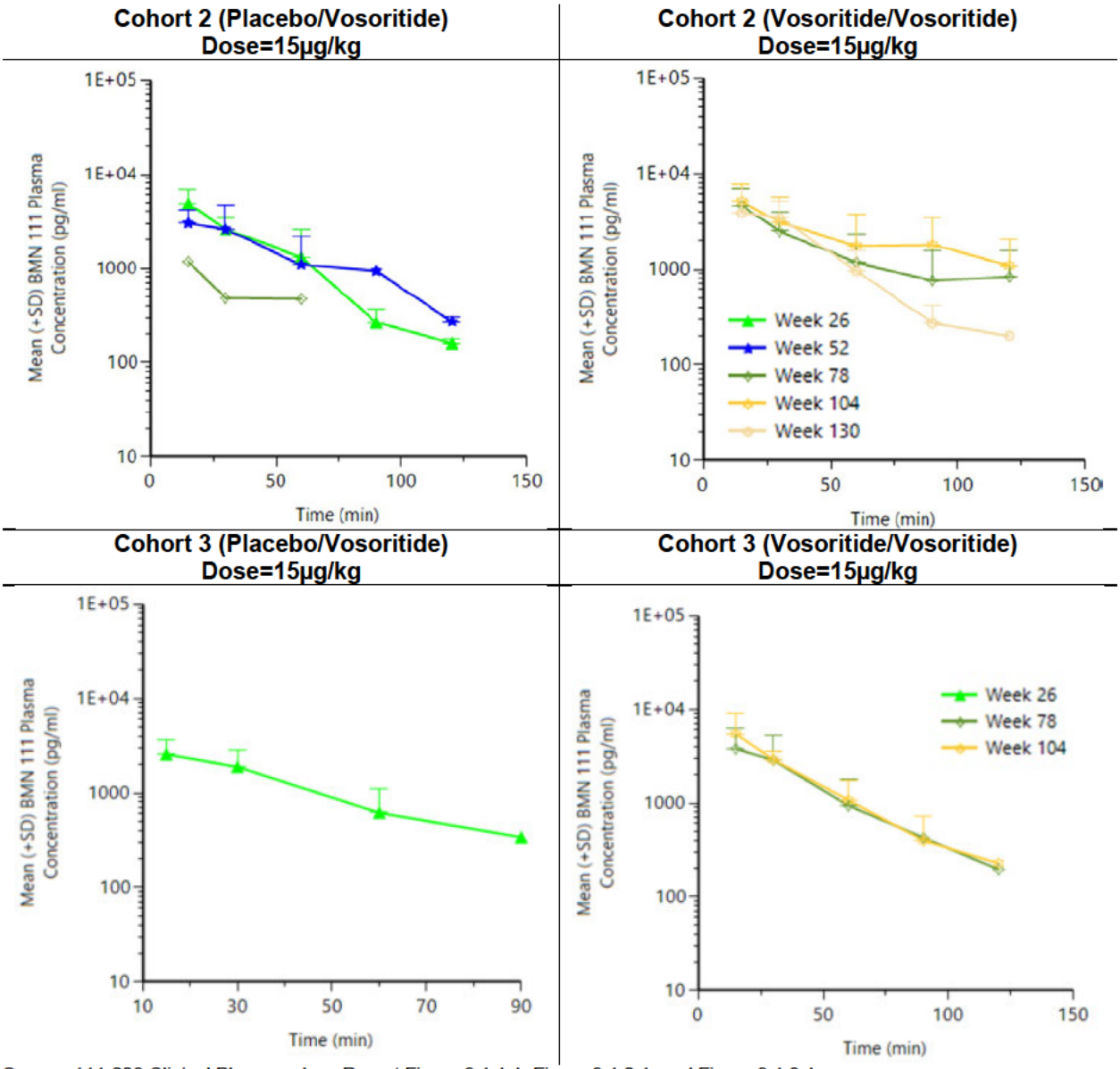
continued into Placebo/vosoritide group, the mean C_{max}, AUC_{0-t}, $AUC_{0-120min}$ and AUC_{0-inf} ranged from 3670 to 6110 pg/mL, 134000 to 450000 pg-min/mL, 135000 to 447000 pg-min/mL, and 150000 to 264000 pgmin/mL respectively. Median T_{max} ranged from 15 to 17 minutes, and mean $t_{1/2}$ ranged from 15 to 26 minutes in the vosoritide/vosoritide group while the median T_{max} ranged from 15 to 35 minutes, and mean $t_{1/2}$ ranged from 23 to 27 minutes in the placebo/vosoritide group.

In Cohort 2, 10 subjects continued into vosoritide/vosoritide group, the mean C_{max}, AUC_{0-t}, $AUC_{0-120min}$ and AUC_{0-inf} ranged from 5160 to 5610 pg/mL, 177000 to 246000 pg-min/mL, 179000 to 246000 pg-min/mL, and 181000 to 368000 pg-min/mL respectively. Median T_{max} ranged from 15 to 19 minutes, and mean $t_{1/2}$ ranged from 16 to 25 minutes. In Cohort 2, 5 subjects continued into Placebo/vosoritide group, the mean C_{max}, AUC_{0-t}, $AUC_{0-120min}$ and AUC_{0-inf} ranged from 1180 to 4880 pg/mL, 36900 to 169000 pg-min/mL, 36900 to 170000 pg-min/mL, and 178000 to 238000 pg-min/mL respectively. Median T_{max} ranged from 15 to 18 minutes, and mean $t_{1/2}$ ranged from 18 to 22 minutes.

In Cohort 3, 4 subjects continued into vosoritide/vosoritide group, the mean C_{max}, AUC_{0-t}, $AUC_{0-120min}$ and AUC_{0-inf} ranged from 5090 to 5480 pg/mL, 181000 to 185000 pg-min/mL, 182000 to 185000 pg-min/mL, and 186000 to 269000 pg-min/mL respectively. Median T_{max} ranged from 18 to 19 minutes, and mean $t_{1/2}$ was 18 minutes. Only 2 subjects continued into Placebo/vosoritide group and only Week 26 was available, the mean values for C_{max}, AUC_{0-t}, $AUC_{0-120min}$ and AUC_{0-inf} were 2570 pg/mL, 97600 pg-min/mL, 101000 pg-min/mL, and 150000 pg-min/mL respectively. Median T_{max} and mean $t_{1/2}$ was 16 and 21 minutes, respectively.

Figure 18. Mean (+SD) Concentration-Time Profiles of Vosoritide by Visit in Trial 111-208





Source: 111-208 Clinical Pharmacology Report Figure 9.1.1.1, Figure 9.1.2.1, and Figure 9.1.3.1.
Each line represents the mean plasma vosoritide concentration across subjects for each visit. Error bars represent the standard deviation of the mean, and only the upper error bars are shown.
Abbreviations: BMN, vosoritide; SD, standard deviation

Reviewer's comment:

In the long-term extension Trial 111-208, the exposures were overall consistent with that observed in Trial 111-206.

14.3. Bioanalytical Method Validation and Performance

For both Studies 111-206 and 111-208, the K3EDTA plasma PK samples containing phosphodiesterase and protease inhibitors were analyzed for concentration of vosoritide using a validated quantitative electrochemiluminescence (ECLA) assay (Validation BMN111-15-095).

The range of quantification for the assay was 137 pg/mL to 100ng/mL. The QC concentrations were 0.3ng/mL, 7.5ng/mL, and 75ng/mL. The assay procedure described in the method (b) (4) 21-252-MTH-001) was used for analysis of Phase 2/3 studies in original NDA submission, was reviewed by the Office of Clinical Pharmacology and available in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) (Reference ID: 4907421).

- The long-term stability in plasma was established for 44 months at a temperature range of -90°C to -65°C and clinical study samples were analyzed within the stability period.
- The cumulative accuracy (% bias) and cumulative precision (% CV) for the calibration curve standards in the analytical runs ranged between 95.5 % to 105.7% and 1.1% to 8.5%, respectively.
- The cumulative accuracy (% bias) and cumulative precision (% CV) for the quality controls in the analytical runs ranged between 89.6 % to 109.5% and 4.3% to 10.1%, respectively.
- For Trial 111-206, the incurred sample reanalysis was performed in 9.7 % of samples (29 of 300 samples) and all samples were equal to or within 30% of original value and met the pre-specified acceptance criterion.

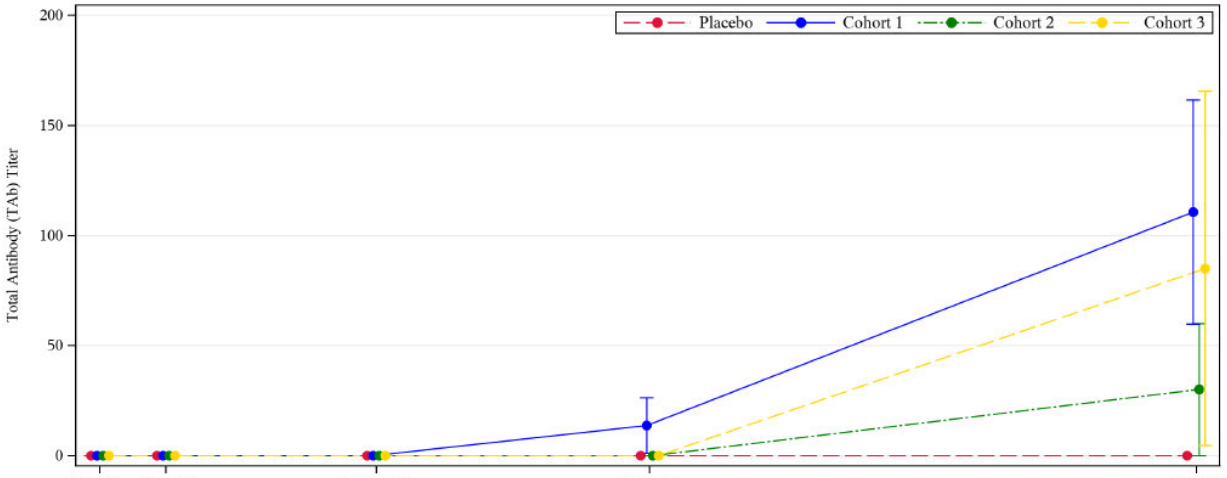
Overall, the performance of bioanalytical method parameters was within the criterion set forth in bioanalytical method validation guidance of FDA and the results of vosoritide concentrations are considered acceptable.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

The serum anti-drug antibody (ADA) response to vosoritide was tested using measurements of total antibody (Tab) and neutralizing antibody (Nab). A tiered approach was used wherein any Tab sample that confirmed positive was further characterized for the presence of Nab to vosoritide and for cross-reactivity with atrial natriuretic peptide (ANP), B type natriuretic peptide (BNP) or CNP. Validated assays were used for quantifying both Tab and Nab. Participants with one or more positive results at any post-baseline visit with a titer value >10 were considered positive for Tab.

In Trial 111-206, 19% (8/43) of all vosoritide-treated subjects tested positive for Tab, however all of the Tab-positive subjects tested negative for Nab at all time points. All placebo-treated participants tested negative for Tab. The incidence of Tab was 26% (5/19) in Cohort 1, 8% (1/12) in Cohort 2 and 17% (2/12) in Cohort 3, respectively. The earliest time to Tab onset was Week 26 in the study and Tab positive subjects were transiently positive at Week 26 and/or Week 52 of the study (Figure 19).

Figure 19. Mean (+/-SE) Total Antibody (Tab) Titer Over Time in Trial 111-206



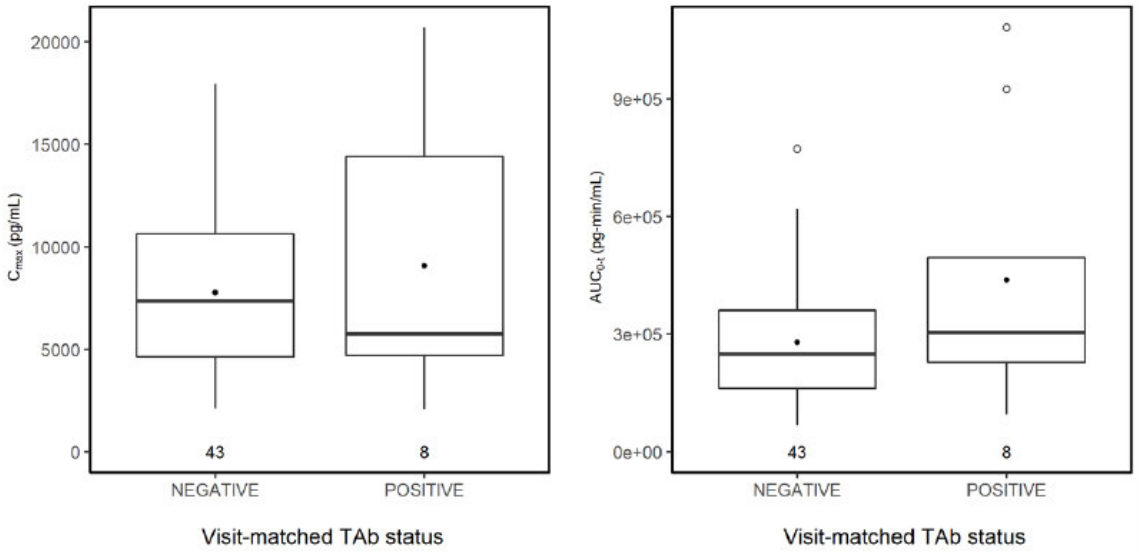
Placebo	31	20	29	29	28
Cohort 1	19	6	17	19	18
Cohort 2	11	10	11	9	8
Cohort 3	7	6	9	8	7

Source: Figure 14.3.6.5.1A of Trial 111-206 CSR.
Abbreviations: SE, standard error; TAb, total antibody

Interim immunogenicity results as of cut-off date in Trial 111-208 indicated presence of Tab in 33% (20/61) of subjects who were all on vosoritide treatment and none of them were Nab. Of the 20 overall Tab positive subjects, 8 subjects had seroconverted to positive status on vosoritide treatment in Trial 111-206 while the remaining 12 who received placebo in Trial 111-206 seroconverted to positive status in Trial 111-208. The earliest time to onset of Tab development was Week 26 in Trial 111-208 and data presented is until Week 130.

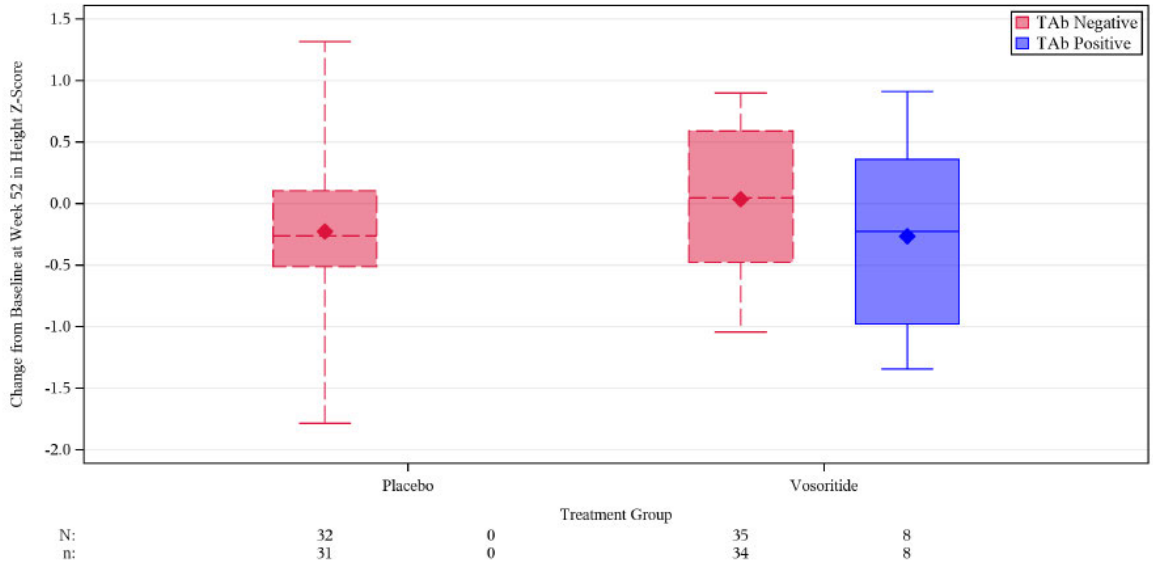
In Trial 111-206, the potential impact of ADAs on the pharmacokinetics, efficacy, and safety of vosoritide was evaluated. The impact of anti-vosoritide Tab on vosoritide PK was evaluated by comparing the mean across visit-matched PK parameters at Tab-negative visits for all vosoritide treated subjects in the study. The results showed the visit-matched PK parameters (C_{max} and AUC_{0-t}) were comparable in the two groups, suggesting there was no impact of anti-vosoritide Tab on plasma exposure of vosoritide (Figure 20). Additionally, there was no obvious association between Tab positivity and the primary treatment outcome as measured by the change from baseline in Height Z-Score to Week 52 (Figure 21).

Figure 20. Vosoritide Plasma Exposure (AUC_{0-t} and C_{max}) vs. TAb Status in Trial 111-206



Source: Figure 9.1.5.1 in Clinical Pharmacology Report of Trial 111-206
The line inside the box represents the median, the box represents the limits of the middle half of the data. The range of the box, from the first quartile (Q1) to the third quartile (Q3), defines the interquartile range (IQR); The mean exposure of the subjects at that visit is shown as a black circle. Within subject mean PK parameters on visits with and without ADA detected were used as representative PK parameters for that subject in the presence and absence of ADA, respectively. As such, each subject is not represented more than once in the negative and positive ADA distributions.
Abbreviations: ADA, anti-drug antibody; AUC_{0-t}, area under the plasma concentration-time curve from 0 to the time of last measurable concentration; C_{max}, total maximum concentration; IQR, interquartile range; Q, quarter; TAb, total antibody

Figure 21. Change From Baseline at Week 52 in Height Z-Score vs. TAb Status in Trial 111-206



Source: Figure 14.3.6.5.2A of Trial 111-206 CSR.
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; Box plot displays the 25th and 75th percentiles (box edges), the median (midline), the mean (diamond symbol) and the 2.5th and 97.5th percentiles (whiskers)
Abbreviations: SD, standard deviation; TAb, total antibody

Overall, the analyses indicate no impact of the ADA development on the PK or efficacy of vosoritide in this ACH population.

14.5. Pharmacometrics Assessment

The population PK model was considered appropriate for describing the observed vosoritide concentrations, and for performing PK simulations to predict vosoritide exposure metrics (AUC and C_{max}) in patients with ACH. More specifically, the PK model was utilized to support the current submission as outlined below:

Table 41. Utility of the Population PK Modelling

	Utility of the Final Model	Reviewer's Comments
Derive exposure metrics and PK parameters	The original PK model developed in pediatric patients with ACH, 1 years to 15 years old. The model was updated with additional patient data from Trial 111-206, with younger patients (4.5 months to <5 years old). The identified covariates and covariate effects on the PK were comparable to the previous model, with body weight as covariate on CL/F and V/F and an exponential increase in bioavailability with time. The PK model was used to simulate vosoritide exposure metrics (AUC_{0-5h} and C_{max}) to provide dosing regimen in in studied and unstudied younger subjects with body weight 3 to 9 kg (mostly <2 years old).	The reviewer's assessment of the PK model and the conducted sensitivity analyses found that the Applicant's PK model reasonably describes and predicts vosoritide PK in patients with ACH from Trial 111-206. The reviewer's updated PK model estimated a correlation of 58% between the random-effects terms of CL/F and V/F. Accounting for the correlation in random effects between PK parameters is critical for PK model-based simulations to avoids outliers and maintains a plausible relationship between CL/F and V/F values. The reviewer's PK model and independent simulations provided comparable individual predicted concentrations and simulated exposure metrics as the Applicant's PK model.

Source: FDA Reviewer.
Abbreviations: ACH, achondroplasia; AUC_{0-5h}, area under the plasma concentration-time curve from 0 to time 5 hours; CL/F, clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; V/F, volume of distribution

14.5.1. Applicant's PK Analysis

The population PK analysis (popPK) used to describe the observed PK data in children and adolescents (4.5 months to 15 years old) with achondroplasia (ACH) was based on PK data from 5 clinical studies (Table 42): 111-202, 111-205, 111-206, 111-301 and 111-302.

The current popPK model was built on the previously developed PK model describing the PK of vosoritide following subcutaneous (SC) administration in pediatric patients with ACH (1 to 15 years old). The model was updated with additional patient data from study 111-206, which included younger patients (4.5 months to <5 years old).

In study 111-206 (a 52-week study), subjects ≥2 years old (Cohort 1) were given a SC daily dose of 15µg/kg vosoritide and subjects <2 years (Cohort 2 and 3) were given 30µg/kg vosoritide or placebo daily. Patients in Cohort 2 (age ≥ 6 to < 24 months) had their daily dose adjusted to 15µg/kg during the visit immediately preceding the 2-year birthday. According to the study protocol, plasma samples were collected pre-dose and at 5, 15, 30, 45-, 60-, 90-, and 120-minutes post-dose on the planned visits (Day 1, Week 13, Week 26, Week 39, and Week 52). On Day 1, additional PK samples were collected at 180- and 240-minutes post-dose.

The final PK dataset used for analysis consisted of 6022 PK samples from 191 subjects, including 925 BLQ (below limit of quantification) observations. Trial 111-206 contributed with 1411 observations from 43 subjects, including 270 BLQ observations. The lower limit of quantification (LLOQ) of the different assays are reported in Table 43. The likelihood-based approach (M3 method) was used to handle BLQ data during PK modelling. Table 44 summarizes the relevant demographic characteristics of all subjects stratified by study.

Table 42. Studies Included in the Population PK Analysis

Study	Study Population	Study Design	Study Drug Dosage Regimens	Number of Subjects Who Received Vosoritide
111-202	Children with ACH	Phase 2: open label, sequential cohort dose-escalation study in children with ACH (age 5- 14)	2.5, 7.5, 15, 30µg/kg/day	35
111-205	Children with ACH	Phase 2: open label extension study in children with ACH who completed 111-202	15 or 30 µg/kg/day	30
111-206	Children with ACH	Phase 2: randomized, double-blind, placebo controlled in infants and young children with ACH (age 0 to < 60 months)	15 or 30 µg/kg/day	43
111-301	Children with ACH	Phase 3: double-blind, randomized placebo-controlled trial in children with ACH (age 5- 18)	15 µg/kg/day	60
111-302	Children with ACH	Phase 3: open label extension study in children with ACH who completed 111-301	15 µg/kg/day	119

Source: Applicant's Population PK Report, Table 1, pages 17-18.
Abbreviations: ACH, achondroplasia; PK, pharmacokinetic

Table 43. Vosoritide Dose Solutions, Assays and Lower Limit of Quantifications by Study

Study	Weight-based Dose	Dose Administered	Solution concentration	Assay	LLOQ
111-202	2.5, 7.5, 15 or 30 µg/kg	< 65 µg	0.2 mg/mL	ELISA	0.391 ug/L
		>= 120 µg	2.0 mg/mL		
111-205	15 or 30 µg/kg	All	2.0 mg/mL		
111-206	15 µg/kg	=< 255 µg (17 kg)	0.8 mg/mL	ECLA	0.137 ug/L
		> 255 µg	2.0 mg/mL		
	30 µg/kg	=< 240 µg (8 kg)	0.8 mg/mL		
		> 240 µg	2.0 mg/mL		
111-301/302	15 µg/kg	=< 480 µg (32 kg)	0.8 mg/mL		
		> 480 µg	2.0 mg/mL		

Source: Applicant's Population PK Report, Table 2, page 19.
Abbreviations: ELISA, enzyme-linked immunosorbent assay; ECLA, electrochemiluminescence assay; LLOQ: lower limit of quantitation

Table 44. Summary of Relevant Demographic Characteristics, Stratified by Study

	Study 202 (N=29)	Study 205 (N=29)	Study 206 (N=43)	Study 301 (N=60)	Study 302 (N=119)
Age (years)					
Mean (SD)	7.66 (1.59)	9.72 (1.58)	2.04 (1.47)	8.35 (2.43)	9.24 (2.46)
Median [Min, Max]	7.00 [5.00, 11.0]	10.0 [7.00, 13.0]	1.82 [0.372, 4.98]	7.79 [5.07, 13.1]	9.00 [6.00, 15.0]
Weight (Kg)					
Mean (SD)	21.3 (4.95)	27.8 (5.84)	10.2 (3.75)	22.9 (7.96)	26.9 (9.65)
Median [Min, Max]	20.6 [15.6, 36.4]	28.0 [19.4, 41.3]	9.40 [5.20, 19.1]	21.3 [13.6, 53.0]	24.9 [13.0, 74.5]
Sex					
Male	13 (44.8%)	13 (44.8%)	25 (58.1%)	31 (51.7%)	63 (52.9%)
Female	16 (55.2%)	16 (55.2%)	18 (41.9%)	29 (48.3%)	56 (47.1%)

Source: FDA Reviewer.
Reviewer's Note: the Summary of Demographic Characteristics is based on the PK dataset used for PK modelling.
Abbreviations: max, maximum; min, minimum; N, number of subjects; SD, standard deviation

Applicant's Final Population PK model

The parameter estimates from the final PK model describing vosoritide PK in pediatric patients (4.5 months to 15 years old) with ACH are listed in Table 45. The final PK model consisted of a 1-compartment disposition model with first-order absorption (with a time-dependent change point in absorption rate constant and time-dependent change in relative bioavailability) and first-order elimination, consistent with the previous structural PK model in patients 5 years old and above (studies 111-202, 111-205, 111-301 and 111-302).

The parameter estimates from the current PK model are within the lower range of those estimated in older children (≥ 5 years old) from the previous model, notably for the apparent clearance (CL/F) and the absorption rate constants. The estimated vosoritide typical CL/F for a 20 kg subject of 31.5 L/h (95%CI: 25.6 – 35.87 L/h) was lower than the estimated CL/F of 47.47 L/h (95%CI: 40.45 – 57.97 L/h) in the previous PK model in older children (≥ 5 years old). Vosoritide SC absorption was modeled using a sequential absorption with a fast absorption rate constant (Ka1 of 1.55 h^{-1}) followed by a slower absorption rate constant (Ka2 of 0.33 h^{-1}). The time of the change from Ka1 to Ka2 (change-point parameter) was estimated to be 0.26 h. The relative bioavailability (F) was modeled to change over time until reaching a plateau using exponential function (see equations Table 45).

Body weight (standardized to 20 kg) was included as a covariate on CL/F and the apparent central volume of distribution (V/F), using estimated allometric scaling exponents (estimated exponent of 0.53 for CL/F and 1.08 for V/F). The estimated allometric exponent on CL/F of 0.53 (95%CI: 0.28 – 0.75) was higher than the estimated exponent (0.356, 95%CI: 0.02 – 0.68) in the previous PK model in older children (≥ 5 years old). Vosoritide solution concentration (SOLNC) was found to be a significant covariate on F, with an estimated 64% increase in bioavailability with the lowest solution concentration of 0.2 mg/mL. Of note, the solution concentration of 0.2 mg/mL has only been used in the dose-escalation study 111-202 and will not be used for commercial formulations.

Anti-drug antibodies (ADA) titers and ADA positivity (categorical variables) were not found to increase vosoritide CL/F.

Between-subject or Inter-individual variability (IIV) in PK parameters was included on CL/F, V/F, and change-point (CP) parameters, with an estimated unexplained IIV of 28.2%, 20.9% for CL/F and V/F and fixed IIV of 22.4% for change-point. The eta-shrinkage on CL/F, V/F and CP was 15.4%, 38.4 and 51.4%, respectively. In addition, the PK model included between-studies or inter-studies variabilities on CL/F (IIV Study CL) and V/F (IIV Study V) to account for the variability in PK parameters and exposure between studies. Some of these studies were extension studies (111-205 and 111-302). The residual error model consisted of an additive residual error model on log-transformed data (i.e., proportional error model on back-transformed data) with an estimated proportional error of 66.9% in studies using the ELISA assay, and 66.7% in studies using the ECLA assay (Table 43). The epsilon shrinkage was 2.8%.

The goodness of fit (GOF) plots from the final PK model are shown in Figure 22 and the prediction-corrected visual predict check (pcVPC), and the dose-normalized VPC stratified by study are shown in Figure 23.

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Table 45. Parameter Estimates From the Final PK Model

Parameter (units)	Typical Value	se (%)	Bootstrap Lower 2.5th	Bootstrap Median	Bootstrap Upper 97.5th
CL/F (L/hr)	31.50	1.70	25.62	31.19	35.87
V/F (L)	13.60	2.70	11.02	13.46	16.06
Ka1 (1/hr)	1.55	19.20	1.20	1.56	2.00
Ka2 (1/hr)	0.03	2.50	0.02	0.03	0.03
Change-point (hr)	0.26	7.30	0.25	0.26	0.28
Residual Error 1 (CV%)	66.90	1.60	61.60	66.50	71.50
Residual Error 2 (CV%)	66.70	1.20	61.80	66.60	71.10
Effect of Solution Concentration (0.2 mg/mL)	1.64	13.20	1.26	1.61	2.16
Effect of Weight on CL/F	0.53	11.40	0.28	0.53	0.75
Effect of Weight on V/F	1.08	5.40	0.91	1.07	1.21
Effect of Time on F	0.24	6.30	0.18	0.24	0.28
IIV CL	28.20	8.20	0.24	0.28	34.50
IIV V	20.90	13.60	13.40	20.40	25.60
IIV StudyCL	22.20	47.90	16.10	22.40	30.60
IIV StudyV	3.30	57.70	1.30	3.30	6.50
IIV change-point (Fixed)	22.4 Fixed	0.0c	NE	NE	NE

CL/F – apparent clearance, V/F – apparent volume of distribution, F – bioavailability, IIV – inter-individual variability, NE – not estimated, L – liter, hr – hour, IIV StudyCL – nested variability based on study identifier number, IIV StudyV – nested variability based on study identifier number, Residual error 1 – for concentrations arising from the ELISA assay, residual error 2 – for concentrations arising from the ECL assay.

$$CL = exp(\theta 1 + \eta 1 + \eta 6) * \left(\frac{WT(Kg)}{20}\right)^{\theta 14}$$

$$Vc = exp(\theta 2 + \eta 2 + \eta 7) * \left(\frac{WT(Kg)}{20}\right)^{\theta 15}$$

$$Ka1 = exp(\theta 5 + \eta 5)$$

$$Ka2 = exp(\theta 6 + \eta 8)$$

$$Change = \theta 7 + \eta 9$$

If(Time After Dose $< Change$) KA= Ka_1 else KA=Ka_2

$$SD1 = \theta 8$$

$$SD2 = \theta 9$$

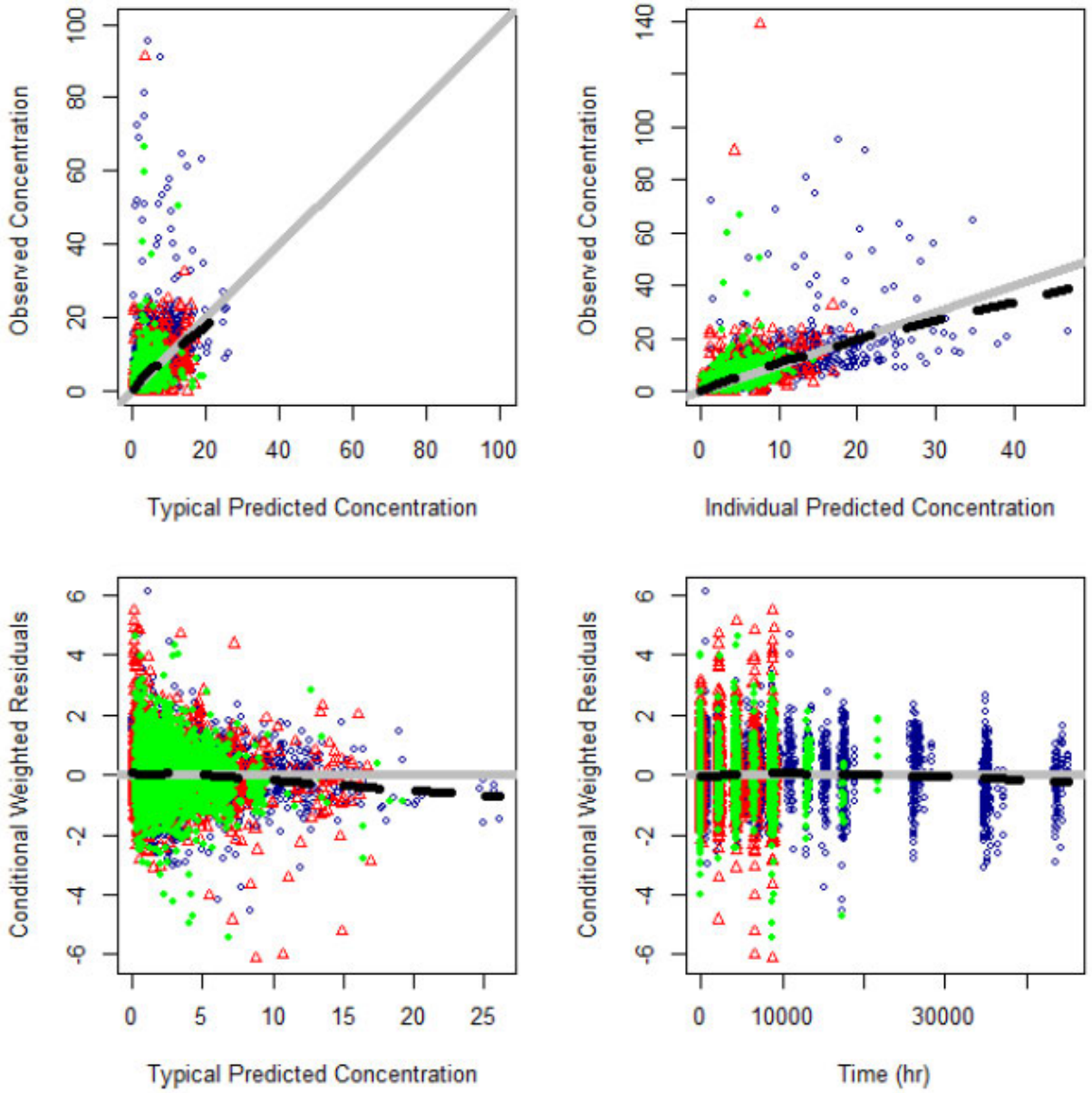
$$Form3 = 1$$

$$IF(SOLNC = 0.2) FORM3 = \theta 11$$

$$F = \exp(\theta 16 * Time/10000) * Form3$$

Source: Adapted from Applicant's Population PK Report, Table 12, page 49, and Equations page 48.
Note: η1, η2 and η9 represent IIV CL, IIV V and IIV change-point, respectively. H6 and η7 represent IIV StudyCL, IIV StudyV, respectively. H5 and η8 were fixed to zero. SOLNC: solution concentration. SD1 and SD2 are the residual error for Assay 1 (ELISA) and Assay 2 (ECLA).

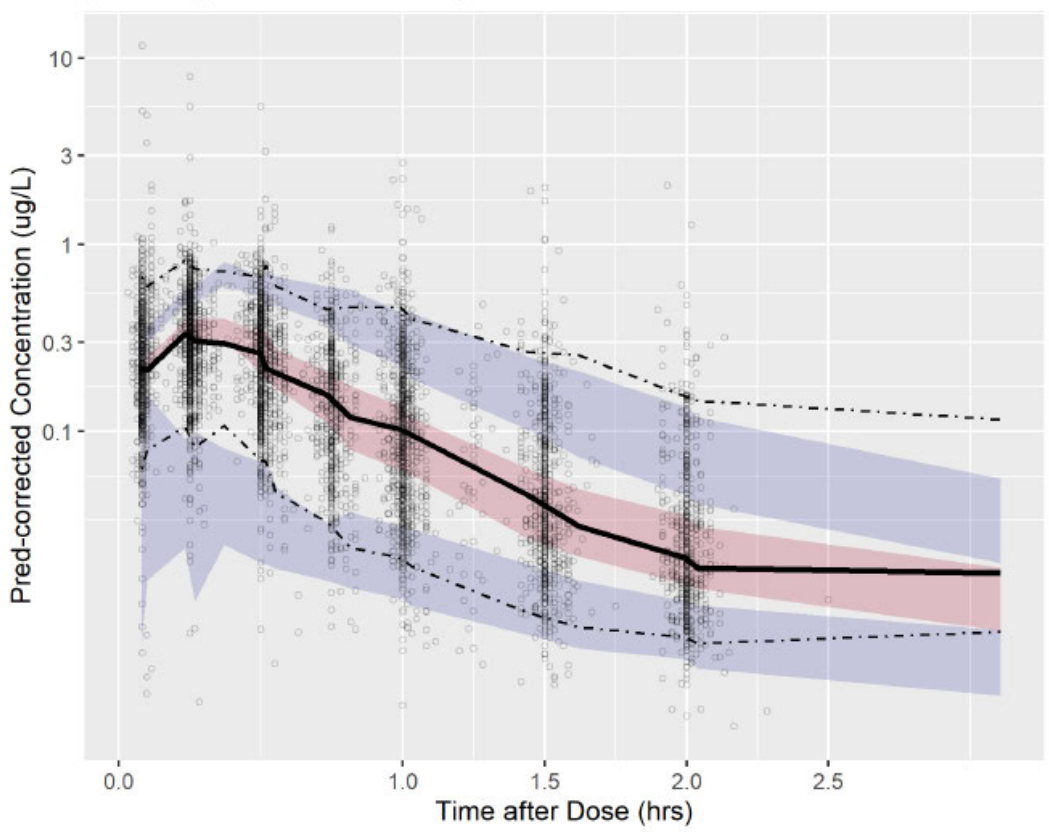
Figure 22. Goodness-of-Fit Plots From the Final PK model



hr –hour Note – Study 111-202/205 are open blue symbols, study 111-206 are open red symbols, Study 111-301/302 are filled green symbols

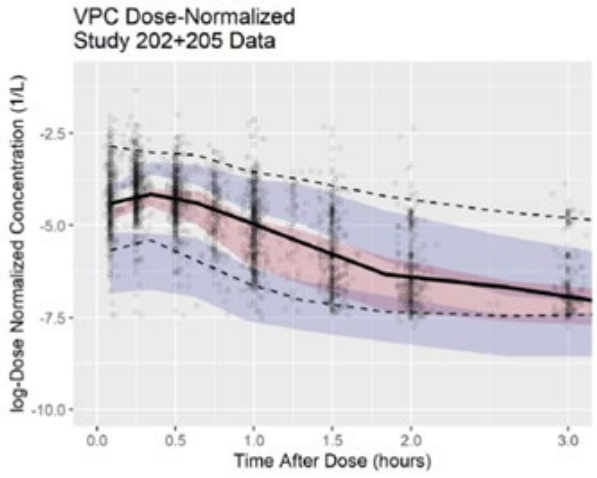
Source: Applicant's Population PK Report, Figure 13, page 50.
Abbreviation: PK, pharmacokinetic

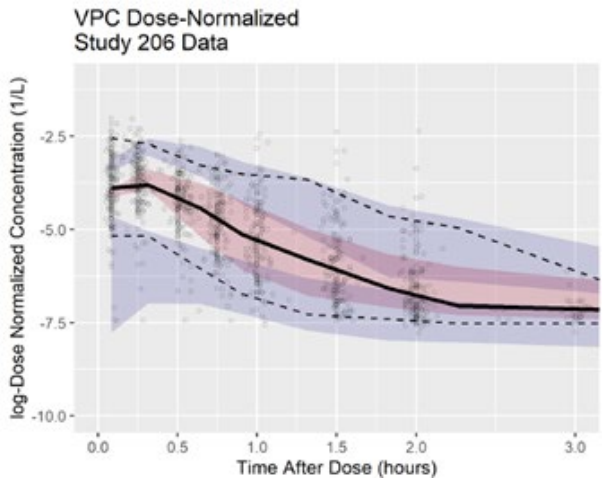
Figure 23. Prediction-Corrected Visual Predictive Check for Final Model, Stratified by Study

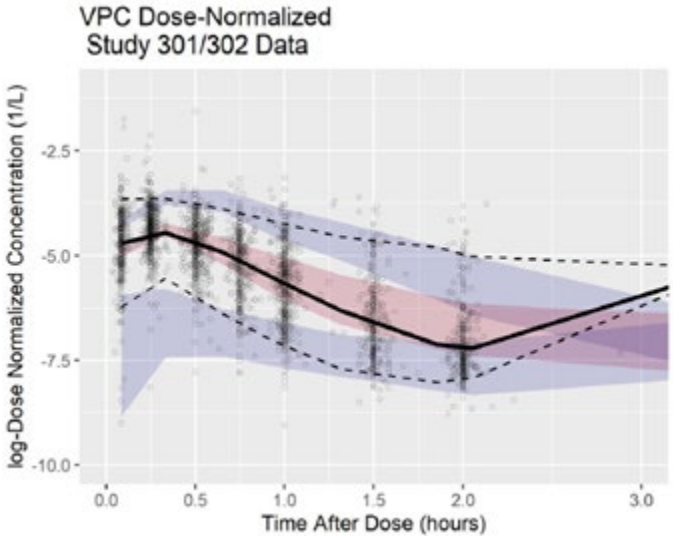


Source: pcVPC_v2.txt, pcVPC_dose-normalized_conc.vs.TAD.updated.png

Note: Black open circles are the observed data; solid black line is the median of the observed data; black dot-dashed lines are the upper and lower 90th percentiles of the observed data, the red ribbon is the 90% confidence interval of the median of the simulated data, blue shaded ribbons are the 90% confidence intervals of the upper and lower 90th percentiles associated with the simulated data.







Source: Applicant's Population PK Report, Figure 34, page 72 and Figure 28-30, pages 66-68.
Note: Vosoritide concentrations are log-transformed
Abbreviations: hrs, hours; VPC, visual predict check

Reviewer's Comments and Assessment of the Population PK model:

- The GOF plots are acceptable indicating that the Applicant's PK model is able to capture and describe the observed vosoritide concentrations in patients with ACH from 5 studies. The pcVPC and dose-normalized VPC by study also shows that the PK model the median PK profile and the PK variability in vosoritide concentrations over-time, with slight underestimation of the C_{max} at the 5 and 95th percentiles.
- The typical PK parameter values and covariate effects from the final model (Table 45) were estimated with good precision (RSE ≤ 30%). The interindividual random error (eta-) shrinkage for CL/F was below 20% and acceptable for reliable for the graphical assessment of covariate effects on CL/F. The eta-shrinkage for the remaining parameters (V/F and CP) was higher than 30%. However, for these PK parameters no covariates were included, other than the physiological body weight effect on V/F. The residual error (Epsilon) shrinkage was low (< 10%), indicating the informativeness of the goodness of fit (GOF) plots to diagnose structural and residual error model misspecifications.
- In the Applicant's PK model, the change point (CP) parameter of 0.26 hours, estimating the time of change of Ka from a fast (Ka1) to a slower (ka2) absorption rate constant, was model as a normally distributed parameter with a truncated typical value to 0.25 hours. The FDA's reviewer re-estimated the PK parameters of the Applicant's model with CP modeled as a log-normally distributed parameter using the following expression (CP=EXP(MU_5+ETA(5)), where MU_5=typical value of CP). The reparametrized PK model resulted in a statistically significant improvement in the objective function value (OFV), with a decrease in OFV of 130 points. However, the estimated typical value for CP 0.2 hours was comparable to the Applicant's PK model estimation (Table 46).
- In addition, the reviewer's updated PK model estimated a correlation of 58% between the random-effects terms of CL/F and V/F. The inclusion of a correlation decreased the OFV by 23 points (1df, $p < 0.001$). Accounting for the correlation in random effects between PK parameters is critical for PK model-based simulations, as it avoids outliers and maintains a

plausible relationship between CL/F and V/F values when sampling from a multivariate normal distribution.

- Table 46 summarizes the parameter estimates from the reviewer's updated PK model. The estimated PK model parameters from the Applicant's PK model and the reviewer's updated PK model were comparable, except CL/F and V/F were within the lower range for the reviewer's updated model. The GOF plots from both models were comparable.

Table 46. Parameter Estimates From the Applicant's and Reviewer's Final PK Model

	Applicant's Model	Reviewer's Updated Final
Parameter (Units)	**Population Estimates (%RSE)**	**Population Estimate (%RSE)**
PK parameter		
CL/F (L/h)	31.5 (1.7)	26.31 (1.8)
Vc/F (L)	13.60 (2.7)	12.06 (2.5)
Ka1 (1/h)	1.55 (19.2)	1.45 (18.6)
Ka2 (1/h)	0.03 (2.5)	0.02 (2.1)
Change point (h)	0.26 (7.3)	0.19 (2.5)
Covariates		
Weight on CL/F (standardized to 20 kg): power exponent	0.53 (11.4)	0.387 (16.1)
Weight on Vc/F (standardized to 20 kg): power exponent	1.08 (5.4)	0.874 (7.4)
Time on bioavailability (F)	0.24 (6.3)	0.208 (7.3)
Solution concentration (0.2 mg/mL) on F	1.64 (13.2)	1.59 (14.5)
Inter-individual variability (%CV)		
CL/F	28.2% (8.2)	39.9% (6.5)
Vc/F	20.9% (13.6)	31.2% (9.5)
Correlation between CL/F and Vc/F variances	NA	58.2%
CL/F by Study	22.2% (47.9)	20.2% (45.5)
Vc/F by Study	3.30% (57.7)	2.5% (60.)
Change Point	22.4% FIXED	22.4% FIXED
Residual error (SD)		
Exponential (log-additive) error (assay 1: ELISA)	0.669 (1.6)	0.675 (1.6)
Exponential (log-additive) error (assay 2: ECL)	0.667 (1.2)	0.668 (1.2)

Source: FDA Reviewer
Abbreviations: CL/F, apparent clearance; Vc/F, apparent central volume of distribution, CV, coefficient of variation; ECL, electrochemiluminescence; ELISA, enzyme-linked immunoassay; F, bioavailability; h, hour; Ka, absorption rate constant; NA, not applicable; RSE, relative standard error; SD, standard deviation

14.5.2. Applicant's PK simulations and Exposure-Efficacy Analyses

14.5.2.1. Population PK Simulations for the Weight-Band Dosing Recommendations

The objective of the PK simulations was to provide dosing recommendations for ACH patients weighing 3 to 9 kg, using the updated vosoritide PK model. The PK model was used to simulate the expected concentration time profiles with dense sampling over the first 5 hrs, using Monte-Carlo simulations (500 replicates) in subject 3 to 90 kg. The simulated individual predicted concentrations (IPRED) were then used to derive exposure metrics ($AUC_{[0\text{-}5h]}$ and C_{max}).

Simulated individuals weighing 3 to 9 kg were given dosages of approximately 30µg/kg. The proposed dose for patients weighing < 10 kg is consistent with study 111-206, in which patients aged <2 years (weight range in the study: 5 to 11 kg) received 30µg/kg of vosoritide.

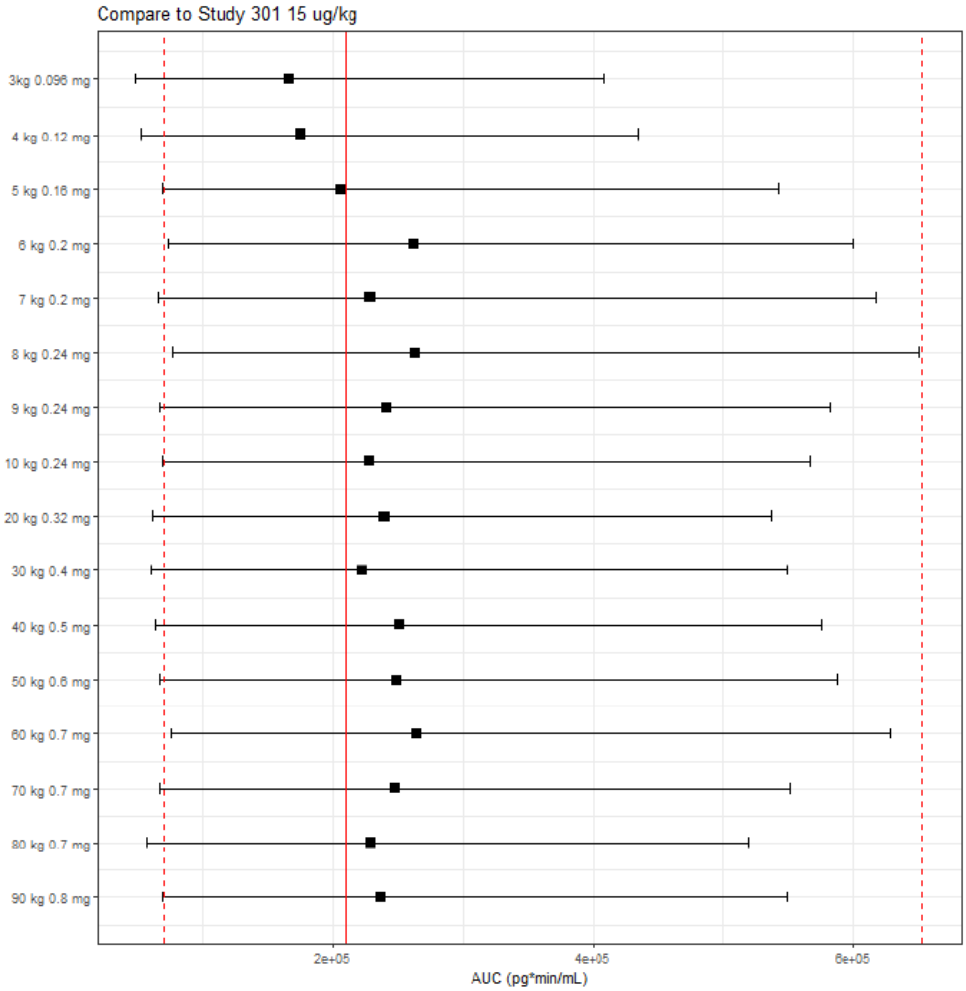
At 30µg/kg, patients weighing 8 and 9 kg should receive 0.24 and 0.27 mg, respectively. However, in the proposed dosing regimen, it was simplified by combining 8 and 9 kg with 10-11 kg for a total dose of 0.24 mg. Simulated individuals weighing 10 to 90 kg were given the dosing regimen that has been already approved.

The median, 5th and 95th percentiles of exposure metrics from simulation were compared with the same exposure metrics derived from the observed data in study 111-301, which evaluated a 15µg/kg daily dose, in ACH patients older than 5 years old (weight range: 14 to 53 kg). Figure 24 and Figure 25 show the distribution of vosoritide AUC[0-5h] and C_{max}, respectively.

According to the Applicant, the results show that the model-predicted 90% prediction interval (5th and 95th percentiles) of the simulated AUC[0-5h] generally fall within the 5th to 95th percentile range of the observed AUC[0-5h] in study 111-301. The median simulated AUC[0-5h] values are within the range and consistent with the observed AUC[0-5h] at 15µg/kg in Study 111-301.

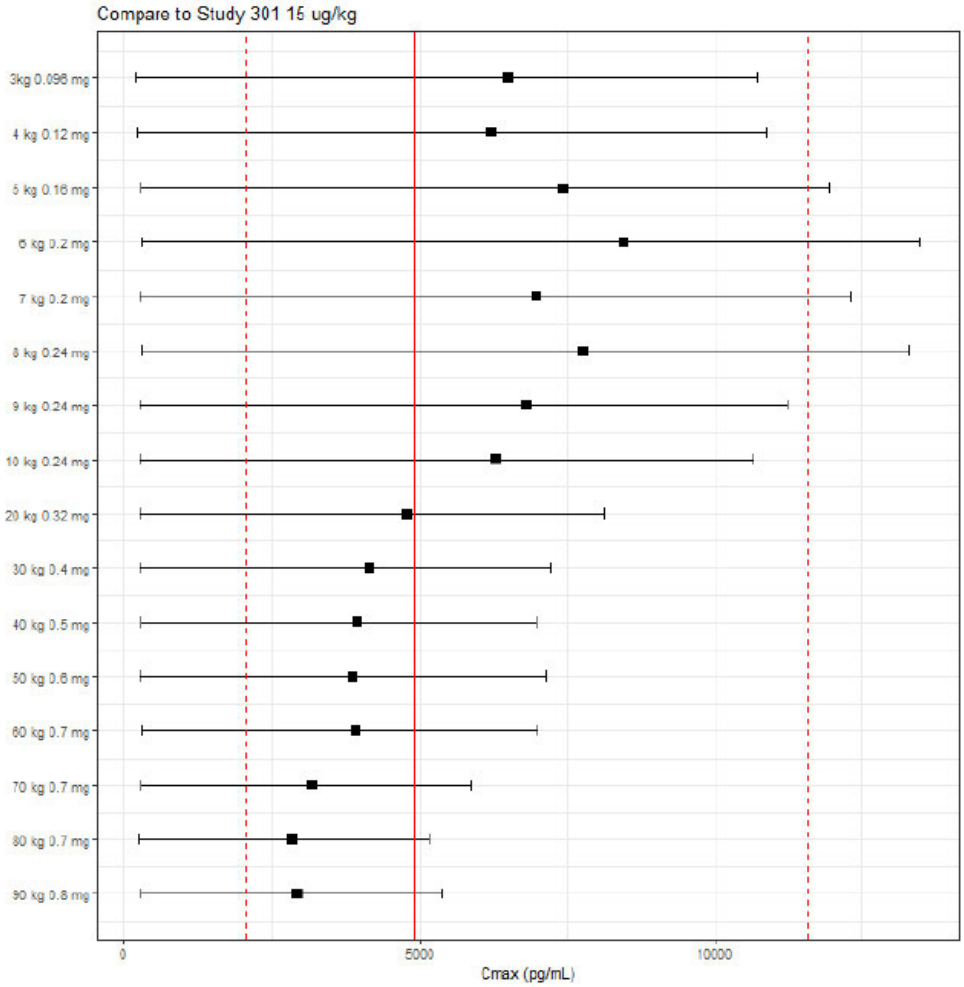
Median model-predicted C_{max} for subjects weighing <10 kg are slightly higher than that of the observed C_{max} in 111-301. However, the data in study 111-206 did not show safety concern in subjects <2 yrs old, receiving a dose of 30µg/kg. The 5th and 95th percentiles of the simulated C_{max} were lower than the 5th and 95th percentiles of the observed C_{max}, likely due to the PK model under-estimating C_{max} as shown in the VPC plots (Figure 23).

Figure 24. Simulated Vosoritide $AUC_{0\text{-}5h}$ for the Proposed Updated Weight-Band Based Dosing in Subject 3 to 9 kg



Source: Applicant's Population PK Simulation Report, Figure 1, page 16.
Note: the 5th percentile, median and 95th percentile of the observed $AUC_{0\text{-}t}$ in study 111-301 are 70500, 210000 and 653000 pg.min/mL, respectively.
Note: Black squares represent the median exposure metrics for each weight, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of exposure. The red dashed lines represent the lower 5th and upper 95th percentiles of observed metrics from the comparison study. The red solid line represents the median of observed metrics from the comparison study.
Abbreviations: AUC, area under the concentration-time curve; PK, pharmacokinetic

Figure 25. Simulated Vosoritide C_{max} for the Proposed Updated Weight-Band Based Dosing in Subject 3 to 9 kg



Source: Applicant's Population PK Simulation Report, Figure 2, page 17.
Note: the 5th percentile, median and 95th percentile of the observed C_{max} in study 111-301 are 2060, 4910 and 11600 pg/mL, respectively.
Note: Black squares represent the median exposure metrics for each weight, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of exposure. The red dashed lines represent the lower 5th and upper 95th percentiles of observed metrics from the comparison study. The red solid line represents the median of observed metrics from the comparison study.
Abbreviations: C_{max}, maximum plasma concentration; PK, pharmacokinetic

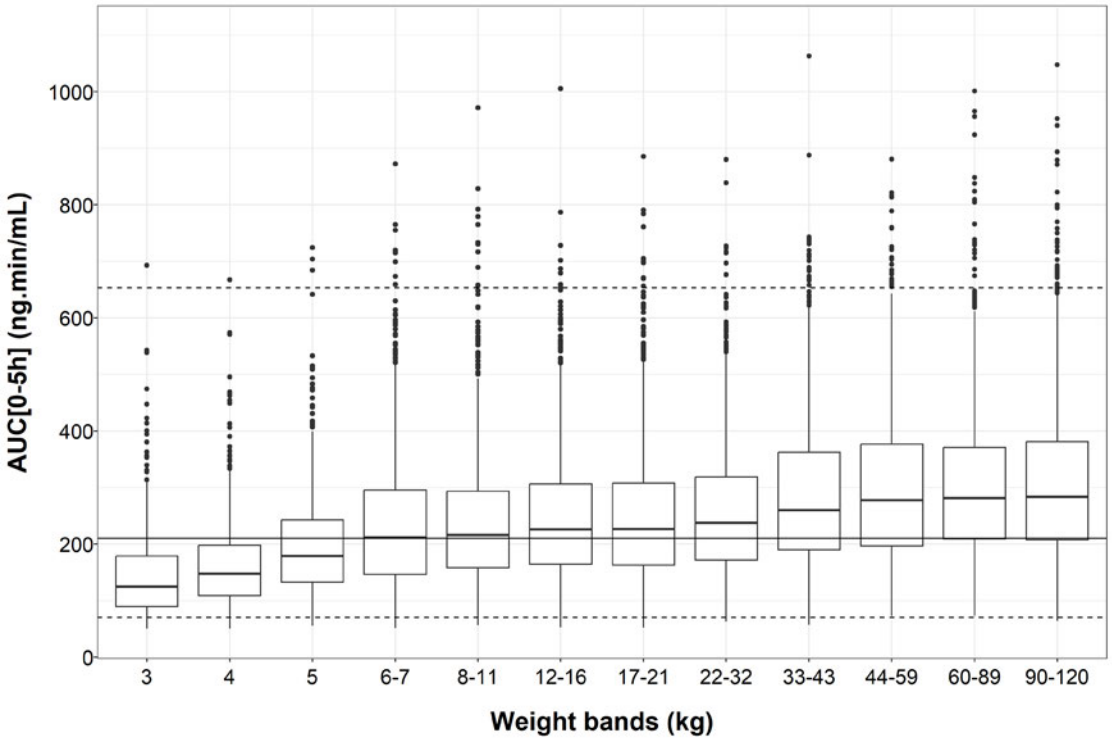
Reviewer's Assessment of PK Simulations and Updated Weight-Band Dosing

- The reviewer's independent simulations using the updated PK model provided comparable results to the Applicant's simulations for the predicted AUC[0-5h] and C_{max} in different weight groups, receiving the proposed vosoritide dosage.
- Trial 111-206 did not enroll ACH patients with a body weight less than 5 kg. In subjects 3 and 4 kg and receiving a dose of 30µg/kg, the range of model-predicted AUC[0-5h] and C_{max} are within the range of exposure metrics observed and predicted in subjects weighing 5 kg and above. However, the predicted median AUC[0-5h] in subjects 3 and 4 kg are within the lower range of the median AUC[0-5h] predicted in heavier subjects (Figure 26 and Figure 27).
- PK simulations using re-estimated PK parameters from a PK model with fixed allometric exponents of 0.75 and 1 on CL/F and V/F (instead of the estimated exponents) predicted

a median and range of exposure in subjects 3 and 4 kg comparable to those observed in heavier patients.

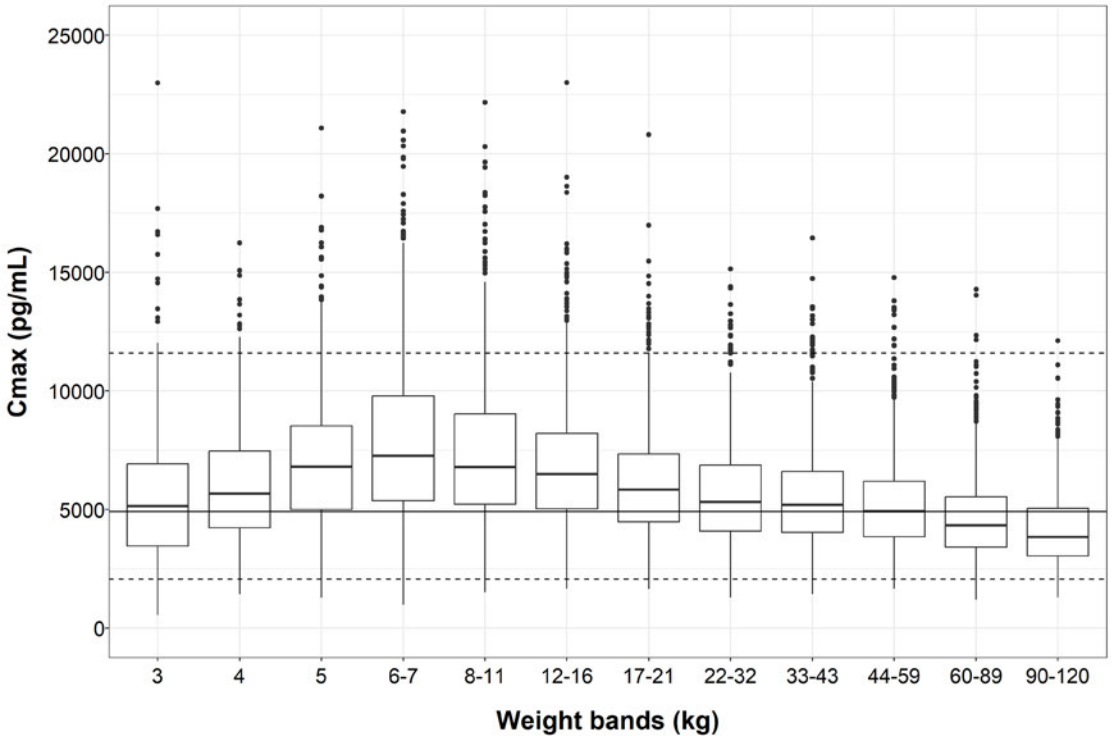
- Given the lack of exposure-efficacy relationship, including in patients older than 2 years old with a body weight higher or equal to 5 kg and an exposure lower than 200ng.min/mL, the proposed vosoritide dose in subjects 3 and 4 kg seems acceptable.

Figure 26. Simulated Vosoritide AUC Using the Reviewer's Updated PK Model



Source: FDA Reviewer
Note: the horizontal dashed and solid lines are 5th percentile, median and 95th percentile of the observed AUC_{0-t} under a dose of 15µg/kg in study 111-301 of 70500, 210000 and 653000 pg.min/mL, respectively.
Abbreviations: AUC, area under the concentration-time curve; PK, pharmacokinetic

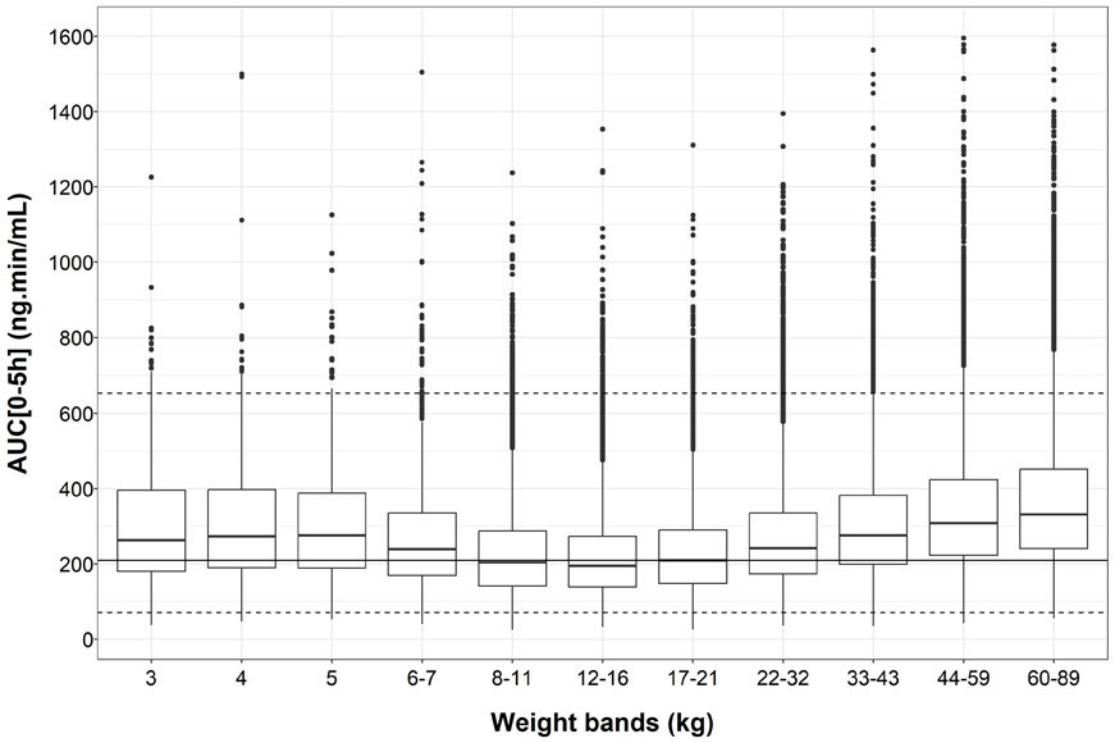
Figure 27. Simulated Vosoritide C_{max} Using the Reviewer's Updated PK Model



Source: FDA Reviewer.
Note: the horizontal dashed and solid lines are 5th percentile, median and 95th percentile of the observed C_{max} under a dose of 15μg/kg in study 111-301 of 2060, 4910 and 11600 pg/mL, respectively.
Abbreviations: C_{max}, maximum plasma concentration; PK, pharmacokinetic

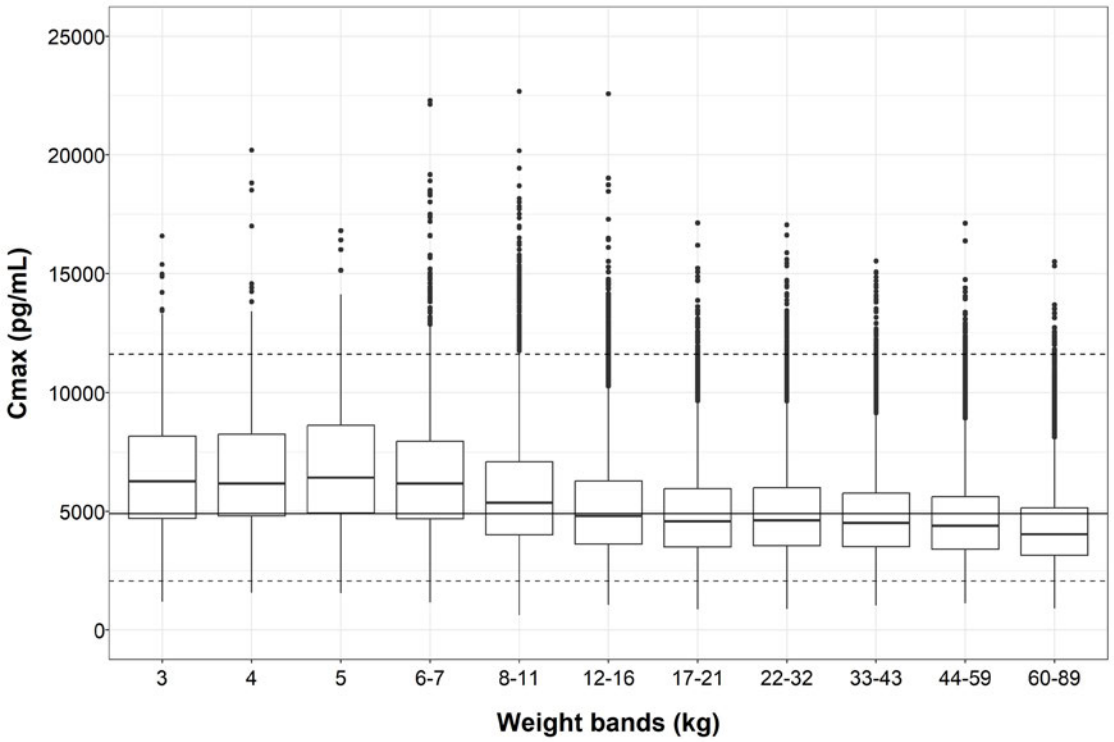
- The extent of elimination of vosoritide by glomerular filtration has not been studied and is unknown, and the Applicant's PK model used for dose extrapolation did not include a renal maturation function to describe the maturation of renal filtration in younger patients < 2 years. A sensitivity analysis was performed to account for the maturation in renal filtration with age in the PK model and to predict vosoritide exposure in infants weighing 3 or 4 kg, with the assumption that vosoritide is eliminated by kidneys.
- The PK model was updated by including a renal maturation function as a covariate on CL/F and fixing the parameters describing the renal maturation (i.e., postmenstrual age associated with 50% maturation of renal filtration of 47.7 weeks and hill coefficient of 3.4) to the literature values (Rhodin et al. 2009). All patients were assumed to be born at full term in the calculation of postmenstrual age. The reviewer's updated PK model with renal function maturation had a 17-point increase in OFV compared with the model without renal function maturation. The PK parameters were comparable between both model except for a lower estimated allometric scaling exponent of 0.236 on CL/F for the model with the renal maturation function. The re-estimated parameters from the updated PK model were used to perform PK simulations using demographic data (age and weight) from the CDC growth chart.
- The sensitivity analysis shows that the proposed dose is expected to remain acceptable, with a predicted AUC[0-5h] and C_{max} in subjects weighing 3 and 4 kg within the range of those values observed and predicted in heavier and older subjects (Figure 28 and Figure 29). The sensitivity analysis evaluated the highest expected exposure in case the vosoritide is completely eliminated by kidneys.

Figure 28. Simulated Vosoritide AUC Using the Reviewer's Updated PK Model With Renal Maturation Function



Source: FDA Reviewer.
Note: the horizontal dashed and solid lines are 5th percentile, median and 95th percentile of the observed AUC_{0-t} under a dose of 15μg/kg in study 111-301 of 70500, 210000 and 653000 pg.min/mL, respectively.
Abbreviations: AUC, area under the concentration-time curve; PK, pharmacokinetic

Figure 29. Simulated Vosoritide C_{max} Using the Reviewer's Updated PK Model With Renal Maturation Function



Source: FDA Reviewer.
Note: the horizontal dashed and solid lines are 5th percentile, median and 95th percentile of the observed C_{max} under a dose of 15μg/kg in study 111-301 of 2060, 4910 and 11600 pg/mL, respectively.
Abbreviations: C_{max}, maximum plasma concentration; PK, pharmacokinetic

14.5.2.2. Exposure-Efficacy Analysis

Exposure-response analyses were conducted for the following efficacy endpoints:

- Change in height Z-score from baseline to Week 52 and
- Change in annualized growth velocity (AGV) from baseline to Week 52).

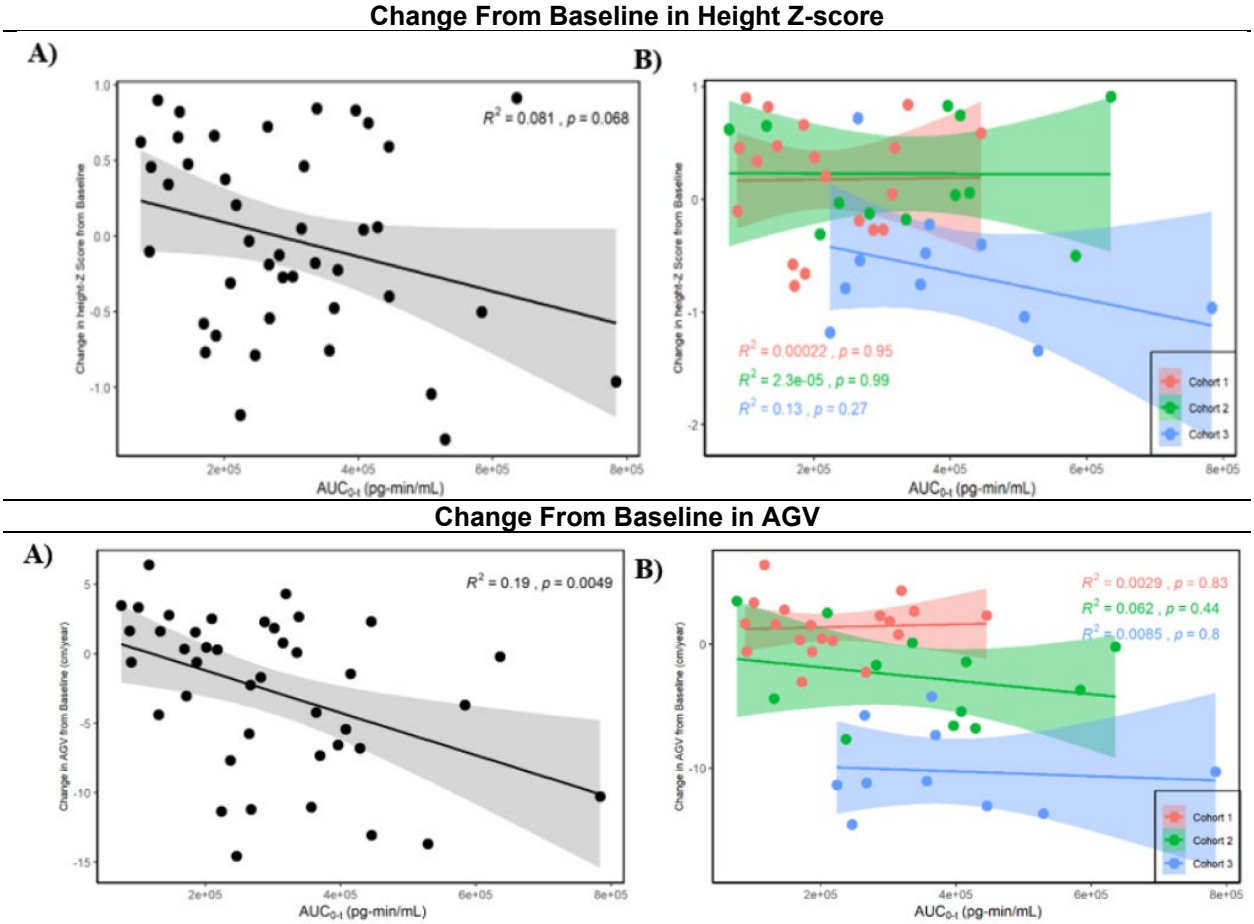
Exposure-response relationships were evaluated for all the subjects together as well as for subjects separated by cohorts, using a linear regression. The exposure metric used in the analyses was the individual mean area under the plasma concentration-time curve from time 0 to last measurable vosoritide concentration (AUC[0-t]), calculated for each subject on available PK data from all visit days. The mean AUC[0-t] value was used as representative measures of a subject's exposure during the entire study, as supported by the short half-life (of about 20 minutes) and lack of accumulation of vosoritide with a daily dosing interval.

Figure 30 shows the exposure-response relationship for the change from baseline in height Z-score and AGV at Week 52. The negative correlations observed in the analyses not adjusted by Cohorts (Figure 30A) are likely due to the confounding effects of differences in the underlying change in growth by age as well as dose adjustment by age. In fact, Cohort 3 (the youngest cohort with age < 6-month-old) had a greater change in height-Z score and AGV than the other cohorts, due to the underlying rapid decline in growth velocity in children during their early development, which makes the exposure analysis for changes in height-Z score and AGV

challenging. In addition, Cohort 3 had a higher exposure due to the highest studied dose of 30µg/kg.

To reduce these confounding effects, the Applicant analyzed the exposure-response by cohorts as shown in Figure 30 B. No apparent and statistically significant correlation was observed between individual exposure and change from baseline in height-Z score or AGV at Week 52 within the different cohorts.

Figure 30. Change From Baseline in Height Z-Score at AGV at Week 52 by Mean AUC_{0-t} in Trial 111-206

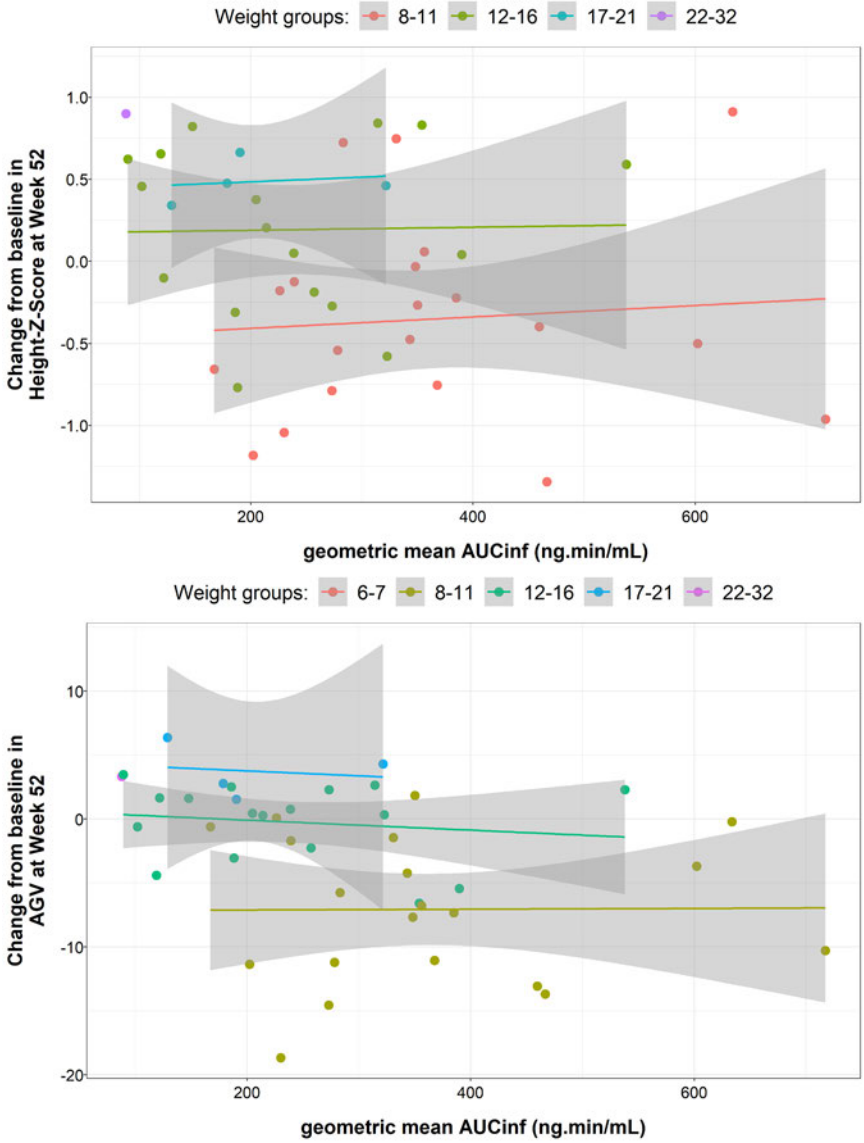


Source: Adapted from Applicant's Clinical Pharmacology Report, Figure 9.3.2.1 and Figure 9.3.2.2, pages 47-48 and, Figure 9.3.2.3 and Figure 9.3.2.4, page 49.
Note: A) Left panel: pooled data from 111-206. B) Right panel: data from 111-206 by Cohort.
Cohort 1: 2 to 5 years old dosed at 15µg/kg, Cohort 2: ≥ 6 to < 24 months old dosed at 30µg/kg, Cohort: 3 to <6 months old dosed at 30µg/kg. Solid lines are the fits through the data and the shaded region the 95% CI.
Abbreviations: AGV, annualized growth velocity (cm/year); AUC_{0-t}, area under the plasma concentration-time curve from 0 to the time of last measurable concentration; R, Pearson's correlation coefficient

Reviewer's Assessment of the Exposure-Response Analysis

The reviewer's independent analysis adjusting for either cohorts (not shown) or body weight groups (Figure 31) did not find a significant relationship between the change from baseline in height-Z score or AGV at Week 52 and the mean AUC_{inf} estimated by NCA for either the observed data (Figure 31) or the model-predicted data (not shown).

Figure 31. Change From Baseline in Height Z-Score at AGV at Week 52 by Mean AUC_{inf} in Trial 111-206



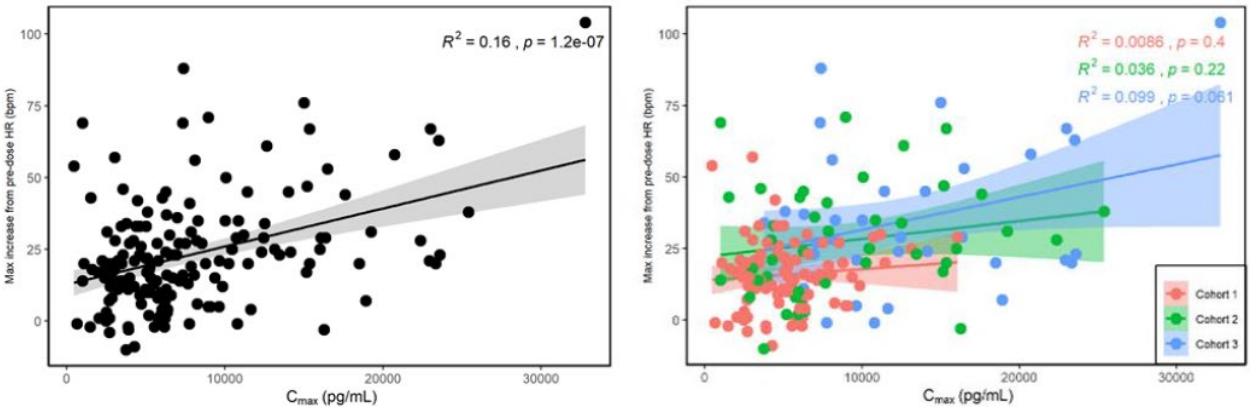
Source: FDA Reviewer.
Note: Solid lines are the fits through the data and the shaded regions are the 95% CI. The data were fit using a linear regression with body weight groups (kg) as an interaction term. At Week 52, the data contained only one subject with body weight 6-7 kg and 22-32 kg and no subject with body weight of 5 kg.
Abbreviations: AGV, annualized growth velocity; AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinite time

14.5.2.3. Exposure-Change in Heart Rate Analysis

The Applicant conducted Exposure-safety analyses for safety endpoints such as maximum change in heart rate (HR) for ACH subjects treated with vosoritide in study 111-206. A weak positive correlation between the maximum increase from each pre-dose in HR and vosoritide C_{max}, was found statistically significant (p value= 0.061) in Cohort 3 only (left panel Figure 32). However, the changes in HR were transient and self-limiting, not associated with an adverse clinical outcome. Therefore, these changes were not considered to be clinically meaningful.

According to the Applicant, no adverse events of tachycardia or events related to change in HR were reported across all cohorts.

Figure 32. Visit-Matched Maximum Change in HR vs. Vosoritide C_{max}, Trial 111-206



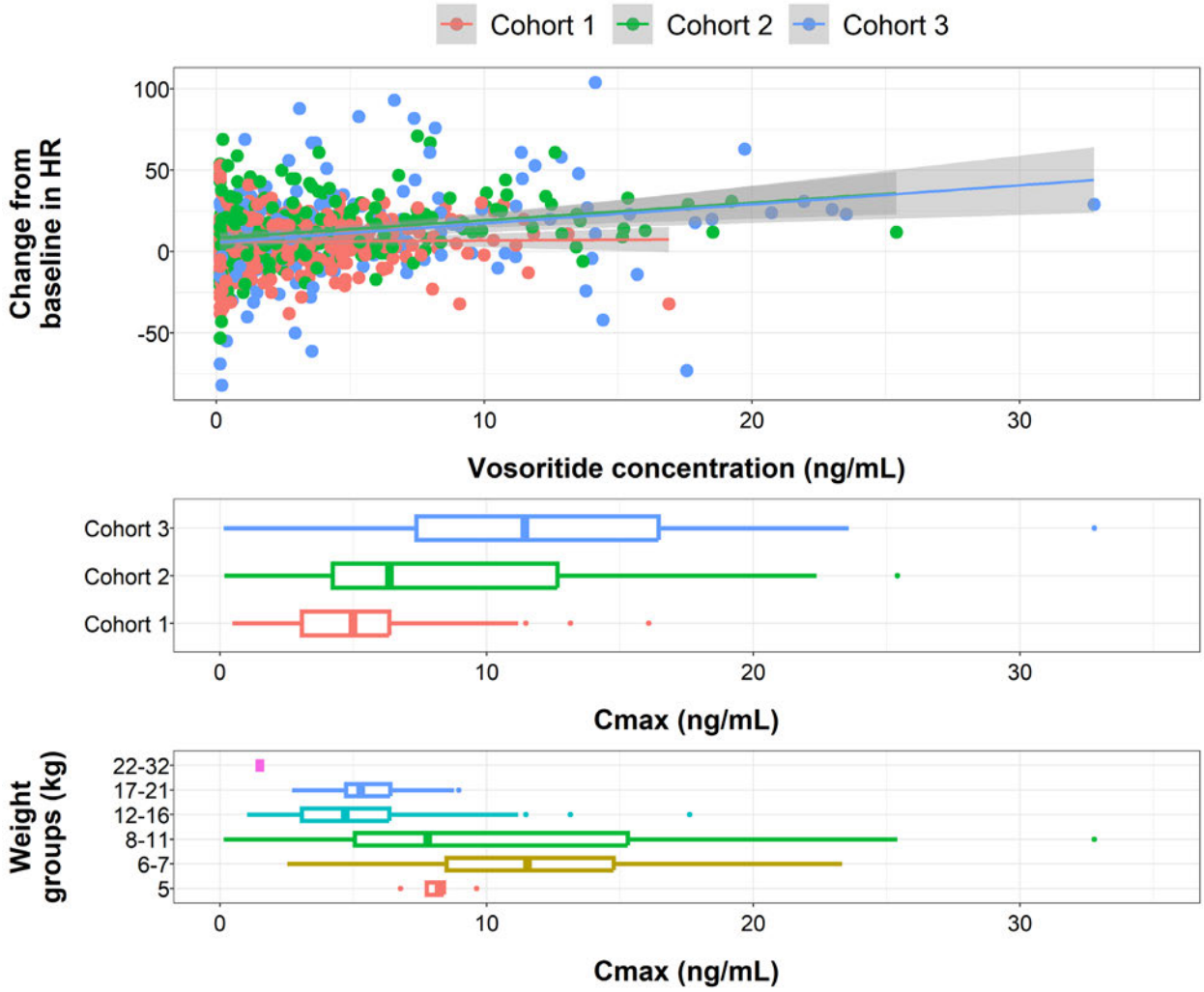
Source: Adapted from Applicant's Summary of Clinical Pharmacology, Figure 2.7.2.3.3.1.3.1, pages 47.
Note: Left panel: pooled data from 111-206. Right panel: data from 111-206 by Cohort.
Cohort 1: 2 to 5 years old dosed at 15µg/kg, Cohort 2: ≥ 6 to < 24 months old dosed at 30µg/kg, Cohort 3: <6 months old dosed at 30µg/kg.
Scatter plots of vosoritide C_{max} in plasma and maximum increase from pre-dose HR. Solid lines represent the linear fits through the data and the shaded regions represent the 95% confidence interval.
Abbreviations: bpm, beats per minute; C_{max}, maximum observed plasma concentration; HR, heart rate; max, maximum; min, minutes; R, Pearson's correlation coefficient

Reviewer's Assessment of the Exposure-Change in Heart Rate Analysis

The Applicant's analysis investigated the relationship between vosoritide Cmax and the maximum change in HR from pre-dose. Each pre-dose HR was considered as a baseline due to the very short half-life of the dug (~20 minutes) compared to the dosing interval.

The reviewer's independent analysis assessed the relationship between all vosoritide concentrations and the time-matched change in HR from pre-dose (i.e., not limited to the maximum increase from pre-dose). A linear mixed-effect model with cohorts as a covariate on the slope was used to describe the relationship (Figure 33, upper panel). A positive by shallow significant slope was estimated for the Cohort 2 and Cohort 3 (< 2 years old), with a slope of 1.19 for Cohort 2 (p value<0.05) and 1.08 for Cohort 3 (p value <0.05). The intercept of 6.3 bpm was statistically different from 0 (p value <0.05), suggesting that the relationship might be better described with an Emax model at the lowest concentrations. However, this linear mixed-effect model is reasonable to describe the increase in HR around Cmax values. According to this model, the mean change from baseline in HR estimated to be around 19 bpm and 32 bpm at the median Cmax (11.4 ng/mL) and 95th percentile of Cmax (23.5 ng/mL) observed in Cohort 3.

Figure 33. Change From Pre-Dose in HR vs. Vosoritide Concentrations (Upper Panel) and Distribution of Vosoritide C_{max} by Cohort and Weight Groups (Lower Panels)



Source: FDA Reviewer.
Note: In the upper panel, the solid lines are the model-predicted mean change in HR by cohort and the shaded areas represent the 95% CI around the model-predicted mean change in HR.
Abbreviations: CI, confidence interval; C_{max}, maximum plasma concentration; HR, heart rate

14.6. Pharmacogenetics

Not applicable

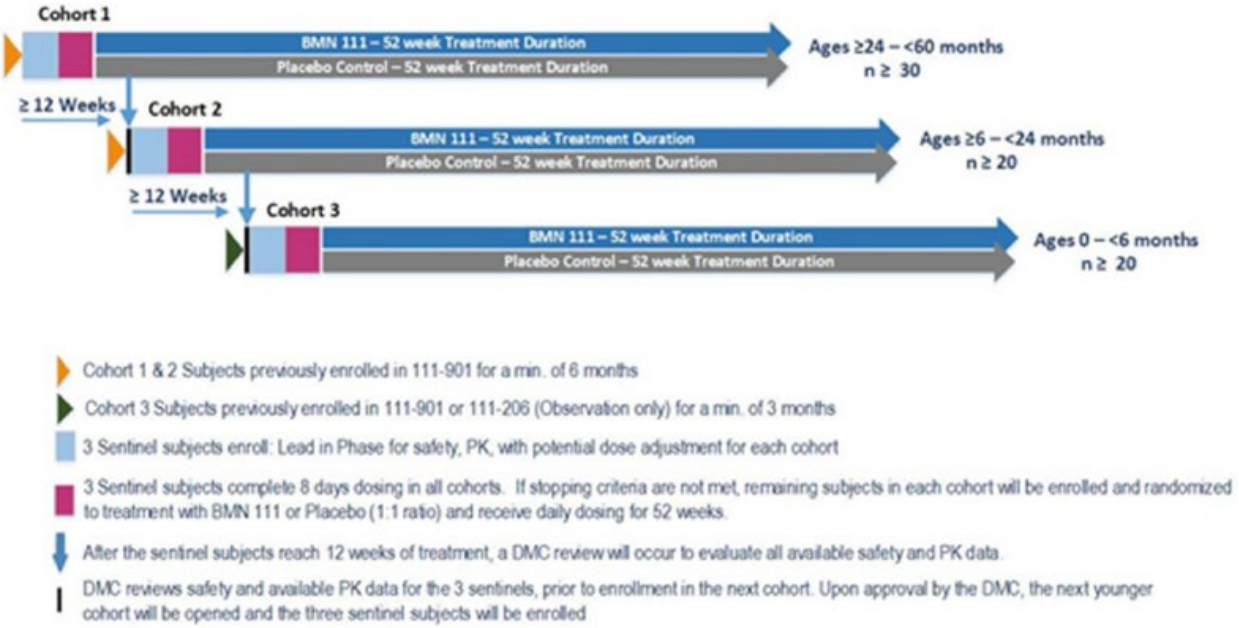
15. Trial Design

15.1. Trial 111-206

Study Design

Subjects in Cohorts 1 (aged ≥ 24 to < 60 months) and 2 (aged ≥ 6 to < 24 months) were further stratified by age into ≥ 24 to < 36 months and ≥ 36 months to < 60 months (Cohort 1) and (≥ 6 months to < 15 months and ≥ 15 months to < 24 months (Cohort 2).

Figure 34. Trial 111-206 Design



Source: Figure 8.1.1, CSR 111-206
Abbreviations: BMN, vosoritide; DMC, data monitoring committee; n, number of subjects; PK, pharmacokinetic

After randomization, the subjects were required to attend clinic for visits on Days 1, 2, 3, 8 and Weks 3, 6, 13, 20, 26, 39, and 52.

Secondary and Exploratory Efficacy Endpoints

Other secondary endpoints included evaluation of change from baseline to Week 52 of: a) Health-Related Quality of Life (HRQoL), developmental status, and functional independence as measured by age-specific QoL and functional independence questionnaires/QoL status: Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III]), Activity of Daily Living Functional Independence Measure (Wee-FIM), Infant Toddler Quality of Life Questionnaire (ITQOL), Child Behavior Checklist (CBCL); b) bone morphology and quality as X-ray and dual X-ray absorptiometry (DXA); c) sleep study to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation pulse rate, and airflow during overnight monitoring and Apnea/Hypopnea Index (AHI); d) skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions as measured by Magnetic resonance imaging (MRI); e) other growth parameters and body proportions, such as:

Upper arm length to lower arm (forearm) length ratio; Upper leg length (thigh) to knee to heel length ratio; Upper leg length (thigh) to tibial length ratio; Arm span to standing height ratio.

Exploratory endpoints include evaluation of genomics including, but not limited to, NPR-2, BRAF, and other genes associated with C-type natriuretic peptide (CNP) signaling, as well as physical and phenotypic changes with clinical photography of the full body, face, spine, and extremities.

Eligibility Criteria

Key Inclusion Criteria

- ACH, diagnosed by clinical assessment and confirmed by genetic testing.
- Age 0 to < 60 months, at study entry (Day 1)
- At least a 6-month period of pretreatment growth assessment in observational Study 111-901 (Cohorts 1 and 2); At least 3 months of observation prior to treatment, either by prior enrollment in observational Study 111-901 or by enrollment in Trial 111-206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment (Cohort 3).

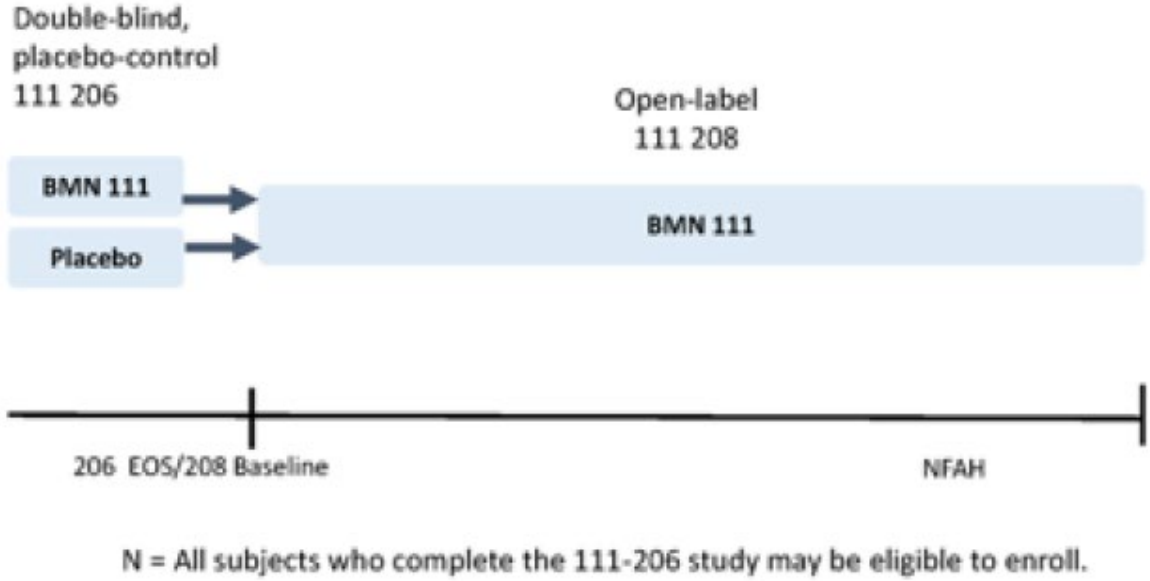
Key Exclusion Criteria

- Hypochondroplasia or short-stature condition other than ACH (e.g., trisomy 21 and pseudochondroplasia).
- Weight <5.0 kg (Cohort 1 and 2) or < 4.0 kg (Cohort 3).
- Conditions that might affect growth (e.g., hypothyroidism or hyperthyroidism, insulin-requiring diabetes mellitus, autoimmune inflammatory diseases, inflammatory bowel disease, renal insufficiency, chronic anemia, cardiac or vascular diseases, vitamin D deficiency, severe untreated sleep apnea or new initiation of sleep apnea treatment within 2 months prior to screening).
- Treatment with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (>3 months) at any time. Regular long-term treatment (> 1 month) with oral corticosteroids in the 12 months prior to screening.
- Baseline SBP below age and gender specified normal range or recurrent symptomatic hypotension or recurrent symptomatic orthostatic hypotension.
- Clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening electrocardiogram (ECG).
- 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 that may impair or enhance compensatory tachycardia, drugs known to alter renal function that is expected to continue for the duration of the study.
- Evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of screening as informed by the following assessments: a) physical exam (e.g., neurologic findings of clonus, opisthotonos, exaggerated reflexes, and dilated facial veins); b) polysomnography (e.g., severe central sleep apnea); c) MRI indicating presence of severe CMC or spinal cord damage.

- Unstable medical condition likely to require surgical intervention during the study, or planned spine or long-bone surgery (i.e., surgery involving significant disruption of bone cortex) during the study period.
- Had cervicomedullary decompression surgery (Cohorts 2 and 3 only), spine or long bone surgery (i.e., surgery involving disruption of bone cortex) or bone-related surgery with chronic complications.
- Limb-lengthening surgery or planned to have limb-lengthening surgery during the study period. Fracture of the long bones or spine within 6 months prior to screening.
- Hip surgery or severe hip dysplasia, or clinically significant hip injury in the 30 days prior to screening. Clinically significant abnormal findings on baseline clinical hip exam or imaging assessments. History of history of slipped capital femoral epiphysis or avascular necrosis of the femoral head.
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin greater than upper limit of normal (ULN) at screening.
- Current malignancy, history of malignancy, or currently under work-up for suspected malignancy.

15.2. Trial 111-208

Figure 35. Study Design, Trial 111-208



Source: Figure 8.1.1, Interim CSR, 111-208
Abbreviations: BMN, vosoritide; EOS, end-of-study; NFAH, near-final adult height

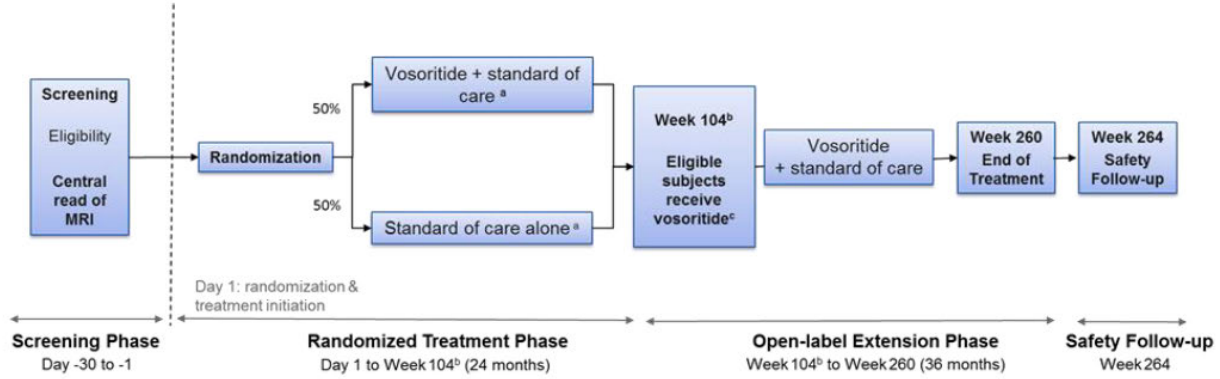
15.3. Trial 111-209

Study Design

This is an ongoing, randomized, controlled, open-label study to evaluate the safety of vosoritide treatment in infants and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery (see below details regarding enrollment criteria). This

study was not submitted to FDA for review prior to initiation. The study includes a screening phase (4 weeks), a Randomized Treatment Phase (104 weeks), an Open-label Extension phase (156 weeks) and a Safety follow up phase (4 weeks) (Figure 36).

Figure 36. Trial Design, Trial 111-209



MRI, magnetic resonance imaging.

[a]Once enrolled, participants will continue randomized treatment for 104 weeks.

[b]The last day of the randomized treatment phase will be the Week 104 visit.

[c]Participants randomized to standard of care alone in the Randomized Treatment Phase will be re-screened at Week 104 to confirm eligibility to receive vosorotide. If eligible, participants will receive in-clinic treatment on Day 1, Day 2, and Day 3 of Week 104.

Source: Figure 9.1.1, Interim CSR, 111-209

Enrolled subjects were stratified based on age (0 to ≤ 6 months, > 6 months to ≤ 12 months) and randomized 1:1 to either open-label, once daily, subcutaneous vosoritide combined with SoC (SoC + vosoritide) or SoC alone. Approximately 20 participants were planned to be enrolled at approximately 4 clinical centers worldwide. Subjects randomized to receive vosoritide were administered a dose of 15µg/kg/day vosoritide for subjects aged ≥ 24 months and 30µg/kg/day for subjects aged <24 months.

Efficacy endpoints

- Frequency of surgical cervicomedullary decompression over the course of the study.
- Change in clinical signs and symptoms (including, but not limited to, neurological assessment) every 6 months.
- Change in MRI measurement of area of foramen magnum and antero-posterior (AP) diameter, brain stem and spinal cord volume and ratio of area of spinal cord to foramen magnum every 6 months.
- Change in MRI measurement of area of spinal canal, transverse and AP diameter, spinal cord volume and ratio of area of spinal cord to spinal canal every 6 months.
- Change in developmental skills (Bayley-III) every 6 months.
- Change in status of sleep apnea including central and obstructive components (sleep study) every 6 months.
- Change in anthropometric measurements every 6 months.

For this abbreviated study report, the Applicant did not perform any analysis of efficacy endpoints. The protocol-specified efficacy endpoint of change in MRI measurement of brain stem/skull and spinal cord volume performed every 6 months was analyzed as a part of the safety endpoint.

Descriptive summaries will be provided by study arm and strata in which subjects are enrolled. Statistical comparisons will be considered descriptive.

Eligibility Criteria

Key Inclusion Criteria

- ACH, documented by genetic testing.
- Age 0 to ≤ 12 months, at study entry.
- Have evidence of CMC that "may" require surgical intervention determined by the Achondroplasia Foramen Magnum Score (AFMS):
    - Baseline MRI assessment showing at least one of the following findings:
        - Narrowing of the foramen magnum with loss of cerebrospinal fluid space surrounding the cord (AFMS 2).
        - Narrowing of the foramen magnum with flattening of the cervical cord without T2 signal change (AFMS 3).
- Note: AFMS is calculated based on MRI findings, and ranges from AFMS 0 to 4, as follows: AFMS 0 = normal foramen magnum; AFMS 1 = constitutional narrowing of the foramen magnum with preserved cerebrospinal fluid space (no cord distortion); AFMS 2 = narrowing of the foramen magnum with loss of CSF space surrounding the cord; AFMS 3 = loss of CSF space with cord compression; AFMS 4 = cord compression and signal changes (myelomalacia).
    - Supported by (but not required for eligibility) the following findings:
        - Baseline physical examination:
            - Gross or fine motor developmental milestone delay compared to expected for ACH (e.g., lifting head when lying on stomach).
            - Abnormal reflex (e.g., brisk reflex / abnormal clonus for age).
            - Weakness (e.g., opisthotonos).
        - Baseline sleep study:
            - Sleep apnea with a primary central component (e.g., not secondary to obstructive sleep apnea).

Key Exclusion Criteria

- Hypochondroplasia or short-stature condition other than ACH (e.g., trisomy 21 and pseudochondroplasia).
- Have CMC that either does not require surgical intervention (for example foramen magnum narrowing with preservation of the cerebrospinal fluid space) or does require immediate surgical intervention (for example narrowing of the foramen magnum with cervical cord signal change).

- Conditions that might affect growth (e.g., untreated congenital hypothyroidism or maternal history of hyperthyroidism, insulin-requiring neonatal diabetes mellitus, autoimmune inflammatory diseases, inflammatory bowel disease, autonomic neuropathy, renal insufficiency, chronic anemia, cardiac or vascular diseases).
- Clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening electrocardiogram (ECG).
- Current treatment with antihypertensive medications, or any medication that may compromise the safety or ability of the subject to participate in this clinical study.
    - Treatment with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (>3 months) at any time. Regular long-term treatment (> 1 month) with oral corticosteroids in the 12 months prior to screening.
    - Fracture of the long bones or spine within 6 months prior to Screening
    - Had cervicomedullary decompression surgery.
    - Hip surgery or severe hip dysplasia, or clinically significant hip injury in the 30 days prior to screening.
    - AST or ALT or total bilirubin greater than upper limit of normal (ULN) at screening.
    - Current malignancy, history of malignancy, or currently under work-up for suspected malignancy.

Subject stopping criteria for safety

- Any treatment-emergent adverse event (AE) of at least National Cancer Institute (NCI) – Common
- Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher assessed as
- related to vosoritide.
- Any two treatment-emergent National Cancer Institute–Common Terminology Criteria for Adverse Event (NCI-CTCAE) Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any NCI-CTCAE Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated).
- Clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of the QTc-F interval > 500 msec.

Study stopping criteria for safety

- Any two subjects have a treatment-emergent AE of Grade 3 or higher, assessed as related to vosoritide.
- Any two subjects have two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any two subjects have a Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated).
- Any two subjects have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F > 500 msec.

16. Efficacy

16.1. Trial 111-206

Table 47. Treatment Compliance, Trial 111-206, FAS

Treatment Compliance	Sentinel (N=11)	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)
Compliance with protocol-specified treatment regimen, %[a]				
n	11	32	32	43
Mean (SD)	99.34 (0.82)	98.69 (2.32)	98.76 (3.9)	98.85 (2.05)
Median	99.69	99.61	99.22	99.67
Min, max	97.7, 100	88.5, 101.0	90.9, 115.8	88.5, 101.0
Compliance with protocol-specified treatment regimen, %[a,b]				
≥80%	11 (100.0)	32 (100.0)	32(100.0)	43 (100.0)
≥90%	11 (100.0)	31 (96.9)	32 (100.0)	42 (97.7)
≥100%	3 (27.3)	8 (25.0)	7 (21.9)	11 (25.6)

Source: adapted from Table 10.3.1, CSR 111-206
[a] Calculated as: (total number of units taken / total number of units planned over actual duration of treatment) x 100.
[b] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator.
Abbreviations: FAS, full analysis set; max, maximum; min, minimum; SD, standard deviation

Table 48. Baseline Demographic Characteristics by Cohort, Trial 111-206, FAS

	Cohort 1		Cohort 2		Cohort 3	
Demographic Characteristic	**All Vosoritide (N=19)**	**Placebo (N=16)**	**All Vosoritide (N=12)**	**Placebo (N=8)**	**All Vosoritide (N=12)**	**Placebo (N=8)**
Age at Screening, months						
n	19	16	12	8	12	8
Mean (SD)	40.2 (11.2)	43.1 (11.5)	15.3 (5.1)	15.8 (6.3)	3.8 (0.8)	4.1 (1.0)
Median	39.0	39.5	15.5	17.5	4.0	4.0
25th, 75th Percentile	29.0, 50.0	33.5, 55.0	10.5, 20.0	9.0, 21.0	3.0, 4.5	4.0, 5.0
Min, max	24, 59	28, 58	8, 22	8, 23	3, 5	2, 5
Age on Day 1, months						
n	19	16	12	8	12	8
Mean (SD)	41.48 (11.07)	44.33 (11.54)	16.59 (5.11)	16.87 (6.21)	5.41 (0.53)	5.76 (0.59)
Median	40.02	40.39	16.54	18.56	5.62	5.91
25th, 75th Percentile	30.19, 51.06	34.55, 56.36	11.63, 21.42	10.46, 22.16	4.86, 5.86	5.72, 5.95
Min, max	25.4, 59.8	29.2, 59.8	8.7, 23.4	8.9, 23.7	4.5, 5.9	4.4, 6.5
Sex, n (%) [a]						
Male	10 (52.6)	7 (43.8)	9 (75.0)	5 (62.5)	6 (50.0)	1 (12.5)
Female	9 (47.4)	9 (56.3)	3 (25.0)	3 (37.5)	6 (50.0)	7 (87.5)
Race, n (%) [a]						
White	12 (63.2)	13 (81.3)	9 (75.0)	6 (75.0)	8 (66.7)	6 (75.0)
Asian	6 (31.6)	3 (18.8)	2 (16.7)	1 (12.5)	3 (25.0)	2 (25.0)
Japanese	2 (10.5)	3 (18.8)	1 (8.3)	1 (12.5)	2 (16.7)	2 (25.0)
Other	4 (21.1)	0	1 (8.3)	0	1 (8.3)	0
Multiple	1 (5.3)	0	1 (8.3)	0	1 (8.3)	0
Native Hawaiian or other Pacific Islander	0	0	0	1 (12.5)	0	0
Ethnicity, n (%) [a]						
Not Hispanic or Latino	18 (94.7)	15 (93.8)	12 (100.0)	8 (100.0)	10 (83.3)	6 (75.0)
Hispanic or Latino	1 (5.3)	1 (6.3)	0	0	2 (16.7)	2 (25.0)

Source: ADSL dataset for study 111-206, Statistical Reviewer's analysis
[a]:Percentages were calculated using the total number of participants in the full analysis set of each column as the denominator. Cohort 1 included participants aged ≥24 to < 60 months, Cohort 2 included participants aged ≥6 to < 24 months and Cohort 3 included participants aged 0 to < 6 months
Abbreviations: FAS, full analysis set; max, maximum; min, minimum; N, number of subjects; SD, standard deviation

Table 49**. ACH-Related Comorbidities, Trial 111-206, FAS**

System Organ Class Preferred Term	Sentinel (N=11)	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)
Participants with any ACH-related medical history condition, n (%)[a]	7 (63.6)	25 (78.1)	22 (68.8)	32 (74.4)
Respiratory, thoracic, and mediastinal disorders, n (%)[a]	6 (54.5)	17 (53.1)	16 (50.0)	23 (53.5)
Adenoidal hypertrophy	1 (9.1)	5 (15.6)	2 (6.3)	6 (14.0)
Tonsillar hypertrophy	1 (9.1)	2 (6.3)	0	3 (7.0)
Nasal disorder	2 (18.2)	0	1 (3.1)	2 (4.7)
Snoring	1 (9.1)	0	4 (12.5)	1 (2.3)
Nervous system disorders, n (%)[a]	4 (36.4)	13 (40.6)	7 (21.9)	17 (39.5)
Hypotonia	3 (27.3)	4 (12.5)	1 (3.1)	7 (16.3)
Hydrocephalus	1 (9.1)	4 (12.5)	1 (3.1)	5 (11.6)
Spinal cord compression	1 (9.1)	4 (12.5)	0	5 (11.6)
Speech disorder	0	4 (12.5)	1 (3.1)	4 (9.3)
Cervical cord compression	0	3 (9.4)	1 (3.1)	3 (7.0)
Cerebral ventricle dilatation	0	2 (6.3)	3 (9.4)	2 (4.7)
Myelomalacia	0	2 (6.3)	1 (3.1)	2 (4.7)
Speech disorder developmental	0	0	3 (9.4)	0
Congenital, familial, and genetic disorders, n (%)[a]	5 (45.5)	8 (25.0)	15 (46.9)	13 (30.2)
Skull malformation	3 (27.3)	5 (15.6)	4 (12.5)	8 (18.6)
Foramen magnum stenosis	1 (9.1)	3 (9.4)	5 (15.6)	4 (9.3)
Musculoskeletal and connective tissue disorders, n (%)[a]	5 (45.5)	12 (37.5)	13 (40.6)	17 (39.5)
Kyphosis	4 (36.4)	8 (25.0)	8 (25.0)	12 (27.9)
Limb deformity	5 (45.5)	5 (15.6)	5 (15.6)	10 (23.3)
Hand deformity	3 (27.3)	3 (9.4)	6 (18.8)	6 (14.0)
Lordosis	2 (18.2)	2 (6.3)	3 (9.4)	4 (9.3)
Bone deformity	1 (9.1)	2 (6.3)	3 (9.4)	3 (7.0)
Joint range of motion decreased	2 (18.2)	1 (3.1)	4 (12.5)	3 (7.0)
Knee deformity	2 (18.2)	0	2 (6.3)	2 (4.7)
Spinal deformity	1 (9.1)	1 (3.1)	1 (3.1)	2 (4.7)
Spinal stenosis	1 (9.1)	1 (3.1)	1 (3.1)	2 (4.7)
Infections and infestations, n (%)[a]	4 (36.4)	11 (34.4)	11 (34.4)	15 (34.9)
Otitis media	3 (27.3)	7 (21.9)	7 (21.9)	10 (23.3)
Otitis media chronic	2 (18.2)	3 (9.4)	3 (9.4)	5 (11.6)
Ear infection	1 (9.1)	2 (6.3)	2 (6.3)	3 (7.0)

System Organ Class Preferred Term	Sentinel (N=11)	Randomized Vosoritide (N=32)	Randomized Placebo (N=32)	All Vosoritide (N=43)
Surgical and medical procedures, n (%)[a]	5 (45.5)	10 (31.3)	12 (37.5)	15 (34.9)
Ear tube insertion	4 (36.4)	4 (12.5)	5 (15.6)	8 (18.6)
Adenoidectomy	3 (27.3)	4 (12.5)	7 (21.9)	7 (16.3)
Tonsillectomy	2 (18.2)	2 (6.3)	5 (15.6)	4 (9.3)
Posterior fossa decompression	0	3 (9.4)	3 (9.4)	3 (7.0)
Spinal decompression	0	3 (9.4)	2 (6.3)	3 (7.0)
Craniectomy	0	2 (6.3)	2 (6.3)	2 (4.7)
Speech rehabilitation	1 (9.1)	1 (3.1)	2 (6.3)	2 (4.7)
Adenotonsillectomy	0	1 (3.1)	2 (6.3)	1 (2.3)
Congenital, familial, and genetic disorders, n (%)[a]	5 (45.5)	8 (25.0)	15 (46.9)	13 (30.2)
Skull malformation	3 (27.3)	5 (15.6)	4 (12.5)	8 (18.6)
Macrocephaly	4 (36.4)	2 (6.3)	5 (15.6)	6 (14.0)
Foramen magnum stenosis	1 (9.1)	3 (9.4)	5 (15.6)	4 (9.3)
Chondrodystrophy	2 (18.2)	1 (3.1)	2 (6.3)	3 (7.0)
Brachydactyly	2 (18.2)	0	3 (9.4)	2 (4.7)
Dysmorphism	0	1 (3.1)	2 (6.3)	1 (2.3)
Ear and labyrinth disorders, n (%)[a]	3 (27.3)	7 (21.9)	9 (28.1)	10 (23.3)
Deafness	2 (18.2)	3 (9.4)	2 (6.3)	5 (11.6)
Conductive deafness	0	3 (9.4)	3 (9.4)	3 (7.0)
Middle ear effusion	1 (9.1)	2 (6.3)	1 (3.1)	3 (7.0)
Eustachian tube dysfunction	0	1 (3.1)	2 (6.3)	1 (2.3)

Source: Excerpted from Table 10.2.2.2. CSR 111-206
[a] Percentages were calculated using the total number of subjects in the full analysis set of each column as the denominator.
Subjects with more than one medical history condition of the same SOC/PT were counted only once for that SOC/PT
Medical history conditions were coded using MedDRA version 24.1.

Abbreviations: ACH, achondroplasia; N, number of subjects; n, number of subjects with specific comorbidities; PT, preferred term; SOC, system organ class Table 50. Change in MRI Parameters From Baseline to Week 52 by Cohort (Safety Population), Trial 111-206

Parameter	Cohort 1 All Vosoritide (N=19)	Cohort 1 Placebo (N=16)	Cohort 2 All-Vosoritide (N=12)	Cohort 2 Placebo (N=8)	Cohort 3 All-Vosoritide (N=12)	Cohort 3 Placebo (N=8)
Volume of calvarium (cm^3)						
Baseline, n	19	16	11	8	8	12
Mean (SD)	1743.377 (180.310)	1734.763 (188.348)	1513.967 (169.677)	1384.816 (147.360)	978.373 (83.428)	1005.745 (112.807)
Week 52, n	16	12	8	6	10	6
Change from BL at W52	47.275 (47.638)	48.676 (53.527)	204.236 (106.927)	203.622 (95.583)	485.427 (78.727)	432.735 (142.515)
% Change at W52	2.83 (2.97)	2.82 (2.83)	13.82 (8.16)	15.02 (7.84)	50.41 (8.94)	45.35 (16.65)

Parameter	Cohort 1 All Vosoritide (N=19)	Cohort 1 Placebo (N=16)	Cohort 2 All-Vosoritide (N=12)	Cohort 2 Placebo (N=8)	Cohort 3 All-Vosoritide (N=12)	Cohort 3 Placebo (N=8)
Area of spinal cord at the foramen magnum level (cm^2)						
Baseline, n	19	16	12	8	12	8
Mean (SD)	0.071 (0.009)	0.070 (0.017)	0.075 (0.029)	0.070 (0.012)	0.047 (0.014)	0.048 (0.018)
Week 52, n	17	12	8	7	10	6
Change from BL at W52	-0.001 (0.018)	0.011 (0.014)	-0.005 (0.026)	-0.004 (0.012)	0.009 (0.017)	0.013 (0.020)
% Change at W52	-0.84 (24.52)	19.13 (26.87)	1.66 (27.99)	-6.53 (15.69)	26.40 (43.74)	51.03 (73.33)
Whole brain total volume (cm^3)						
Baseline, n	18	16	11	7	12)	8
Mean (SD)	1309.365 (123.154)	1312.861 (119.078	1109.785 (131.475)	1052.374 (121.499)	756.528 (63.029)	748.348 (79.227)
Week 52, n	16	12	8	6	10	6
Change from BL at W52	46.752 (79.899)	53.412 (44.711)	180.820 (79.590)	177.942 (44.896)	376.896 (38.840)	300.223 (66.118)
% Change at W52	3.95 (6.59)	4.27 (3.63))	16.88 (8.87)	16.72 (5.02)	50.16 (7.18)	42.29 (12.39)
Ventricles total volume (cm^3)						
Baseline, n	18	16	12	8	12	8
Mean (SD)	95.289 (65.801)	84.562 (70.350)	50.688 (22.301)	46.658 (25.491)	29.302 (13.979)	23.333 (6.834)
Week 52, n	16	12	8	7	10	6
Change from BL at W52	1.272 (12.314)	3.158 (10.457	15.595 (27.704)	4.614 (11.476)	24.230 (17.253)	23.782 (22.600)
% Change at W52	-0.02 (11.24)	11.12 (32.83)	21.63 (36.97)	10.19 (26.75)	96.44 (48.82)	94.41 (52.03)
Area of spinal cord at the foramen magnum level (cm^2)						
Baseline, n	19	16	12	8	12	8
Mean (SD)	0.071 (0.009)	0.070 (0.017)	0.075 (0.029)	0.070 (0.012)	0.047 (0.014)	0.048 (0.018)
Week 52, n	17	12	8	7	10	6
Change from BL at W52	-0.001 (0.018)	0.011 (0.014)	-0.005 (0.026)	-0.004 (0.012)	0.009 (0.017)	0.013 (0.020)
% Change at W52	-0.84 (24.52)	19.13 (26.87)	1.66 (27.99)	-6.53 (15.69)	26.40 (43.74)	51.03 (73.33)
Ratio of face volume to calvarium						
Baseline, n	15	14	11	7	11	8
Mean (SD)	0.353 (0.024)	0.314 (0.097)	0.304 (0.033)	0.316 (0.039)	0.347 (0.044)	0.356 (0.035)
Week 52, n	13	8	7	6	9	6
Change from BL at W52	0.007 (0.030)	0.028 (0.015)	0.019 (0.013)	0.000 (0.028)	-0.019 (0.033)	-0.028 (0.031)
% Change at W52	1.82 (8.89)	8.62 (5.04)	6.33 (4.60)	0.61 (9.10)	-5.04 (9.28)	-7.74 (9.08)
Ratio of area of spinal cord to foramen magnum						
Baseline, n	19	16	12	8	12	8
Mean (SD)	0.517 (0.070)	0.509 (0.104)	0.524 (0.129)	0.548 (0.090)	0.537 (0.069)	0.499 (0.092)
Week 52, n	17	12	8	7	10	6
Change from BL at W52	0.039 (0.109)	0.078 (0.096)	-0.031 (0.109)	-0.043 (0.064)	-0.025 (0.139)	0.047 (0.100)
% Change at W52	8.72 (22.60)	18.90 (23.04)	-1.73 (20.48)	-7.25 (11.66)	-3.41 (26.58)	10.25 (23.10)
Ratio of face volume to sinus						
Baseline, n	16	14	12	8	11	8
Mean (SD)	83.346 (54.453)	64.391 (35.636)	565.495 (1067.857)	204.790 (267.7112417)7	719969.649 (136.525)	207.725 (133.753)

	Cohort 1		Cohort 2		Cohort 3	
Parameter	**All Vosoritide (N=19)**	**Placebo (N=16)**	**All-Vosoritide (N=12)**	**Placebo (N=8)**	**All-Vosoritide (N=12)**	**Placebo (N=8)**
Week 52, n	8	14	7	7	6	9
Change from BL at W52	-25.684 (45.236)	-13.700 (22.610)	105.979 (324.013)	-102.499 (256.939)	-65.133 (119.128)	188.615 (433.627)
% Change at W52	-17.19 (32.29)	-15.16 (29.77)	19.02 (76.11)	4.29 (65.28)	-5.95 (81.29)	338.06 (598.22)

Source: Table 10.4.2.13.1 of CSR 111-206.
Change from baseline and percent change from baseline was based on the participants with available measurements at both time points. Baseline is defined as Day 1 or screening if a Day 1 assessment is not available.
Abbreviations: BL, baseline; N, number of subjects; SD, standard deviation; W, week

Table 51. Sleep Study Indices by Cohort, Analysis Population, FAS

	Cohort 1		Cohort 2		Cohort 3	
Mean (SD) Change From Baseline to Week 52	**All Vosoritide (N=19)**	**Placebo (N=16)**	**All Vosoritide (N=12)**	**Placebo (N=8)**	**All Vosoritide (N=12)**	**Placebo (N=8)**
n	16	14	9	5	10	7
Apnea Hypopnea Index (number per hour)	-1.45 (4.63)	-0.54 (2.70)	-0.72 (1.41)	1.06 (4.80)	-0.94 (2.78)	1.89 (6.31)
Apnea Index (number per hour)	-0.83 (1.93)	-1.07 (2.12)	-0.71 (1.61)	0.40 (2.34)	-0.36 (2.54)	-1.09 (1.22)
Central Apnea Index (number per hour)	-0.74 (1.86)	-1.26 (2.66)	-0.71 (1.61)	-0.28 (0.89)	0.50 (0.92)	-1.00 (0.97)
Hypopnea Index (number per hour)	-0.61 (3.63)	0.52 (1.35)	-0.01 (1.32)	0.66 (2.53)	-0.56 (0.54)	2.97 (5.45)
Desaturation per Hour ≥3% (number per hour)	-1.24 (3.98)	-0.41 (1.51)	-0.69 (1.30)	0.98 (3.60)	-0.93 (2.60)	1.71 (6.63)
Obstructive Index (number per hour)	-0.09 (0.45)	0.19 (0.73)	-0.01 (0.08)	0.68 (1.52)	-0.86 (2.08)	-0.07 (0.64)

Source: Table 10.4.2.10.1 of CSR 111-206
Change from baseline was based on the participants with available measurements at both time points.
Abbreviations: N, number of subjects; n, number of subjects within specific sleep study indices; SD: standard deviation

Subgroup Analysis of the Primary Endpoint by Sex and Race:

There were small differences in the proportion of male and female participants between groups, with a higher proportion of males (17/32) in the vosoritide arm compared to placebo. Most participants (46 out of 64) were categorized as White. There were small differences in the proportion of white participants between groups, with a lower proportion of white participants in the vosoritide arm (21/46) compared to placebo (25/46). The difference between treatment group LS means within these subgroups (estimated as vosoritide – placebo), and the 95% CI for the treatment difference, at Week 52 for the randomized full analysis set (FAS) are provided in Table 52. The point estimate of treatment effect was in favor of vosoritide in all subgroups and the height Z score achieved significance for Asian subgroups.

Table 52. ANCOVA of Height Z-Score at Week 52 by Sex and Race, Analysis Population: FAS (Randomized)

	N		LSM Change From Baseline		
Parameter	Placebo (N=32)	Vosoritide (N=32)	Placebo	Vosoritide	Treatment Difference[a]
Sex					
Male	13	17	-0.16	0.07	0.26 (-0.15, 0.67)
Female	19	15	-0.47	-0.15	0.32 (-0.02, 0.66)
Race					
White	25	21	-0.27	0.00	0.26 (-0.08, 0.61)
Asian	6	10	-0.48	-0.04	0.44 (0.11, 0.77)
Other	1	1	-	-	-
Ethnicity					
Hispanic/Latino	3	3	-	-	-
Japanese	4	4	-	-	-

Source: Statistical Reviewer's analysis.
[a] Difference is vosoritide minus placebo. Least square means (LSM) were obtained only for subgroups with sufficient number of subjects.
Abbreviations: ANCOVA, CI, confidence interval; FAS, full analysis set; SD, standard deviation

Subgroup Analysis using Bayesian shrinkage prior

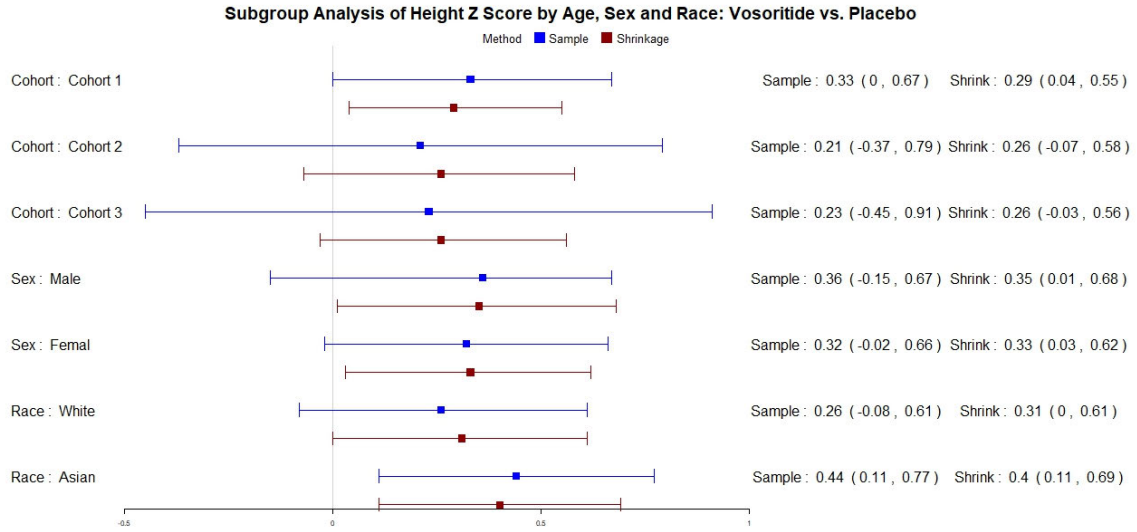
In Section 6.2.1.4.2.3, subgroup analyses of height Z score and AGV by age cohort are provided. There were likely some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimates of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage).

For $I = 1, 2\ldots, n$; Y_i represents the observed sample estimate of treatment effect in a subgroup level I, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where:

- σi2 are the observed variance for sample estimates,

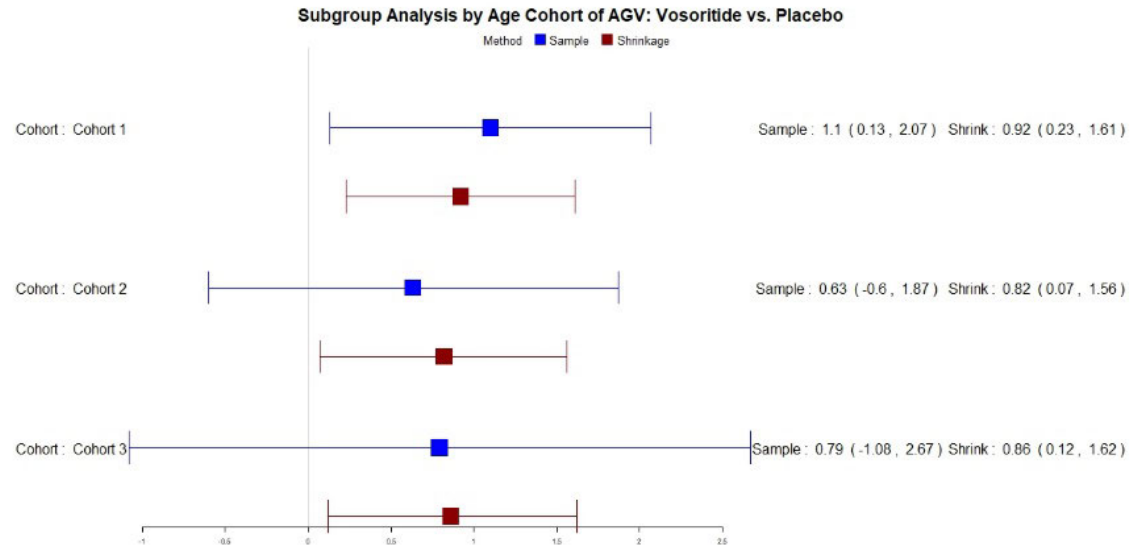
- $\mu i \sim N(\mu, \tau 2)$, and
- $\mu \sim N(0, 202)$, $1/\tau 2 \sim$ Gamma(0.001, 0.001).

Figure 37. Subgroup Analysis of Height Z-Score by Age Cohort



Source: Statistical Reviewer's analysis

Figure 38. Subgroup Analysis of AGV by Age Cohort



Source: Statistical Reviewer's analysis.
Abbreviations: AGV, annualized growth velocity

For AGV, all age subgroups reported the lower limit of the 95% CI greater than zero, in favor of Vosoritide, except for Cohort 3. However, with a shrinkage estimate, the lower limit of the 95% credible interval was positive, in favor of Vosoritide. Note that for Height Z score, the credible intervals produced by the Bayesian shrinkage method failed to exclude 0 in Cohort 2 and 3.

16.2. Studies With External Controls

16.2.1. Eligibility Criteria and Follow-up, Studies With External Controls

Table 53 presents the selected inclusion and exclusion criteria and study follow-up of ACH subjects included in the comparative studies with external controls.

Table 53. Selected Study Design Elements in Vosoritide Comparative Analysis With External Controls

Design Element	AchNH Control	Observational/Placebo Control	Vosoritide Arms (111-206/208)
Inclusion	ACH, clinical or molecular diagnosis Had clinical genetics visit Receiving care or had received care in the study sites	ACH, clinical or molecular diagnosis Age <60 months at baseline Ambulatory and able to stand (for subjects ≥5 years)	ACH, genetically confirmed Age 0 to <60 months Growth assessment before screening for 111-206 At least one year of follow-up in 111-208 for 111-206 placebo arm
Exclusion	Enrolled in any vosoritide interventional studies or 111-901 Ever exposed to growth hormone Having had limb-lengthening	Medical conditions[a] Ever exposed to growth hormone, IGF-1, anabolic steroids, antihypertensive drugs Having had bone related surgery	
Follow-up	Up to age 8 years old until subjects met the exclusion criteria or participated into Study 111-901 or vosoritide interventional study	7-year follow-up, until subjects withdraw from study, transition into vosoritide interventional study, or loss to follow-up	Until subjects attain near final adult height[b], withdraw from study or loss to follow-up

Source: natural history integrated analysis report Version 2.0
[a] Medical conditions may include hypothyroidism, hyperthyroidism, renal insufficiency, anemia, cardiac or vascular disease, inflammatory bowel disease, type 1 diabetes, autoimmune neuropathy, autoimmune inflammatory disease
[b] Evidence of growth plate closure and < 1.5 cm/year annualized growth velocity
Abbreviations: ACH, achondroplasia; IGF-1, insulin-like growth factor 1

16.2.2. Statistical Analysis Plan, Studies With External Controls

The original version of the statistical analysis plan (SAP) for the analyses using external controls in this sNDA was dated April 20, 2022, which was after the unblinding of Trial 111-206 on

February 14, 2022. The SAP was considered *post-hoc*, however, majority of the analysis methods were similar to those in the SAP for the original NDA.

The Applicant conducted two types of analyses: cross-sectional and longitudinal. The cross-sectional analyses did not use baseline and post-baseline visits from the same control subjects to compute change from baseline, whereas the longitudinal analyses did. We only focused on the longitudinal analyses in our review since results from the cross-sectional analyses were difficult to interpret due to lack of within subject change from baseline. Unless otherwise stated, the comparative analyses using external controls refer to the longitudinal analyses.

In the analyses using the Achondrolpasia Natural History (AchNH) control, controls were matched to treated subjects by age (±1 month), sex (exact), baseline height (±5 cm), and baseline Z-score (±1). The matching algorithm required each control to have at least 3 height assessments, including (1) baseline, (2) post baseline follow-up, and (3) several months prior to baseline to derive the baseline AGV. The baseline (index date) in an AchNH control was defined as the visit that matched to the baseline of a treated subject. An Analysis of Covariance (ANCOVA) model was used to estimate the treatment difference between the treated and control groups in change in height Z-score or height from baseline. The model included treatment, matching ID, baseline age strata (same as the randomization age strata used in Trial 111-206), baseline AGV, and baseline height Z-score or height.

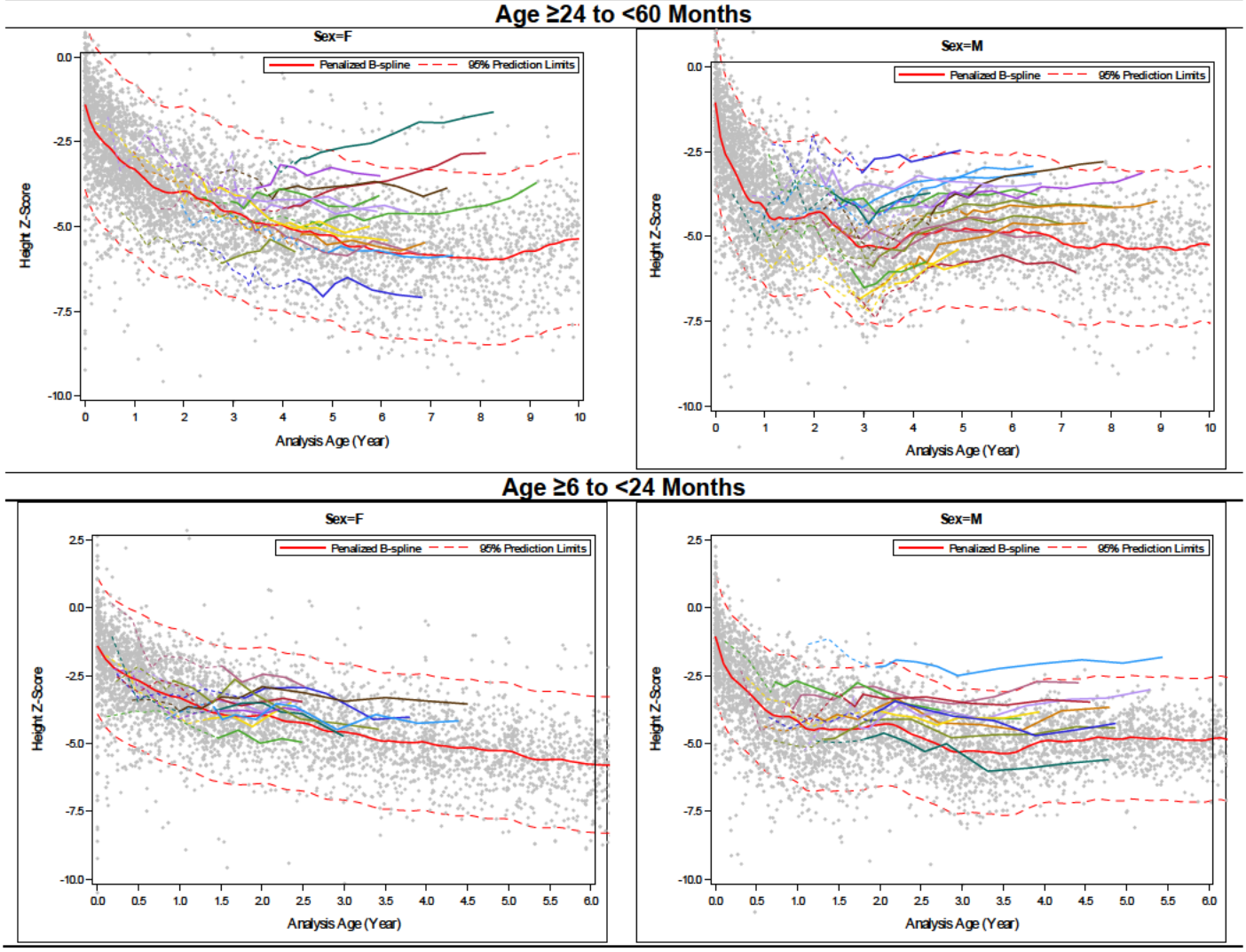
In the analyses using the observational/placebo control, a subject would be excluded from the control group for a specific analysis if the subject was already in the treated group. Matching was not performed due to inadequate sample size. The baseline (index date) in an observational/placebo control was defined as the first visit that met the age requirement in a specific analysis. An ANCOVA model similar to the model used in the AchNH control analyses was used to estimate the treatment difference. The model included treatment, baseline age strata, and baseline height Z-score or height. Baseline AGV was not included due to limited follow-up time.

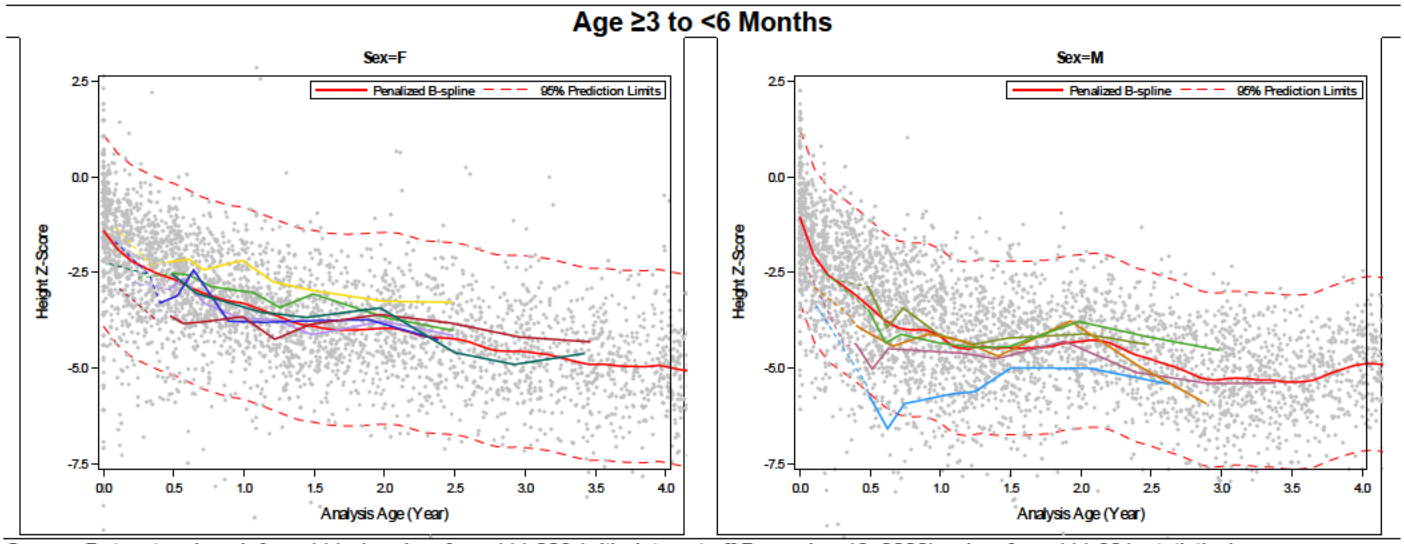
For the analyses with external controls, assessments were censored at limb lengthening procedure or growth therapies for both the treated arm and control arms. No imputation for missing data were performed except for linear interpolation for intermediate missing values in the Applicant's clinical studies. Statistical adjustment for multiplicity was not considered.

In general, body length took priority for subjects aged <24 months and standing height took priority for subjects aged ≥24 months. A like-to-like rule, similar to the one used in Trial 111-206, was applied at Year 1 in the treated group as well as the observational/placebo control. The AchNH control lacked the information on whether the height measurement was body length or standing height, and therefore the like-to-like rule could not be applied.

16.2.3. Results of Analyses, Studies With External Controls

Figure 39. Height Z-Score in Individual Vosoritide-Treated Subjects in Trials 111-206/111-208 vs. Average From AchNH Controls by Age and Sex Subgroup[1]





Source: Datasets adgmnh from 111-nh, adgm from 111-208 (with data cut-off December 19, 2022), adgm from 111-901, statistical reviewer's analysis.
Each colored spaghetti line represents height Z-scores from a Vosoritide-treated subject, where the solid part is the treated period, and the dotted part is the pre-treatment period. Age subgroup is defined by the subject's age at the start of treatment (baseline). The grey dots represent height Z-scores from AchNH controls, and the red reference lines represent the average and 95% prediction limits computed based on these dots.
Abbreviations: AchNH, achondroplasia Natural History; F, female; M, male

Table 54. Treatment Difference in Change in Height Z-Score and Height at Year 1, Trial 111-206 Randomized Vosoritide-Treated Versus Different Control Groups

Control Arm	N (Vosoritide, Control)	Treatment Difference Vosoritide – Control (95% CI)	
		Height Z-Score	Height (cm)
111-206 Placebo[1]	32, 32	0.25 (-0.02, 0.53)	0.77 (-0.02, 1.56)
AchNH (Matched)[2]	31, 285	0.51 (0.24, 0.78)	1.69 (0.79, 2.59)
Observational/Placebo[3]	31, 106	0.46 (0.29, 0.63)	1.28 (0.71, 1.85)

Source: Applicant's integrated summary of efficacy, verified by statistical reviewer
[1] ANCOVA model included treatment, baseline age strata, baseline AGV and baseline height Z-score or height.
[2] ANCOVA model included treatment, matching ID, baseline age strata, baseline AGV and baseline height Z-score or height.
[3] ANCOVA model included treatment, baseline age strata, and baseline height Z-score or height.
Abbreviations: AchNH, achondroplasia Natural History; CI, confidence interval; N, number of subjects

Table 55. Treatment Difference in Change in Height Z-Score at Year 1 by Age Subgroup, Trial 111-206 Randomized Vosoritide-Treated Versus Different Control Groups

Age Group	Number of Treated	Treatment Difference Vosoritide – Control (95% CI)[1]	
		111-206 Placebo	AchNH (Matched)
≥24 to <60 Months (Cohort 1)	15	0.33 (0.00, 0.67)	0.48 (0.16, 0.79)
≥6 to <24 Months (Cohort 2)	8	0.21 (-0.37, 0.79)	0.88 (0.38, 1.37)
≥3 to <6 Months (Cohort 3)	9[2]	0.23 (-0.45, 0.91)	0.14 (-0.49, 0.77)

Source: Summarized from Applicant's Integrated Summary of Efficacy.
[1] For the placebo control, ANCOVA model included treatment, baseline age strata, baseline AGV and baseline height Z-score. For the AchNH control, matching was performed for each age subgroup, and ANCOVA model included treatment, matching ID, baseline age strata, baseline AGV and baseline height Z-score.
[2] One of the 9 treated subjects in 111-206 with imputed height using multiple imputation was not included in the analyses using the AchNH control.
Abbreviations: AchNH, achondroplasia Natural History; CI, confidence interval; N, number of subjects

The Applicant conducted comparative analyses of the randomized placebo arm in Trial 111-206 versus the AchNH control in change in height Z-score, height and AGV at Year 1. Their

ANCOVA model includes matching ID, which can hurt the precision of the estimate due to the large number of matching IDs in the model. The FDA used weighted generalized estimating equations (GEE) to re-analyze the data. In the FDA's analyses, variable ratios in the matched sets were accounted for by weighting instead of adjusting for matching ID in the model. The FDA's analyses yielded smaller SEs and narrower confidence intervals, and the estimated treatment differences were significantly greater than 0, suggesting better growth in the placebo arm compared to the matched AchNH control.

Table 56**. Difference in Change From Baseline at Year 1 in Growth Parameters Between Trial 111-206 Randomized Placebo Versus AchNH**[1]

	Difference Placebo – AchNH (95% CI)	
Endpoint	**ANCOVA[2]**	**Weighted GEE[3]**
Height Z-Score	0.18 (-0.06, 0.42)	0.20 (0.08, 0.31)
Height (cm)	0.57 (-0.23, 1.37)	0.59 (0.22, 0.96)
AGV (cm/year)	0.63 (-0.19, 1.45)	0.62 (0.23, 1.01)

Source: Applicant's integrated summary of efficacy, statistical reviewer's analysis
[1] The 32 subjects who were randomized to placebo in Trial 111-206 were matched to 276 AchNH controls on sex, age, height, and height Z-score.
[2] Analysis conducted by the Applicant. ANCOVA model included treatment, matching ID, baseline age strata, baseline AGV and baseline height Z-score or height if the endpoint is height Z-score or height.
[3] Analysis conducted by FDA. Generalized estimating equations (GEE) model included treatment, baseline age strata, baseline AGV and baseline height Z-score or height if the endpoint is height Z-score or height. Matching ID was used as cluster ID. The analysis was weighted by weight=1 for treated and weight=1/n for controls, where n is the number of controls in a matched set.
Abbreviations: AchNH, achondroplasia Natural History; AGV, annualized growth velocity; ANCOVA, analysis of covariance; CI, confidence interval; GEE, generalized estimating equations

Table 57. Baseline Covariates in Trial 111-206 Placebo Arm and Matched AchNH

Baseline Covariate	**Mean in Trial 111-206 Placebo N=32**	**Weighted Mean in Matched AchNH[1] N=276**	**SMD[2]**
Age (Months)	27.80	27.85	-0.003
Sex (Male)	41%	41%	0
Height Z-Score	-4.28	-4.18	-0.063
Height (cm)	70.8	71.0	-0.019
AGV (cm/year)	9.60	9.50	0.013

Source: statistical reviewer's analysis
1 AchNH subjects were weighted by $weight = \frac{1}{n}$, where n is the number of AchNH controls in a matched set.
2 Standardized mean difference (SMD) was calculated by $\frac{\overline{X_1}-\overline{X_2}}{\sqrt{\frac{s_1^2+s_2^2}{2}}}$, where $\overline{x_1}$ and $\overline{x_2}$ are sample means for the treated and control groups, and s_1^2 and s_2^2 are sample variances for the treated and control groups in the weighted population.
Abbreviations: AchNH, achondroplasia Natural History; AGV, annualized growth velocity; N, number of subjects; SMD, standardized mean difference

Table 58. Number of Subjects at Each Follow-up Visit in Observational/Placebo Control[1]

	Number of Subjects at Visit Month				
Age at Baseline[2]	**0**	**12**	**18**	**24**	**36**
≥3 to <6 months	23	7	6	2	0
≥6 <15 months	26	13	10	5	1
≥15 <24 months	15	11	11	9	4
≥24 to <36 months	25	17	18	13	7
≥36 to <60 months	70	51	48	35	11

Source: Statistical reviewer's analysis
[1] This analysis included Study 111-901 and extension to the placebo arms in Studies 111-206 and 111-301.
[2] Baseline in this analysis was the first visit in a subject in Study 111-901 that was between 3 and 60 months of age.

16.2.4. Assessment of Review Issues, Studies with External Controls

Background

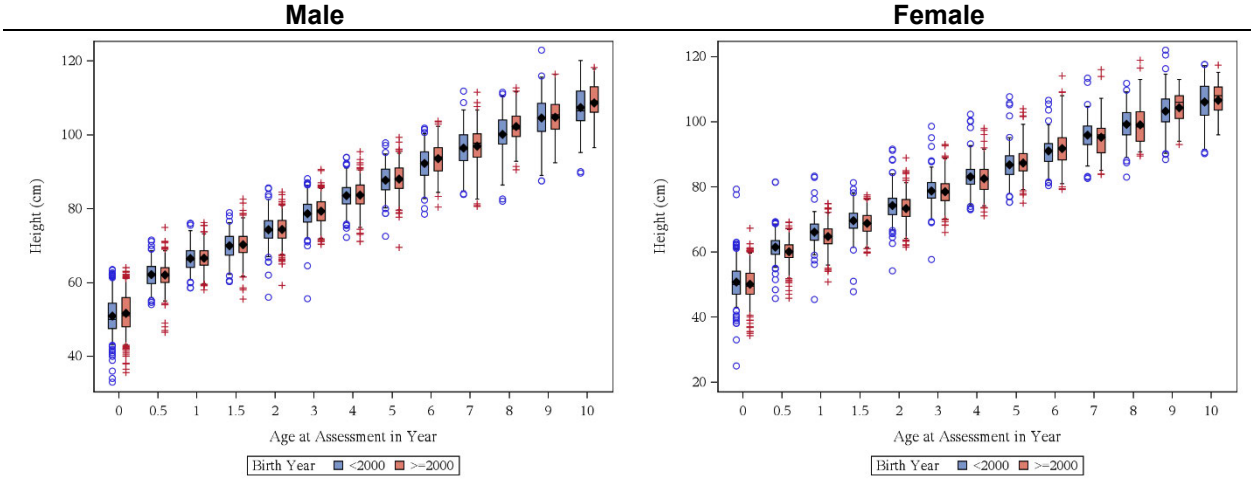
Most subjects in the vosoritide clinical trials were recruited directly from the observational Study 111-901. The study had regular 3-month scheduled visits and similar inclusion/exclusion criteria as the clinical trials, making it a potentially suitable external comparator. However, the early dropout from 111-901 and enrollment into clinical trials resulted in a short follow-up time, limiting its use for evaluating long-term efficacy, particularly in subjects younger than 24 months.

Compared to Study 111-901, the AchNH study has a larger sample size and longer follow-up time. However, the study retrospectively retrieved data from medical records, and therefore outcomes of interest were not measured in regularly scheduled visits. Some important information, such as whether the subject was measured in standing height or body length, was undocumented, and some AchNH data are not contemporaneous to the trial data. Absence of contemporaneous data in the external control arm may introduce bias when comparing height data, since differences in dietary habits, and other environmental factors at various points in time may affect growth.

16.2.4.1. Contemporaneousness of Height Data in AchNH

Of the 1,213 subjects aged 0 to 18 years in AchNH, 636 (52.4%) were born before 2000 and 577 (47.6%) after 2000. The Applicant did not find any temporal trend in height comparing the subjects born before 2000 with those born after 2000 by sex and age, with a generally comparable mean height between these subjects (Table 59). FDA statistical reviewer confirmed these findings (Figure 40).

Figure 40. Boxplot of Heights of Subjects Born Before Year 2000 vs. After Year 2000 by Sex and Age in AchNH



Source: statistical reviewer's analysis
Black diamond markers indicate mean height.
Abbreviations: AchNH, achondroplasia Natural History

The FDA team conducted a sensitivity analysis comparing vosoritide-treated subjects in Trial 111-206 with the AchNH control in change in height Z-score or height from baseline by restricting matched AchNH controls to those born after 2000 (Table 60). The treatment difference in change in height Z-score or height from baseline closely resembled that from the original analysis including all matched AchNH controls. These results suggest that including the historic data before year 2000 in AchNH did not introduce substantial bias into the analyses.

Table 59. Mean Height in Subjects Born Before vs. After Year 2000 by Sex and Age in AchNH

Age (years)	Female				Male			
	Participants Born Before 2000		Participants Born After 2000		Participants Born Before 2000		Participants Born After 2000	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
0	541	50.75 (5.43)	692	50.10 (4.91)	497	50.91 (4.93)	782	51.65 (5.07)
0.5	255	61.48 (3.80)	371	60.08 (3.62)	210	62.14 (3.18)	433	62.03 (3.50)
1	218	66.10 (4.03)	270	64.74 (3.73)	173	66.48 (3.38)	364	66.57 (3.21)
1.5	149	69.61 (4.25)	205	68.80 (3.54)	130	69.96 (3.61)	269	70.23 (3.90)
2	263	74.26 (4.45)	325	73.35 (4.40)	236	74.28 (3.75)	427	74.34 (3.52)
3	216	78.74 (4.47)	265	78.52 (4.54)	224	78.63 (3.93)	368	79.30 (3.58)
4	229	83.08 (4.48)	224	82.54 (4.61)	203	83.51 (3.73)	292	83.66 (3.89)
5	220	86.78 (4.75)	160	87.33 (4.63)	174	87.67 (4.06)	245	88.00 (4.14)
6	161	91.03 (4.63)	135	91.77 (6.13)	128	92.23 (4.41)	170	93.54 (4.48)
7	149	95.89 (4.83)	91	95.23 (5.99)	116	96.39 (5.42)	132	96.90 (5.82)
8	128	99.20 (5.36)	86	99.06 (5.85)	113	100.10 (5.42)	115	102.22 (4.60)
9	146	103.25 (6.16)	73	104.30 (5.33)	115	104.53 (6.10)	77	104.73 (5.76)
10	118	106.09 (6.48)	53	106.60 (5.76)	102	107.35 (6.16)	74	108.61 (5.10)
11	119	110.66 (6.43)	50	110.53 (5.51)	105	110.30 (6.13)	65	111.09 (5.49)
12	88	112.59 (7.97)	24	112.28 (5.34)	88	113.90 (6.47)	54	115.57 (5.12)
13	94	117.72 (5.89)	34	116.03 (6.35)	70	118.54 (6.82)	42	121.65 (6.29)
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)
17	52	120.12 (6.52)	3	118.80 (1.93)	75	129.44 (6.86)	0	0
18	50	121.06 (4.07)	0	0	46	129.00 (5.96)	0	0

Source: Applicant's natural history integrated analyses report
Abbreviations: AchNH, achondroplasia Natural History; n, number of subjects; SD, standard deviation

Table 60. Treatment Difference in Change in Height Z-Score and Height When Included and Excluded AchNH Controls Born Before 2000 – Trial 111-206 Randomized Vosoritide-Treated Versus AchNH

Subjects in AchNH	N (Vosoritide, Control)	Treatment Difference Vosoritide vs. Control (95% CI)[1]	
		Height Z-Score	Height (cm)
All	31, 285	0.51 (0.24, 0.78)	1.69 (0.79, 2.59)
Born after 2000	31, 159	0.53 (0.24, 0.81)	1.76 (0.82, 2.69)

Source: statistical reviewer's analysis
[1] ANCOVA model included treatment, matching ID, baseline age strata, baseline AGV and baseline height Z-score or height.
Abbreviations: AchNH, achondroplasia Natural History; AGV, annualized growth velocity; CI, confidence interval; N, number of subjects

16.2.4.2. Confounding

The observed potential confounders in comparative analyses using external controls include sex, age, baseline height or height Z-score, and baseline AGV. Since the number of AchNH controls

far exceeded the number of Vosoritide-treated subjects, coarsened exact matching (CEM) for each baseline covariate is feasible. The Applicant's original analyses with the AchNH control did not include baseline AGV as a matching variable but included the other factors. The Applicant argued that the range in AGV was large in subjects aged <5 years (i.e., Baseline AGV ranged from 0.3 to 30.2 cm/year in Trial 111-206) and therefore it was difficult to match on baseline AGV. In response to the FDA's request, the Applicant performed a sensitivity analysis by including baseline AGV in matching and applying a ± 4 cm/year matching threshold. Results from the sensitivity analysis were consistent to those from the original analyses (Table 61).

In response to the FDA's request, the Applicant used standardized mean difference (SMD) to evaluate the balance in baseline covariates between two matched groups. SMD appeared to be reasonably small considering the small sample sizes (Table 62), suggesting that matching had achieved good balance of the observed confounders. Nevertheless, in the absence of randomization, unmeasured and residual confounding was still possible.

Matching, particularly CEM, is not feasible in analyses using the observational/placebo control because of its small sample size. Covariate adjustment in the outcome regression model alone would likely be inadequate to control for confounding since it is subject to model misspecification. In addition, baseline AGV was not adjusted for in the outcome regression. Therefore, analyses using the observational/placebo control were likely subject to residual confounding. The Applicant performed a sensitivity analysis using the latest age rather than the earliest age within the age cohort with sufficient follow-up as baseline and a second sensitivity analysis adjusting for baseline AGV in the outcome regression. The estimates of treatment difference from these sensitivity analyses were noticeably smaller than those from the original analysis (Table 63). However, baseline covariates appeared to be less balanced in these sensitivity analyses than in the original analysis. For example, the mean baseline age was 25.0 months in the treated arm but was > 40 months in the control arm in two sensitivity analyses.

Table 61. Treatment Difference in Change From Baseline in Height Z-Score and Height When Included and Excluded Baseline AGV in Matching in Analyses with AchNH

Time	Study/ Treatment	Age Group	Baseline AGV Included for matching	N (Active, Control)	Height Z Score - Difference (Vosoritide/Placebo – AchNH) in LSM (95% CI)	Height – Difference (Vosoritide/Placebo – AchNH) in LSM (95% CI)
Year 1	111-206/Placebo	All (< 60 M)	No[1]	32, 276	0.18 (-0.06, 0.42)	0.57 (-0.23, 1.37)
			Yes[2]	**32, 234**	**0.19 (-0.06, 0.43)**	**0.57 (-0.23, 1.37)**
Year 1	111-206/Vosoritide	All (< 60 M)	No[1]	31, 285	0.51 (0.24, 0.78)	1.69 (0.79, 2.59)
			Yes[2]	**31, 239**	**0.44 (0.19, 0.70)**	**1.43 (0.62, 2.24)**
Year 1	111-206/208 Vosoritide	≥24 to < 60 M	No[1]	33, 191	0.48 (0.30, 0.65)	1.85 (1.18, 2.52)
			Yes[2]	**32, 153**	**0.36 (0.18, 0.53)**	**1.38 (0.71, 2.05)**
		≥6 to < 24 M	No[1]	14, 201	0.83 (0.46, 1.21)	2.54 (1.30, 3.79)
			Yes[2]	**14, 139**	**0.85 (0.48, 1.22)**	**2.64 (1.40, 3.87)**
		0 to < 6 M	No[1]	11, 169	0.12 (-0.44, 0.68)	0.44 (-1.22, 2.10)
			Yes[2]	**11, 124**	**0.13 (-0.42, 0.68)**	**0.47 (-1.07, 2.01)**
Year 2	111-206/208 Vosoritide	≥24 to < 60 M	No[1]	21, 124	0.63 (0.38, 0.89)	3.01 (1.85, 4.17)
			Yes[2]	**20, 108**	**0.64 (0.38, 0.90)**	**3.02 (1.82, 4.22)**
		≥6 to < 24 M	No[1]	11, 144	0.79 (0.29, 1.28)	2.69 (1.00, 4.38)
			Yes[2]	**11, 94**	**0.79 (0.27, 1.32)**	**2.73 (0.97, 4.50)**

Source: Applicant's May 5, 2023, response to FDA's April 04, 2023, information request
Abbreviations; AchNH, achondroplasia Natural History external control; AGV, annualized growth velocity; CI, confidence interval; LSM, least square mean, M, month

Table 62. Standardized Mean Difference[1] in Matched Population of Trial 111-206/111-208 Vosoritide-Treated Versus AchNH[2]

		Standardized Mean Difference			
Age Group	**Year**	**Age**	**Height**	**Height Z-Score**	**AGV**
≥24 to <60 Months	1	0.00	-0.13	-0.16	-0.17
	2	0.00	-0.16	-0.20	-0.36
	3	-0.00	-0.22	-0.28	-0.32
≥6 to <24 Months	1	-0.00	-0.12	-0.15	-0.37
	2	0.02	-0.08	-0.13	-0.49
	3	0.01	-0.04	-0.03	-0.55
≥3 to <6 Months	1	0.06	0.30	0.29	-0.47
	2	0.09	0.36	0.32	-0.39

Source: Applicant's August 4, 2023, response to FDA's July 25, 2023, information request
[1] SMD was calculated by $\frac{\overline{x_1}-\overline{x_2}}{\sqrt{\frac{s_1^2+s_2^2}{2}}}$, where $\overline{x_1}$ and $\overline{x_2}$ are sample mean for the treated and control groups, and s_1^2 and s_2^2 are sample variance for the treated and control groups in the weighted population.
[2] Subjects were weighted by weight $= \frac{1}{n}$ for controls, where n is the number of controls in a matched set, and $weight = 1$ for treated.
Abbreviations: AchNH, achondroplasia Natural History; AGV, annual growth velocity; SMD, standardized mean difference

Table 63. Treatment Difference in Change in Height Z-Score and Height in Original and Sensitivity Analyses – Trial 111-206 Randomized Vosoritide-Treated Versus Observational/Placebo

Analysis	N (Vosoritide, Control)	Treatment Difference Vosoritide – Control (95% CI)[1]	
		Height Z-Score	Height (cm)
Original	31, 106	0.46 (0.29, 0.63)	1.28 (0.71, 1.85)
Sensitivity Analysis 1[1]	31, 109	0.29 (0.10, 0.47)	1.03 (0.44, 1.62)
Sensitivity Analysis 2[2]	31, 72	0.33 (0.12, 0.54)	1.18 (0.53, 1.82)

Source: Applicant's June 23, 2023, response to FDA's May 26, 2023, information request
[1] This sensitivity analysis considered latest age rather than the earliest age with sufficient follow up as baseline in the control arm.
[2] This sensitivity analysis included baseline AGV in the outcome regression model.
Abbreviations: CI, confidence interval; AGV, annual growth velocity

16.2.4.3. Selection Bias

In comparative analyses using the observational/placebo external control, there is a potential concern of selection bias resulting from differential loss to follow-up between the external control and the Vosoritide-treated arm. In Study 111-901, subjects' decision of early termination of Study 111-901 or participation into a vosoritide interventional study (i.e., Studies 111-202, 111-206, and 111-301) may potentially be affected by factors related to outcomes of interest (e.g., disease progression at the transition time). In contrast, there were no such early termination in Trial 111-206/208 at the time of data cut-off for comparative analyses. Matching and adjustment on baseline variables may not address such selection bias.

The Applicant's comparative analyses excluded (1) subjects who did not reach the required follow-up time, assuming missing completely at random, and (2) subjects who transitioned into any interventional study from the external group. Although such analyses are inadequate to address selection bias described above (given that patients remaining in Study 111-901 with complete follow-up were per selection), the Applicant's analysis indicated that Study 111-901 subjects aged 24 to <60 months who finished the Study 111-901 follow-up had a slower decrease in height Z-score in 6 months from baseline, as compared to subjects who transitioned into study 206/208 vosoritide arm or who were lost to follow-up (Table 64). These results suggest that for subjects aged 24 to <60 months, selection bias, if present, is likely to result in an underestimated treatment effect of vosoritide on height increase. For subjects aged 6 to <24 months or aged <6 months, the impact of potential selection bias could not be readily assessed because of the small sample size.

Table 64. Change From Baseline in Height Z-Score at Six-Months Among Study 111-901 Subjects[1]

Change in Height Z-Score From Baseline at 6-Months in Each Age Group	Number of Subjects at Baseline/6-Months; Mean (SD) Change in Height Z-Score From Baseline				
	Finished 1-Year Follow-Up		Transitioned or Dropped Out by 1-Year[2]		
	External Control	Vosoritide Arm (Trials 111-206/111-208)	Transitioned to Vosoritide Arm (Trials 111-206/111-208)	Transitioned to Other Vosoritide Interventional Trials (Trials 111-202 or 111-301)	Dropped Out of Study 111-901[3]
24 to <60 months	72/72	20/20	13/7	5/5	15/7
Height Z-score	-0.07 (0.26)	-0.27 (0.40)	-0.08 (0.10)	-0.24 (0.35)	-0.20 (0.62)
6 to <24 months	33/32	1/1	13/9	3/2	14/5
Height Z-score	-0.37 (0.57)	-0.03 (NA)	0.09 (0.67)	0.30 (0.35)	-0.56 (0.69)

0 to <6 months	13/12	0/0	8/0	5/2	13/2
Height Z-score	-0.97 (0.44)	NA	NA	-0.98 (1.14)	-1.32 (0.42)

Source: Applicant's May 5, 2023, responses to FDA's April 04, 2023, information request. *NA* Not Applicable
[1] Subjects who enrolled directly into study 111-206 and did not participate in study 111-901 are not included, which explains the few subjects in the Vosoritide arm in the 6 to < 24 months and < 6 months groups.
[2] The observational/placebo control in 1-year comparative analyses excluded Study 111-901 subjects in these groups.
[3] This group includes 111-901 subjects who dropped out of Study 111-901 before 1 year without enrolling into any Vosoritide interventional studies.
Abbreviation: SD, standard deviation

The Applicant conducted sensitivity analyses that 1) included Study 111-901 subjects who transitioned into Trials 111-206/208 as the control, and 2) excluded transition subjects from the vosoritide arm and included them in the control. Results from these sensitivity analyses and the original analyses were consistent (Table 65). Of note, these sensitivity analyses did not consider subjects who dropped out of Study 111-901 or transitioned to other vosoritide interventional study (i.e., Studies 111-202 and 111-301) before 1 year.

In general, potential selection bias due to subjects transfer from Study 111-901 to Trial 111-206 is less of a concern, given that subjects transferring into Trial 111-206 were randomized when entering Trial 111-206 and those who were randomized to the placebo group were combined with the subjects remaining in Study 111-901 as external control. Overall, sensitivity analyses appear to provide consistent findings, and descriptive analysis results did not suggest potential selection bias would overestimate the treatment effect on height increase.

Therefore, although the impact of potential selection bias from differential loss to follow-up cannot be readily assessed, it does not constitute a major concern in this study scenario based on study design characteristics and potential direction of bias.

Table 65. Treatment Difference in Change From Baseline in Height Z-Score in One-Year Comparing Trials 111-206/208 Vosoritide-Treated Arm With Observational/Placebo Control

Treatment Difference in Each Age Group[1]	Original Analysis: Controls Excluding Transition Subjects		Sensitivity Analysis: Controls Including Transition Subjects		Sensitivity Analysis: Vosoritide Arm Excluding Transition Subjects	
	Vosoritide	Control	Vosoritide	Control	Vosoritide	Control
24 to <60 months						
Subjects excluded, n	0	20	0	0	20	0
Subjects, n	33	72	33	92	13	92
Treatment difference (95% CI)	0.46 (0.30,0.62)		0.45 (0.29,0.62)		0.54 (0.28,0.79)	
6 to <24 months						
Subjects excluded, n	0	1	0	0	1	0
Subjects, n	14	35	14	36	13	36
Treatment difference (95% CI)	0.65 (0.31,0.99)		0.65 (0.31,0.99)		0.66 (0.32,1.01)	

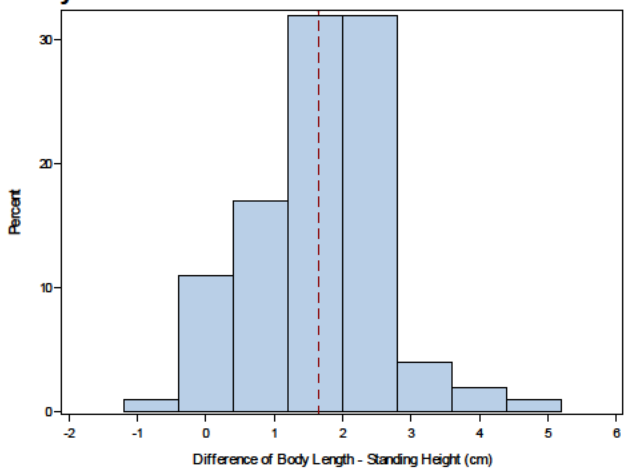
Source: Applicant's May 5, 2023, responses to FDA's April 04, 2023, information request. NA Not Applicable, CI confidence interval
[1] No transition subjects among subjects aged <6 months.
Abbreviations: CI, confidence interval; n, number of subjects

16.2.4.4. Discrepancy Between Body Length and Standing Height

Figure 41 shows the difference between paired measures of body length and standing height among visits in Trial 111-206 FAS where both measures were available. Body length was

generally greater than standing height at the same visit, with an average difference of 1.65 cm (95% CI: 1.46, 1.85).

Figure 41. Histogram of Difference Between Body Length and Standing Height, Trial 111-206, Full Analysis Set[1]



Source: statistical reviewer's analysis
[1] This analysis included visits at baseline, Week 26 and 52 in Trial 111-206 from both treatment groups.
The dotted line indicates the average difference of body length minus standing height.

The impact of the difference between body length and standing height on treatment difference was mitigated in Trial 111-206 by the like-to-like rule (refer to Section 6.2.1.1 for details) and the use of randomization. However, it might have affected the comparative analyses with external controls, particularly the AchNH control. vosoritide-treated subjects aged < 24 months at baseline (Cohorts 2 and 3) likely had body length as height measure at baseline. The like-to-like rule ensured that body length was also prioritized at Year 1 (e.g., among all Cohorts 2 and 3 subjects in Trial 111-206, only 1 vosoritide-treated Cohort 2 subject had standing height at Year 1). However, the like-to-like rule could not be applied in the AchNH external control, which lacked documentation of whether height measurement was body length or standing height. It is possible that some AchNH Cohort 2 subjects had standing height as height measure at Year 1 since the mean age at Year 1 for this cohort was >2 years. This could potentially make the AchNH control arm appear shorter in height at Year 1 and overestimate the treatment effect in this cohort, compared to Trial 111-206 (Table 55). Cohort 3 was expected to be less affected, since most subjects aged < 6 months at baseline would have body length as height measure at Year 1 regardless of the like-to-like rule. In addition, the lack of increase in treatment difference at Year 2 compared to that at Year 1 in Cohorts 2 and 3 in the analyses with the AchNH control (Figure 5, Section 6.2.3.2) could also be attributed to the inconsistent use of the like-to-like rule in the treated and control groups. However, AchNH did not report the height measurement method information to verify this speculation. Such an impact is expected to be less pronounced in the analyses at Year 3 and beyond since all subjects would likely have standing height as height measure by Year 3.

In the observational/placebo control, the same like-to-like rule was applied at Year 1.

17. Clinical Safety

17.1. Trial 111-206

Table 66. Duration of Exposure to Vosoritide[1], Safety Population From All Trials

Duration of exposure	Trials 111-206/111-208 N=74	Trial 111-209 N=9	Trials 111-301/111-302 N=121	Trials 111-202/111-205 N=35	All Trials N=239
Person-years of exposure	146.85	4.41	371.80	192.84	715.89
Duration of treatment, months					
Mean (SD)	23.81 (10.79)	5.88 (4.94)	36.87 (9.00)	66.11 (28.21)	35.94 (20.13)
Median	24.72	4.53	35.55	76.52	32.69
Min-max	0.0, 43.5	0.1, 12.1	0.2, 62.5	0.4, 97.4	0.0, 97.4
Duration of treatment, months, n (%)					
<6 months	6 (8.1)	5 (55.6)	2 (1.7)	3 (8.6)	16 (6.7)
≥6 months	68 (91.9)	4 (44.4)	119 (98.3)	32 (91.4)	223 (93.3)
≥1 year	64 (86.5)	1 (11.1)	119 (98.3)	31 (88.6)	215 (90.0)
≥2 years	37 (50.0)	0	117 (97.7)	30 (85.7)	184 (77.0)
≥3 years	9 (12.2)	0	60 (49.6)	29 (82.9)	98 (41.0)
≥4 years	0	0	10 (8.3)	29 (82.9)	39 (16.3)
≥5 years	0	0	1 (0.8)	27 (77.1)	28 (11.7)
≥6 years	0	0	0	23 (65.7)	23 (9.6)
≥7 years	0	0	0	10 (28.6)	10 (4.2)
≥8 years	0	0	0	1 (2.9)	1 (0.4)
≥9 years	0	0	0	0	0

Source: Applicant's response to Agency's Information Request dated July 13, 2023
[1] Duration of exposure includes subjects exposed to vosoritide in Studies 111-206, 111-208, 111-301, 111-302, 111-202, 111-205, 111-209, with exposure data up January 26, 2022, for Trial 111-208 (the data cut-off applied to the 111-208 Interim CSR) and up to February 25, 2022 (the data cut-off applied to the 111-302, 111-205, and 111-209 Interim CSRs)
Abbreviations: N, number of subjects; SD, standard deviation

Table 67. Adverse Events by System Organ Class, Safety Population, Trial 111-206

System Organ Class	Randomized Vosoritide N=32 n (%)	Randomized Placebo N=32 n (%)	Sentinel Vosoritide N=11 n (%)	All Subjects Vosoritide N=43 n (%)	All Subjects Vosoritide vs. Randomized Placebo Risk Difference (%) (95% CI)
General disorders and administration site conditions	29 (90.6)	24 (75.0)	9 (81.8)	38 (88.4)	13.4
Immune system disorders	3 (9.4)	2 (6.2)	2 (18.2)	5 (11.6)	5.4
Eye disorders	1 (3.1)	0	0	1 (2.3)	2.3
Reproductive system and breast disorders	1 (3.1)	0	0	1 (2.3)	2.3
Psychiatric disorders	2 (6.2)	1 (3.1)	0	2 (4.7)	1.5
Vascular disorders	1 (3.1)	1 (3.1)	1 (9.1)	2 (4.7)	1.5
Investigations	4 (12.5)	3 (9.4)	0	4 (9.3)	-0.1
Skin and subcutaneous tissue disorders	11 (34.4)	12 (37.5)	5 (45.5)	16 (37.2)	-0.3
Blood and lymphatic system disorders	1 (3.1)	1 (3.1)	0	1 (2.3)	-0.8
Respiratory, thoracic, and mediastinal disorders	18 (56.2)	19 (59.4)	7 (63.6)	25 (58.1)	-1.2
Injury, poisoning and procedural complications	9 (28.1)	11 (34.4)	5 (45.5)	14 (32.6)	-1.8
Cardiac disorders	0	1 (3.1)	0	0	-3.1
Endocrine disorders	0	1 (3.1)	0	0	-3.1
Musculoskeletal and connective tissue disorders	6 (18.8)	7 (21.9)	2 (18.2)	8 (18.6)	-3.3
Metabolism and nutrition disorders	1 (3.1)	3 (9.4)	0	1 (2.3)	-7.0
Infections and infestations	26 (81.2)	30 (93.8)	11 (100)	37 (86.0)	-7.7
Ear and labyrinth disorders	8 (25.0)	12 (37.5)	3 (27.3)	11 (25.6)	-11.9
Nervous system disorders	4 (12.5)	8 (25.0)	0	4 (9.3)	-15.7
Gastrointestinal disorders	18 (56.2)	26 (81.2)	7 (63.6)	25 (58.1)	-23.1

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.
Duration is 1 year treatment period.
Risk difference is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 68. Adverse Events Occurring at ≥2% Frequency by Age Subgroups, Safety Population, Trial 111-206

Preferred Term	Cohort 1 Randomized Vosoritide N=15 n (%)	Cohort 1 Randomized Placebo N=16 n (%)	Cohort 2 Randomized Vosoritide N=8 n (%)	Cohort 2 Randomized Placebo N=8 n (%)	Cohort 3 Randomized Vosoritide N=9 n (%)	Cohort 3 Randomized Placebo N=8 n (%)
Any AE	15 (100)	16 (100)	8 (100)	8 (100)	9 (100)	8 (100)
Injection site reaction	12 (80.0)	6 (37.5)	6 (75.0)	2 (25.0)	8 (88.9)	5 (62.5)
Injection site erythema	10 (66.7)	4 (25.0)	7 (87.5)	3 (37.5)	8 (88.9)	6 (75.0)
Upper respiratory tract infection	8 (53.3)	6 (37.5)	2 (25.0)	3 (37.5)	2 (22.2)	2 (25.0)
Injection site swelling	6 (40.0)	1 (6.2)	1 (12.5)	0	0	1 (12.5)
Pyrexia	5 (33.3)	7 (43.8)	4 (50.0)	4 (50.0)	5 (55.6)	8 (100)
Arthropod bite	4 (26.7)	2 (12.5)	1 (12.5)	0	1 (11.1)	0
Diarrhea	4 (26.7)	5 (31.2)	0	0	3 (33.3)	2 (25.0)
Injection site induration	4 (26.7)	0	0	0	1 (11.1)	0
Rhinorrhea	4 (26.7)	2 (12.5)	0	0	2 (22.2)	4 (50.0)
Ear infection	3 (20.0)	5 (31.2)	1 (12.5)	0	1 (11.1)	1 (12.5)
Fall	3 (20.0)	1 (6.2)	0	2 (25.0)	0	0
Injection site bruising	3 (20.0)	4 (25.0)	1 (12.5)	1 (12.5)	0	1 (12.5)
Pain in extremity	3 (20.0)	1 (6.2)	0	0	0	0
Vomiting	3 (20.0)	9 (56.2)	1 (12.5)	3 (37.5)	1 (11.1)	5 (62.5)
Constipation	2 (13.3)	0	0	0	0	2 (25.0)
Cough	2 (13.3)	6 (37.5)	0	0	1 (11.1)	1 (12.5)
Dermatitis diaper	2 (13.3)	0	0	0	0	1 (12.5)
Ear pain	2 (13.3)	4 (25.0)	0	0	0	0
Epistaxis	2 (13.3)	0	0	0	0	0
Gastroenteritis	2 (13.3)	2 (12.5)	0	1 (12.5)	0	2 (25.0)
Impetigo	2 (13.3)	0	0	0	0	0
Injection site hemorrhage	2 (13.3)	1 (6.2)	0	1 (12.5)	1 (11.1)	0
Injection site urticaria	2 (13.3)	1 (6.2)	1 (12.5)	0	1 (11.1)	0
Nasal congestion	2 (13.3)	1 (6.2)	0	1 (12.5)	3 (33.3)	4 (50.0)
Nasopharyngitis	2 (13.3)	6 (37.5)	3 (37.5)	2 (25.0)	2 (22.2)	1 (12.5)
Otitis media acute	2 (13.3)	1 (6.2)	0	1 (12.5)	0	0
Rash	2 (13.3)	1 (6.2)	1 (12.5)	1 (12.5)	1 (11.1)	2 (25.0)
Acetonemic vomiting	1 (6.7)	0	0	0	0	0
Allergy to animal	1 (6.7)	0	0	0	0	0
Asthma	1 (6.7)	0	0	0	0	1 (12.5)
Balanoposthitis	1 (6.7)	0	0	0	0	0
Blood pressure decreased	1 (6.7)	1 (6.2)	0	1 (12.5)	0	0
Body tinea	1 (6.7)	0	0	0	0	0

Preferred Term	Cohort 1 Randomized Vosoritide N=15 n (%)	Cohort 1 Randomized Placebo N=16 n (%)	Cohort 2 Randomized Vosoritide N=8 n (%)	Cohort 2 Randomized Placebo N=8 n (%)	Cohort 3 Randomized Vosoritide N=9 n (%)	Cohort 3 Randomized Placebo N=8 n (%)
Cheilitis	1 (6.7)	0	0	0	0	0
Conjunctivitis	1 (6.7)	3 (18.8)	3 (37.5)	3 (37.5)	2 (22.2)	0
Croup infectious	1 (6.7)	2 (12.5)	0	0	0	0
Dermatitis contact	1 (6.7)	0	0	0	0	0
Dizziness	1 (6.7)	0	0	0	0	0
Erythema infectiosum	1 (6.7)	0	0	0	0	0
Gastritis	1 (6.7)	0	0	0	0	0
Gastroenteritis viral	1 (6.7)	1 (6.2)	0	0	0	1 (12.5)
Hand-foot-and-mouth disease	1 (6.7)	1 (6.2)	1 (12.5)	1 (12.5)	1 (11.1)	0
Head injury	1 (6.7)	0	0	1 (12.5)	0	0
Hypermetropia	1 (6.7)	0	0	0	0	0
Hypersensitivity	1 (6.7)	0	0	0	0	0
Influenza	1 (6.7)	2 (12.5)	2 (25.0)	1 (12.5)	0	0
Injection site injury	1 (6.7)	0	0	0	0	0
Injection site mass	1 (6.7)	1 (6.2)	2 (25.0)	0	0	1 (12.5)
Injection site pain	1 (6.7)	0	0	0	0	0
Lower respiratory tract infection	1 (6.7)	0	2 (25.0)	1 (12.5)	0	0
Lymphadenopathy	1 (6.7)	0	0	0	0	1 (12.5)
Mechanical urticaria	1 (6.7)	0	0	0	0	0
Middle ear effusion	1 (6.7)	1 (6.2)	0	0	0	0
Oropharyngeal pain	1 (6.7)	3 (18.8)	1 (12.5)	0	0	0
Otitis externa	1 (6.7)	1 (6.2)	0	0	0	0
Oxygen saturation decreased	1 (6.7)	0	0	0	0	0
Post-traumatic headache	1 (6.7)	0	0	0	0	0
Procedural anxiety	1 (6.7)	0	0	0	0	0
Rhinitis	1 (6.7)	0	2 (25.0)	0	0	0
Rhinitis allergic	1 (6.7)	0	0	0	0	0
Seasonal allergy	1 (6.7)	0	0	0	0	0
Upper respiratory tract inflammation	1 (6.7)	0	0	1 (12.5)	0	0
Viral infection	1 (6.7)	1 (6.2)	2 (25.0)	0	2 (22.2)	3 (37.5)
Viral upper respiratory tract infection	1 (6.7)	0	0	0	1 (11.1)	0
Abdominal discomfort	0	1 (6.2)	0	0	0	0
Abdominal distension	0	1 (6.2)	0	0	0	0
Adenoidal hypertrophy	0	0	0	1 (12.5)	0	0
Allergic oedema	0	0	0	1 (12.5)	0	0

Preferred Term	Cohort 1 Randomized Vosoritide N=15 n (%)	Cohort 1 Randomized Placebo N=16 n (%)	Cohort 2 Randomized Vosoritide N=8 n (%)	Cohort 2 Randomized Placebo N=8 n (%)	Cohort 3 Randomized Vosoritide N=9 n (%)	Cohort 3 Randomized Placebo N=8 n (%)
Arthralgia	0	0	1 (12.5)	0	0	0
Aspiration	0	0	0	0	1 (11.1)	0
Asymptomatic COVID-19	0	0	0	0	0	1 (12.5)
Autism spectrum disorder	0	0	0	1 (12.5)	0	0
Back pain	0	1 (6.2)	0	0	0	0
Body temperature increased	0	1 (6.2)	1 (12.5)	0	0	0
Bronchiolitis	0	0	0	0	0	1 (12.5)
Cerebral ventricle dilatation	0	0	0	0	1 (11.1)	0
Chemical burn	0	0	1 (12.5)	0	0	0
Conductive deafness	0	0	1 (12.5)	0	0	0
Contusion	0	2 (12.5)	0	0	0	0
COVID-19	0	0	0	0	0	1 (12.5)
Deafness	0	0	0	1 (12.5)	1 (11.1)	0
Deafness unilateral	0	1 (6.2)	0	0	0	0
Decreased appetite	0	1 (6.2)	0	0	0	0
Dehydration	0	0	0	0	1 (11.1)	0
Dermatitis allergic	0	0	0	0	1 (11.1)	0
Discomfort	0	0	1 (12.5)	1 (12.5)	0	2 (25.0)
Dry skin	0	1 (6.2)	0	0	0	2 (25.0)
Dysphonia	0	0	1 (12.5)	0	0	0
Eczema	0	1 (6.2)	1 (12.5)	1 (12.5)	0	1 (12.5)
Emotional distress	0	0	1 (12.5)	1 (12.5)	0	0
Enterobiasis	0	0	1 (12.5)	0	0	0
Erythema	0	0	0	1 (12.5)	1 (11.1)	0
Eustachian tube dysfunction	0	0	0	1 (12.5)	0	0
Excessive cerumen production	0	0	0	1 (12.5)	0	0
Eye contusion	0	1 (6.2)	0	0	0	0
Eye infection	0	0	1 (12.5)	1 (12.5)	0	0
Eyelid injury	0	1 (6.2)	0	0	0	0
Febrile convulsion	0	0	0	0	0	1 (12.5)
Food allergy	0	0	0	0	0	1 (12.5)
Fracture pain	0	0	0	0	0	1 (12.5)
Fungal infection	0	0	1 (12.5)	0	0	0
Hematoma	0	0	0	1 (12.5)	0	0
Headache	0	4 (25.0)	0	0	0	0

Preferred Term	Cohort 1 Randomized Vosoritide N=15 n (%)	Cohort 1 Randomized Placebo N=16 n (%)	Cohort 2 Randomized Vosoritide N=8 n (%)	Cohort 2 Randomized Placebo N=8 n (%)	Cohort 3 Randomized Vosoritide N=9 n (%)	Cohort 3 Randomized Placebo N=8 n (%)
Hypoacusis	0	1 (6.2)	0	0	0	0
Hypoglycemia	0	1 (6.2)	0	0	0	0
Hypotension	0	0	0	0	1 (11.1)	0
Infusion site extravasation	0	1 (6.2)	0	0	0	0
Ingrowing nail	0	1 (6.2)	0	0	0	0
Injection site rash	0	0	0	0	1 (11.1)	0
Inner ear disorder	0	0	0	0	1 (11.1)	0
Irritability	0	0	0	0	1 (11.1)	0
Knee deformity	0	0	0	0	1 (11.1)	0
Kyphosis	0	0	0	0	1 (11.1)	2 (25.0)
Lactose intolerance	0	0	0	0	0	1 (12.5)
Limb injury	0	1 (6.2)	1 (12.5)	0	0	0
Lymphadenitis	0	0	0	0	0	1 (12.5)
Malaise	0	2 (12.5)	0	0	0	0
Medical device site bruise	0	1 (6.2)	0	0	0	0
Middle ear disorder	0	0	1 (12.5)	0	0	0
Middle ear inflammation	0	0	0	0	1 (11.1)	0
Miliaria	0	0	0	0	1 (11.1)	0
Musculoskeletal discomfort	0	0	1 (12.5)	0	0	0
Neck pain	0	1 (6.2)	0	0	0	0
Oral contusion	0	1 (6.2)	0	0	0	0
Oral mucosal eruption	0	0	0	0	0	1 (12.5)
Oral pain	0	0	0	0	0	2 (25.0)
Otitis media	0	2 (12.5)	3 (37.5)	2 (25.0)	1 (11.1)	2 (25.0)
Otitis media chronic	0	1 (6.2)	0	0	0	1 (12.5)
Otorrhea	0	1 (6.2)	1 (12.5)	0	0	1 (12.5)
Papule	0	0	1 (12.5)	0	0	1 (12.5)
Parainfluenza virus infection	0	0	0	0	0	1 (12.5)
Perioral dermatitis	0	1 (6.2)	0	0	0	0
Peripheral swelling	0	0	0	0	0	1 (12.5)
Petit mal epilepsy	0	1 (6.2)	0	0	0	0
Pharyngitis	0	1 (6.2)	0	0	0	0
Pneumonia	0	0	0	0	1 (11.1)	0
Pneumonia mycoplasmal	0	0	1 (12.5)	0	0	0
Post-tussive vomiting	0	0	0	1 (12.5)	0	0

Preferred Term	Cohort 1 Randomized Vosoritide N=15 n (%)	Cohort 1 Randomized Placebo N=16 n (%)	Cohort 2 Randomized Vosoritide N=8 n (%)	Cohort 2 Randomized Placebo N=8 n (%)	Cohort 3 Randomized Vosoritide N=9 n (%)	Cohort 3 Randomized Placebo N=8 n (%)
Precocious puberty	0	0	0	0	0	1 (12.5)
Pyelonephritis acute	0	0	0	0	0	1 (12.5)
Rash macular	0	0	1 (12.5)	0	0	0
Respiratory distress	0	0	0	1 (12.5)	0	1 (12.5)
Respiratory syncytial virus bronchiolitis	0	0	0	0	1 (11.1)	0
Respiratory syncytial virus infection	0	0	0	0	1 (11.1)	0
Respiratory syncytial virus test positive	0	0	0	0	1 (11.1)	0
Respiratory tract infection	0	0	0	1 (12.5)	0	0
Rhinovirus infection	0	0	0	1 (12.5)	0	1 (12.5)
Salivary gland enlargement	0	0	0	0	1 (11.1)	0
Scoliosis	0	0	0	1 (12.5)	0	0
Sinusitis	0	2 (12.5)	0	0	0	1 (12.5)
Skin abrasion	0	1 (6.2)	0	0	0	0
Skin disorder	0	1 (6.2)	0	0	0	0
Skin hypopigmentation	0	0	0	0	0	1 (12.5)
Skin induration	0	1 (6.2)	0	0	0	0
Skin swelling	0	0	0	0	1 (11.1)	0
Skull fracture	0	0	0	0	0	1 (12.5)
Sleep apnea syndrome	0	0	1 (12.5)	0	1 (11.1)	0
Sleep study abnormal	0	1 (6.2)	0	0	0	0
Speech disorder	0	0	1 (12.5)	0	0	0
Speech disorder developmental	0	0	0	0	0	1 (12.5)
Subdural effusion	0	0	0	0	0	1 (12.5)
Sudden infant death syndrome	0	0	0	0	1 (11.1)	0
Supraventricular extrasystoles	0	1 (6.2)	0	0	0	0
Teething	0	0	3 (37.5)	6 (75.0)	5 (55.6)	4 (50.0)
Tonsillitis	0	0	0	0	0	1 (12.5)
Toothache	0	0	0	0	0	1 (12.5)
Trigger finger	0	1 (6.2)	0	0	0	0
Tympanic membrane perforation	0	1 (6.2)	0	0	0	0
Tympanosclerosis	0	0	0	1 (12.5)	0	0
Upper-airway cough syndrome	0	1 (6.2)	0	0	0	0
Urticaria	0	1 (6.2)	0	0	0	0
Vaccination site pain	0	0	0	0	1 (11.1)	0
Varicella	0	0	1 (12.5)	0	0	0

Preferred Term	Cohort 1 Randomized Vosoritide N=15 n (%)	Cohort 1 Randomized Placebo N=16 n (%)	Cohort 2 Randomized Vosoritide N=8 n (%)	Cohort 2 Randomized Placebo N=8 n (%)	Cohort 3 Randomized Vosoritide N=9 n (%)	Cohort 3 Randomized Placebo N=8 n (%)
Varicella virus test positive	0	0	1 (12.5)	0	0	0
Venomous sting	0	0	0	0	0	1 (12.5)
Ventricular extrasystoles	0	1 (6.2)	0	0	0	0
Vessel puncture site bruise	0	0	0	1 (12.5)	0	0
Vessel puncture site swelling	0	0	0	1 (12.5)	0	0
Viral rash	0	0	1 (12.5)	0	0	0
Wheezing	0	0	0	1 (12.5)	0	0

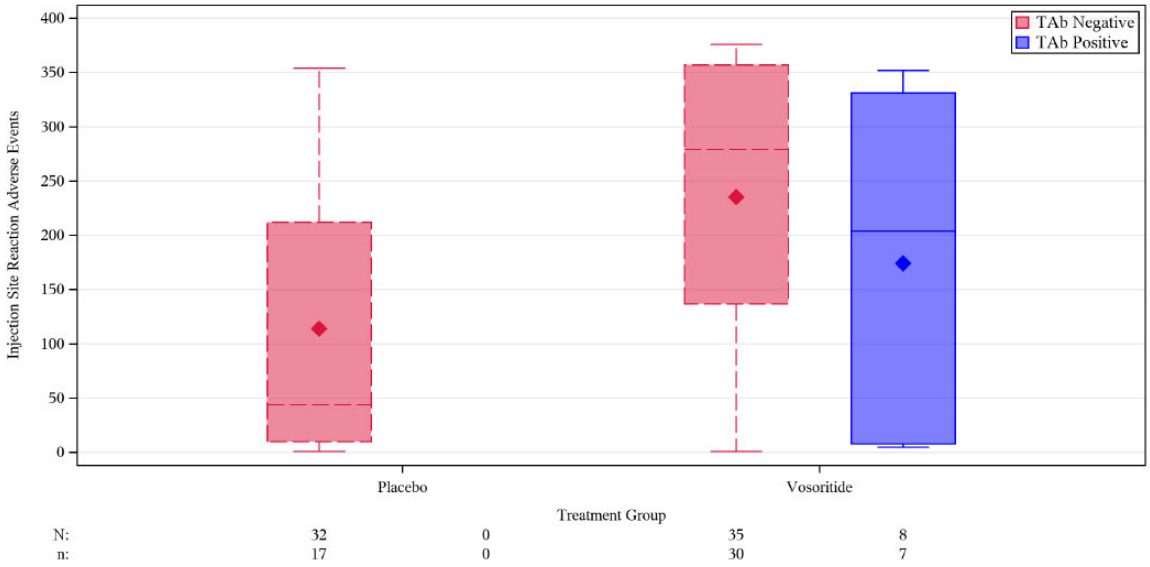
Source: adae.xpt; Software: R
Abbreviations: Cohort 1, included participants aged ≥24 months and <60 months; Cohort 2, included participants aged ≥6 months and <24 months; Cohort 3, included patients aged 0 to <6 months; COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 69. Laboratory Abnormalities – Shift in CTCAE Grade From Baseline to Worst Post-Baseline Values Occurring With Higher Incidence in Vosoritide Than Placebo, Safety Population, Trial 111-206

Laboratory Test	Placebo N=32 n (%)	All Vosoritide N=43 n (%)	Risk Difference[a] Vosoritidev – Placebo
Hemoglobin (g/L) decreased			
Any grade	2 (6.3)	7 (16.7)	10.4
Grade 3 or 4	0	0	0
White blood cell count (10^9/L) decreased			
Any grade	4 (12.5)	18 (41.8)	29.3
Grade 3 or 4	0	0	0
Lymphocyte count (10^9/L) increase			
Any grade	2 (6.3)	12 (27.9%)	21.6
Grade 3 or 4	0	0	0
Alkaline phosphatase (U/L) increased			
Any grade	5 (15.6)	9 (20.9)	5.4
Grade 3 or 4	2 (6.2)	1 (2.3)	-3.9
Alanine aminotransferase (U/L) increased			
Any grade	3 (9.4)	9 (20.9)	11.5
Grade 3 or 4	0	0	0

Source: Excerpted by clinical review team from Tables 14.3.5.2.1.1 and 14.3.5.2.2.1, CSR 111-206
[a] Risk difference column shows difference between All vosoritide and placebo percentages.
Grading Scale: CTCAE v4
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Event; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality

Figure 42. Injection Site Reaction Events by ADA Status, Immunogenicity Population, Trial 111-206



Source: Figure, 14.3.6.5.4A, CSR 111-206
Abbreviations: ADA, antidrug antibodies; N, number of subjects in TAb positive or TAb negative groups; respectively; n, number of subjects reporting injection site reaction events; TAb, total antibody

Table 70. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial 111-206

Characteristic	Randomized Vosoritide N=32 n/N_s (%)	Randomized Placebo N=32 n/N_s (%)	Sentinel Vosoritide N=11 n/N_s (%)	All Subjects Vosoritide N=43 n/N_s (%)
Sex, n (%)				
Female	15/15 (100)	19/19 (100)	3/3 (100)	18/18 (100)
Male	17/17 (100)	13/13 (100)	8/8 (100)	25/25 (100)
Age group, months, n (%)				
0 months to <6 months	8/8 (100)	8/8 (100)	0/0 (N/A)	8/8 (100)
≥6 to <24 months	7/7 (100)	7/7 (100)	7/7 (100)	7/7 (100)
≥24 to <36 months	13/13 (100)	13/13 (100)	13/13 (100)	13/13 (100)
Missing	4/4 (100)	4/4 (100)	11/11 (100)	15/15 (100)
Race, n (%)				
Asian	10/10 (100)	6/6 (100)	1/1 (100)	11/11 (100)
Multiple	1/1 (100)	0/0 (NA)	2/2 (100)	3/3 (100)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	1/1 (100)	0/0 (N/A)	0/0 (NA)
White	21/21 (100)	25/25 (100)	8/8 (100)	29/29 (100)
Ethnicity, n (%)				
Hispanic or Latino	3/3 (100)	3/3 (100)	0/0 (N/A)	3/3 (100)
Not Hispanic or Latino	29/29 (100)	29/29 (100)	11/11 (100)	40/40 (100)
Is in United States, n (%)				
United States	17/17 (100)	18/18 (100)	6/6 (100)	23/23 (100)
Non-United States	15/15 (100)	14/14 (100)	5/5 (100)	20/20 (100)

Source: adae.xpt; Software: R
Risk difference is shown between total treatment and comparator.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; N/A, not applicable; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 71. Postdose Changes in DBP (mmHg), SBP (mmHg), HR (Beats/Mins) From Predose Values, Trial 111-206

Predose Value and Postdose Change From Baseline Value [Mean (SD)]	DBP		SBP		HR	
	Placebo N=32	All Vosoritide N=43	Placebo N=32	All Vosoritide N=43	Placebo N=32	All Vosoritide N=43
Day 1						
Predose	63.3 (13.5)	62.8 (10.6)	105.2 (14.8)	103.3 (13.3)	122.8 (19.7)	125.2 (21.7)
15 min postdose	1.6 (15.5)	2.7 (11.9)	4.4 (14.0)	5.7 (13.0)	-2.4 (18.6)	11.9 (23.1)
30 min postdose	1.0 (16.1)	0.2 (12.8)	3.7 (13.5)	7.0 (11.7)	-2.1 (19.6)	10.3 (20.0)
60 min postdose	-3.2 (16.8)	-2.8 (14.0)	-0.2 (15.7)	2.4 (11.5)	0.6 (18.7)	4.7 (18.9)
90 min postdose	-2.7 (15.5)	-1.2 (15.1)	0.0 (14.7)	4.6 (13.3)	-0.3 (19.9)	1.0 (19.7)
120 min postdose	-1.7 (15.4)	-3.3 (13.5)	1.4 (16.1)	5.0 (15.7)	0.8 (20.6)	-0.3 (22.4)
Day 2						
Predose	59.0 (10.5)	61.7 (10.9)	104.8 (22.3)	101.3 (12.7)	124.3 (19.5)	128.1 (19.5)
15 min postdose	7.0 (16.2)	1.3 (12.8)	3.7 (13.7)	1.5 (15.4)	-1.0 (16.7)	3.7 (24.5)
30 min postdose	0.8 (10.3)	-3.9 (14.7)	0.3 (15.2)	0.3 (14.2)	-4.9 (14.1)	6.0 (17.9)
60 min postdose	4.1 (13.2)	-1.8 (14.9)	5.6 (19.5)	0.6 (13.0)	-2.1 (20.9)	0.3 (22.0)
90 min postdose	3.3 (11.6)	-5.6 (14.3)	0.2 (16.6)	0.8 (14.7)	-3.7 (14.4)	-2.5 (21.5)
120 min postdose	4.0 (15.0)	0.3 (11.7)	3.2 (16.8)	3.5 (14.4)	-1.2 (14.8)	-4.1 (18.4)
Day 8						
Predose	62.2 (12.1)	59.3 (10.1)	103.4 (13.0)	100.3 (14.6)	123.5 (15.2)	128.1 (16.2)
15 min postdose	3.4 (12.6)	-0.7 (11.8)	5.4 (17.0)	2.5 (13.2)	-0.2 (11.0)	5.8 (15.3)
30 min postdose	1.3 (13.9)	0.1 (11.1)	1.5 (15.7)	3.2 (12.2)	2.5 (11.7)	5.7 (16.0)
60 min postdose	1.8 (12.9)	-3.0 (12.5)	5.6 (15.6)	2.3 (14.1)	1.8 (14.3)	-3.5 (17.2)
Week 26						
Predose	61.1 (8.1)	64.2 (11.9)	106.6 (15.4)	105.1 (14.6)	119.4 (21.9)	117.8 (18.1)
15 min postdose	4.4 (14.1)	0.7 (12.5)	1.9 (16.8)	4.1 (14.0)	0.6 (16.7)	13.4 (23.4)
30 min postdose	6.7 (15.5)	-2.1 (16.4)	5.2 (13.6)	1.2 (14.1)	2.6 (16.3)	12.6 (24.2)
60 min postdose	1.6 (11.2)	-5.7 (19.2)	1.3 (17.4)	-1.3 (17.5)	3.6 (21.9)	8.2 (18.4)
Week 52						
Predose	66.2 (9.5)	67.2 (10.1)	108.6 (17.0)	105.8 (17.0)	116.1 (17.7)	116.9 (23.1)
15 min postdose	3.1 (10.7)	-0.7 (13.8)	6.8 (15.8)	4.8 (13.7)	-0.6 (13.5)	8.8 (19.8)
30 min postdose	2.5 (18.5)	-5.4 (16.2)	10.6 (18.3)	2.1 (13.3)	3.3 (21.7)	12.9 (21.4)
60 min postdose	-0.7 (12.1)	-7.7 (15.7)	0.8 (20.4)	0.5 (16.3)	-2.2 (14.3)	4.9 (20.4)

Source: Excerpted by clinical review team from Table 14.3.6.1.2.1, CSR, Trial 111-206
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; min, minutes; SBP, Systolic blood pressure; SD, standard deviation

Table 72. Change From Baseline to Week 52 in Lower Limb X-Rays

Measure (unit)	All Vosoritide N=43	Vosoritide N=32	Placebo N=32
Left femur length (cm)			
n	17	16	14
Mean (SD)	2.29 (0.58)	2.29 (0.60)	2.01 (0.62)
Median	2.30	2.25	2.10
Min, max	1.5, 3.2	1.5, 3.2	1.1, 2.9
Right femur length (cm)			
n	17	16	14
Mean (SD)	2.35 (0.49)	2.34 (0.51)	2.20 (0.73)
Median	2.30	2.20	2.20
Min, max	1.7, 3.2	1.7, 3.2	1.2, 3.2
Left fibula length (cm)			
n	40	30	27
Mean (SD)	2.00 (0.61)	2.03 (0.64)	1.97 (0.69)
Median	2.00	2.10	2.00
Min, max	0.3, 3.0	0.3, 2.9	0.9, 4.1
Right fibula length (cm)			
n	39	29	27
Mean (SD)	2.00 (0.64)	2.07 (0.64)	1.89 (0.75)
Median	2.10	2.10	1.80
Min, max	0.6, 3.2	0.6, 3.2	1.0, 4.5
Left tibia length (cm)			
n	40	30	27
Mean (SD)	1.92 (0.55)	1.93 (0.58)	1.69 (0.70)
Median	2.05	2.10	1.60
Min, max	0.7, 2.8	0.7, 2.8	0.5, 3.4
Right tibia length (cm)			
n	39	29	27
Mean (SD)	1.96 (0.57)	1.97 (0.62)	1.68 (0.77)
Median	2.00	2.10	1.50
Min, max	0.7, 3.0	0.7, 3.0	0.6, 4.0
Left femur length (cm) to tibia length (cm) ratio			
n	17	16	14
Mean (SD)	-0.03 (0.06)	-0.04 (0.06)	-0.05 (0.05)
Median	-0.02	-0.03	-0.05
Min, max	-0.1, 0.1	-0.1, 0.1	-0.1, 0.0
Right femur length (cm) to tibia length (cm) ratio			
n	17	16	14
Mean (SD)	-0.05 (0.06)	-0.05 (0.06)	-0.02 (0.03)
Median	-0.06	-0.06	-0.03
Min, max	-0.2, 0.1	-0.2, 0.1	-0.1, 0.0

Source: Table 14.3.6.4.1.1, CSR 111-206
Abbreviations: max, maximum; min, minimum; N, number of subjects; n, number of subjects with specific lower limb; SD, standard deviation

Table 73. Lumbar Spine Angles by Cohort and Overall, in Trial 111-206 (Safety Population)

	Sacral Tilt Angle (deg)		Lordosis Angle (deg)		Kyphosis Angle (deg)	
Age cohort	**Placebo**	**Vosoritide**	**Placebo**	**Placebo**	**Vosoritide**	**Placebo**
All						
N	32	32	32	32	32	32
Baseline, mean (SD)	26.1 (14.7)	23.2 (13.6)	38.8 (14.8)	31.4 (16.0)	24.6 (13.5)	22.5 (11.1)
Change at Week 52, mean (SD)	5.7 (15.9)	13.4 (12.5)	8.4 (14.2)	15.2 (17.4)	-2.1 (10.3)	-5.1 (12.9)
Cohort 1 (≥24 to <60m)						
N	16	15	16	15	16	15
Baseline, mean (SD)	31.8 (12.7)	30.0 (15.3)	46.6 (12.2)	40.3 (14.1)	21.9 (16.7)	17.9 (7.9)
Change at Week 52, mean (SD)	5.2 (15.0)	8.9 (10.0)	4.1 (14.7)	5.5 (11.3)	-4.6 (9.6)	-6.1 (9.1)
Cohort 2 (≥6 to <24m)						
N	8	8	8	8	8	8
Baseline, mean (SD)	21.3 (11.1)	14.3 (7.7)	33.1 (12.7)	24.6 (15.5)	27.1 (10.6)	32.8 (9.5)
Change at Week 52, mean (SD)	6.7 (7.8)	27.0 (7.1)	11.3 (9.5)	25.9 (17.3)	-1.0 (8.3)	-13.0 (11.5)
Cohort 3 (3-<6m)						
N	8	9	8	9	8	9
Baseline, mean (SD)	19.5 (18.2)	19.7 (8.4)	29.0 (14.4)	22.7 (12.3)	27.3 (7.8)	21.1 (11.9)
Change at Week 52, mean (SD)	5.9 (22.6)	7.5 (10.8)	13.4 (15.8)	21.6 (18.6)	1.3 (12.7)	3.4 (16.0)

Source, Applicant's response to Agency's IR dated May 26, 2023
Change from baseline is based on the subjects with available measurements at both time points.
Abbreviations: deg, degree; m, months; N, number of subjects; SD, standard deviation

Table 74. Proportion of Subjects With a Change in Lumbar Spine Angles of ≥5 to <10 and ≥10 Degrees by Cohort and Overall, in Trial 111-206 (Safety Population)

	All		Cohort 1 (≥24 to <60mo)		Cohort 2 (≥6 to <24mo)		Cohort 3 (3 to <6mo)	
Parameter	**Vosoritide (N=32)**	**Placebo (N=32)**	**Vosoritide (N=15)**	**Placebo (N=16)**	**Vosoritide (N=8)**	**Placebo (N=8)**	**Vosoritide (N=9)**	**Placebo (N=8)**
Subjects with an increase in sacral tilt (deg) at Week 52, n (%)[a]								
≥5 to <10	2 (6.3)	6 (18.8)	2 (13.3)	2 (12.5)	0	3 (37.5)	0	1 (12.5)
≥10	21 (65.6)	10 (31.3)	8 (53.3)	5 (31.3)	8 (100.0)	1 (12.5)	5 (55.6)	4 (50.0)
Subjects with an increase in lordosis angle (deg) at Week 52, n (%)[a]								
≥5 to <10	3 (9.4)	1 (3.1)	1 (6.7)	0	0	0	2 (22.2)	1 (12.5)
≥10	17 (53.1)	14 (43.8)	5 (33.3)	5 (31.3)	7 (87.5)	4 (50.0)	5 (55.6)	5 (62.5)
Subjects with an increase in kyphosis angle (deg) at Week 52, n (%)[a]								
≥5 to <10	2 (6.3)	2 (6.3)	0	2 (12.5)	0	0	2 (22.2)	0
≥10	4 (12.5)	4 (12.5)	2 (13.3)	0	0	1 (12.5)	2 (22.2)	3 (37.5)

Source, Applicant's response to Agency's IR dated May 26, 2023
Percentages calculated using the total number of subjects in the safety population (N for each treatment groups) as the denominator
All increases are comparing results at Week 52 relative to the baseline assessment
Abbreviations: deg, degree; mo, months; N, number of subjects assessed; n, number of subjects with event

17.2. Trial 111-209

Table 75. Magnetic Resonance Imaging of Brain Stem/Skull, Trial 111-209, Safety Population

Measure (Unit)	Treatment Group	Baseline	Change From Baseline to Week 52	Percent Change From Baseline to Week 52	Change From Baseline to Week 104	Percent Change From Baseline to Week 104
Volume of Face (cm^3)	SoC alone (N=9)	n=9	n=7	n=7	n=5	n=5
		350.223 (47.614)	121.664 (28.111)	34.16 (11.44)	220.480 (62.629)	62.79 (23.04)
	SoC + vos (N=11)	n=11	n=6	n=6	n=2	n=2
		357.456 (98.698)	155.303 (46.701)	52.93 (36.66)	208.385 (65.796)	56.12 (23.51)
Volume of Sinus (cm^3)	SoC alone (N=9)	n=9	n=7	n=7	n=5	n=5
		1.707 (0.814)	2.481 (2.606)	128.64 (109.11)	6.998 (5.206)	327.52 (230.01)
	SoC + vos (N=11)	n=11	n=6	n=6	n=2	n=2
		1.012 (0.637)	1.650 (1.145)	306.65 (343.23)	4.265 (2.906)	369.16 (329.15)
Volume of Calvarium (cm^3)	SoC alone (N=9)	n=9	n=7	n=7	n=5	n=5
		1050.938 (215.393)	462.410 (151.073)	46.70 (26.35)	650.258 (225.808)	67.28 (40.37)
	SoC + vos (N=11)	n=11	n=6	n=6	n=2	n=2
		1025.060 (277.608)	452.753 (208.414)	56.16 (46.09)	666.600 (17.565)	61.31 (0.83)
Area of Foramen Magnum (cm^2)	SoC alone (N=9)	n=9	n=7	n=7	n=5	n=5
		1.144 (0.347)	0.171 (0.243)	20.20 (26.57)	0.340 (0.416)	41.59 (46.59)
	SoC + vos (N=11)	n=11	n=6	n=6	n=2	n=2
		1.164 (0.329)	0.033 (0.308)	4.62 (22.31)	0.550 (0.354)	50.00 (42.43)
Area of Spinal Cord at the Foramen Magnum Level (cm^2)	SoC alone (N=9)	n=9	n=7	n=7	n=5	n=5
		0.544 (0.113)	0.014 (0.135)	3.47 (26.57)	0.040 (0.089)	0.150 (0.212)
	SoC + vos (N=11)	n=11	n=6	n=6	n=2	n=2
		0.536 (0.150)	0.050 (0.187)	11.51 (33.77)	10.00 (22.36)	21.43 (30.30)
Whole Brain Total Volume (cm^3)	SoC alone (N=9)	n=9	n=7	n=7	n=5	n=5
		757.940 (146.736)	307.604 (108.279)	42.38 (24.08)	432.804 (166.835)	60.70 (36.76)
	SoC + vos (N=11)	n=11	n=6	n=6	n=2	n=2
		753.074 (197.292)	324.528 (123.926)	52.44 (37.90)	608.495 (28.899)	74.37 (0.86)

Measure (Unit)	Treatment Group	Baseline	Change From Baseline to Week 52	Percent Change From Baseline to Week 52	Change From Baseline to Week 104	Percent Change From Baseline to Week 104
Ventricles Total Volume (cm^3)	SoC alone (N=9)	n=9	n=7	n=7	n=5	n=5
		45.322 (43.705)	49.734 (38.857)	187.28 (187.81)	55.596 (41.656)	258.71 (218.21)
	SoC + vos (N=11)	n=11	n=6	n=6	n=2	n=2
		35.656 (28.146)	10.595 (16.161)	137.49 (213.50)	10.615 (0.870)	32.21 (1.66)

Source: Excerpted from Table IR230814Q1.14.2.3.3, Response to Agency Information Request, dated August 25, 2023
Abbreviations: N, number of subjects; n, number of subjects with specific change; SoC, standard of care; vos, vosoritide

APPEARS THIS WAY
ON ORIGINAL

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The inspection for this sNDA consisted of two domestic clinical study sites, namely Drs. John Phillips (Site #0003) and William Wilcox (Site #0184). Based on the inspection of the two clinical sites, the Office of Scientific Investigation (OSI) concluded that the inspectional findings support validity of data as reported by the Applicant under this sNDA. Refer to Clinical Inspection Summary report in DARRTS, dated July 27, 2023, for further details.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 76). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 76. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	NA
1 INDICATIONS AND USAGE	Applicant proposed to remove "who are 5 years of age and older" in the indication statement to permit use of Voxzogo in all pediatric patients. DGE concurs with the updated indication based upon the results of Studies 206 and 208
2 DOSAGE AND ADMINISTRATION	Section 2.2: DGE reformatted Table 1 recommended dosage table to have the dosing column follow the weight column. Table 1 includes dosage recommendation for pediatric patients with weight between 3 to 9 kg. DGE added Table 2 to include reconstitution volume for each vial strength.
4 CONTRAINDICATIONS	NA
5 WARNINGS AND PRECAUTIONS	NA
6 ADVERSE REACTIONS	Applicant proposed to update section 6.1 to include summary of adverse reactions for pediatric patients less than 5 years of age. DGE concurs with description of the study design, including the age of the youngest patient. In text, rash was added as a new adverse reaction in patients less than 5 years of age, compared to greater than 5 years. Also, DGE agreed with Applicant's addition of laboratory data reflecting an increase in alkaline phosphatase levels-based data from Study 111-301.
7 DRUG INTERACTIONS	NA
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Section 8.4 revised to incorporate establishment of safety and effectiveness in entire pediatric population statement in the first sentence. The second paragraph summarized the evidence supporting approval of Voxzogo for the approved pediatric population.
9 DRUG ABUSE AND DEPENDENCE	NA
10 OVERDOSAGE	NA
12 CLINICAL PHARMACOLOGY	Section 12.3: Based upon PK in patients less than 5 years, age was determined to have no effect on PK. The summary sentence under Specific Populations was updated with age and weight from the 5 years and younger ped pts to reflect the effect of age in all pediatric populations on PK. Results from in vitro studies with transporters were added. Section 12.6: Applicant moved summary of immunogenicity in patients aged 5 years and older from section 6.2 to 12.6 and included summary from patients less than 5 years of age. DGE edited the introductory statement, per the Immunogenicity labeling guidance. ADA rates for pediatric patients less than 5 years were updated based upon studies 206 and 208.
13 NONCLINICAL TOXICOLOGY	No revisions
14 CLINICAL STUDIES	(b) (4) [redacted]
17 PATIENT COUNSELING INFORMATION	NA
Product Quality Sections (i.e.,	Section 3: DGE added drug name "vosoritide" following the listed

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	strengths in the description of the product. Sections 11: OPQ recommended the Applicant list the inactive ingredients in alphabetical order.

Source: [Please provide a source for this table.]
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): PI, Prescribing Information; OPQ, Office of Pharmaceutical Quality

23.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information

24. Postmarketing Requirements and Commitments

NDA 214938 was approved on 11/19/2021 under accelerate approval (AA) for the indication to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. This approval letter included AA PMR 4134-1:

> *Conduct an open-label, external-controlled trial in subjects with achondroplasia (ACH) 5 years of age and older with open epiphyses to measure the effect of vosoritide on final adult height. The trial should also evaluate disproportionality and bone age as secondary endpoints. The safety endpoints related to the drug (e.g., blood pressure) or to the disease itself that may improve or worsen with long-term treatment (e.g., Neurological complications, bone deformities, sleep apnea) should also be included. The total exposure to vosoritide for each patient should be sufficient to meet the study's stated objectives. The vosoritide-treated trial population should include subjects who are already enrolled and treated with vosoritide in Studies 111-2024 /2055, and 111-3016 /3027 and/or treatment-naïve subjects with a genetically confirmed ACH diagnosis.*

The current supplement proposes to expand the originally approved indication to pediatric patients with achondroplasia who are less than 5 years of age with open epiphyses. Since NDA 214938/S-002 will be also granted accelerated approval for this new indication and because postmarketing requirement (PMR) 4134-1 describes only patients older than 5 years of age, the review team proposed and discussed with the Applicant a new PMR for the expanded indication:

> *Conduct an open-label, external-controlled trial in subjects with achondroplasia (ACH) with open epiphyses to measure the effect of vosoritide on final adult height. The trial should also evaluate disproportionality and bone age as secondary endpoints. The safety endpoints related to the drug (e.g., blood pressure) or to the disease itself that may improve or worsen with long-term treatment (e.g., neurological complications, bone*

deformities, sleep apnea) should also be included. The total exposure to vosoritide for each patient should be sufficient to meet the study's stated objectives. The vosoritide-treated trial population should include subjects who are already enrolled and treated with vosoritide in Studies 111-202 /205, 111-301/302 and 111-206/208, and/or treatment-naïve subjects with a genetically confirmed ACH diagnosis.

Therefore, PMR 4134-1 will be released and superseded by a new PMR 4134-2 which will expand the PMR description to require collection of data from the trial for all ages.

25. Financial Disclosure

Table 77. Covered Clinical Studies: [111-206/208]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 236		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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27. Review Team

Table 78. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Linda Galgay, Elisabeth Hanan
Nonclinical reviewer	Daniel Minck
Nonclinical team leader	David Carlson
OCP reviewers	Hari Thanukrishnan, Elyes Dahmane
OCP team leaders	Li Li, Justin Earp
Clinical reviewer	Geanina Roman-Popoveniuc
Clinical team leader	Marina Zemskova
Biometrics reviewers	Satyajit Ghosh, Jiwei He,
Biometrics team leaders	Feng Li, Yong Ma, Clara Kim
Cross-disciplinary team leader	Marina Zemskova
Division director, Deputy (clinical)	Naomi Lowy

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 79. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Rohit Kolhatkar, Sarah Zimmermann, Ramesh Raghavachari,
OPDP	Charuni Shah
OSI	Ling Yang, Min Lu
OSE/DEPI	Po-Yin Chang, Yandong Qiang, Wei Hua
OSE/DMEPA	Peggy Rahbani, Madhuri Patel
DPMH	Ethan Hausman, Shetarra Walker, Jeannie Limpert, Tamara Johnson

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH Division of Pediatric and Maternal Health

Reviewer Signatures

See next page

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Deputy Director	Naomi Lowy, MD Office of Cardiology, Hematology, Endocrinology, and Nephrology Division of General Endocrinology	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: ALL	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: {See appended electronic signature page}				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Cross-Disciplinary Team Lead	Marina Zemskova, MD Office of Cardiology, Hematology, Endocrinology, and Nephrology Division of General Endocrinology	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: ALL	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: {See appended electronic signature page}				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Primary Reviewer	Geanina Roman-Popoveniuc, MD Office of Cardiology, Hematology, Endocrinology, and Nephrology Division of General Endocrinology	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1, 3, 4, 6, 7, 8.3, 8.4, 10, 11, 15, 16.1, 17, 22, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Geanina Roman-popoveniuc -S Digitally signed by Geanina Roman-popoveniuc -S Date: 2023.10.15 19:41:01 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Management CPMS	Elisabeth A. Hanan, MS Other Division of Regulatory Operations for Cardiology, Hematology, Endocrinology and Nephrology	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Section:12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature/date/time stamp: Elisabeth Hanan -S Digitally signed by Elisabeth Hanan -S Date: 2023.10.17 12:49:43 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Management Regulatory Project Manager	Linda V. Galgay, RN, MSN Other Division of Regulatory Operations for Cardiology, Hematology, Endocrinology and Nephrology	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Section: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature/date/time stamp: Linda V. Galgay -S Digitally signed by Linda V. Galgay -S Date: 2023.10.15 14:15:27 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biometrics Team Leader	Feng Li, PhD Office of Biostatistics Division of Biometrics II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 16.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Feng Li -S Digitally signed by Feng Li -S Date: 2023.10.16 09:01:09 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biometrics Primary Reviewer	Satyajit Ghosh, PhD Office of Biostatistics Division of Biometrics II	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 16.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Satyajit Ghosh -S (Affiliate) Digitally signed by Satyajit Ghosh -S (Affiliate) Date: 2023.10.16 09:13:21 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Team Leader	Li Li, PhD Office of Clinical Pharmacology/Genome Targeted Therapy Group Division of Cardiometabolic and Endocrine Pharmacology	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Li Li -S Digitally signed by Li Li -S Date: 2023.10.16 09:22:50 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Primary Reviewer	Harisudhan Thanukrishnan, PhD Office of Clinical Pharmacology/Genome Targeted Therapy Group Division of Cardiometabolic and Endocrine Pharmacology	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Harisudhan Thanukrishnan -S Digitally signed by Harisudhan Thanukrishnan -S Date: 2023.10.16 13:04:20 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology/Pharmacometrics Team Leader	Justin Earp, PhD Office of Clinical Pharmacology/Genome Targeted Therapy Group Division of Pharmacometrics	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.1, 8.1, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Justin C. Earp -S Digitally signed by Justin C. Earp -S Date: 2023.10.17 15:52:32 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology/Pharmacometrics Primary Reviewer	Elyes Dahmane, PhD Office of Clinical Pharmacology/Genome Targeted Therapy Group Division of Pharmacometrics	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.1, 8.1, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature/date/time stamp:

Elyes Dahmane -S Digitally signed by Elyes Dahmane -S
Date: 2023.10.16 15:35:54 -04'00'

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacology/Toxicology Team Leader	David B. Carlson, PhD Office of Cardiology, Hematology, Endocrinology, and Nephrology Division of Pharmacology Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature/date/time stamp:

David B. Carlson -S Digitally signed by David B. Carlson -S
Date: 2023.10.16 15:48:44 -04'00'

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacology/Toxicology Primary Reviewer	Daniel R. Minck, PhD Office of Cardiology, Hematology, Endocrinology, and Nephrology Division of Pharmacology Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Daniel R. Minck -S Digitally signed by Daniel R. Minck -S Date: 2023.10.16 13:33:18 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Deputy Director	Wei Hua, MD, PhD, MS, MHS Office of Surveillance and Epidemiology Division of Epidemiology I	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Wei Hua -S Digitally signed by Wei Hua -S Date: 2023.10.17 13:14:53 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Team Leader	Yandong Qiang, MD, PhD, MHS, MPH Office of Surveillance and Epidemiology Division of Epidemiology I	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature/date/time stamp:

Yandong Qiang -S

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Date: 2023.10.17 11:56:07 -04'00'

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Primary Reviewer	Po-Yin Chang, PhD Office of Surveillance and Epidemiology Division of Epidemiology I	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature/date/time stamp: Yandong Qiang as Proxy

Yandong Qiang -S

Digitally signed by Yandong Qiang -S
Date: 2023.10.17 11:57:38 -04'00'

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Supervisor	Clara Y. Kim, PhD Office of Biostatistics Division of Biometrics VII	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature/date/time stamp:

Clara Y. Kim -S
Digitally signed by Clara Y. Kim -S
Date: 2023.10.17 13:28:40 -04'00'

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Team Leader	Yong Ma, PhD Office of Biostatistics Division of Biometrics VII	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature/date/time stamp:

Yong Ma -S
Digitally signed by Yong Ma -S
Date: 2023.10.16 16:24:54 -04'00'

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Primary Reviewer	Jiwei He, PhD Office of Biostatistics Division of Biometrics VII	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Jiwei He -S Digitally signed by Jiwei He -S Date: 2023.10.16 16:10:50 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Product Quality Supervisor	Ramesh Raghavachari, PhD Other Division of Post Marketing Activities I	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Section: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Ramesh Raghavachari -S Digitally signed by Ramesh Raghavachari -S Date: 2023.10.17 15:23:08 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Product Quality Primary Reviewer	Sarah Zimmermann, PhD Office of Pharmaceutical Quality Division of Post Marketing Activities I	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Section: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature/date/time stamp:

Sarah C. Zimmermann -S

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Date: 2023.10.17 14:37:31 -04'00'

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/s/

MARINA ZEMSKOVA
10/19/2023 09:47:29 AM

NAOMI N LOWY
10/20/2023 11:32:32 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214938Orig1s002

OTHER REVIEWS

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Application: NDA 214938/S-002

Name of Drug: Voxzogo (vosoritide) for injection

Applicant: Biomarin Pharmaceuticals, Inc.

Material Reviewed:

S-002 Submission Date: December 21, 2022
Amendments (Labeling): April 20, September 6, 28, and October 12, 19, 2023

Background and Summary

NDA 214938, approved under accelerated approval on November 19, 2021, provides for the use of Voxzogo (vosoritide) for injection to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses.

NDA 214938/S-002 provides for expansion of the approved indication to include pediatric patients less than 5 years of age.

Review

The PI and PPI proposed in S-002 were compared to the currently approved PI and PPI approved November 19, 2021. A comparison is attached to this review.

Changes to the Prescribing Information and PPI were found acceptable by OPDP (August 1, 2023), DMPP (August 3, 2023), DMEPA (April 12, 2023), and the Division of General Endocrinology (Naomi Lowy, LaiMing Lee, Marina Zemskova).

Recommendations

- Issue an approval letter for NDA 214938/S-002.

Linda Galgay October 20, 2023

_____

Senior Regulatory Project Manager Date

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/s/

LINDA V GALGAY
10/20/2023 04:49:59 PM

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:	August 3, 2023
To:	Linda V. 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)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC 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)
Drug Name (established name):	VOXZOGO (vosoritide)
Dosage Form and Route:	for injection, for subcutaneous use
Application Type/Number:	NDA 214938
Supplement Number:	S-002
Applicant:	BioMarin Pharmaceutical Inc.

1 INTRODUCTION

On December 21, 2022, BioMarin Pharmaceutical Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy for New Drug Application 214938/ S-002 VOXZOGO (vosoritide) for injection, for subcutaneous use. The purpose of this PAS is to propose the indication for the treatment of pediatric patients with achondroplasia less than 5 years of age with open epiphyses.

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 December 29, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VOXZOGO (vosoritide) for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft VOXZOGO (vosoritide) PPI received on December 21, 2022, and received by DMPP and OPDP on July 26, 2023.
- Draft VOXZOGO (vosoritide) Prescribing Information (PI) received on December 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 26, 2023.

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 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 we:

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

4 CONCLUSIONS

The PPI is 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 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.

Please let us know if you have any questions.

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/s/

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CHARUNI P SHAH
08/03/2023 10:49:32 AM

MARCIA B WILLIAMS
08/03/2023 10:57:28 AM

LASHAWN M GRIFFITHS
08/03/2023 01:27:15 PM

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

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

Memorandum

Date: August 1, 2023

To: Geanina Roman-Popoveniuc, MD., Clinical Reviewer
Division of General Endocrinology (DGE)

Linda Galgay, Regulatory Project Manager (DGE)

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

CC: Susannah O'Donnell, Team Leader, OPDP

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

NDA: 214938

Background:

In response to DGE's consult request dated December 22, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and Patient Information (PPI) for VOXZOGO (vosoritide) for injection, for subcutaneous use (Voxzogo). This supplement provides for a new indication for children greater than 4.4 months of age.

PI/MG:

OPDP's review of the proposed PI is based on the draft labeling provided via email by DGE on July 26, 2023, and we have no comments at this time.

OPDP comments on the proposed PPI will be sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP).

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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/s/

CHARUNI P SHAH
08/01/2023 09:48:16 AM

Clinical Inspection Summary

Date	July 27, 2023
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Geanina Roman-Popoveniuc, Physician, Clinical Reviewer Marina Zemskova, Physician, Clinical Team Leader Linda Galgay, Senior Regulatory Health Project Manager Division of General Endocrinology
NDA #	214938/S-002
Applicant	BioMarin Pharmaceutical Inc.
Drug	Voxzogo for injection (vosoritide, BMN111)
NME (Yes/No)	No
Review Priority	Priority
Proposed Indication(s)	To increase linear growth in pediatric patients younger than 5 years of age with achondroplasia and with open epiphyses
Consultation Request Date	January 20, 2023
Summary Goal Date	August 21, 2023
Action Goal Date	October 20, 2023
PDUFA Date	October 21, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 111-206 entitled “A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months” were submitted to support this supplemental New Drug Application (sNDA) for Voxzogo for injection indicated to increase linear growth in pediatric patients with achondroplasia (ACH) who are younger than 5 years old with open epiphyses. Two domestic clinical investigators (CIs): Drs. John Phillips (Site #0003) and William Wilcox (Site #0184) were inspected for the submitted study.

Based on the overall inspection results of these two CIs and the regulatory assessments, the data generated by these two CI sites are verifiable. Study 111-206 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Achondroplasia (ACH), caused by a gain-of-function mutation in FGFR3, a negative regulator of chondrocyte proliferation and differentiation, is a rare disease with a prevalence of 1/25000 in the US.

Voxzogo (vosoritide; BMN 111) for injection was approved on 11/19/2021 under NDA 214938 for a subset of ACH patients to increase linear growth in pediatric patients older than 5 years with ACH and open epiphyses.

BioMarin Pharmaceutical, Inc. (BioMarin) submitted an efficacy supplement S-002 to NDA 214938 Voxzogo (vosoritide, BMN111) on 12/21/2022 to extend the indication to pediatric patients younger than 5 years of age with ACH and open epiphyses. The submission meets the mission critical criteria as there is an unmet medical need.

Study 111-206

Study 111-206 was a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of BMN 111 in infants and young children aged 0 to < 60 months with ACH.

The primary study objectives were to evaluate the safety and tolerability of vosoritide in children aged 0 to < 60 months with ACH; and to evaluate the effect of vosoritide on the length/height Z-score changes from baseline.

The primary efficacy endpoint was the change from baseline in height Z-score at Week 52.

Study Procedures:

- Enrolled subjects entered one of the three cohorts based on age:
  - Cohort 1: age ≥ 24 to < 60 months stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
  - Cohort 2: age ≥ 6 to < 24 months stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
  - Cohort 3: age 0 to < 6 months; treatment begins at ≥ 3 months to < 6 months after 3 months of observation.
- Non-interventional baseline growth data were collected for at least 6 months for Cohorts 1 and 2; and at least 3 months for Cohort 3 (Observational Study 111-901).
- Subjects were randomized at a 1:1 ratio to receive daily subcutaneous (SC) injection of either vosoritide or placebo. At each cohort, at least three sentinel subjects received vosoritide for short-term safety and PK evaluation, before the rest of the subjects were randomized.
- The daily SC vosoritide dose was determined after evaluation of the PK data of sentinel participants for each cohort.
  - Cohort 1: 15 μg/kg/day
  - Cohort 2: initially 15 μg/kg/day; adjusted to 30 μg/kg/day
  - Cohort 3: 30 μg/kg/day.
- Study duration: 52 weeks of double-blind treatment + 2 weeks of safety follow up.
- Following completion of the study, all subjects were eligible to participate the open-label extension study 111-208 to evaluate the long term safety and efficacy.

The study enrolled 75 subjects [35 subjects (4 sentinel, 15 vosoritide and 16 placebo) in Cohort 1; 20 subjects (4 sentinel, 8 vosoritide and 8 placebo) in Cohort 2; and 20 subjects (3 sentinel, 9 vosoritide and 8 placebo) in Cohort 3] and randomized 64 subjects at 16 study sites in four countries: US, Australia, United Kingdom and Japan. The first subject was enrolled on (b) (6)

and the last subject's last visit was on (b) (6) A total of 73 subjects completed the study (11 sentinel, 31 on vosoritide and 31 on placebo).

III. RESULTS

1. John A. Phillips III, M.D. (Sites #0003)
DD-2205 Medical Center North
1161 21st Avenue South
Nashville, TN 37232-0001

This CI was inspected on 03/20-24/2023 as a data audit for Study 111-206. This was the second FDA inspection of Dr. Phillips.

For the inspected study, the site screened 9 subjects and enrolled 7 subjects, with 6 subjects completed the study. (b) (6) (b) (6) (b) (6). The first subject consented on (b) (6) and the last subject completed the study on (b) (6). Source records for all 9 screened subjects were reviewed.

The inspection reviewed the study protocol and amendments, Informed Consent Forms (ICFs)/ child assent and versions, documentation of eligibility criteria and enrollment logs, medical records [including visit data, laboratory tests, physical exam results, adverse events (AEs) and serious AEs (SAEs) reports], investigational product (IP) accountability records, paper Case Report Forms (CRFs) with electronic CRFs (eCRFs) entries, electronic data capture (EDC) system and the audit trail, protocol deviations and related regulatory documents [e.g., Institutional Review Board (IRB) approvals and communications, staff trainings, monitoring log, ClinicalTrials.gov registration, records retention, financial disclosures and delegation of authority].

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint of change from baseline in height Z-score was verified with no discrepancy noted. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected study subjects, with no deficiencies reported.

2. William R. Wilcox, M.D., Ph.D. (Site #0184)
101 Woodruff Circle, Suite 7130
Atlanta, GA 30322

This CI was inspected on 03/20-23/2023 as a data audit for Study 111-206. This was the second FDA inspection of Dr. Wilcox.

The study site screened 10 subjects, enrolled 8 subjects, with 7 subjects completed the study. The first subject consented on (b) (6) and the last subject's last visit was on (b) (6). Source records for all 10 screened subjects were reviewed.

The inspection reviewed the study protocol and amendments, ICFs/child assent and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, concomitant medications, AEs and SAEs reports), IP accountability records, subjects' diaries, paper CRFs with eCRFs entries and the audit trails, the EDC system, protocol deviations and related regulatory documents (e.g., IRB approvals and communications, staff trainings, monitoring procedure and logs, ClinicalTrials.gov registration, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint of change from baseline in height Z-score was verified with no discrepancies noted. There were no underreporting of AEs or SAEs.

There was one discussed item that Subject # (b) (6) (b) (6) was not assessed with a follow up.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\NDA 214938/S-002
DGE\CDTL\Marina Zemskova
DGE\Reviewer\Geanina Roman-Popoveniuc
DGE\Project Manager\Linda Galgay
OSI\Director\David Burrow
OSI\Deputy Director\Laurie Muldowney
OSI\DCCE\Division Director\Kassa Ayalew
OSI\DCCE\GCPAB\Branch Chief\Jenn Sellers
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

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MIN LU
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JENN W SELLERS
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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:	April 12, 2023
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 214938/S-002
Product Name and Strength:	Voxzogo (vosoritide) for injection, 0.4 mg/vial, 0.56 mg/vial, and 1.2 mg/vial
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	BioMarin Pharmaceutical Inc.
FDA Received Date:	December 21, 2022
TTT ID #:	2023-3461
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

BioMarin Pharmaceutical Inc. submitted a supplement for Voxzogo (vosoritide) for injection, to expand the label to include treatment of pediatric patients with achondroplasia less than 5 years of age with open epiphyses. Subsequently, the Division of General Endocrinology (DGE) requested that we review Voxzogo Prescribing Information (PI) and Patient Information (PPI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note this supplement provides for revisions to the Prescribing Information (PI) and Patient Information (PPI) for the proposed indication of pediatric patients with achondroplasia less than 5 years of age with open epiphyses. The currently approved dosage form and strengths support the proposed new indication and proposed dose.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Voxzogo Prescribing Information (PI) and Patient Information (PPI) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Voxzogo (vosoritide) for injection received on December 21, 2022, from Biomarin Pharmaceutical Inc.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Voxzogo (vosoritide) for injection</th></tr>
<tr><td>Initial Approval Date</td><td>November 19, 2021</td></tr>
<tr><td>Active Ingredient</td><td>vosoritide</td></tr>
<tr><td>Indication</td><td>Current:
to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses

Proposed:
to increase linear growth in pediatric patients with achondroplasia with open epiphyses</td></tr>
<tr><td>Route of Administration</td><td>subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>for injection</td></tr>
<tr><td>Strength</td><td>0.4 mg/vial, 0.56 mg/vial, and 1.2 mg/vial</td></tr>
<tr><td>Dose and Frequency</td><td>Recommended dosage based on patient’s actual body weight. Administered by subcutaneous injection once daily.

Table 1: Recommended VOXZOGO Daily Dosage and Injection Volume
<table>
<tr><th>Actual Body Weight*</th><th>Vial Strength for Reconstitution**</th><th>Dose</th><th>Injection Volume</th></tr>
<tr><td>3 kg</td><td>0.4 mg</td><td>0.096 mg</td><td>0.12 mL</td></tr>
<tr><td>4 kg</td><td>0.4 mg</td><td>0.12 mg</td><td>0.15 mL</td></tr>
<tr><td>5 kg</td><td>0.4 mg</td><td>0.16 mg</td><td>0.2 mL</td></tr>
<tr><td>6-7 kg</td><td>0.4 mg</td><td>0.2 mg</td><td>0.25 mL</td></tr>
<tr><td>~~10~~8-11 kg</td><td>0.4 mg</td><td>0.24 mg</td><td>0.3 mL</td></tr>
<tr><td>12-16 kg</td><td>0.56 mg</td><td>0.28 mg</td><td>0.35 mL</td></tr>
<tr><td>17-21 kg</td><td>0.56 mg</td><td>0.32 mg</td><td>0.4 mL</td></tr>
<tr><td>22-32 kg</td><td>0.56 mg</td><td>0.4 mg</td><td>0.5 mL</td></tr>
<tr><td>33-43 kg</td><td>1.2 mg</td><td>0.5 mg</td><td>0.25 mL</td></tr>
<tr><td>44-59 kg</td><td>1.2 mg</td><td>0.6 mg</td><td>0.3 mL</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>white to yellow lyophilized powder for reconstitution and is provided as a co-pack which includes ten:
• Sterile, single-dose 2 mL glass vials containing VOXZOGO
• Diluent (Sterile Water for Injection, USP) in a single-dose prefilled syringe
• Diluent transfer needles (23 gauge)</td></tr>
</table>

<table>
<tr><td></td><td>• Single-dose administration syringes (30 gauge) both with needle retraction safety devices
<table>
<tr><th>Strength (mg)</th><th>Diluent (mL)</th><th>Co-pack NDC Number</th><th>Flip Cap Color</th></tr>
<tr><td>0.4</td><td>0.5</td><td>NDC 68135-082-36</td><td>White</td></tr>
<tr><td>0.56</td><td>0.7</td><td>NDC 68135-119-66</td><td>Magenta</td></tr>
<tr><td>1.2</td><td>0.6</td><td>NDC 68135-181-93</td><td>Grey</td></tr>
</table></td></tr>
<tr><td>Storage</td><td><u>Storage</u>
Refrigerate vials and prefilled diluent syringes at 2°C to 8°C (36°F to 46°F). Do not freeze.
Can be stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) for 90 days. Do not return to the refrigerator once stored at room temperature.
After reconstitution, can be held in the vial at room temperature 20°C to 25°C (68°F to 77°F) for a maximum of 3 hours [see Dosage and Administration (2.4)].
Record the starting date of room-temperature storage clearly on the unopened product carton.
Do not use beyond expiration date on the label.
Store in the original package to protect from light.
<u>Handling</u>
Reconstituted VOXZOGO must be administered within 3 hours of reconstitution</td></tr>
<tr><td>Container Closure</td><td>single-dose 2 mL glass vials containing VOXZOGO
diluent (Sterile Water for Injection, USP) in a single-dose prefilled syringe
diluent transfer needles (23 gauge)
single-dose administration syringes (30 gauge) both with needle retraction safety devices</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 2, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Voxzogo. Our search identified two previous reviews[a,b], and we confirmed that our previous recommendations were implemented.

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[a] Flint, J. Human Factors and Label and Labeling Review for Voxzogo (NDA 214938). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Aug 04. RCM No.: 2020-1758.

[b] Flint, J. Memorandum Label and Labeling Review for Voxzogo (NDA 214938). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Sep 13. RCM No.: 2020-1758-1.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

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

- Patient Information received on December 21, 2022 \\CDSESUB1\EVSPROD\nda214938\0086\m1\us\114-labeling\1141-draft-labeling\11412-annotated-draft-labeling-text\pi-us-draft-annotated-21dec2022.pdf
- Prescribing Information (Image not shown) received on December 21, 2022, available from insert EDR link: \\CDSESUB1\EVSPROD\nda214938\0086\m1\us\114-labeling\1141-draft-labeling\11412-annotated-draft-labeling-text\prescribe-info-us-draft-annotated-21dec2022.pdf

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

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