CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214938Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	214938
Priority or standard	Priority
Submit date(s)	8/20/2020
Received date(s)	8/20/2020
PDUFA goal date	11/20/2021
Division/office	Division of General Endocrinology (DGE)
Review completion date	See electronic signature page
Established/proper name	Vosoritide
(Proposed) proprietary name	VOXZOGO
Pharmacologic class	C-type natriuretic peptide (CNP) analog
Code name	86268005 Achondroplasia (disorder)
Applicant	BioMarin
Dosage form(s)/formulation(s)	(b) (4)
Dosing regimen	Daily subcutaneous injection
Applicant proposed indication(s)/ population(s)	Treatment of achondroplasia in children (b) (4) whose epiphyses are not closed
Proposed SNOMED indication	Achondroplasia
Regulatory action	Accelerated approval
Approved dosage (if applicable)	Weight based dosing
Approved indication(s)/ population(s) (if applicable)	Increase in linear growth in children with achondroplasia ages 5 and older with open epiphyses
Approved SNOMED term for indication (if applicable)	86268005 Achondroplasia (disorder)

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Glossary

AC	advisory committee
ACE	angiotensin-converting enzyme
ACH	achondroplasia
AchNH	achondroplasia natural history
ADA	antidrug antibody
ADAE	AE page
ADCE	ISR symptom page
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AGV	annualized growth velocity
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANP	atrial natriuretic peptide
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BLQ	below the limit of quantitation
BMC	bone mineral content
BMD	bone mineral density
BMN-111	vosoritide
BNP	B-type natriuretic peptide
BP	blood pressure
BSA	body surface area
BSAP	bone-specific alkaline phosphatase
BV/TV	bone volume
CDER	Center for Drug Evaluation and Research
CDM	Common Data Model
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CNP	C-type natriuretic peptide
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSR	clinical study report
CXM	collagen type X biomarker
DBP	diastolic blood pressure
DCN	Division of Cardiology and Nephrology
DCOA	Division of Clinical Outcome Assessment
DEPI	Division of Epidemiology

DEXA	dual energy X-ray absorptiometry
DMEPA	Division of Medication Error Prevention and Analysis
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECLA	electrochemiluminescence assay
eCRF	electronic case report form
EDC	electronic data capture
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
EOP2	end-of-phase 2
E-R	exposure-response
ERK1/2	extracellular signal-regulated kinases 1 and 2
F	bioavailability
FAS	full analysis set
[redacted]	(b) (4)
FDA	U.S. Food and Drug Administration
FGFR3	Fibroblast Growth Factor Receptor 3
FMQ	FDA MedDRA query
GCP	good clinical practice
GH	growth hormone
GHD	growth hormone deficiency
GI	gastrointestinal
GLP	good laboratory practice
GnRH	gonadotropin-releasing hormone
GQ	grouped query
HD	high dose
HF	Human Factor
HLM	human liver microsomes
HR	heart rate
HRQoL	Health Related Quality of Life
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IM	intramuscular
IND	investigational new drug
IIV	interindividual variability
ISR	injection site reaction
IV	intravenous
LD	low dose
MAPK	mitogen-activated protein kinase
MD	mid dose
Md.V/TV	mineralized bone volume
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
MRI	magnetic resonance imaging
NAb	neutralizing antibodies
NADPH	nicotinamide adenine dinucleotide phosphate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NDA	new drug application
NEP	neutral endopeptidase
NFAH	near final adult height
NH	natural history
NHP	nonhuman primate
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NPR	natriuretic peptide receptor
Ob.S/BS	osteoblast surface
Oc.S/BS	osteoclast surface
OPQ	Office of Pharmaceutical Quality
OS/BS	osteoid surface
OSI	Office of Scientific Investigations
OV/BV	osteoid volume
P1NP	N-terminal propeptide of procollagen I
PAC	Pediatric Advisory Committee
PCH	Partial Clinical Hold
PD	pharmacodynamic
PDE	permissible daily exposure
PedsQL	Pediatric Quality of Life Inventory
PET	positron emission tomography
PK	pharmacokinetic
popPK	population PK
PMC	postmarketing commitment
PMR	postmarketing requirement
PPD	postpartum day
PRO	patient-reported outcome
PT	preferred term
QD	once daily
QoLISSY	Quality of Life in Short Stature Youth
RD	risk difference
RWE	Real-World Evidence
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SCFE	slipped capital femoral epiphysis
SD	standard deviation
SDS	standard deviation score
SDTM	Standard Data Tabulation Model
SMD	standardized mean difference
SOC	System Organ Class
TAb	total anti-vosoritide antibodies
T_{max}	time to maximum concentration
TQT	thorough QT
UAT	User Acceptance Testing
ULN	upper limit of normal

V/F	apparent volume of distribution at steady state
Vc/F	apparent volume of central compartment
Vd/F	apparent volume of distribution
WeeFIM	Pediatric Functional Independence Measure
WPW	Wolf Parkinson White syndrome

I. Executive Summary

1. Summary of Regulatory Action

Vosoritide is proposed for the treatment of achondroplasia in children (b) (4) whose epiphyses are not closed. The new drug application (NDA) was reviewed by the multidisciplinary review team. Each discipline recommended 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: to increase linear growth in children with achondroplasia ages 5 years of age and older with open epiphyses. The Applicant will be required to conduct a postapproval trial to verify the clinical benefit of improved final adult height based on the intermediate clinical endpoint of improved annualized growth velocity. Vosoritide is the first pharmacologic treatment proposed for the treatment of any manifestation of achondroplasia.

The Applicant submitted one adequate and well-controlled trial and confirmatory evidence providing substantial evidence of efficacy for the approved indication. The available safety data show that vosoritide is safe for its intended use. 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.

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., spinal cord compression, 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, including mobility, self-care, and performance at school.	• ACH is a serious medical condition that is associated with disproportional and delayed growth, leading to severely short final adult height, bone-related complications, and impaired functional and social performance.
Current treatment options	• There are no approved pharmacologic treatments for ACH. • Recombinant human growth hormone has been used off-label. However, no clear long-term benefit on final height has been established. • Surgical limb lengthening has been used to increase stature. However, the procedure is controversial as it often requires repeat procedures, long-term use of orthopedic appliances, and is associated with surgical complications.	• ACH is a condition with an unmet medical need; currently, there is no cure or specific treatment for ACH. • 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. In addition, treatment that improves disproportionality could also decrease ACH complications.
Benefit	• Efficacy was established from a single adequate and well-controlled trial (Study 111-301). Annualized growth velocity (AGV) at Week 52 was the primary endpoint in Study 111-301 which enrolled subjects ages 5 and older. – Vosoritide was superior to placebo in improving AGV (treatment difference was 1.57 cm/year [95% confidence interval (CI): 1.22, 1.93], p<0.0001).	• Substantial evidence of effectiveness was established from study 111-301 (adequate and well-controlled) and confirmatory evidence from Studies 111-202/205 and 111-302. • AGV is an intermediate clinical endpoint. Verification of the clinical benefit on final adult height is needed. Although final adult height may not normalize in patients with ACH,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Height Z-score increased in the vosoritide group by 0.26 (treatment difference was 0.28 [95% CI: 0.17, 0.39], p<0.0001) after 1 year of treatment. • Confirmatory evidence consists of data provided from Studies 111-202/205 and 111-302 that demonstrated durability of the effect on growth for up to 5 years in subjects ages 5 and older. • Comparative analyses of the data from Studies 111-202/205 and 111-302 and from age and sex-matched ACH subjects from the natural history data demonstrate a height difference ranging between 7 and 8 cm at 5 years and approximately 9 cm at 6 years, in favor of vosoritide-treated subjects. • Only 4 vosoritide-treated subjects achieved near final adult height. • Disproportionality, as assessed by the upper to lower body segment ratio, was not different—neither worsened nor improved—in the vosoritide treated-group compared to placebo after 1 year of treatment in Study 111-301 (treatment difference was -0.011 [95% CI: -0.045, 0.022], p=0.506) • The upper to lower body segment ratio improved over time in long-term Studies 111-302 and 111-202/205. However, there is no comparator arm, and upper to lower body segment ratio naturally improves with age. • The effect of vosoritide on other important clinical endpoints were either not evaluated properly (e.g., clinical outcome assessments) or not evaluated at all (e.g., neurological complications, sleep apnea, etc.)	any magnitude of increase in final height is a benefit for this population with severe short stature. • Treatment with vosoritide increases AGV at Week 52 in children ages 5 and older. • Supportive data demonstrated that improvement in AGV was sustained up to 6 years during the vosoritide treatment when compared to natural history data. (b) (4) . • Vosoritide-induced growth did not appear to have an effect on disproportionality in the Phase 3 study. • The effect of vosoritide on final adult height is not established. • Longer-term follow-up is needed to demonstrate that other factors, such as disproportionality and bone-age acceleration, will not attenuate the long-term treatment effect. • There is no evidence of benefit on other manifestations of ACH beyond height. The data do not support the proposed broad indication of treatment of ACH, since the effect of the drug on other important aspects of the disease related to abnormal bone growth, including neurologic complications, sleep apnea, and otitis media, have not been evaluated in the clinical program.
Risk and risk management	• The most common adverse events (AEs) associated with vosoritide in Study 111-301 were injection site erythema (75%), injection site swelling (62%), injection site urticaria (25%), vomiting (27%), arthralgia (15%), decreased blood pressure (13%), diarrhea (10%), ear pain (10%), influenza (10%), and dizziness (10%). • Injection site reactions were the most frequent adverse reactions observed in the clinical program. All reactions	• The safety profile of vosoritide has been sufficiently characterized in the clinical program. • No concerning or unexpected safety signals were identified with vosoritide treatment up to 6 years. • Vosoritide-induced decreases in blood pressure are asymptomatic in the majority of patients or are associated with mild symptoms that quickly resolve and do not require medical intervention. Monitoring and intervention will be recommended in labeling to address this risk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	were nonserious, mild, resolved within short period of time, and did not lead to treatment discontinuation. • Increase in linear growth carries a potential risk of worsening skeletal disproportionalities in patients with disproportional short stature. – No new or worsening skeletal deformities (hip, lower extremities, spine) were detected on x-ray during the first year of treatment with vosoritide in Study 111-301 or up to 6 years of treatment in Studies 111-202/205. – No adverse events that may potentially be associated with vosoritide-induced worsening of bone deformities, such as spinal stenosis, fractures, or osteonecrosis, were reported. • Vosoritide induces vascular muscle relaxation. Therefore, treatment with vosoritide carries a potential risk of hypotension, which was an adverse event of interest. – All changes in blood pressure parameters from baseline at prespecified time points during treatment with vosoritide were small, were without clear clinical signficance, were resolved within a short period of time, and did not require drug discontinuation. – The majority of subjects with decreased blood pressure were asymptomatic. In Study 111-301, 2 subjects had nonserious adverse events of symptomatic hypotension and 2 out of 6 subjects with an adverse event of dizziness had low blood pressure (BP) at the time of the event (4 subjects did not have BP measurments at time of the event). In Studies 111-202/205, 4 out of 14 subjects with adverse events of decreased blood pressure had associated mild symptoms of dizziness and presyncope. All AEs resolved within a short period of time and did not require medical treatement/drug discontinuation. – No serious adverse events of hypotension were reported in the clinical program. • Patients with ACH have a delay in bone age relative to chronological age, and bone age is expected to improve with vosoritide treatment. However, there is a potential risk	• Tolerability issues are mild. Treatment with vosoritide is associated with injection site reactions, arthralgia, vomiting, and diarrhea. All risks are monitorable. Monitoring and interventions will be recommended in labeling to address these risks. • The risk of worsening of bone deformities was not detected in the clinical program and does not require additional labeling at this time. • As expected, bone age was delayed at baseline in all subjects with ACH and improved with treatment. There were no changes in the bone age/chronological age ratio that suggested that vosoritide treatment advances bone age relative to chronological age more than expected. • The current device user interface is acceptable to support the safe and effective use of the product because the consequences of the user errors are of low clinical impact. If the Applicant changes the user interface than a new HF validation study would be useful to determine if the design changes were successful in reducing the user errors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of an acceleration in bone age that may lead to the premature closure of growth plates with all growth-promoting products. In the vosoritide clinical program, bone age improved as expected, and there were no concerning changes in the bone age/chronological age ratio. Therefore, there is no suggestion of undue acceleration of bone age. – In Study 111-301, no clinically meaningful changes were seen in the bone age/chronological age ratio that would suggest that vosoritide treatment advances bone age relative to chronological age more than expected. – In Study 111-202/205, no concerning bone age changes suggesting acceleration were found. • The immunogenicity data did not raise any concerns. No severe allergic reactions were reported. • Errors and difficulties associated with administration of the drug using the to-be-marketed syringe were identified during the review of the results of the Human Factor (HF) studies. – The risk associated with a potential underdose is not critical; the expected doses are still within the dose range of a flat exposure-response curve and a 15% underdose (worst case scenario) is not expected to affect efficacy. – The risk of adverse events with overdose is minimal. The doses of up to 30 µg/kg were used in Study 111-202/205 and no dose-dependent adverse events were identified to date.	

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. There is no approved pharmacological therapy of ACH in the United States. 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 or other ACH manifestations 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.

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. The clinical data submitted demonstrated that vosoritide increased annualized growth velocity (AGV, an intermediate clinical endpoint) compared to placebo. The benefit on final height will be confirmed postmarketing. However, the data submitted in this NDA is insufficient to support a broad indication of treatment of ACH, since the Applicant did not evaluate the effect of the drug on other aspects of the condition, including neurological sequelae.

The safety database for vosoritide was adequate for the proposed dosing regimen and intended patient population. Overall, vosoritide has a favorable safety profile, and safety findings can be adequately addressed in labeling and by routine pharmacovigilance. The drug was well-tolerated, and there were no deaths in the clinical program. The most frequent adverse reactions (AR) were injection site reactions; all ARs were nonserious, resolved within short period of time, and did not lead to treatment discontinuation. No worsening in disproportionality or adverse events potentially associated with vosoritide-induced worsening of bone deformities, such as spinal stenosis, fractures, and osteonecrosis were reported. Vosoritide-induced blood pressure changes (hypotension) were asymptomatic, small, and did not have apparent clinical significance. Human factor studies showed there may be errors in self-administration with the device that could cause under- or over-dosing. Taking into consideration the flat dose-response curve, potential underdosing or overdosing as a result of user errors are unlikely to have an effect on the efficacy or safety of the drug. Thus, the current user interface is acceptable to support the safe and effective use of the product. If the Applicant changes the user interface, then a new HF validation study would be useful to determine if the design changes were successful in reducing the use errors.

Based upon review of all available efficacy and safety data, the benefits of vosoritide outweigh the risks for treatment of short stature in pediatric patients with ACH who are at least 5 years old, the population of children in which the safety and efficacy of the drug has been established in the vosoritide clinical program. The availability of vosoritide will provide the first pharmacologic treatment option for this patient population. Given the available data, it is not expected that vosoritide will lead to normalization of final adult height in this population. However, any magnitude of increase in final height is a benefit for this population with extreme short stature, and it is expected that patients will accept the tradeoff between the adverse reactions observed in the clinical studies, which seem to be limited to tolerability issues, and the opportunity for any improvement in height.

II. Interdisciplinary Assessment

3. Introduction

The Applicant, BioMarin, submitted this new drug application (NDA) for vosoritide in support of the following proposed indication: *for the treatment of achondroplasia in patients* (b) (4) *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. There is an unmet medical need for treatment of ACH as there is no approved pharmacological therapy in United States. Therapies that address short stature in ACH children include human growth hormone and surgical limb lengthening. The long-term benefit of growth hormone therapy 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 nonskeletal 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 (b) (4) administered subcutaneously daily.

The Applicant submitted the Investigational New Drug (IND) application 111299 for vosoritide in November 2011. The U.S. Food and Drug Administration (FDA) and the Applicant discussed the development clinical program for vosoritide (including indication, design of phase 2 and 3 studies, endpoints, duration of the studies, etc.) on multiple occasions. Refer to Section 12 for details. On May 11, 2018, a Pediatric Advisory Committee (PAC)/Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting was held to identify therapeutic goals of the ACH community and to further discuss the appropriate elements of the clinical development program of vosoritide for treatment of ACH, such as study design, duration, efficacy endpoints, and number of studies needed. The Advisory Committee members agreed that annualized growth velocity (AGV) could be used as a primary endpoint; however, data on final adult height should be obtained to evaluate long-term clinical efficacy. In addition, they stated that improvement in disease complications should be evaluated as key secondary endpoints. All Committee members also recommended to conduct at least 2 randomized, double-blind, placebo-controlled trials in 2

different age groups (with mention that the greatest benefit would likely be seen in the youngest subjects). Committee members stated that a trial of at least 2 years duration would be most appropriate for evaluation of the primary efficacy endpoint of change in AGV, since a shorter trial may miss growth velocity attenuation over a relatively short time frame. On July 30, 2018, FDA communicated these recommendations to the Applicant via an Advice Letter.

The Applicant submitted an NDA for vosoritide for the treatment of achondroplasia on August 20, 2020. The Applicant included data from 3 clinical studies and from natural history (NH) studies to support the efficacy and safety of the drug for the proposed indication. Study 111-301 (conducted for registrational purposes) was a phase 3 randomized, placebo-controlled, 12-month study evaluating efficacy and safety of the drug compared to placebo in children ages 5 and older, whose epiphyses were not closed. Study 111-202 was a 6-month, phase 2, open-label, single arm, safety and dose finding study comparing the efficacy, safety, and pharmacokinetics (PK) of 3 different doses of vosoritide in pediatric subjects with ACH followed by extension Study 111-205, evaluating long-term efficacy and safety of vosoritide in subjects with ACH. The information from this study was considered as confirmatory. 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 these studies further (long-term treatment with placebo in pediatric subjects with ACH was considered not feasible).

Lastly, on March 31, 2021, the Applicant submitted an amendment to the NDA that included 1 additional year data from Study 111-302 (the extension of Study 111-301) and 1 additional year of data from Study 111-205. This submission was coded as a Major Amendment and the User Fee goal date was extended by 3 months to November 20, 2021.

3.1. Review Issue List

The review team identified 9 key review issues that had a significant impact on the overall determination of the approvability of vosoritide. Some of these issues were identified prior to submission of the NDA, whereas others emerged during the NDA review. In depth analyses of the benefit and risk issues can be found in Section 6.3 and Section 7.7, respectively.

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- Proposed broad indication, i.e., treatment of ACH
- Intended population: (b) (4)
- Adequacy of the efficacy data to provide “substantial evidence of effectiveness”
- Use of AGV as surrogate marker to demonstrate the efficacy of vosoritide in subjects with disproportional short stature (primary endpoint)
- Final adult height versus AGV as clinical benefit
- Quality of data from NH studies used as external control to support the evaluation of the drug effect on growth parameters

3.1.2. Key Review Issues Relevant to Evaluation Risk

- Blood pressure decrease/hypotension
- Abnormal skeletal growth
- Bone age
- Use errors and difficulties associated with use of the proposed user interface of the device constituent

3.2. Approach to the Review

Table 3 provides an overview of the clinical trials reviewed to assess the efficacy and safety of vosoritide.

The phase 3 Study 111-301 was the primary source of evidence for efficacy. This study was 52-weeks in duration, conducted in subjects ages 5 to 18, and was placebo-controlled. Because ACH is a serious and rare disease with an unmet medical need, FDA accepted a single adequate and well-controlled study.

AGV was the primary efficacy endpoint in Study 111-301 and in other trials to evaluate the benefit of vosoritide in subjects with ACH. Documentation of a drug-induced improvement in AGV has been used historically as a validated surrogate of benefit to support the approval of drugs for the treatment of proportional short stature (e.g., due to growth hormone [GH] deficiency), since there are sufficient data from long-term clinical trials to date demonstrating that improvement in AGV in patients with proportional short stature translates into improvement in final height. However, AGV has not been validated as surrogate marker in conditions associated with disproportional growth. Although the Applicant presupposes that improvement in AGV will translate into improvement in final adult height, there are concerns that growth in patients with ACH can attenuate over time due to various factors, including worsening of disproportionality or accelerated bone age. Thus, in line with advisory committee (AC) recommendations, the Division accepted AGV as an objective intermediate endpoint to demonstrate benefit in patients with ACH with disproportional short stature. However, data on final height is required to validate long-term efficacy.

No effect of the drug on other ACH-related complications (spinal stenosis, neurological complications, chest deformities, sleep apnea, etc.) was evaluated in the clinical program.

Confirmatory evidence generated from Studies 111-202/205 in the same age group was reviewed to establish substantial evidence of efficacy. The objective of Studies 111-202/205 was to evaluate the safety of vosoritide and effect of the drug on AGV and other growth parameters (key secondary endpoints). These studies provide longer-term data on vosoritide-induced AGV to address uncertainties of whether the improvement in growth is sustained with longer treatment. This uncertainty could not be addressed in Study 111-301 due to its relatively short duration. However, Studies 111-202/205 were open-label, single-arm studies without a concurrent control group. There was no prespecified testing for efficacy endpoints and the studies were purely descriptive in nature. Study 111-302, which followed subjects previously enrolled in Study 111-301, was reviewed as supportive evidence of efficacy.

It should also be noted that in the absence of a control group in Studies 111-202/205, it is challenging to distinguish the effect of vosoritide on growth from natural growth. Thus, real

world data from the achondroplasia natural history (AchNH) study was used as an external control to help understand the effect of vosoritide on growth in these studies (long-term treatment with placebo in pediatric subjects with ACH was considered not feasible). The Real-World Evidence (RWE) Subcommittee discussed the AchNH data on April 6, 2021 and concluded that they appear to be fit for use and can be used to support efficacy in the clinical program. However, Study 111-202/205 along with the external control should not be considered an adequate and well-controlled trial.

The review of clinical safety considered all data from clinical trials using vosoritide.

(b) (4)

Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations[a] for Vosoritide

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[b]	Number of Trial Sites
111-301	Pediatric subjects ages 5 to <18 years with achondroplasia	Control type: Placebo concurrent Randomization: Stratified randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug (established name): vosoritide Dose: 15 µg/kg daily subcutaneous injection Number treated: 60 vosoritide, 61 placebo Duration (quantity and units): 52 weeks	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	Centers: 24 Countries: 7
111-202	Pediatric subjects ages 5 to 14 years with ACH	Control type: No treatment concurrent (single-arm) Randomization: No randomization (single-arm) Blinding: Open-label Biomarkers: None Innovative design features: None	Drug (established name): vosoritide Dose: 2.5, 7.5, 15, or 30 µg/kg daily SC injection with escalation after 6 months in 2.5 and 7.5 µg/kg groups Number treated: 35 (Initial dosage: 8 on 2.5 µg/kg, 8 on 7.5 µg/kg, 10 on 15 µg/kg, and 9 on 30 µg/kg) Duration (quantity and units): 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
111-205	Subjects with ACH 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 Biomarkers: None Innovative design features: None	Drug (established name): vosoritide Dose: 15 or 30 µg/kg daily SC injection Number treated: 30 (6 on dose of 2.5 to 7.5 to 15 µg/kg in Study 111-202, then 15 µg/kg in 205; 6 on dose of 7.5 to 15 µg/kg in Study 111-202, then 15 µg/kg in 205; 10 on 15 µg/kg; 8 on 30 µg/kg) Duration (quantity and units): 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

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[b]	Number of Trial Sites
111-302	Subjects with ACH who completed Study 111-301	Control type: No treatment concurrent (single arm) Randomization: No randomization (single arm) Blinding: Open-label Biomarkers: None Innovative design features: None	Drug (established name): vosoritide Dose: 15 µg/kg daily SC injection Number treated: 119 vosoritide Duration (quantity and units): 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: 1) Change from baseline in height Z-score 2) Change from baseline in upper to lower body segment ratio	Actual: 119	Centers: 24 Countries: 7
111-206	Pediatric subjects from birth to <60 months old with ACH	Control type: Placebo concurrent Randomization: Stratified randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug (established name): vosoritide Dose: Ages ≥2 to <5 years: 15 µg/kg daily SC injection; Ages ≥6 months to <2 years: 30 µg/kg daily SC injection Number treated: 60 vosoritide, 61 placebo Duration (quantity and units): 52 weeks	Primary: Safety/tolerability, Change from baseline in height Z-score at Week 52. Key secondary: 1) Change from baseline in AGV at 52 weeks 2) Change from baseline in upper to lower body segment ratio at Week 52	44: 8 sentinel subjects 36 randomized subjects (efficacy data included from sentinel subjects only)	Centers: 16 Countries: 4
111-208	Pediatric subjects with ACH who completed Study 111-206	Control type: No treatment concurrent (single arm) Randomization: No randomization (single arm) Blinding: Open-label Biomarkers: None Innovative design features: None	Drug (established name): vosoritide Dose: Ages ≥2 to <5 years: 15 µg/kg daily SC injection; Ages ≥6 months to <2 years: 30 µg/kg daily SC injection Number treated: 4 vosoritide Duration (quantity and units): until subject attains NFAH (evidence of growth plate closure and 6-month interval AGV <1.5 cm/year)	Primary: Safety/tolerability, Change from baseline in height Z-score Secondary: 1) Change from baseline in AGV 2) Change from baseline in upper to lower body segment ratio	Actual: 4	Centers: 16 Countries: 4
AchNH	All prior or current subjects of all ages with a diagnosis of ACH at participating study sites	Observational, retrospective	Drug: not applicable	Anthropometry data collection (height, height velocity, weight, BMI, head circumference)	Actual: 1374	Centers: 4

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[b]	Number of Trial Sites
111-901	Pediatric subjects with ACH 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: 352	Centers: 27
LIAISE	ACH subjects of all ages at participating EU study sites	Observational, retrospective	Drug: not applicable	Track impact on QoL, clinical burden healthcare resource use, socioeconomic burden, and psychosocial burden in ACH	Actual: 128	Centers: 11
KAISER	ACH subjects in Kaiser Permanente, Northern California Skeletal Dysplasia Program	Observational, retrospective	Drug: not applicable	Investigator-sponsored study to determine baseline characteristics and natural history in ACH	Actual: 114	Centers: 1

Source: Reviewer
[a] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[b] If no randomization, then replace with "Actual Enrolled"
Abbreviations: AchNH, Achondroplasia Natural History; AGV, annualized growth velocity; BID, twice daily; BMI, body mass index; DB, double-blind; EU, European Union; LTE, long-term extension study; MC, multicenter; N, number of subjects; NFAH, near final adult height; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized; SC, subcutaneous; QoL, quality of life

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	See Section 16.1
☒	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	See Section 4 and 6.3.46
☒	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**	
☐	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

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	C-type natriuretic peptide (CNP) analog[a]
Mechanism of action	Binding of vosoritide to natriuretic peptide receptor-B (NPR-B) antagonizes fibroblast growth factor receptor 3 (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).
Active moieties	Vosoritide
QT prolongation	At the maximum approved recommended dose, vosoritide does not prolong the QT interval to any clinically relevant extent. In nonclinical investigations, there were no effects on the hERG current.
	General Information
Bioanalysis	A total of 16 bioanalytical methods were developed to support analysis of pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity in vosoritide clinical studies. Vosoritide PK assays and antidrug antibody assays were validated for potential cross-reactivity with human endogenous natriuretic peptides (ANP, BNP, and CNP).
Healthy subjects versus patients	Pediatric achondroplasia (ACH) subjects appeared to have a shorter vosoritide half-life (21.0±4.67 min vs. 69.5±61.2 min), higher CL/F (104±98.8 mL/min/kg vs. 20.3±11.3 mL/min/kg) and larger Vz/F (2.88±2.45 L/kg vs. 1.50±0.53 L/kg) compared to healthy adults.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Following administration of 15 µg/kg once daily dose, the PK parameters were (Mean ± SD): AUC: 161±98.1 ng*min/mL (Week 13) and 290±235 ng*min/mL (Week 52) C_{max}: 4.71±2.32 ng/mL (Week 13) and 6.52±7.89 ng*min/mL (Week 26)
Range of effective dosage(s) or exposure	7.5-30 µg/kg once daily (Study 202/205) In subjects who are ages 5 to <18 years, the efficacy endpoint (changes in annualized growth velocity [AGV] from baseline) reaches the plateau of the exposure-response curve at exposures obtained at 15 µg/kg once daily.
Maximally tolerated dosage or exposure	30 µg/kg once daily (Study 202/205)
Dosage proportionality	In the dose range of 7.5-30 µg/kg, vosoritide shows greater than dose proportional PK. The mean single-dose AUC increased from 32.2 ng*min/mL at 7.5 µg/kg to 689 ng*min/mL at 30 µg/kg.
Accumulation	No accumulation with repeat dosing between Day 1 and Day 10
Time to achieve steady state	Predose plasma concentration of vosoritide is below the limit of quantitation. No drug accumulation is expected. Population PK analysis showed that the exposure of vosoritide increased with the duration of treatment.
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed commercial formulation of vosoritide was used in the phase 3 trials. No bioequivalence study was conducted.

Characteristic	Drug Information
	Absorption
Bioavailability	Absolute bioavailability for vosoritide following subcutaneous (SC) injection was not determined.
T_{max}	15 mins (median)
Food effect (fed/fasted) Geometric least square mean and 90% CI	Vosoritide is subcutaneously administered. A food effect study was not conducted.
	Distribution
Volume of distribution	Vz/F=2880±2450 mL/kg on Day 1; Vz/F=3020±1980 mL/kg at Week 26
Plasma protein binding	Not determined due to the hydrolysis of vosoritide in human plasma
Drug as substrate of transporters	Not evaluated
	Elimination
Mass balance results	Mass balance study was not conducted.
Clearance	Subjects with ACH ages 5-18 years receiving 15 µg/kg across 52 weeks: 79.4-104 mL/min/kg; Subjects with ACH ages 2-8 years receiving 15 µg/kg across 52 weeks: 82.1-150 mL/min/kg
Half-life	Subjects with ACH ages 5-18 years receiving 15 µg/kg across 52 weeks: 21-28 min; Subjects with ACH ages 2-5 years receiving 15 µg/kg across 52 weeks: 15-29 min
Metabolic pathway(s)	Protease-mediated catabolism
Primary excretion pathways	Vosoritide and its metabolites are expected to be primarily excreted into urine based on high levels of radioactivity in the kidney and bladder of rats following SC administration of ^{124}I-vosoritide.
	Intrinsic Factors and Specific Populations
Body weight	Population PK analysis showed that the apparent clearance and volume of distribution of vosoritide increased with increasing body weight in subjects with ACH. The dose of vosoritide is adjusted based on the body weight of subjects with ACH.
Age	Population PK analysis showed that age was not a significant covariate for vosoritide clearance or volume of distribution. No age-based dose adjustment is needed.
Renal impairment	No dedicated PK study was conducted in subjects with renal impairment. No subjects with moderate-to-severe renal impairment were enrolled in clinical studies. The exposure of vosoritide did not increase in subjects with ACH with mild renal impairment. No dose adjustment is needed for subjects with mild renal impairment.
Hepatic impairment	Vosoritide is mainly eliminated by protease-mediated catabolism. The PK of vosoritide is not expected to change in subjects with hepatic impairment. No dedicated PK study was conducted in subjects with hepatic impairment. Subjects with moderate-to-severe hepatic impairment were excluded from clinical studies. Population PK analysis showed that hepatic function was not a significant covariate for vosoritide clearance or volume of distribution. No dose adjustment is needed for subjects with any degree of hepatic impairment.

Characteristic	Drug Information
	Drug Interaction Liability (drug as perpetrator)
Inhibition/induction of metabolism	In vitro microsome stability study showed that cytochrome P450 (CYP) enzymes were not involved in the elimination of vosoritide. In vitro CYP inhibition and induction studies indicated that vosoritide did not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, nor induce CYP 1A2, 2B6, or 3A4/5 at clinically relevant concentrations. In vivo CYP-mediated drug-drug interactions for vosoritide are unlikely.
Inhibition/induction of transporter systems	Transporter inhibition or induction studies were not conducted with vosoritide. Considering the rapid hydrolysis of vosoritide ($T_{1/2}$<30 min), and once daily dose regimen, vosoritide is unlikely to affect the PK of concomitantly administered transporter substrates.
	Immunogenicity (if applicable)
Bioanalysis	Immunogenicity assays were validated for semiquantitative measurement of antidrug antibodies (ADAs), including assays for total anti-vosoritide antibodies (TAb), neutralizing antibodies (NAb), and anti-vosoritide IgE in serum.
Incidence	Overall, immunogenicity findings in phase 2 and 3 studies revealed that ADA responses were detected in approximately 34% to 63% of subjects across studies with the incidence being 38% (59/156) in subjects with ACH who received any dose of vosoritide. NAb responses were detected in 2% (3/156) of subjects with ACH who received vosoritide treatment.
Clinical impact	The observed higher AUC of vosoritide in subjects with positive ADA in Study 111-202 was likely due to 1 outlier. No obvious impact of ADA or NAb on predose urine cyclic guanosine monophosphate (cGMP) or efficacy (change from baseline in AGV) was observed.

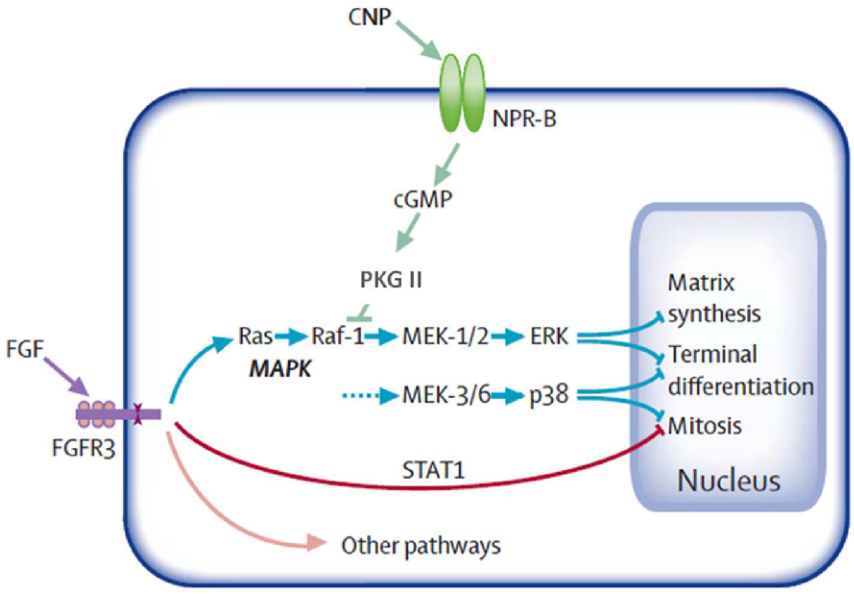
Source: Reviewer's summary
[a] The basis for this EPC is that vosoritide binds specifically to natriuretic peptide receptor B (NPR-B) that is primarily located in skeletal tissues, which is where the pharmacologic effect is manifested. This differs from the action of natriuretic peptides that bind to other NPRs to exert pharmacologic effects on other systems

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Target Affinity

Achondroplasia is an autosomal dominant condition caused by a gain-of-function mutation in the FGFR3 receptor. FGFR3 is a negative regulator of endochondral bone growth, and overactivity suppresses proliferation of the chondrocytes in the growth plate, leading to reduction in the size of the growth plate which results in a reduction in bone elongation. The binding of CNP to its receptor natriuretic peptide receptor B (NPR-B) acts as a regulator of this pathway. Vosoritide (BMN-111) is a recombinant human CNP that has been modified by the addition of 2 amino acids to the N-terminus for resistance to neutral endopeptidase (NEP) proteolysis, thereby increasing its biological half-life. It binds to NPR-B and antagonizes FGFR3 downstream signaling that is a negative regulator of endochondral bone growth. By down-regulating the activity of this pathway through inhibiting the extracellular signal-regulated kinases 1 and 2 (ERK1/2) mitogen-activated protein kinase (MAPK) pathway at the level of rapidly accelerating fibrosarcoma serine/threonine protein kinase (RAF-1), BMN-111 is expected to promote endochondral bone growth by stimulating chondrocyte proliferation and allowing for bone growth to occur. These pathways are summarized in Figure 1.

Figure 1. Pathway of CNP Activity



ANP, atrial natriuretic peptide; cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; FGF, fibroblast growth factor; MAPK, mitogen-activated protein kinase; NPR, natriuretic peptide receptor.

Modified from Horton 2007.

Source: Applicant figure (fig 2.6.2.2.1.1 from Pharmacology Written Summary)

Analogous to endogenous CNP-22 (the CNP found in plasma), vosoritide binds with similar potency to NPR-B and NPR-C but not to NPR-A, as summarized in Table 6.

Table 6. Estimated EC_{50} for Binding to NPR Receptors

Peptide	EC_{50} NPR-B (nM)	EC_{50} NPR-A (nM)	EC_{50} NPR-C (nM)	EC_{50} NPR-C/EC_{50}	n
CNP-22	13.4 ± 11.2	> 1 µM	57.5 ± 35.8	7.2 ± 8.1	4
vosoritide	3.5 - 10	> 1 µM	20.6 - 113.5	5.9 - 11.4	2
ANP	> 1 µM	0.04 - 0.14	5 - 8.7	62.1 - 125	2

Source: Applicant table (Table 2.6.2.2.3.1 from Pharmacology Written Summary)
Abbreviations: ANP, atrial natriuretic peptide; CNP, C-type natriuretic peptide; EC_{50}, 50% effective concentration; NPR, natriuretic peptide receptor

5.1.2. Effects on Bone Growth Parameters

Pharmacologic activity was demonstrated in a series of in vitro and in vivo studies where vosoritide affected bone formation. In human growth plate tissue obtained from normal or achondroplastic sources, vosoritide was shown to prevent FGF-mediated increases in MAPK phosphorylation (ERK1/2). In bone explants from mutant achondroplastic mice, vosoritide treatment was associated with increased bone length and expansion of the hypertrophic zone of the growth plates as compared to untreated mutant animals.

Studies evaluating effects on bone were conducted in both normal (mouse, rat, nonhuman primate [NHP]) and achondroplastic (mouse) models with open or incompletely fused growth plates. In both types of models, chondrocyte proliferation and differentiation occurred leading to widening of the growth plate and bone growth. These effects were characterized by increased height/thickness of the growth plate, proliferating zone, and hypertrophic zone, disorganization of the chondrocytes, increased levels of biomarkers of bone growth, and/or increases in bone length. Increases in foramen magnum length and width were also evident. Secondary to bone overgrowth, limited limb usage, gait abnormalities, paw curvature, joint swollen joints, and/or hunched posture were observed in normal rodents. In achondroplastic models, treatment with vosoritide was associated with partial to complete normalization of phenotypic appearance. In the pharmacology studies, the effects on bone parameters were evident in normal mice, rats, and NHPs at dosages >20, 80, and 9 µg/kg, respectively (0.2x, 1.3x, and 0.3x the maximum recommended human dose [MRHD] based on body surface area [BSA], respectively) and achondroplastic mutant mice at dosages >240 µg/kg (2x the MRHD based on BSA), with the number of bone parameters showing evidence of growth and the magnitude of change increasing with dose. Refer to Section 13.1.1 for further details.

6. Assessment of Effectiveness

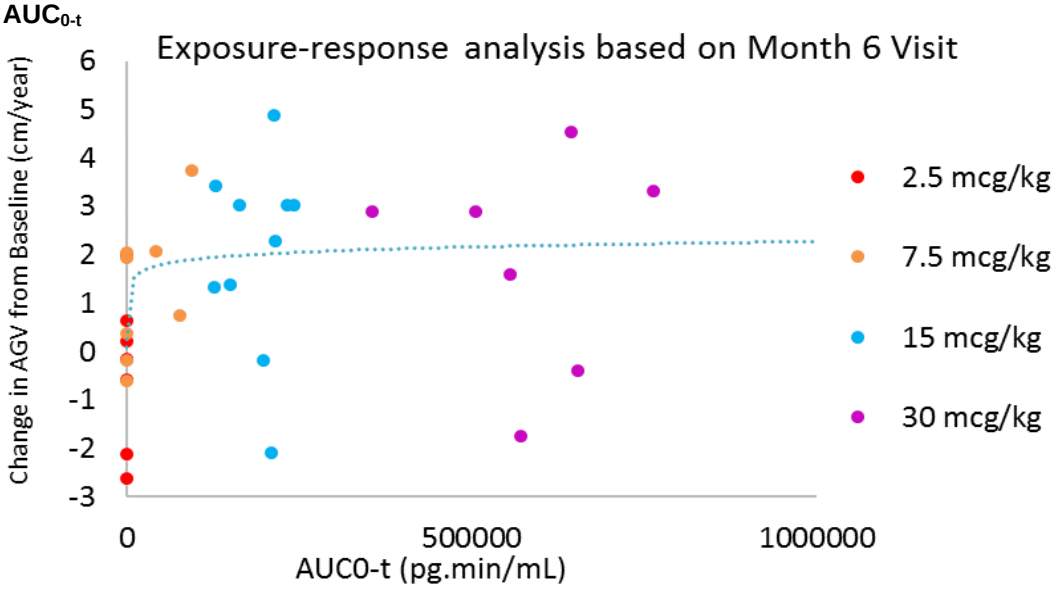
6.1. Dose and Dose Responsiveness

The 15 µg/kg once daily (QD) dose selected for evaluation in the pivotal trial (Study 111-301) was based on dose-response and exposure-response analyses from efficacy, biomarker, and safety data from 2 phase 2 trials (Studies 111-202 and 111-205) in subjects with ACH.

Study 111-202 was a dose-escalation trial that evaluated vosoritide 2.5, 7.5, 15, and 30 µg/kg in subjects with ACH ages 5 to 14 years during the initial 6-month dosing period. Study 111-205 is an ongoing extension trial that is evaluating the long-term safety and efficacy of vosoritide 15 µg/kg and 30 µg/kg in subjects with ACH who completed Study 111-202.

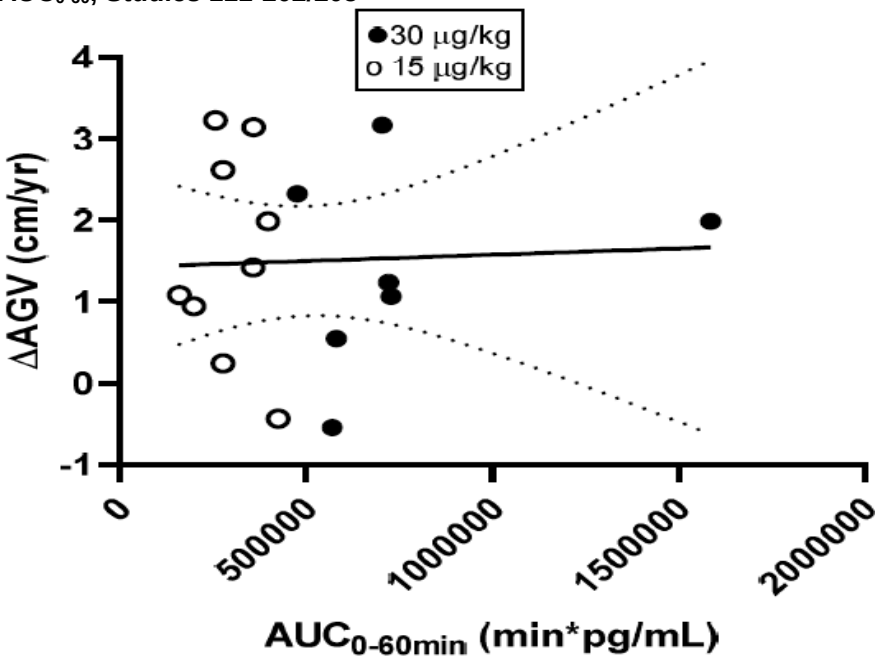
The Applicant performed an exposure-response (E-R) analysis using AGV, serum collagen type X biomarker (CXM, a biomarker of growth plate activity), and safety data from Studies 111-202 and 111-205. In Study 111-202, vosoritide exhibited a flat E-R (AGV) relationship in the dose range of 7.5 to 30 µg/kg, and the change in AGV at Month 6 plateaued at an exposure of 15 µg/kg (Figure 2). Maximal CXM response was observed at exposures obtained with daily doses ≥15 µg/kg (refer to Section 14.2, Appendix). The E-R analysis based on Study 111-205 (Figure 3) showed no obvious improvements in AGV for subjects receiving vosoritide 30 µg/kg compared to 15 µg/kg at Month 48.

Figure 2. Change in Annualized Growth Velocity From Baseline at Month 6 by Individual Mean AUC_{0-t}



Source: Clinical pharmacology reviewer's analysis.
Note: Subject (b) (6) 30 µg/kg group (outlier) with high individual mean AUC_{0-60} (3699 ng-min/mL) was not shown in the figures. The dash represents a regression between change in AGV from baseline at Month 6 and individual AUC_{0-t}.
Abbreviations: AGV, annualized growth velocity

Figure 3. Change in Annualized Growth Velocity From Baseline at Month 48 by Individual Mean AUC_{0-60}, Studies 111-202/205



Source: Applicant's Supportive Pharmacokinetic and Pharmacodynamic Analysis Report (Module 5.3.4.2).
Note: Solid line represents the linear fit through the data and the broken lines represents the 95% confidence interval. AUC_{0-60}, area under the curve up to 60 mins postdose. The average AUC_{0-60} across all visits of 111-202 and 111-205 up to Month 48 visit was computed for each individual subject.
Abbreviations: AGV, annualized growth velocity

E-R and dose-response analyses for safety showed no obvious correlations between vital signs (heart rate and systolic and diastolic blood pressure) and vosoritide maximum plasma concentration (C_{max}) in subjects with ACH treated with vosoritide at 2.5 to 30 µg/kg once daily (refer to Section 14.2, Appendix). No serious adverse events were reported in subjects with ACH receiving daily doses of 15 µg/kg or 30 µg/kg.

(b) (4)

On October 22nd, 2021, in the Applicant's response to the Agency's information request, the Applicant submitted an eight-body weight-band dosing approach (b) (4) (0.24 mg for 10-12 kg subjects, 0.28 mg for 12-16 kg subjects, 0.32 mg for 17-21 kg subjects, 0.4 mg for 22-32 kg subjects, 0.5 mg for 33-43 kg subjects, 0.6 mg for 44-59 kg subjects, 0.7 mg for 60-89 kg subjects, and 0.8 mg for subjects weighing 90 kg or higher). (b) (4) Based on population PK simulation, the proposed new eight-weight-band-based dosing regimen is acceptable. Refer to Section 8.1 and Section 14.3 for more information.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Study 111-301 (Registrational Trial)

6.2.1.1. Design, Study 111-301

The Applicant conducted 1 randomized, double-blind, controlled trial.

Because ACH is a serious and rare disease with an unmet medical need, FDA accepted the single adequate and well-controlled Study 111-301 conducted in subjects ages 5 to 18 years to demonstrate efficacy of the drug in patients with ACH ages 5 to 18 years.

Study 111-301 was designed as a 52-week, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the effect of vosoritide on AGV in children with ACH. The subjects were randomized in a 1:1 ratio to receive vosoritide 15 µg/kg or placebo. The randomization was stratified by sex and Tanner stage of pubertal development. The subjects were required to have at least 6 months of baseline growth data collected in observational Study 111-901 prior to enrollment in Study 111-301.

Primary Endpoint

The primary efficacy endpoint was the change from baseline in AGV at Week 52.

As discussed during the vosoritide development program and during the AC meeting on May 11, 2018 (refer to Section 12, Appendix), AGV is a reasonable primary endpoint for a clinical trial in this population. However, it is considered an intermediate clinical endpoint. Data on final height is required to assess long-term efficacy. Refer to the further discussion on use of AGV in subjects with ACH in Sections 6.3.3 and 6.3.4.

Key Secondary and Exploratory Endpoints

Key secondary endpoints included the change from baseline in height Z-score at Week 52 and the change from baseline in upper to lower body segment ratio at Week 52. These endpoints are typically considered in clinical practice for treatment optimization. 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 secondary and exploratory endpoints included evaluation of other parameters of growth (e.g., standing height) and disproportionality and evaluation of quality of life by various questionnaires. It should be noted that none of the patient-reported outcome measures used in the clinical program have been validated in this patient population. Refer to Section 15.1, Appendix, for full list of endpoints.

6.2.1.2. Eligibility Criteria, Study 111-301

Overall, the inclusion and exclusion criteria were consistent with the indication sought in this application (treatment of ACH). The study included subjects ages 5 to 17 years with a confirmed

diagnosis of ACH by genetic testing, (b) (4) 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, Appendix, for a detailed list of inclusion and exclusion criteria.

6.2.1.3. Statistical Analysis Plan, Study 111-301

The efficacy analysis population is the full analysis set (FAS), which consists of all randomized subjects and same as the usual intention-to-treat population.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was change from baseline in AGV (cm/year) at Week 52. For a given interval [Date 1, Date 2], the AGV was defined as follows:

$$AGV(cm/year) = \frac{\text{Standing Height at Date 2} - \text{Standing Height at Date 1}}{Interval\ Length\ of\ Date2 - Date1(Days)} X365.25$$

For AGV at Week 52, Date 2 is Week 52 and Date 1 is baseline. The baseline AGV was established in the observational run-in period of Study 111-901, based on the standing height at least 6 months prior to enrollment to Study 111-301.

An analysis of covariance (ANCOVA) model was used to determine the treatment difference between vosoritide and placebo at Week 52. It included the following baseline factors:

- Treatment group
- Stratum: Male Tanner Stage I, Female Tanner Stage I, Male Tanner Stage > I, Female Tanner Stage > I
- Age at baseline
- AGV at baseline
- Height Z-score at baseline

Key Secondary Efficacy Endpoint Analyses

Key secondary endpoints included:

- Change from baseline in height Z-score at Week 52
- Change from baseline in upper to lower body segment ratio at Week 52

Each measurement of standing height was converted to an age-and sex-appropriate SDS, also referred to as a height Z-score, by comparison with reference data available for normal average stature children from the Centers for Disease Control and Prevention (CDC).

The upper to lower body segment ratio was calculated as the follows:

$$Upper\ to\ Lower\ Body\ Ratio = \frac{\text{Sitting Height (cm)}}{Standing\ Height(cm) - Sitting\ Height\ (cm)}$$

The key secondary endpoints were analyzed using a similar ANCOVA model as the primary efficacy endpoint. Hierarchical testing was used to control the type I error.

Method for Handling Intercurrent Events and Missing Data

Subjects who discontinued from study drug were encouraged to remain in the study. All available measurements were included in the primary efficacy analysis regardless of treatment discontinuation or switching to rescue medication. This is consistent with the concept of intention-to-treat.

The prespecified method for handling missing data was to apply multiple imputations based on subjects in the same treatment group who also discontinued treatment prematurely and had their height measured post-treatment discontinuation. Since only 2 treated subjects discontinued treatment and both discontinued the study, it was not feasible to apply this approach. Missing standing and sitting heights at Week 52 were imputed by applying the baseline AGV to what the change would be from the last observed height assessment to Week 52. The height Z-score and AGV at Week 52 were calculated based on the imputed standing height. The upper to lower body segment ratio was calculated based on the imputed standing height and sitting height.

The Applicant's imputation approach is overall acceptable. FDA conducted a conservative sensitivity analysis for the primary efficacy endpoint by assuming the subjects who discontinued the study did not have any growth in the period with missing height values after discontinuing treatment.

Sample Size Calculation

With 55 subjects planned in each group (vosoritide and placebo), the power to detect a difference between them of 1.75 cm/year in change from baseline in AGV at 12 months was approximately 90%.This assumes the pooled standard deviation (SD) of the change from baseline in AGV is 2.80 using a two-sided two-sample t-test at the 0.05 significance level.

Subgroup Analysis

Subgroup analysis for change in AGV from baseline at Week 52 was performed for the following baseline factors: sex, age group, race, baseline AGV, height Z-score, and Tanner Stage. Missing data were imputed in the same way as the primary efficacy analysis. A similar ANCOVA model was fit, including the additional factors of subgroup and subgroup-by-treatment interaction. In addition, we performed shrinkage analyses to obtain estimates from a Bayesian hierarchical model. Subgroup results from both approaches are presented in the Appendix, Section 15.1.

6.2.1.4. Results of Analyses, Study 111-301

6.2.1.4.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Out of the 124 subjects who were screened, 121 subjects were enrolled, randomized, received at least 1 dose of the study drug, and were included in FAS population: 60 subjects received vosoritide and 61 subjects received placebo. The 3 subjects not enrolled in the study failed the screening because they were at a Tanner stage >1. According to study protocol, no more than

20% of subjects should have Tanner stage >1 at enrollment. The completion rate of the study was high: 119/121 subjects completed the study. Only 2 subjects in the vosoritide group and none in the placebo group discontinued the study prematurely. One of these subjects discontinued due to an adverse event (AE) (Table 7).

Table 7. Patient Disposition, Study 111-301

Disposition Outcome	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)
Patients randomized	60	61
FAS population	60	61
Safety population	60	61
Discontinued study drug	2 (3.3)	0
Adverse event	1 (1.7)	0
Subject's request	1 (1.7)	0
Discontinued study	2 (3.3)	0
Withdrawal by subject	2 (3.3)	0

Source: adds.xpt; Software: R
Abbreviations: FAS, full analysis set; N, number of subjects in treatment arm; n, number of subjects in specified population or group; VOS, vosoritide

All 119 subjects were enrolled into the extension Study 111-302 and were treated with vosoritide. By the cut-off date, of the 58 subjects who were in the vosoritide/vosoritide (vos/vos) arm enrolled in Study 111-302, 2 subjects discontinued study treatment: 1 due to an AE and the other at the "subject's request" (see Section 7.6.4 for details). No subjects in the placebo/vosoritide (plc/vos) arm discontinued study drug.

The adherence rate with the treatment regimen was high in both treatment arms (99.1% vosoritide versus 98.7% placebo), with ≥80% of the subjects reporting a 100% adherence rate in both treatment arms (Table 106, Appendix).

Baseline demographics and growth characteristics were generally well-balanced between treatment arms (Table 8 and Table 9). Subjects in the vosoritide arm were slightly younger (mean [SD] age: 8.35 [2.43] vosoritide versus 9.06 [2.47] placebo) with 51% of the subjects in the vosoritide arm enrolled in the ≥5 to <8 year age bracket versus 39% in placebo arm, while the ≥8 to <11 year age bracket had 28% subjects in vosoritide arm and 39% in placebo arm. Most subjects (79%) were prepubertal (Tanner Stage I). Males and females were both well-represented in the study. The majority (71%) of the subjects were white and approximately 45% of the enrolled subjects were from the United States.

The mean baseline AGV was slightly higher in the vosoritide group compared to placebo, consistent with the slightly younger age of the subjects in that group.

Table 8. Baseline Demographic Characteristics, Full Analysis Set, Study 111-301

Characteristic	15 µg/kg VOS N=60	Placebo N=61
Sex, n (%)		
Female	29 (48.3)	28 (45.9)
Male	31 (51.7)	33 (54.1)
Age, years		
Mean (SD)	8.3 (2.4)	9.0 (2.5)
Median (min, max)	7.7 (5.0, 13.0)	9.2 (5.0, 14.8)

Characteristic	15 µg/kg VOS N=60	Placebo N=61
Ethnicity, n (%)		
Hispanic or Latino	1 (1.7)	6 (9.8)
Not Hispanic or Latino	59 (98.3)	55 (90.2)
Race, n (%)		
Asian	10 (16.7)	13 (21.3)
Black or African American	3 (5.0)	2 (3.3)
Multiple	2 (3.3)	5 (8.2)
White	45 (75.0)	41 (67.2)
Country		
Australia	11 (18.3)	11 (18.0)
Germany	5 (8.3)	5 (8.2)
Spain	5 (8.3)	8 (13.1)
Great Britain	8 (13.3)	5 (8.2)
Japan	3 (5.0)	4 (6.6)
Turkey	1 (1.7)	2 (3.3)
United States	27 (45.0)	26 (42.6)

Source: adsl.xpt; Software: Python
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; VOS, vosoritide

Table 9. Baseline Growth Characteristics, Full Analysis Set, Study 111-301

Characteristic Variable	15 µg/kg VOS (N=60)	Placebo (N=61)
AGV (cm/year)		
Mean (SD)	4.26 (1.53)	4.06 (1.20)
Median	4.14	4.13
Min, max	−0.1, 6.9	1.5, 6.7
Height z-score		
Mean (SD)	−5.13 (1.11)	−5.14 (1.07)
Median	−5.27	−5.15
Min, max	−7.7, −1.1	−7.9, −2.7
Upper to lower body segment ratio		
Mean (SD)	1.98 (0.20)	2.01 (0.21)
Median	2.01	1.99
Min, max	1.3, 2.3	1.5, 2.6

Source: CSR of Study 111-205, verified by statistical reviewer
Abbreviations: AGV, annualized growth velocity; min, minimum; max, maximum; SD, standard deviation; VOS, vosoritide

The 2 arms were balanced in terms of ACH comorbidities. The most common conditions reported were sleep apnea syndrome (45% vosoritide versus 50% placebo), otitis media (40% vosoritide versus 44% placebo), ear tube insertion (45% vosoritide versus 36% placebo), and adenoidectomy (33% vosoritide versus 31% placebo) (Table 105, Appendix).

A review of concomitant medications did not reveal an imbalance in medications that might affect growth. There was no reported use of hormonal contraceptive therapy. One subject in the placebo group received a prohibited medication (triptorelin) to delay puberty, which may augment growth. However, this would be expected to skew the results of the primary efficacy analysis in favor of placebo.

6.2.1.4.2. Primary and Key Secondary Efficacy Results

Primary Endpoint

The vosoritide-treated group demonstrated superiority to placebo in terms of change in AGV from baseline to Week 52 (Table 10). The difference in LS mean change from baseline between the 2 groups was 1.57 cm/year (95% confidence interval [CI]: 1.22, 1.93; p-value<0.0001). Conclusion from FDA's sensitivity analysis for missing data imputation assuming subjects did not grow during the period with missing data was consistent with that from the primary efficacy analysis (Table 11). The point estimate for treatment difference was slightly smaller in this analysis due to the conservative method of imputation of missing data in 2 treated subjects.

Differences in AGV between the 2 groups were notable as early as the Week 13 visit. The difference was maintained until Week 52 (Figure 65 and Figure 66, Appendix). The pronounced effect on growth observed in the first 3 to 6 months is explained by the well-known catch-up growth phenomenon that occurs when the cause of the growth deficit is removed (Wit and Boersma 2002). The same effect was observed in the early phase 2 studies. However, the conclusion regarding final height cannot be made based on this short-term exaggerated growth response because growth rate usually decreases (but remains within improved range) during the subsequent years of treatment, based on experience with other growth promoting therapies (i.e., hGH).

Table 10. Primary Endpoint: Change From Baseline in AGV at Week 52[a], Full Analysis Set, Study 111-301

AGV (cm/year)	15 µg/kg VOS (N=60)	Placebo (N=61)
Baseline		
Mean (SD)	4.26 (1.53)	4.06 (1.20)
Week 52		
Mean (SD)	5.61 (1.05)	3.94 (1.07)
Change from baseline[b]		
LS Mean (95% CI)	1.40 (1.15, 1.66)	-0.17 (-0.42, 0.08)
Difference in change from baseline[b]		
LS Mean (95% CI)	1.57 (1.22, 1.93)	
P-value	<0.0001	

Source: statistical reviewer
[a] Standing height from the 2 subjects with missing data was imputed assuming baseline growth rate for the period with missing data. AGV was calculated based on the imputed standing height.
[b] ANCOVA model includes treatment, stratum defined by sex and Tanner stage, baseline age, baseline AGV and baseline height Z-score. LS mean for each group was adjusted according to the distribution of baseline covariates.
Abbreviations: AGV, annualized growth velocity; ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; SD, standard deviation; VOS, vosoritide

Table 11. Sensitivity Analysis for Change From Baseline in AGV at Week 52[a], Full Analysis Set, Study 111-301

AGV (cm/year)	15 µg/kg VOS (N=60)	Placebo (N=61)
Baseline		
Mean (SD)	4.26 (1.53)	4.06 (1.20)
Week 52		
Mean (SD)	5.48 (1.39)	3.94 (1.07)
Change from baseline[b]		
LS Mean (95% CI)	1.33 (1.06, 1.60)	-0.17 (-0.44, 0.10)
Difference in change from baseline[b]		
LS Mean (95% CI)	1.50 (1.12, 1.88)	
P-value	<0.0001	

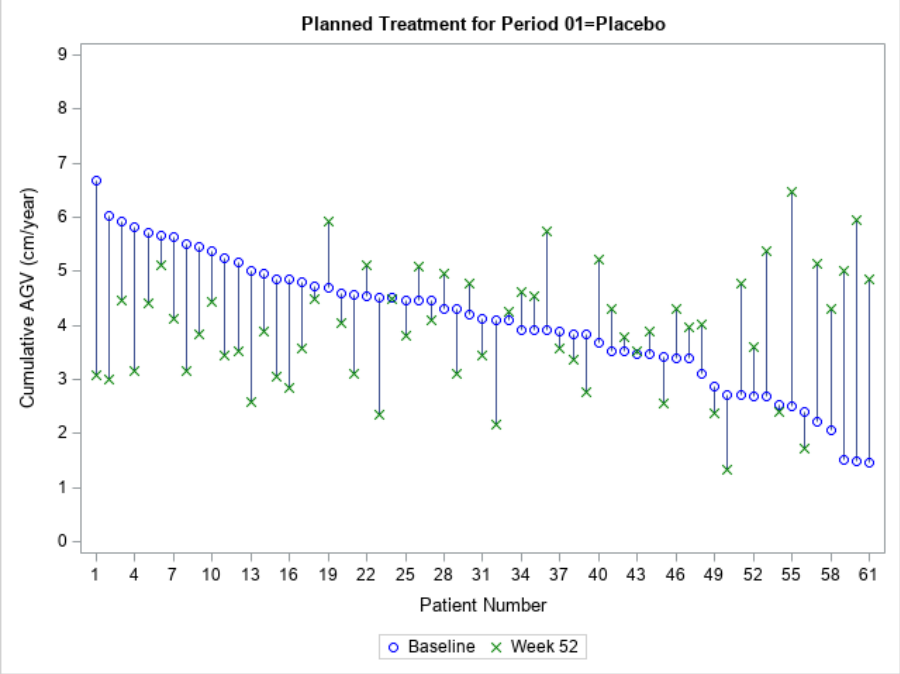
Source: statistical reviewer
[a] Standing height for the 2 subjects with missing data at Week 52 was imputed using last nonmissing height measurement. AGV was calculated based on the imputed standing height.
[b] The same ANCOVA model used by the Applicant was applied. LS mean for each group was adjusted according to the distr bution of baseline covariates.
Abbreviations: AGV, annualized growth velocity; ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; SD, standard deviation; VOS, vosoritide

Figure 4 below illustrates the changes in AGV from baseline to Week 52 in individual subjects in both the placebo and vosoritide groups. It was noted that the subjects in the placebo group with lower baseline AGV (i.e., approximate AGV ≤4.5 cm/year) tended to have an increase in AGV from baseline at Week 52, while subjects with higher baseline AGV (i.e., approximate AGV >4.5 cm/year) tended to have a decrease in AGV from baseline at Week 52. This could be related to the regression to the mean phenomenon. A similar trend was also noted in the vosoritide arm (i.e., subjects with lower AGV at baseline had a higher increment in AGV at Week 52 compared to subjects with higher AGV at baseline).

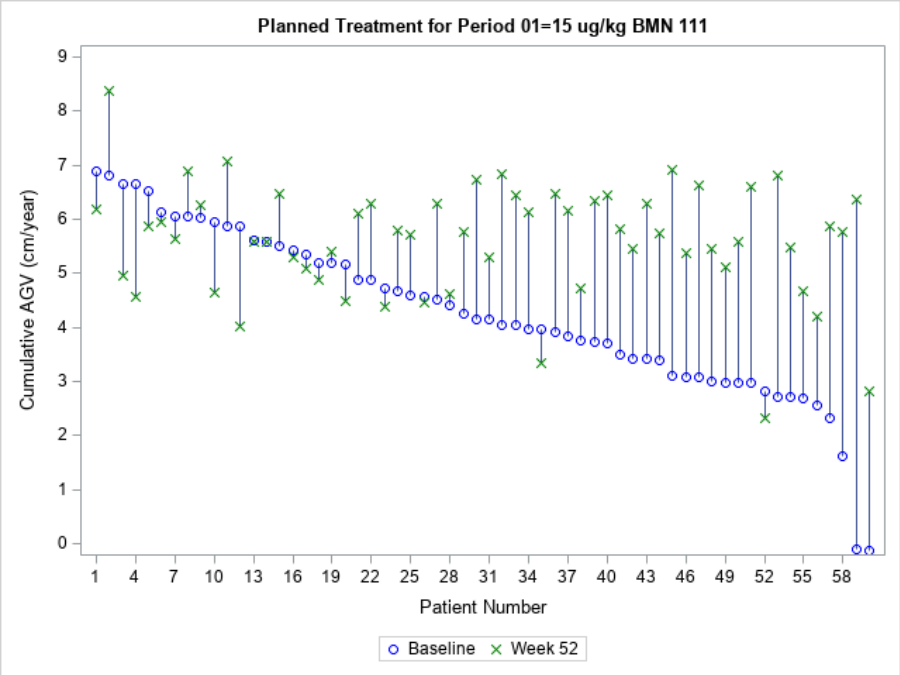
Overall, the subjects in the vosoritide group had a relative increase in AGV at Week 52 compared to subjects in the placebo group of similar baseline AGV across all levels. This is also supported by the subgroup analysis by baseline AGV, which showed little difference among the subgroups (Figure 67, Appendix).

Figure 4. Waterfall Plots of Change in AGV From Baseline at Week 52 in Individual Subjects in Placebo (A) and Vosoritide-Treated (B) Groups, Full Analysis Set, Study 111-301

A



B.



Source: statistical reviewer
Abbreviations: AGV, annualized growth velocity

Subgroup Analyses

The treatment effect of vosoritide relative to placebo in the various subgroups (e.g., by sex, age, race, AGV at baseline, height Z-score at baseline, and Tanner stage at baseline) appeared to be

consistent with the overall group (Figure 67, Appendix). There was no qualitative difference among any of the subgroups examined. The most noticeable difference was observed among the age subgroups, where the middle age category (≥8 to <11 years) appeared to have a larger treatment effect (treatment difference of 2.28 cm/year) compared to the other 2 categories (treatment difference 1.32 cm/year for age category ≥5 to <8, and 1.08 cm/year for age category ≥11 to <15, respectively). The treatment by age subgroup interaction was nominally significant (p-value=0.031). The results for differences among subgroups should be interpreted with caution considering lack of multiplicity adjustment.

Key Secondary Endpoints

The vosoritide-treated group demonstrated superiority to placebo in terms of change in height Z-score from baseline to Week 52 (Table 12). The difference in LS mean change from baseline between the 2 treatment arms was 0.28 (95% CI: 0.17, 0.39; p-value<0.0001).

Table 12. Key Secondary Endpoint 1: Change From Baseline in Height Z-Score at Week 52[a], Full Analysis Set, Study 111-301

Height Z-score	15 µg/kg VOS (N=60)	Placebo (N=61)
Baseline		
Mean (SD)	−5.13 (1.11)	−5.14 (1.07)
Week 52		
Mean (SD)	−4.89 (1.09)	−5.14 (1.09)
Change from baseline[b]		
LS Mean (95% CI)	0.26 (0.18, 0.33)	-0.02 (-0.09, 0.05)
Difference in change from baseline[b]		
LS Mean (95% CI)	0.28 (0.17, 0.39)	
P-value	<0.0001	

Source: statistical reviewer
[a] Standing height from the 2 subjects with missing data was imputed assuming baseline growth rate for the period with missing data. Height Z-score was calculated based on the imputed standing height.
[b] ANCOVA model includes treatment, stratum defined by sex and Tanner stage, baseline age, baseline AGV and baseline height Z-score. LS mean for each group was adjusted according to the distribution of baseline covariates.
Abbreviations: AGV, annualized growth ratio; ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; SD, standard deviation; VOS, vosoritide

The vosoritide-treated group failed to achieve superiority to placebo in terms of change in upper to lower body segment ratio from baseline to Week 52 (Table 13). The estimated treatment difference was close to 0, suggesting the observed increase in growth occurred proportionally in the upper and lower body segments and had no impact on the ratio of the 2. These findings suggest that disproportionality neither improved nor worsened after 1 year of treatment with vosoritide.

Table 13. Key Secondary Endpoint 2: Change From Baseline in Upper to Lower Body Segment Ratio at Week 52[a], Full Analysis Set, Study 111-301

Upper to Lower Body Segment Ratio	15 µg/kg VOS (N=60)	Placebo (N=61)
Baseline		
Mean (SD)	1.98 (0.20)	2.01 (0.21)
Week 52		
Mean (SD)	1.95 (0.20)	1.98 (0.18)
Change from baseline[b]		
LS Mean (95% CI)	-0.035 (-0.059, -0.012)	-0.024 (-0.047, -0.001)
Difference in change from baseline[b]		
LS Mean (95% CI)	-0.011 (-0.045, 0.022)	
P-value	0.506	

Source: statistical reviewer
[a] Standing height and sitting height from the 2 subjects with missing data were imputed assuming no growth for the period with missing data. AGV was calculated based on the imputed standing height and sitting height.
[b] ANCOVA model includes treatment, stratum defined by sex and Tanner stage, baseline age, baseline AGV and baseline height Z-score as well as baseline upper to lower body segment ratio. LS mean for each group was adjusted according to the distribution of baseline covariates.
Abbreviations: AGV, annualized growth ratio; ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; SD, standard deviation; VOS, vosoritide

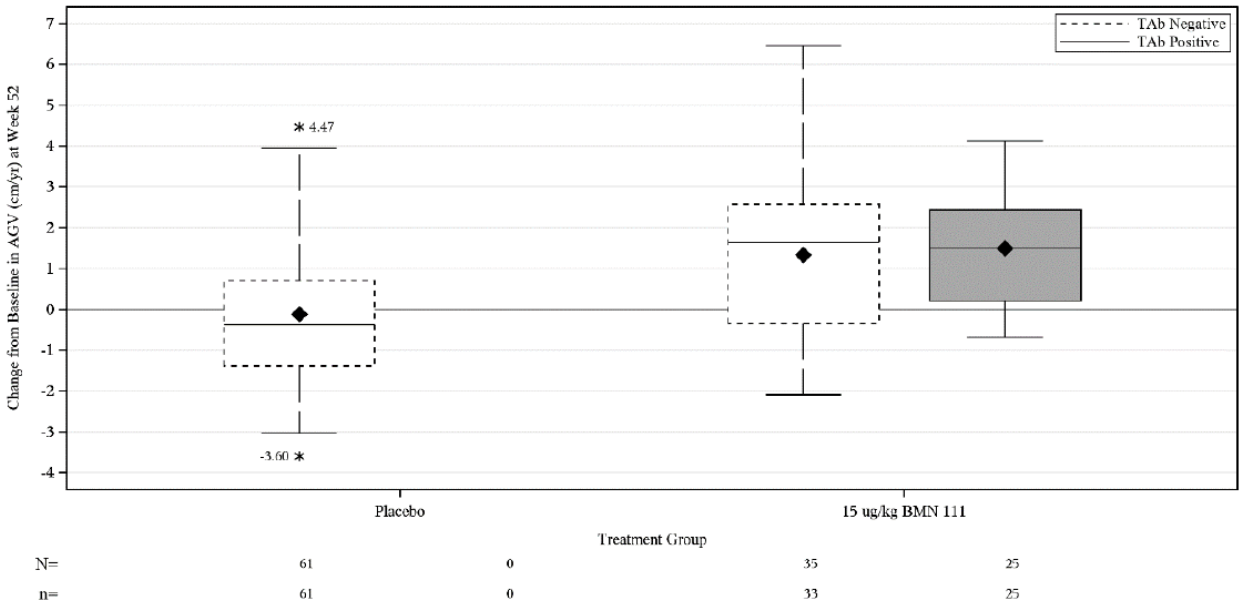
Other Secondary Efficacy Endpoints

The changes in other secondary endpoints were consistent with the results of the primary and key secondary analyses. There was no worsening in disproportionality as assessed by other body proportion ratios (Table 109, Appendix).

Insufficient information was included to support the use of the patient-reported outcomes (PROs) in the intended patient population. Nevertheless, there was no observed difference in change from baseline between the vosoritide and placebo arms in any of the PROs (see detailed review by Division of Clinical Outcome Assessment (DCOA) in Appendix, Section 16.1).

Lastly, the effect of immunogenicity on efficacy was assessed by a comparison of AGV in total anti-vosoritide antibody (TAb)-negative and-positive subjects in the treatment arm. There does not appear to be an association between TAb positivity and treatment outcome (Figure 5).

Figure 5. Change From Baseline in Annualized Growth Velocity at Week 52 by TAb Status (Immunogenicity Population)



Source: Applicant's Figure 11.5.8.2.1, CSR 111-301
Abbreviations: AGV, annualized growth velocity; BMN 111, vosoritide; TAb, total anti-vosoritide antibody

6.2.2. Study 111-302

Study 111-302 is an ongoing, phase 3, open-label uncontrolled extension study of Study 111-301, to evaluate the long-term safety and efficacy of vosoritide in children with ACH. Subjects who completed 1 year of vosoritide or placebo treatment in Study 111-301 were eligible to enroll in Study 111-302 and were administered vosoritide 15 µg/kg as a daily subcutaneous (SC) injection. Participation continues for either 5 years or until subjects reach near final adult height (NFAH), whichever comes first (see Section 3.2 for details and Figure 63, Appendix). The eligibility criteria were similar to that of Study 111-301 (see Section 6.2.1.2 for details).

Because of restrictions related to the coronavirus disease 2019 (COVID-19) pandemic, home visits and virtual visits were implemented. Sitting height was not collected at home visits. At the virtual visits, no anthropometric measurements were collected. This could explain the higher amount of missing data in the second year, particularly for the upper to lower body segment ratio which requires sitting height. There was no formal prespecified statistical inference for the second-year growth data. To visualize the trend, the average AGV, height Z-score, and upper-to-lower body segment ratio over time were depicted based on available data for subjects who were enrolled in Study 111-302. In cases with a lot of missing data in the second year, the graphs should be viewed jointly with analyses that only included subjects who had measurements at both Year 1 and Year 2.

6.2.2.1. Results of Analyses, Study 111-302

6.2.2.1.1. Primary and Key Secondary Efficacy Endpoint Results

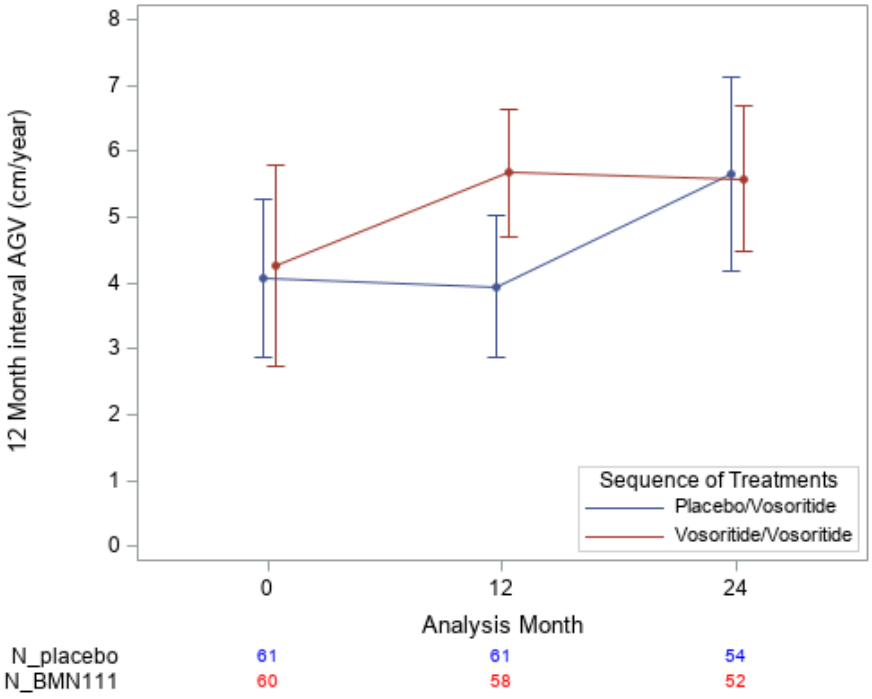
Fifty-six subjects treated with vosoritide in Study 111-301 completed 104 weeks (2 years) of vosoritide treatment (vos/vos arm), and 61 subjects in the placebo arm in Study 111-301 completed 52 weeks of vosoritide treatment (plc/vos arm). Among them, 54 in plc/vos arm and 52 in vos/vos arm had standing height assessments, and 47 in plc/vos arm and 45 in vos/vos arm had both standing and sitting height assessments at Week 52 of Study 111-302.

The results from Study 111-302 are presented in the following figures (Figure 6, Figure 7, and Figure 8). The same data are presented in Table 110, Table 111, and Table 112 in the Appendix. Only observed data were included in these explorat**ory analyses.**

For the vos/vos arm from Year 1 to Year 2, the 12-month interval AGV (i.e., AGV over the previous 12-month period) stayed roughly the same and height Z-score continued to improve. There appeared to be a slightly larger decrease in upper to lower body segment ratio in the vos/vos arm compared to plc/vos arm during the second year of treatment (Figure 8). However, because of missing data and lack of placebo control for the second year, a treatment effect on the decrease in the upper to lower body segment ratio cannot be confirmed.

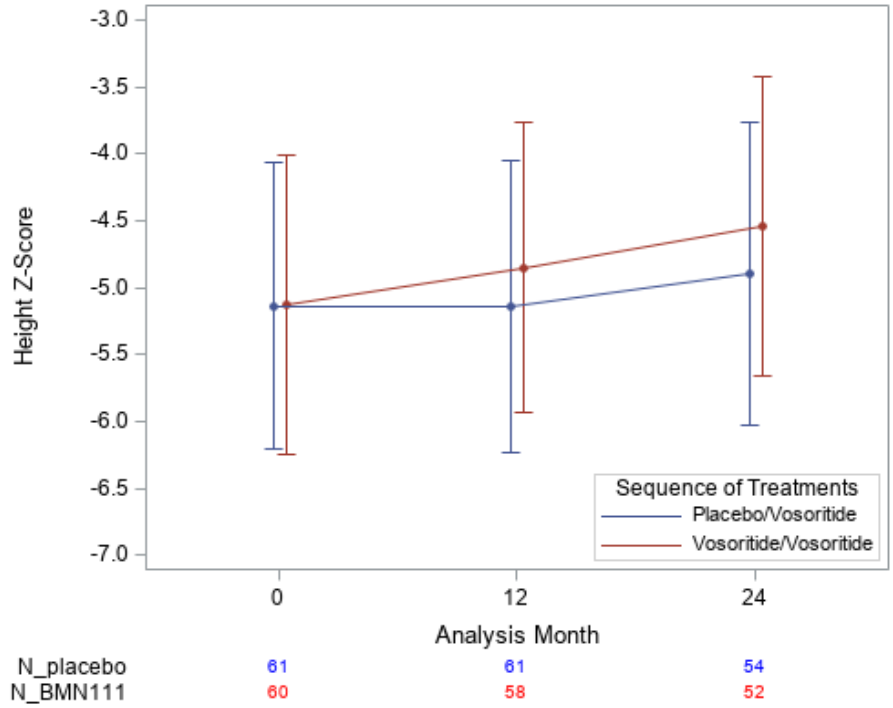
The changes in AGV, height Z-score, and upper to lower body segment ratio in the plc/vos arm from Year 1 to Year 2 were similar to the changes in vosoritide arm in Study 111-301 from baseline to Year 1.

Figure 6. AGV (cm/year) (Mean ± SD) Over 2 Years in 12-Month Intervals, Full Analysis Set, Study 111-301/302



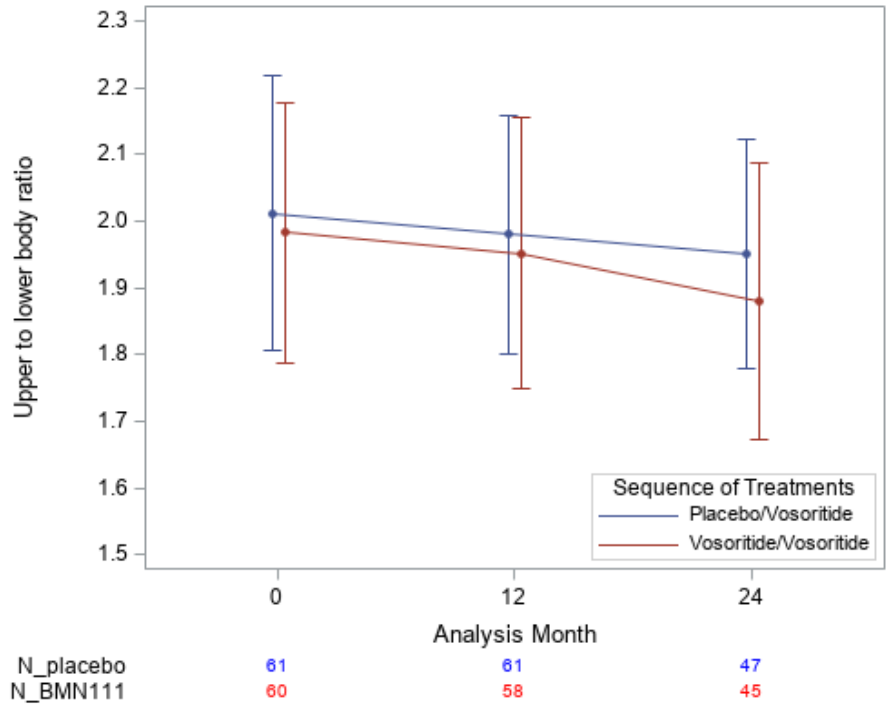
Source: statistical reviewer
Abbreviations: AGV, annualized growth velocity; BMN111, vosoritide; SD, standard deviation

Figure 7. Height Z-Score (Mean ± SD) Over Time, Full Analysis Set, Study 111-301/302



Source: statistical reviewer
Abbreviations: BMN111, vosoritide; SD, standard deviation

Figure 8. Upper to Lower Body Segment Ratio (Mean ± SD) Over Time, Full Analysis Set, Study 111-301/302



Source: statistical reviewer
Abbreviations: BMN111, vosoritide; SD, standard deviation

In summary, the efficacy data from Study 111-302 demonstrated a sustained growth effect of similar magnitude during the second year of vosoritide treatment as that observed during the first year of treatment during Study 111-301. The effect on growth in the placebo arm when exposed to vosoritide for 1 year was similar to the growth effect observed for the subjects exposed to vosoritide after 1 year in Study 111-301.

6.2.3. Studies 111-202/205 (Confirmatory Trials)

6.2.3.1. Design, Studies 111-202/205

Study 111-202 was a phase 2, multicenter, open-label, single-arm, baseline-controlled, dose-escalation, proof-of-concept study of 24 months duration in 35 children with ACH ages 5 to 14 years.

The primary objective of the study was evaluation of safety and tolerability of vosoritide.

The secondary objectives included evaluation of change from baseline in AGV, other growth parameters, body proportions, and PK profiles.

The key inclusion and exclusion criteria were similar to Study 111-301 (refer to Section 15.3, Appendix, for details).

Similar to Study 111-301, the subjects were required to have at least a 6-month period of pretreatment growth assessment in the observational Study 111-901 before entry into Study 111-202. The subjects were enrolled in 4 cohorts and were treated with fixed doses for 6 months as follows: Cohort 1: 2.5 µg/kg/day (n=8), Cohort 2: 7.5 µg/kg/day (n=8), Cohort 3: 15 µg/kg/day (n=10), and Cohort 4: 30 µg/kg/day (n=9). Dose escalation to 15 µg/kg was allowed during the following 18-month extension treatment period for Cohorts 1 and 2; Cohorts 3 and 4 continued on previous doses. All growth parameters were collected at screening, Day 43, Day 85, Day 127, Day 183, Month 8, Month 10, Month 12, and every 13-weeks thereafter.

Subjects who participated in the open-label extension phase of Study 111-202 were eligible to be enrolled in the long-term extension Study 111-205 at Month 24 and continue treatment with doses they were on in the extension period of Study 111-202 (Figure 64, Appendix). Study 111-205 is an ongoing single-arm study that continues to evaluate safety, tolerability, and growth in subjects with ACH for 5 years or until subjects have reached NFAH, whichever comes first. NFAH was defined as evidence of AGV <1.5 cm/year and growth plate closure.

6.2.3.2. Statistical Analysis Plan, Studies 111-202/205

There was no prespecified testing for efficacy endpoints in Studies 111-202/205. Changes in growth parameters (AGV, height Z-scores and upper/lower body segment ratio) were evaluated and presented as descriptive statistics and graphs.

Growth parameters were measured 2 times for each assessment. The mean of these 2 assessments is used for the summaries and analyses. In the event only 1 is available, that individual assessment is used.

All efficacy endpoints are assessed on the FAS, defined as all enrolled subjects who consented for Study 111-205. Efficacy results are presented as descriptive statistics and graphs.

6.2.3.3. Results of Analyses, Studies 111-202/205

6.2.3.3.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Study 111-202 enrolled 35 subjects who were randomized to 1 of 4 treatment cohorts: cohort 1 (2.5 µg/kg starting dose): 8 subjects; cohort 2 (7.5 µg/kg starting dose): 8 subjects; cohort 3 (15 µg/kg starting dose): 10 subjects; cohort 4 (30 µg/kg starting dose): 9 subjects. The demographics of these subjects are presented in Table 114.

Of the 35 subjects enrolled in Study 111-202, 30 subjects continued in Study 111-205. The 5 subjects who discontinued the study drug during Study 111-202 were not exposed to vosoritide, or were exposed to a vosoritide dose of 15 µg/kg/day for a very short period of time. Therefore, they were not included in the evaluation of long-term efficacy of the study drug (Table 113, Appendix). Note that 8 subjects were treated with 30 µg/kg, (b) (4) The disposition, demographics, and clinical characteristics (based on their baseline data at the time of enrollment in Study 111-202) for the remaining 22 subjects treated in Study 111-205 with 15 µg/kg are summarized below.

Of the 22 subjects, 11 (36.6%) subjects discontinued treatment before the cut-off date (Table 14). Of the 11 subjects who discontinued treatment, only 1 subject discontinued the study due to an AE (transaminase increase, see Section 7 for details). Four subjects discontinued study drug as they reached NFAH. To assess if lack of efficacy could have contributed to study drug discontinuation, the AGV data for the 6 subjects who discontinued study drug for other reasons than NFAH or AE were reviewed in detail. Except for 1 subject (b) (6), all the other 5 subjects had a noticeable and sustained improvement in AGV compared to baseline. Subject (b) (6) (Cohort 1, (b) (6) at baseline) had a baseline AGV of 4.01 cm/year that remained stable (between 3.8 and 4.6 cm/year) during the study, suggesting lack of treatment efficacy as a possible reason for discontinuation.

Table 14. Subject Disposition in Study 111-205 (Subjects Rolled Over From Study 111-202)

Disposition	Cohort 1 2.5 µg/kg Starting Dose	Cohort 2 7.5 µg/kg Starting Dose	Cohort 3 15 µg/kg Starting Dose
FAS[a]	6	6	10
Ongoing	2	3	7
Discontinued treatment	4	3	4
Reason for discontinuation of treatment			
Subject reached near-final adult height	1	2	2[b]
Withdrawal by subject	3	1	0
Adverse event	0	0	1
Physician decision	0	0	1

Source: Statistical Reviewer
[a] All enrolled subjects who consented for 111-205
[b] Include 1 subject who discontinued treatment due to erroneous diagnosis of NFAH
Abbreviations: FAS, full analysis set

Treatment adherence was high during Studies 111-202/205, with all subjects having ≥80% adherence rate (Table 117, Appendix).

The demographic characteristics of subjects in these studies were similar to the demographic characteristics of subjects enrolled in Study 111-301. Mean (SD) age of subjects exposed to a

maximum dose of vosoritide 15 µg/kg/day (herein referred to as pooled cohorts 1, 2, 3) was 8.4 (1.7) years, with half of the subjects being ages ≥5 to <8 years at the time of enrollment. Overall, the distribution of sex was balanced, with 54.5% females enrolled. Majority of enrolled subjects were white (68.1%) (Table 115, Appendix).

All but 1 (Tanner stage not reported) subjects had Tanner stage I at enrollment. Mean (SD) baseline AGV was 3.58 (1.29) cm/year, mean height Z-score (SD) was -5.09 (1.09), and mean upper-to-lower body segment ratio was 2.01 (0.20) (Table 116, Appendix).

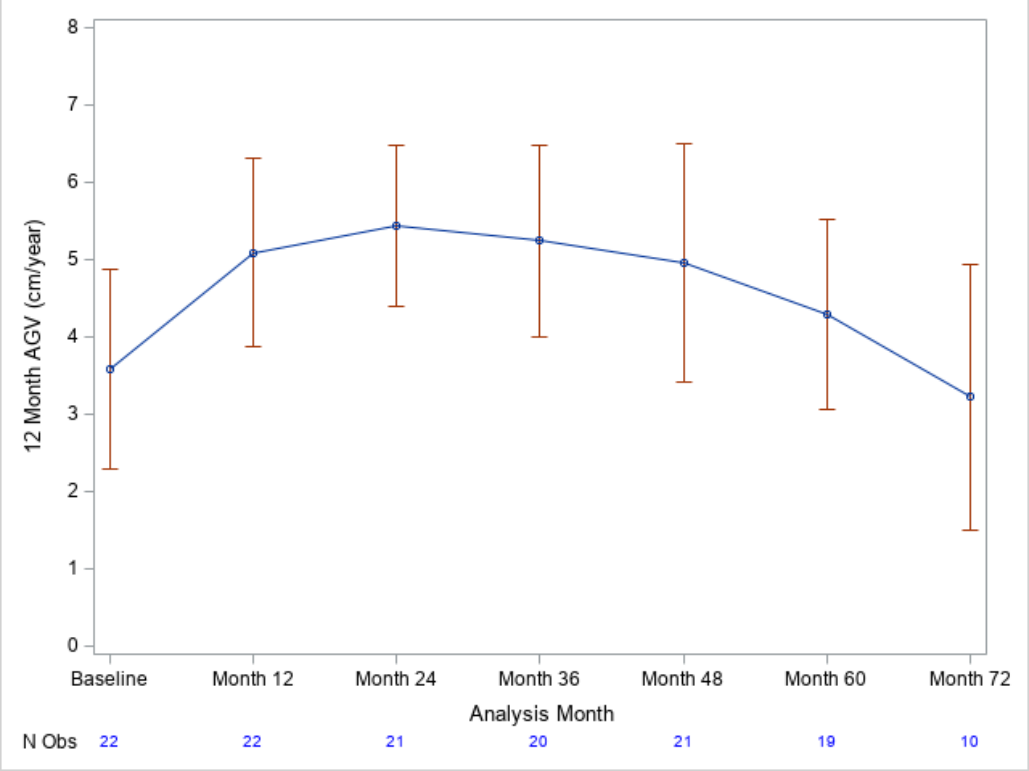
The majority of subjects (96.7%) reported an ACH-related medical history condition at baseline (e.g., otitis, skeletal, deformities, sleep apnea, foramen magnum stenosis, etc.). Refer to Section 16.1.3, Appendix, for details.

6.2.3.3.2. Primary and Key Secondary Efficacy Endpoint Results

AGV

Figure 9 shows the 12-month interval AGV over time for pooled cohorts 1, 2, and 3.

Figure 9. 12-Month Interval AGV Over Time in Pooled Cohorts 1, 2, and 3 (Mean ± SD), Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: AGV, annualized growth velocity; SD, standard deviation

The mean (SD) change from baseline in AGV in the pooled cohorts at the end of the first year (1.51 [1.20] cm/year) is consistent with AGV changes observed in Study 111-301 in the vosoritide-treated group (Table 118, Appendix).

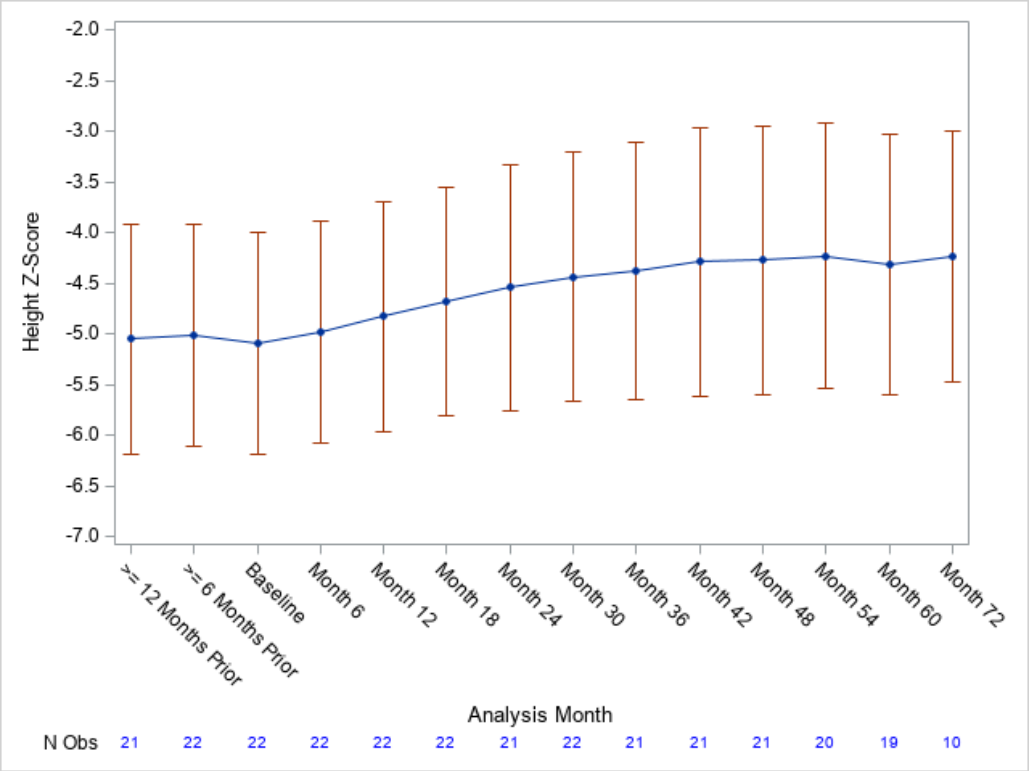
The changes in 12-month interval AGV during the 6-year treatment period were: 1.93 (1.36) cm/year at Year 2, 1.80 (1.37) cm/year at Year 3, 1.44 (1.69) cm/year at Year 4, 0.65 (1.45) cm/year at Year 5, and -0.81(2.12) cm/year at Year 6 (Table 118, Appendix). The largest increase in 12-month interval AGV from baseline was observed at Year 2, when all subjects were exposed to vosoritide 15 µg/kg daily for at least 1 year. A slight decline in the growth rate after the first 2 years was noted, which may reflect, in part, the natural decline in growth velocity with age. A positive change in AGV from baseline was maintained until Year 5. It is difficult to interpret the negative change from baseline in AGV observed at Year 6. At this timepoint, there were a lot of missing data (only 10 out of 19 subjects had data at Year 6) and subjects were older and closer to reaching their NFAH, which is when a natural decline in AGV expected. One of the 10 subjects (subject (b) (6)) with AGV assessed at Year 6 had reached NFAH according to the protocol-defined criteria. Seven of the 10 subjects were female, with 5 of them being ages 13 and older. Epidemiologic data (Hoover-Fong et al. 2008) show females having a significant decline in AGV around age 13, while males continue to grow at the same rate up to at least age 16. All 5 females who were age 13 and older at Year 6 had a decline in AGV from the previous year of more than 1 cm/year (range of AGV decline: 1.6 cm/year to 5 cm/year), while the remaining 2 female subjects who were 12 years old at Year 6 had a relatively stable (≤0.5 cm/year decline) AGV compared to the previous year, consistent with the epidemiological data. The 3 male subjects with AGV data at Year 6 had ages ranging between 11 and 14 years, with 2 of them having relatively stable AGV at Year 6 compared to the previous year, while the 3rd male subject, age 11, had a decline in AGV of 1.6 cm/year.

In summary, the observed decline in AGV at Year 6 is likely explained by a preponderance of females ages 13 older in the cohort analyzed, who have a natural decline in AGV at this age, according to epidemiological data. Therefore, no conclusions with regards to the effect of vosoritide on growth beyond 5 years can be drawn.

Height Z-score

As expected with improvement in AGV, improvement in height SDS was also observed. Mean (SD) change from baseline in height Z-scores over time in the pooled cohorts were +0.26 (0.21) at Year 1, +0.57 (0.38) at Year 2, +0.77 (0.64) at Year 3, +0.88 (0.73) at Year 4, +0.78 (0.7) at Year 5, and +0.78 (0.62) at Year 6 (Figure 10 and Table 120, Appendix). These data suggest that height Z-score gain from baseline reached a peak of approximately 0.7 to 0.8 SDS at Year 3 without much additional change (Figure 10).

Figure 10. Height Z-Score Over Time in Pooled Cohorts 1, 2, and 3 (Mean ± SD), Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: N Obs, number of observations

Lack of additional improvement does not necessarily suggest declining efficacy. Rather, subjects were entering pubertal years and when children with ACH reach puberty, their height Z-scores naturally decline. As such, even if there was no additional beneficial effect of vosoritide treatment on growth, the Z-score would be expected to naturally decline during pubertal years.

In using average stature children as a reference population to assess height Z-scores in subjects with ACH, changes due to a vosoritide treatment effect may be confounded with changes due to differences in growth patterns between ACH and average stature children.

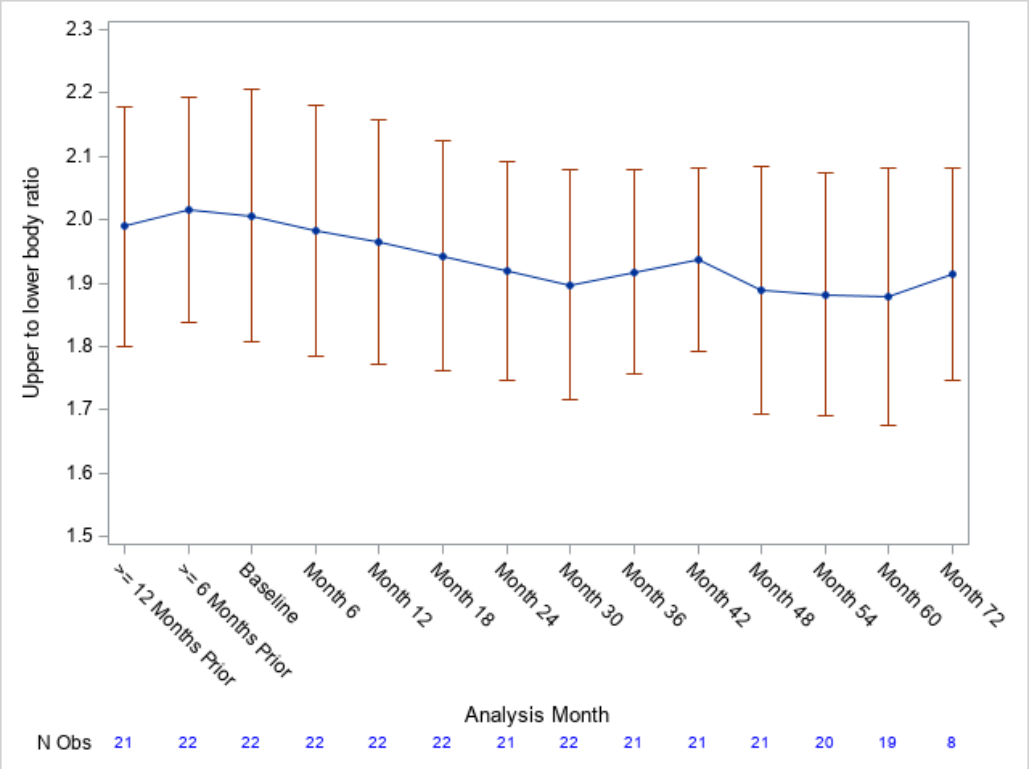
For example, during prepubertal years (e.g., ages 2 to 10 years of) both children with ACH and children of average stature have a relatively stable growth velocity (e.g., 4 to 5 cm/year for children with ACH and 5 to 7 cm/year for children of average stature). However, average stature children experience a growth spurt during puberty (e.g., median peak height velocity in boys reaches 9.3 cm/year at age 13.5 years and 8.3 cm/year in girls at age 12) whereas children with ACH have a steady growth velocity throughout puberty, similar to that of the prepubertal period (Hoover-Fong et al. 2008). As a result, height Z-scores are relatively stable (e.g., mean height Z-score is approximately 5 SDS) during prepuberty and drop during pubertal years (e.g., -5.5 SDS to – 6 SDS) in children with ACH (Merker et al. 2018). This makes for a challenging interpretation of height Z-score changes in response to vosoritide treatment when children reach puberty, such that a certain change in height Z-score as a result of treatment may be underestimated in pubertal children. This problem is further complicated by a lack of a control in Study 111-205.

In conclusion, the effects observed on height Z-scores are consistent with the effects on AGV, and the plateau in the height Z-score values after Year 3 does not necessarily represent a diminished treatment effect on growth but rather an ACH population who reached puberty and in whom height Z-score naturally declines.

Upper to Lower Body Segment Ratio

Data from Study 111-202/205 showed a slight trend towards improvement in the upper to lower body ratio over time when compared to baseline in the pooled cohorts (Figure 11) and in each treatment cohort (Figure 76, Appendix)

Figure 11. Upper to Lower Body Ratio Over Time in Pooled Cohorts 1, 2, and 3 (Mean ± SD), Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: N Obs, number of observations; SD, standard deviation

However, upper to lower body ratio naturally declines with age in ACH (Hoover-Fong et al. 2008). Since there is no comparator arm, it remains unknown whether the observed changes in disproportionality are an effect of vosoritide treatment or are just reflections of the natural evolution of upper to lower body segment ratio in ACH. However, it is reassuring that a negative effect on the upper to lower body segment ratio (e.g., ratio increasing) was not noted for the duration of treatment.

Immunogenicity and Efficacy

A comparison of TAb-negative and TAb-positive subjects showed no association between TAb positivity and treatment outcome as measured by change from baseline in 12-month interval AGV at the end of the study period (Figure 80, Appendix).

6.2.4. Comparative Analyses of Growth Parameters Between Treated Subjects and External Control (From NH Studies)

Studies 111-205 and 111-302 were submitted to demonstrate long-term efficacy of vosoritide. Because both were uncontrolled, the Applicant proposed to use external control data as a comparator. The Applicant used data from the AchNH study as the primary source for their comparative analyses and used pooled data from 3 other NH sources for supportive analyses. The AchNH study is an Investigator-initiated, observational, retrospective study that evaluated longitudinal anthropometry data in subjects with ACH at 4 specialized centers in the United States.

The Applicant's prespecified primary analysis was a 5-year cross-sectional analysis to compare the change in height from baseline to Year 5 between the vosoritide group (from Study 111-205) and the AchNH control group. Additional analyses include 5-year longitudinal analyses, 4-year cross-sectional analyses, and 2-year longitudinal analyses, as well as comparisons with other supportive NH data sources. In the cross-sectional analyses, exact matching on sex and integer age was performed at both baseline and at the end of follow-up (Year 5 in primary analysis). For the longitudinal analyses, matching was performed at baseline only among the pool of AchNH subjects with available height data at Year 5 in the 5-year longitudinal analysis, Year 4 in the 4-year longitudinal analysis, or Year 2 in the 2-year longitudinal analysis. The sensitivity analyses included simulations, a tighter age matching time interval, and analyses using an external control without matching.

The results of the primary analysis (5-year cross-sectional analysis) demonstrated that vosoritide-treated subjects (Study 111-205, Cohort 3, n=10) were on average 4.97 cm taller than AchNH control subjects (n=559) at baseline. At Year 5, the mean difference in height between the 2 groups reached 14.04 cm. The baseline-adjusted mean height difference between subjects exposed to vosoritide (n=10) and the matched external AchNH control (n=360 at Year 5) was 9.08 cm (95% CI: 5.77 to 12.38). Use of the secondary external control pool that represents a combination of the remaining 3 NH databases (n=84 at Year 5) yielded a similar height difference of 8.74 cm (95% CI: 5.37 to 12.11). In the 5-year longitudinal analysis, the mean difference in change from baseline height between subjects exposed to vosoritide (Study 111-205, Cohort 3, n=10) and the matched external AchNH control (n=98) was 8.40 cm (95% CI: 6.13 to 10.67, Table 15). Sensitivity analyses were generally consistent with results from the primary analysis, with height differences after 5 years ranging from 7.50 cm to 9.08 cm across these analyses.

Table 15. 5-Year Comparative Analyses for Change in Height, Study 111-205 Versus NH Control

Analysis[a]	Vosoritide Exposure Cohort	NH Control	Mean Height Difference (cm) (95% CI)	Height Z-Score Difference (95% CI)
Primary analysis				
Cross-sectional	Cohort 3: Vosoritide 15 µg/kg, N=10	AchNH, N=559/360[b]	9.08 (5.77, 12.38)	0.77 (0.40, 1.14)
Cross-sectional	Cohort 3: Vosoritide 15 µg/kg, N=10	Supportive Pool, N=84	8.74 (5.37, 12.11)	0.75 (0.35, 1.15)
Longitudinal	Cohort 3: Vosoritide 15 µg/kg, N=10	AchNH, N=98	8.40 (6.13, 10.67)	0.78 (0.44, 1.11)
Cross-sectional	Cohorts 1,2,3 Vosoritide 15 µg/kg, N=20	AchNH, N=658/423[b]	8.36 (6.38, 10.33)	0.85 (0.59, 1.10)
Longitudinal	Cohorts 1,2,3 Vosoritide 15 µg/kg, N=20	AchNH, N=97	7.50 (5.83, 9.17)	
Sensitivity analysis 1: 5,000 iterations				
Cross-sectional	Cohort 3: Vosoritide 15 µg/kg, N=10	AchNH	9.05 (5.60, 12.50)	
Longitudinal	Cohort 3: Vosoritide 15 µg/kg, N=10	AchNH	8.72 (6.57, 10.87)	
Sensitivity analysis 2: age-matching by 6 months				
Cross-sectional	Cohort 3: Vosoritide 15 µg/kg, N=10	AchNH	8.55 (4.95, 12.14)	
Longitudinal	Cohort 3: Vosoritide 15 µg/kg, N=10	AchNH	8.36 (6.21, 10.50)	
Sensitivity analysis 3: without matching				
Longitudinal	Cohort 3: Vosoritide 15 µg/kg, N=10	AchNH, N=217	8.57 (6.50, 10.63)	

Source: summarized from Applicant's natural history integrated analyses report. Results from primary analyses were verified by FDA.
[a] Cross-sectional analysis method: t-test of difference at Year 5 and difference at baseline between 2 groups. Longitudinal analysis method: ANCOVA model that includes treatment and matching ID as fixed factors.
[b] Number of NH control subjects matched at baseline and 5 year respectively.
Abbreviations: AchNH, Achondroplasia Natural History; CI, confidence interval; NH, natural history

The Applicant also performed 4-year cross-sectional analyses and 2-year and 4-year longitudinal analyses. The results are presented in Table 122 and Table 123 (Appendix). In these analyses, subjects' height measurements were "rebaselined", i.e., measured from the time when a subject's vosoritide dose was escalated to 15 µg/kg. Therefore, subjects in cohorts 1 and 2 of Study 111-205 were already treated with low dose vosoritide for 6 months at the baseline for analyses and were not comparable with the treatment-naïve AchNH subjects.

Per FDA's request, the Applicant performed additional analyses for Study 111-205 that excluded a cohort 3 subject who underwent limb lengthening surgery prior to study entry into the study since the height assessments from this subject do not reflect his natural height. The external controls have already excluded such subjects. In addition, FDA requested that the 4-year and 2-year analyses use height measurements that were not rebaselined, i.e., using the original untreated baseline for all cohorts so that results from these analyses would not be confounded by the difference in treatment status between the 2 groups at baseline. Table 124 (Appendix) summarizes the results for the revised 5-year and 4-year cross-sectional analyses. The baseline-adjusted mean height difference remains highly significant in these analyses. Refer to Section 16.1.4, Appendix, for additional longitudinal analyses that excluded limb lengthening surgery, were not rebaselined, and were matched on additional baseline covariates. Overall, results from these analyses suggest the improvement in height in vosoritide-treated subjects versus matched external control subjects was incremental over time through the 5 years of treatment.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Broad Proposed Indication, i.e., Treatment of ACH

Issue

Sufficiency of data to demonstrate that drug improves signs and symptoms of ACH other than linear growth.

Background

The Applicant's proposed indication for vosoritide is treatment of ACH in patients ages 5 to 18 years. However, the vosoritide clinical program evaluated the effect of vosoritide on height only; other signs and symptoms of ACH (e.g., spinal stenosis, otitis, improvement in daily activities evaluated by validated instruments, etc.) that are clinically important were not assessed in the clinical studies.

Assessment

Although the most striking clinical features of ACH are short stature and disproportional growth manifested as a long narrow trunk and shortened extremities, there are other serious signs and symptoms of the disease. Patients with ACH are at risk for multiple complications that are a consequence of abnormal bone growth. These include internal hydrocephalus, intracranial

hypertension, cervicomedullary cord compression, foramen magnum stenosis, and spinal stenosis.

Cervicomedullary cord compression can result in hypotonia, respiratory insufficiency, central sleep apnea, and, rarely, quadriplegia. Less severe but more common complications include recurrent ear infections, conductive hearing loss, speech delay, developmental motor delays, and dental abnormalities. The combination of impairments in body structure and function can present significant challenges in performance of activities of daily living. Major areas of participation that are affected for children with ACH are mobility, self-care, education, and performance at school. Furthermore, these challenges, along with their altered abnormal physical appearance, can result in psychosocial stress for the patients and their families.

The effect of vosoritide on linear growth was the primary efficacy endpoint demonstrated in Study 111-301 and confirmatory Studies 111-302 and 111-202/205. Disproportionality, evaluated by the measurement of upper-to-lower body segment ratio, is the only other manifestation of ACH included in the clinical trials. There was no clinically meaningful improvement in disproportionality in Studies 111-301 and 111-202/205. Absence of a control group in Studies 111-202/205 further complicates the assessment of drug-attributable improvement in disproportionality with long-term vosoritide treatment (refer to Section 6.2.3 for details).

Sleep apnea was assessed as an exploratory endpoint. The assessment was optional at baseline and at Week 52. Only 3 subjects (2 placebo, 1 vosoritide) had evaluable data and no meaningful conclusions could be made. Lastly, the effect of vosoritide on health-related quality of life and functional measures were evaluated as exploratory endpoints (i.e., not controlled for multiplicity) in Study 111-301 only. There was insufficient information included in the submission on the adequacy of the selected COA instruments (see review by DCOA in Appendix, Section 16.1). Nevertheless, the review team analyzed the results of the COAs, which showed no difference between vosoritide and placebo arms in any of the assessments.

Conclusion

The indication should be limited to improvement in linear growth in patients with short stature due to ACH. Improvement in other signs or symptoms of the disease were either not assessed or not demonstrated in the clinical program.

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6.3.3. Adequacy of the Efficacy Data to Provide "Substantial Evidence of Effectiveness"

Issue

Although the AC and FDA provided specific recommendations on the number and duration of studies needed to provide substantial evidence of vosoritide, the Applicant did not follow the recommendations as discussed during the AC meeting on May 11, 2018, and outlined in the FDA's Advice Letter to the Applicant on July 30, 2018 (refer to Regulatory History Section 12). Therefore, whether the data submitted provides substantial evidence for the treatment of patients with achondroplasia is a central issue in this review.

Background

During development of vosoritide for the proposed indication, the Agency and the Applicant held extensive discussions about the appropriate elements of the vosoritide clinical development program. To help with the complex issues related to the program, the division convened an AC during the IND stage of development. On May 11, 2018, a Joint Meeting of the PAC and the EMDAC was held to discuss the clinical development program for vosoritide. Based on the extensive AC conclusions and comments, FDA provided the following recommendations to the Applicant on July 30, 2018: 1) conduct a randomized, placebo-controlled study to provide statistically and clinically significant efficacy data and sufficient safety data in the intended population to support the drug's approval; 2) if placebo cannot be used in the planned study(s) due to the small number of potential participants and potential unwillingness of subjects and/or caregivers to take the placebo, another option is to use historical control data as a comparator; 3) the study should be of at least 2-years duration in order to evaluate the change in growth velocity, since a shorter trial may miss growth velocity attenuation over a relatively short time frame should it occur. Refer to the Regulatory History in Section 12 of the Appendix.

Assessment

The data intended to provide substantial evidence of effectiveness of vosoritide in the intended population comes from the single adequate and well-controlled phase 3 Study 111-301 plus confirmatory evidence from Studies 111-202/205 and 111-302. Natural history data were used as an external control for Studies 111-202/205 and 111-302. Overall, many elements of the design of the phase 3 study were consistent with FDA and AC recommendations, although the study duration was shorter than recommended by the AC (1 year versus 2 years). Study 111-301 met its primary endpoint and demonstrated that the effect of vosoritide on AGV was statistically superior compared to placebo after the first year of treatment. There was no effect on disproportionality after 1 year of treatment with vosoritide and other important clinical endpoints were either not evaluated properly (e.g., functional assessments) or not evaluated at all (e.g., neurological complications, obstructive sleep apnea, etc.) (refer to Section 6.2.1.4.2 above).

Study 111-301 was not long enough to evaluate the sustainability of drug-induced growth, and there remains a concern that growth velocity attenuation may be missed over a relatively short

time frame. Therefore, to address the concern of whether the effect is sustained, the Applicant submitted long-term growth data of up to 6 years from Studies 111-202/205, conducted in a small number of subjects (N=22). The Applicant also provided uncontrolled data from a second year of treatment from Study 111-302, submitted on March 31, 2021 (Major Efficacy Amendment). These studies demonstrated overall that the drug-induced effect on growth was sustained for up to 5 years and was similar to growth during the first year of treatment (refer to Sections 6.2.2.1.1 and 6.2.3.3.2).

Because Studies 111-302 and 111-202/205 were uncontrolled, conclusions regarding efficacy are challenging. To better understand long-term efficacy, data from Studies 111-205 and 111-302 were compared with data obtained from the NH studies to compare growth in the vosoritide group compared to untreated subjects. The results of the initial comparative analyses and the additional analyses performed by the Applicant at FDA's request supported the conclusion that the improvement in AGV observed with long-term treatment is most likely attributable to the drug (refer to Section 6.3.4 for details). It should also be noted that the quality of the primary NH data (AchNH study) was reviewed by the Division of Epidemiology (DEPI) team and also discussed with the RWE Subcommittee on April 6, 2021 (refer to Sections 6.3.3, 6.3.6, and the Epidemiology Review in DARRTS dated July 25, 2021) and was found to be fit for use and overall acceptable to be used as an external comparator arm to support efficacy of vosoritide.

Conclusion

The review team concludes that the submitted data provides substantial evidence of effectiveness. Refer to Section 6.3.1 for discussion of the indication supported by these data.

Whether or not substantial evidence was provided was also discussed at an MPPRC meeting on June 16, 2021. Overall, the Council agreed with the Division that the Applicant has provided substantial evidence of effectiveness. In addition, the members also agreed that data on final height are required to validate AGV as an intermediate clinical endpoint in ACH (refer to Section 6.3.4). Lastly, the members also indicated that although final height data could be obtained via postmarketing commitment (PMC), PMCs are not always robust, reliable, or followed through, and use of the accelerated approval pathway with a postmarketing requirement (PMR) would be important to generate reliable data on final height, which are critical to patients and prescribers.

6.3.4. Use of AGV as Surrogate Marker to Demonstrate Efficacy of Vosoritide in Patients With Disproportional Short Stature (Primary Efficacy Endpoint)

Issue

Acceptability of the AGV as a surrogate endpoint for the evaluation of the drug for the treatment of disproportional short stature associated with ACH.

Background

Improvement in AGV was used as an efficacy endpoint (as primary efficacy endpoint in Study 111-301 and secondary endpoint in Studies 111-202/205).

AGV is a validated surrogate endpoint in conditions associated with proportional short stature due to GH deficiency as well as some other non-GH deficient states. For these conditions in pediatric patients, AGV has been accepted by FDA as a surrogate endpoint to support efficacy. There are sufficient data from long-term clinical trials to date demonstrating that improvement in AGV in patients with proportional short stature translates to improvement in final height. In addition, initially approved GH therapy for treatment of growth hormone deficiency (GHD) (Humatrope) and many GHs for treatment of non-GHD short stature were evaluated in long-term studies to demonstrate the effect of the drug on final height. Lastly, in many of these conditions, the treatment normalized or near-normalized final height (e.g., GHD, Turner syndrome, idiopathic short stature, small for gestational age syndrome, etc.). The mean final height gains observed in these conditions ranged from 5 to 9 cm (Turner syndrome, idiopathic short stature), 9 to 11 cm (Noonan syndrome), and/or final height was similar to the height of children of normal average stature: 170 cm (males), 159 cm (females) (small for gestational age syndrome).

In contrast, ACH is a severe short-stature condition characterized by disproportionate growth in which use of AGV as a surrogate marker has not been validated to date, and there are no validated growth prediction models to final adult height based on AGV.

Assessment

The use of AGV as an efficacy endpoint in achondroplasia was discussed a number of times by the Applicant and FDA during the vosoritide development program and was also a topic of discussion during the AC meeting on May 11, 2018 (refer to Regulatory History Appendix and Section 12). The AC concluded that AGV is an acceptable objective endpoint to demonstrate clinical benefit of the drug in the intended population. The recommendations were based on the assumption that improvement in AGV will likely result in some improvement in final height and that any improvement in final height, even without normalization, will most likely improve functionality of these patients and their quality of life. However, there was a concern that AGV in this population may be affected by other factors, including disproportionality, and that short-term studies may not capture growth attenuation over time. Thus, the AC recommended to evaluate the long-term effect of the drug on growth (refer to the discussion in Section 6.3.5).

Improvement in AGV was observed in children with ACH in all vosoritide clinical trials, and the magnitude of improvement was consistent between trials. Study 111-301 demonstrated superiority of vosoritide compared to placebo after 1 year of treatment, with a treatment benefit on AGV (primary endpoint) of 1.57 cm/year (refer to Section 6.2.1). The effect on growth appeared to be sustained over time as demonstrated by the changes from baseline in AGV and height Z-scores after 1 additional year of treatment in Study 111-302 and up to 6 years in Studies 111-202/205, although the number of subjects followed during the sixth year in Study 111-205 was much smaller (n=10) than the year prior (n=19). The mean (SD) changes from baseline in AGV after 1 additional year of exposure to vosoritide in Study 111-302 was 1.29 (1.83) cm/year. The highest observed change from baseline in AGV (mean [SD]) in Studies 111-202/205 was 1.93 (1.36) cm/year at Year 2, slightly diminishing with time. The height Z-score gain from

baseline in Studies 111-202/205 reached a peak of approximately 0.8 at Year 3 and remained stable afterwards (refer to Section 6.2.3).

The interpretation of drug-induced changes observed in the uncontrolled trials is further supported by the comparative analyses of the drug-induced changes in growth parameters with NH data. The results of these analyses demonstrated a mean (95% CI) height difference in favor of vosoritide ranging between 7.1 (5.4, 8.8) cm and 7.5 (4.8, 10.1) cm at Year 5 and 8.75 (6.32, 11.18) cm and 9.19 (6.19, 12.18) cm at Year 6, respectively (cohort 3 versus AchNH comparison in Table 130 and Table 134), suggesting that there was an improvement in growth measures in Studies 111-202/205 due to vosoritide in addition to natural growth, and that the vosoritide-induced improvement was sustained after 5 years of use.

It should be noted that the observed vosoritide-induced effects on growth in subjects with ACH were smaller compared to the effects observed with other growth promoting drugs in proportional nongrowth hormone deficient short stature conditions. Changes in AGV ranged between 3.5 and 6 cm/year after 1 year of vosoritide treatment, while changes in height Z-scores ranged between 1 and 1.7 in patients with Turner syndrome, idiopathic short stature, Prader Willi syndrome, small for gestational age disorder, etc. However, even if it is not expected that vosoritide will normalize the final height (due to the severe short stature at baseline and small drug-induced growth changes), the demonstrated cumulative growth achieved after up to 6 years of treatment is likely to be clinically meaningful in this patient population with severe short stature. For this population, even small height gains may translate into improved abilities to perform activities of daily living, most likely having a positive psycho-social impact as well. In addition, the observed height gains after 6 years of treatment with vosoritide are similar to the effects of growth hormone therapy on final adult height in patients with Turner syndrome (between 5.0 and 8.3 cm) and idiopathic short stature (5 cm in males and 6.9 cm in females).

No worsening in disproportionality or acceleration in bone age that may affect vosoritide-induced growth was noted during the 6 years of treatment. However, the effect of final height remains unknown (refer to Section 6.3.5 below for details).

Conclusion

The team considers AGV to be an intermediate clinical endpoint and not a validated surrogate endpoint in this population with disproportional growth, because sufficient data on final height was not provided (see Section 6.3.5 for details) to validate the use of AGV in this population, and no predictive validation model exists. It remains unknown whether other factors, such as worsened disproportionality and acceleration in bone age, may occur with longer treatment and attenuate the effect of the drug on growth and achievement of final adult height.

Thus, based on these limitations, the submitted data support accelerated approval, but data on final height are needed to confirm that changes in the intermediate clinical endpoint of AGV ultimately translate into the intended clinical benefit of improved final adult height.

6.3.5. Final Adult Height

Issue

The effect of vosoritide on final adult height in patients with disproportional growth due to ACH is unknown.

Background

Final adult height is the clinically meaningful endpoint of interest in the evaluation of growth-promoting drugs in children with short stature conditions.

As noted above, the first approved GH formulations were required to demonstrate the effect of the drug on final adult height in long-term studies to validate the use of AGV in GHD and non-GHD short stature conditions. These studies convincingly demonstrated that improvement in AGV in patients with proportional short stature translate into improvement and/or normalization of final adult height.

In contrast, ACH is a severe short stature condition characterized by disproportionate growth for which use of AGV as a surrogate marker has not been validated, and there are no validated growth prediction models to final adult height based on AGV. In general, pharmacologically induced effects on growth are largest during the first 1 to 2 years of treatments and tend to diminish over time; thus, in severe short stature conditions, such as ACH, an effect of vosoritide on final adult height may be less than expected based on the growth seen initially. In addition, there are also concerns that other factors, such as drug-induced disproportional growth, may attenuate the effect of vosoritide on final adult height. For example, the drug may have a predominant effect on the lower body segment (i.e., lower extremities) with no significant effect on the upper body segment (body length) or overall final standing height. Thus, as discussed with the Applicant during the development program, and also emphasized during the AC meeting, data on final adult height is needed and “improving final height is a key goal of treatment in the target population” (refer to the Division’s Advice letter from July 30, 2018).

Assessment

The Applicant provided data on near final adult height from 4 subjects (3 females and 1 male) treated with vosoritide in the open-label, single-arm Study 111-205. NFAH was defined as a decrease in AGV <1.5 cm/year over a period of at least 6 months and the fusion of growth plates, assessed by radiographic imaging of the distal femur and proximal tibia.

In Study 111-205, subjects were 9.5 to 10.8 years at baseline and were treated from 5.3 to 6 years. Three subjects had notable changes in AGV compared to baseline values for at least 3 consecutive years. Subject (b) (6) had only 2 years of notable changes from baseline in AGV.

Table 16. Subjects Reaching NFAH, Study 111-205, Full Analysis Set

Parameter	Subj. (b) (6) [a]	Subj (b) (6) [b]	Subj (b) (6)	Subj. (b) (6)
Sex				(b) (6)
Age at baseline, age at last assessment (years)				
Duration of follow-up (years)	6.06	5.26	5.6	5.3
Baseline height (cm)	100.2	102.1	113.2	106.6
Height at last measurement (cm)	121.2	121.4	141.9	124.7
Cumulative growth (cm)	21.0	19.2	28.7	18.1
AGV baseline (cm/year)	1.81	2.88	3.54	2.62
AGV Month 12 (cm/year)	1.64	3.99	7.44	4.57
AGV Month 24 (cm/year)	5.1	5.64	4.93	5.95
AGV Month 36 (cm/year)	5.55	4.59	7.50	2.83
AGV Month 48 (cm/year)	4.21	3.76	5.39	1.30
AGV Month 60 (cm/year)[d]	1.36	1.36	3.83	0.28
AGV at last height assessment (cm/year)	1.0	1.16	0.92	0.97

Source: adapted from Applicant's Efficacy Addendum submission, Listing 16.2.6.1a
[a] Subject (b) (6) has been on vosoritide doses 2.5 µg/kg from start of treatment to Month 10 and 7.5 µg/kg from Month 11 to Month 15 and on vosoritide 15 µg/kg starting with Month 16
[b] Subjects (b) (6) have been on vosoritide 7.5 µg/kg from start of treatment to Month 10, then on vosoritide 15 µg/kg
[c] Subject (b) (6) has been on vosoritide dose of 15 µg/kg from start of treatment
[d] Imagistic evidence of growth plate closure
AGV was derived over the previous 6-months. For example, Month 24 Interval = [(Height at Month 24 Visit- Height at Month 18 Visit)/(Date of Month 24 Visit – Date of Month 18 Visit)] x 365.25
Abbreviations: AGV, Annualized growth velocity; F, female; M, male; NFAH, near final adult height

To help understand whether the height changes in this single-arm study were drug-related, the data for evolution of height percentiles for these 4 subjects were compared against age and sex-matched population from natural history data (AchNH study), which the review team and the FDA RWE Subcommittee found to be fit for use as an external control arm for standing height data evaluation (refer to Section 6.3.3 and Section 6.3.6 below discussing appropriateness of use NH data as an external control and Figure 85, Appendix). Based on this analysis, the 4 subjects demonstrated improvement in final adult height compared to age- and sex-matched external controls.

Subjects (b) (6) had a baseline height below the 25th percentile of the age- and sex-matched untreated population. At the time of the last assessment, standing height for these 2 subjects was at or above the mean value for age and sex-matched comparators in the untreated population. Subjects (b) (6) had a baseline height that was approximately 75th percentile of the age and sex-matched untreated population. At the time of the last assessment, standing height for these 2 subjects was above the 97.5th percentile (subject (b) (6)) and 75th percentile (subject (b) (6)) of the age- and sex-matched untreated ACH population.

Conclusion

Data from the 4 subjects who achieved predefined NFAH are encouraging, in that the benefit of vosoritide may continue beyond the first year of treatment. An effect on near final adult height over the entire height percentile spectrum at baseline (e.g., from below 25th percentile to above 75th percentile) was noted when comparative analyses against age- and sex-matched external controls (from AchNH study) were performed, as demonstrated by the improved height percentiles from baseline to last height assessment in each subject. Since height percentiles are

expected to remain relatively the same throughout a child's growing period, the data suggest that the observed changes were most likely due to the drug and not due to natural growth.

Nevertheless, the small number of subjects who achieved NFAH (n=4) during the development program preclude firm conclusions regarding the beneficial effect of vosoritide on final adult height in this population.

6.3.6. Quality of Data From NH Studies Used as an External Control to Support the Evaluation of the Drug Effect on Growth Parameters

Issue

Studies 111-202/205 and 111-302 were externally controlled using data from NH studies. Whether these NH studies are adequate to serve as an external control is a review issue.

Background

As discussed during the 2018 AC meeting, long-term controlled data were required to demonstrate that possible growth velocity attenuation is not missed due to a short study period (requires at least a 2-year study duration). AC members also noted that if placebo cannot be used in the planned study(s) due to the small number of potential participants and potential unwillingness of patients and/or caregivers to take the placebo for extended periods, another option is to use historical control data as a comparator.

The Applicant also provided long-term growth data from Studies 111-202/205 to demonstrate the durability of the effect of the drug on growth. Since these studies did not include a long-term placebo arm the Applicant submitted and proposed to use data from NH studies as an external control. The Applicant obtained the NH data from 4 different studies of subjects with ACH; the primary NH data source (AchNH study, an Investigator-initiated study) provided the majority of subjects who served as controls. This was the primary source used for FDA analyses. The AchNH is a protocol-driven, retrospective, observational, multicenter registry designed to primarily characterize natural growth in subjects with ACH. Data, including anthropometric data, were collected from 791 subjects with ACH, ages 5 to 16 years, as part of routine specialist care in 4 established skeletal dysplasia centers across the United States. The 3 remaining data sources were pooled to provide a supportive NH control pool.

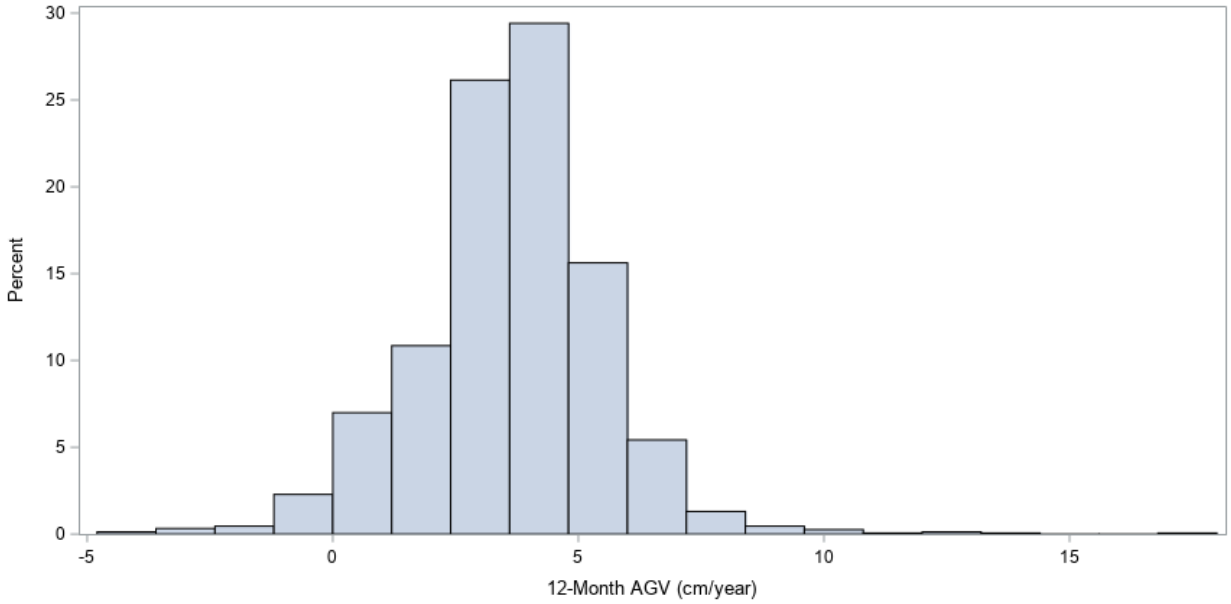
Assessment

The AchNH data were reviewed by the DEPI-I team (refer to Dr. Christian Hampp's Epidemiology Review in DARRTS dated July 25, 2021) to assess its quality. The team confirmed that even though there are limited data on genetic diagnosis, medical history, and medications in the study, these factors are unlikely to skew results in favor of vosoritide.

The statistical team noticed errors in all NH studies, including the AchNH study. There were a number of negative 12-month AGV values at some visits that translate into negative changes in height (Figure 83, Appendix). The Applicant indicated that less than 5% of the assessments for subjects between ages 4 and 18 years were associated with height decreases >1 cm, and only 0.26% (14/5394) were associated with the maximum 4 to 5 cm decrease (Table 125, Appendix).

The Applicant also stated that predefined algorithms, as well as visual inspections, to identify outliers and implausible values were applied to the data cleaning process for all values. This procedure could have reduced the amount of erroneous data values. The statistical reviewer reanalyzed these data and concluded that measurement errors were not expected to have a significant impact on the analyses. As shown below, there was only a small percentage of negative AGV values, and the extreme outliers were equally distributed in both positive and negative directions, suggesting measurement error does not favor a certain direction in this study (Figure 12).

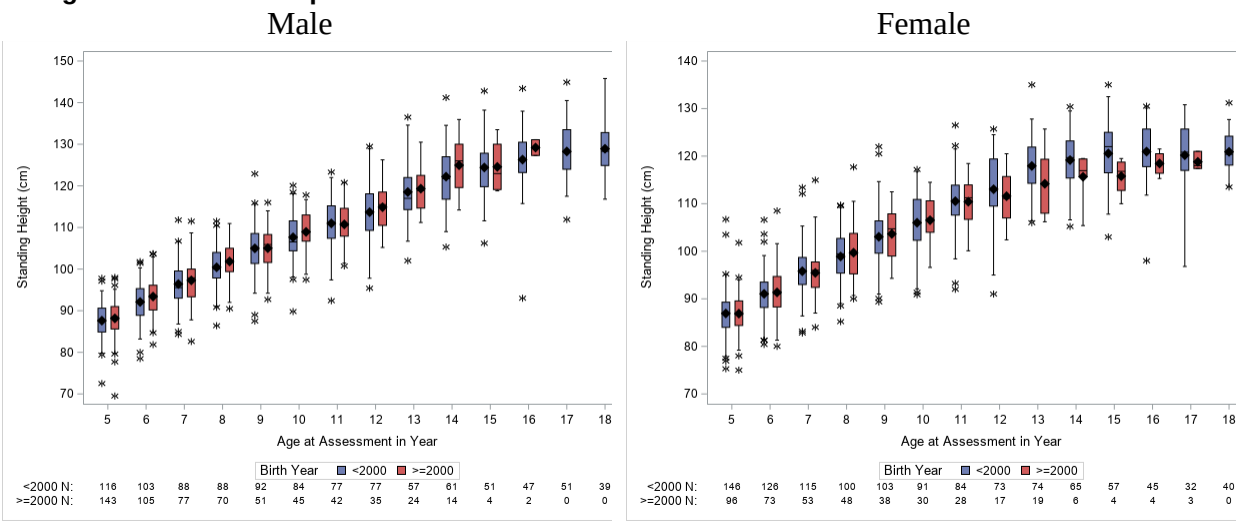
Figure 12. Histogram of 12-Month AGV Assessment From Subjects Between 5 and 17 Years in AchNH Population



Source: statistical reviewer
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity

The team was also concerned that some of the data from AchNH were not contemporaneous and were therefore not a reasonable comparator to the recent clinical trial participants. There were 747 (56.2%) subjects ages 5 to 16 years born before the year 2000, including some born before 1980 (Table 108, Appendix). The Applicant compared the height of subjects who were born before 2000 with the height of subjects who were born on or after 2000 by sex and age and did not identify any temporal trend. The mean height of subjects was generally comparable in the 2 groups (Table 127, Appendix). Their finding was confirmed by the FDA statistical reviewer (Figure 13). The FDA also conducted analyses that adjusted for birth time (<2000 versus ≥2000). These analyses do not suggest that a control cohort with a blend of historic and contemporaneous data introduced bias into the results (Table 130, Appendix).

Figure 13. Boxplot of Heights of Subjects Born Before Year 2000 Versus After Year 2000 by Sex and Age in the AchNH Population



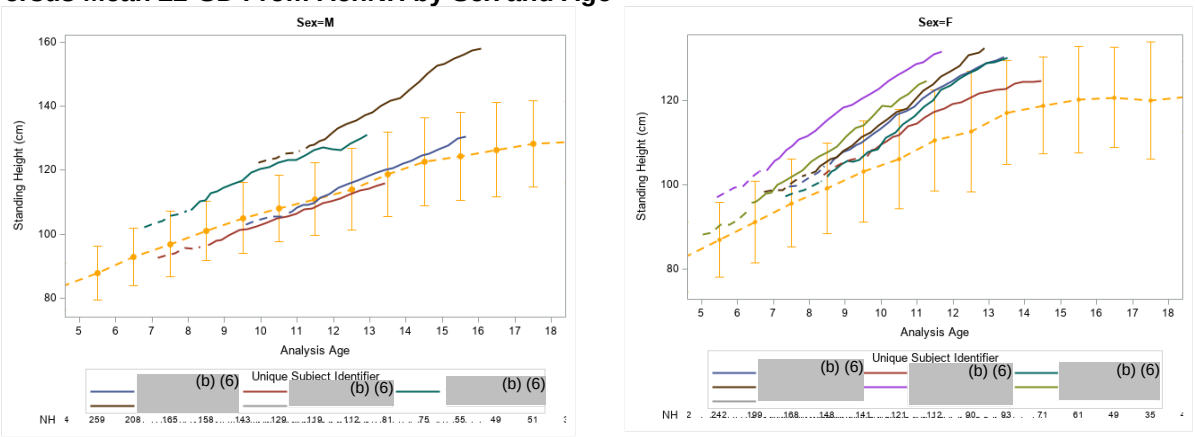
Source: statistical reviewer
Abbreviations: AchNH, achondroplasia natural history

The other issues raised during the review of the comparative analyses between treated subjects and subjects from NH studies were the potential inadequacy of matching between the vosoritide group (from Study 111-205) and the external control (from AchNH) in the Applicant's analyses of 5-year data (Table 15, in Section 6.2.4), and potential selection bias that could occur if NH controls with slow growth have more years with available height measurements, which could underestimate growth among controls. These issues are discussed below.

Inadequate Matching

Upon initial review, we noticed an imbalance in baseline height between Cohort 3 of Study 111-205 and the AchNH source matched on sex and integer age only (mean difference of 5 cm). The Applicant claimed that it was only because of 1 Cohort 3 subject who underwent limb lengthening surgery prior to entry into the study (b) (6), but this does not appear to be the sole reason. Several other Cohort 3 subjects had much higher baseline height compared to the mean height from AchNH subjects of the same sex and age (Figure 14). In the AchNH source, for subjects of the same sex and age, the SD for height was as large as 6.15 cm and the SD for AGV was as large as 2.12 cm/year. The large variability suggested matching on sex and integer age alone may not be adequate for balancing these potential prognostic factors.

Figure 14. Standing Height Over Time From Individual Subjects in Cohort 3 of Study 111-205 Versus Mean ±2*SD From AchNH by Sex and Age



Source: statistical reviewer
Note: For cohort 3 subjects, dotted lines represent pretreatment period, solid lines represent treatment period.
Abbreviations: AchNH, achondroplasia natural history; SD, standard deviation

At FDA's request, the Applicant performed additional longitudinal analyses that further matched baseline height and baseline AGV using selected threshold differences, in addition to exact match on sex and integer age. Nine of the 10 subjects from Cohort 3 were included in these analyses. The subject who underwent limb lengthening surgery was excluded per FDA's request.

The treatment effects on change in AGV and height at Year 5 using different matching thresholds were consistent and highly significant (Table 17). Since the threshold of baseline AGV difference (2 cm/year) and baseline height difference (10 cm) achieved reasonable balance in important prognostic factors (Table 129, Appendix) and provided the largest control arm among the different thresholds explored, the Applicant applied it in the other requested analyses. After matching, the adjusted mean difference in height at baseline was -2.39 cm (standardized mean difference SMD = -0.44); the adjusted mean difference in AGV at baseline was 0.16 cm/year (SMD =0.13). Although the magnitude of SMDs were greater than 0.1, they are considered reasonable given the small sample size.

Table 17. 5-Year Longitudinal Analyses of Change in AGV and Height Under Different Threshold Values for Matching, Study 111-205 Cohort 3 Exclude Limb Lengthening vs. AchNH

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

Source: Table ir201117.q05.2.10.1, Table ir201117.q05.2.10.2, Table ir201117.q05.2.10.1.t1, Table ir201117.q05.2.10.2.t1, Table ir201117.q05.2.10.1.t2 and Table ir201117.q05.2.10.2.t2
AGV: annualized growth velocity; CI: confidence interval.
Source: Applicant's response to FDA's IR, dated November 17, 2020
Baseline height and baseline AGV in the header of this table refer to threshold differences between treated subjects and NH subjects at baseline. For example, baseline height =10 cm means the difference between a treated subject and matched NH subjects should be no more than 10 cm.
Analysis method: ANCOVA model that includes treatment and matching ID as fixed factors
Abbreviations: AchNH, Achondroplasia Natural History; AGV, Annualized growth velocity

We performed several additional analyses to examine the robustness of the Applicant's results including:

- Adjust for additional covariates in the ANCOVA model after matching
  - Adjust for baseline AGV and baseline height
  - Adjust for birth time categories (≥2000 versus <2000), since all subjects in Study 111-205 were born after 2000
- Use nearest neighbor matching for baseline height and baseline AGV based on Mahalanobis distance (or propensity score) in addition to exact matching on sex and integer age to find the best matched pairs for comparison
- Repeat all the analyses above for combined Cohorts 1, 2, 3 of Study 111-205 versus AchNH

Results from the sensitivity analyses were summarized in Table 130 in Appendix**.** All these analyses gave consistent results with the Applicant's results. Per FDA's request, the Applicant performed additional sensitivity analyses related to selection among repeated measures from a NH subject matched to multiple active subjects (Table 131, Appendix). These analyses also gave consistent results.

The Applicant's 2-year, 4-year, and 6-year longitudinal analyses that similarly matched on sex, baseline height, AGV, and age and excluded limb lengthening were presented in the Appendix (Table 132, Table 133 and Table 134). The height difference between Cohort 3 of Study 111-205 and AchNH at Year 6 did not attenuate compared to that at Year 5, suggesting the treatment effect was sustained in the long term.

Per FDA's request, the Applicant compared change in AGV at 1 year between placebo subjects in Study 111-301 and subjects in AchNH that were matched on sex, baseline height, AGV, and age. The results from this analysis showed no statistically significant difference between the groups in baseline-adjusted AGV at 1 year (Table 18).

Table 18. Longitudinal Analyses of Change From Baseline in AGV at 1 Year, Study 111-301 Placebo Group vs. AchNH

Change from Baseline in AGV at Year 1	External Control (Primary)[a] (N=273)	Placebo in 111-301[b] (N=61)
Mean (SD)	-0.25 (2.10)	-0.12 (1.74)
Median (min, max)	-0.30 (-8.0, 9.5)	-0.37 (-3.6, 4.5)
25th, 75th percentile	-1.52, 1.01	-1.39, 0.70
LS Means of Change from Baseline (95% CI)	-0.26 (-0.54, 0.02)	-0.12 (-0.57, 0.33)
Difference in LS Means Change from Baseline (95% CI)[c]	**0.14 (-0.39, 0.68)**	
Two-sided p-value	**0.6007**	

Source: Table ir201117.q06.4.7.1
AGV: annualized growth velocity; CI: confidence interval; max: maximum; min, minimum; SD: standard deviation.
a AchNH Control Arm for 1-Year Longitudinal Comparative Analysis includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex, baseline AGV, baseline height, and age to the sex, baseline AGV, baseline height, and age at Baseline from Subjects in the 111-301 Placebo Arm who had at least one height assessment between 6 to 12 months prior to the baseline and at least one height assessment at 12 ± 3 months relative to the baseline.
b 111-301 Placebo Arm includes subjects in the placebo arm in Study 111-301 who had at least 1 year of follow-up.
c Difference is 111-301 Placebo Arm minus AchNH Control Arm from ANCOVA model with fixed effects of treatment and matching ID.
AGV at baseline is defined as [(Height at Baseline -Height at 6 Months Prior to Baseline)/(Date of Baseline -Date of 6 Months Prior to Baseline Assessment)] x 365.25.
AGV at Year 1 is defined as ((Height at Month 12 -Height at Baseline)/(Date of Month 12 -Date at Baseline)) x 365.25.
Source: Applicant's response to FDA's IR dated November 17, 2020
Analysis method: ANCOVA model that includes treatment and matching ID as fixed factors
Abbreviations: AchNH, Achondroplasia Natural History; AGV, annualized growth velocity; CI, confidence interval; SD, standard deviation

Potential Selection Bias if Slow Growth is Associated With More Years With At Least 1 Height Measurement Among NH Controls

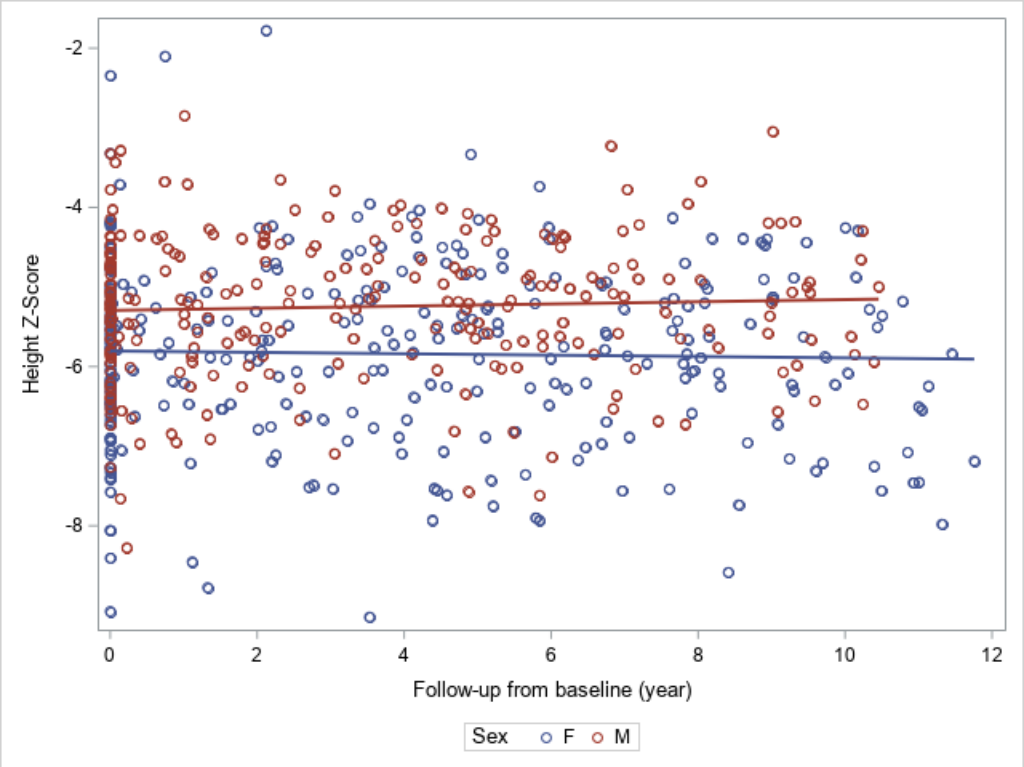
In theory, if children in the AchNH study with slower-than-expected growth have more years with at least 1 height measurement compared to children with average or above average growth, they may be more likely to be selected as controls both in the cross-sectional and longitudinal analyses. In this case, average growth among controls would be underestimated, resulting in bias favoring vosoritide.

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

(1) A comparison of mean baseline height by the number of years until the last height measurement to explore whether subjects with longer follow-up tend to have a lower baseline height than subjects with shorter follow-up duration (n=500 AchNH subjects from 5-year cross-sectional analysis)
(2) An analysis to test whether there are height differences at Year 2 of follow-up between subjects who have height measurements at Year 5 versus those who do not have height measurements at Year 5 (AchNH subjects from 5-year cross-sectional analysis with height values available at 2 year ±6 months)
(3) An analysis to explore whether the number of previous height assessments is associated with subjects' heights prior to reaching final adult height

The first analysis (Figure 15) included available height measurements from baseline and up to 18 years. It was notable that a large proportion of subjects did not have measurements after their baseline measurement. The results of the first analysis did not reveal any association between baseline height and duration of follow-up.

Figure 15. Baseline Height Z-Score Versus Follow-Up Time From Baseline by Sex, AchNH Subjects From 5-Year Cross-Sectional Analysis



Source: statistical reviewer
Note: A linear regression line is fit for each sex group. The flat slope suggests no association.
Abbreviations: AchNH, Achondroplasia Natural History

In the second analysis, height values at Year 2 were compared between subjects who had and who did not have another height measurement at Year 5 (Analysis 1) or at Year 5 or later (Analysis 2), while adjusting for baseline age. Results (Table 135, Appendix) indicate that subjects with 5 years of follow-up were not consistently shorter at Year 2 compared to subjects without 5 years' of follow-up. In Analysis 1, boys who had Year 5 height measurements available were on average 1.45 cm shorter at Year 2 than those who did not have Year 5 height measurements. Yet, the reverse was the case in Analysis 2, as males who had height measurements at Year 5 or later were on average 2.04 cm taller at Year 2 than those who did not have Year 5 or later height measurements. Differences in height were less pronounced among girls, and no height differences among boys or girls were statistically significant.

The third analysis explored whether the number of previous height assessments is associated with subjects' heights prior to reaching final adult height. The analysis was conducted using a dataset which consisted of subject-level data from the AchNH database with height measurements for each year of age. The results of this analysis demonstrated that the subjects with more previous years of height measurements are not consistently shorter at ages 12, 13, or 14 compared to subjects with less frequent prior height measurements (Figure 84, Appendix).

Conclusion

Based on these analyses, the review team concluded that the AchNH data appear to be fit for use.

Data collection in the AchNH study followed a systemic approach to ensure uniform data collection that utilized centralized site monitoring, data management, and analysis. Data cleaning procedures followed an algorithmic and individual visual examination approach to identify erroneous data. Identified measurement errors are few and are not expected to have significant impact on the results of the analyses. Although part of the data from AchNH is not contemporaneous, it does not appear to differ much from the contemporaneous data in AchNH. Height data appear to be reliable and complete.

The treatment effect on growth in comparison with the NH data obtained through various matched analyses were consistent with 1-year findings from the adequate and well-controlled Study 111-301 using a placebo control. The team did not find evidence that the observed treatment difference of vosoritide versus an external control was attributable to an imbalance of a known prognostic factor at baseline (age, sex, baseline height, AGV). The results of comparative analyses between the AchNH population and Study 111-301 placebo group were also supportive, i.e., had there been an impactful unmeasured confounder whose distribution differed between these 2 untreated groups, one would expect to see a difference in change in AGV, but that was not seen. However, it is not possible to rule out the impact of prognostic factors completely, especially given the limited information for subjects in the AchNH study other than basic demographics and height.

Lastly, we did not find evidence for selection bias for AchNH control subjects who had more years with at least 1 height measurement during follow-up.

Overall, the data from the AchNH were acceptable for use as an external control in order to help interpret the results from open-label, single-arm studies evaluating long-term efficacy of the drug in the intended population. The results of the comparative analyses supported the use of these data in this context. The quality of AchNH data and the results of the comparative analyses using AchNH data were also discussed at an RWE meeting on April 6, 2021. The RWE Subcommittee agreed with the Division's conclusion that RWE appear to be fit for use and can be used to provide supportive evidence of the efficacy of vosoritide in patients with ACH.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical profile of vosoritide was characterized in a series of pharmacology, pharmacokinetic/toxicokinetic, and toxicology studies. 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).

7.1.1. Safety Pharmacology-Related Functional Effects

NPR-B, the receptor that CNP binds to, is expressed on vascular smooth muscle (where it induces muscle relaxation) and cardiac fibroblasts. Therefore, multiple cardiovascular safety

pharmacology studies were performed with BMN-111.[1] 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 (50 µg/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 MRHD.

7.1.2. Toxicology Observations

Nonclinical safety was evaluated in single- and repeat-dose studies in the adult rat and NHP with durations of up to 26 and 44 weeks, respectively, in studies of up to 26 weeks in juvenile rats and juvenile/adolescent NHPs, and in a battery of reproductive studies in the rat and rabbit. The NHP is considered the most relevant species based on the high sequence homology of CNP and the NPR-B receptor, the similarity in the orientation of the foramen magnum, and the hindlegs being weight bearing in NHPs and humans. More detailed summations of the toxicology studies are summarized in Section 13.1.3.

In the repeat dose toxicity studies in both species, the primary effects noted were on skeletal tissues. BMN-111 induced dose- and time-dependent skeletal changes associated with bone growth, particularly at the growth plates. The promotion of endochondral bone formation in the animals used in these studies led to clinical signs associated with bone overgrowth (e.g., kinking of the tail/hunched posture, valgus deformity, swollen limbs, degeneration and dysfunction of joints, etc.) that resulted in limited mobility. These effects and the associated microscopic changes to skeletal tissues/growth plates that were not reversible were the basis for the determination of the no observed adverse effect level (NOAEL), which ranged from less than the MRHD to approximately 10-fold the MRHD based on BSA (see Section 13). In general, the NOAEL decreased with study duration. These effects also occurred at lower dosages/exposures in juvenile rat and adult NHPs as compared to that reported in adult rats and younger NHPs. However, these exaggerated pharmacologic effects are not considered to be a safety concern in the targeted population where enhanced bone growth is the desired outcome. Potential clinically relevant nonbone-related effects noted in the nonclinical repeat dose toxicity studies included a slightly increased heart rate at high doses in the chronic NHP study. Refer to Section 13.1.3.1 for details.

Genetic toxicity studies were not conducted because it is not expected that BMN-111 would interact directly with DNA or other chromosomal material. In vivo carcinogenicity studies were not conducted with BMN-111 for the following reasons:

(1) In ‘normal’ animal toxicity studies, dose-limiting bone overgrowth (NOAELs and LOAELs occurring at less than or low multiples of the clinical exposure) inhibited the

[1] BMN-111 is the identification of the test article administered in the nonclinical studies

movement of animals within a few months of dose initiation that precludes the use of either standard 2-year or 6-month rodent models that were related to the pharmacologic activity of BMN-111,

(2) Use of a mutant mouse disease model of achondroplasia was considered but rejected because a) there is a lack of historical and tumor incidence data that would make interpretation of any findings difficult, and b) aggressive progressive blindness occurs in the background of one model and lifespan is limited to 6 weeks in another, and

(3) There was an absence of off-target proliferative effects in toxicity studies. While in vivo carcinogenicity studies were considered likely to be infeasible and/or uninterpretable, vosoritide is not expected to be tumorigenic, based on its mechanism action and lack of preneoplastic lesions in long-term toxicity studies.

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. Further details are provided in Sections 8.4 and 13.1.3.4.

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

Vosoritide is a first-in-class drug and thus, there are no established safety concerns with this drug.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Vosoritide has not been approved in any country; therefore, there has been no postmarketing experience with vosoritide.

7.4. FDA Approach to the Safety Review

7.4.1. Source of Data for Clinical Assessment

The safety data are derived from 1 completed phase 3 trial (Study 111-301) in subjects ages 5 to <18 years and its ongoing open-label single arm long-term extension trial (Study 111-302), 1 completed phase 2 open-label single arm trial (Study 111-202) in subjects ages 5 to 14 years and its ongoing long-term extension trial (Study 111-205) and 1 ongoing double-blind, placebo-controlled phase 2 trial (Study 111-206) in subjects ages 0 to <5 years and its ongoing open-label long-term extension trial (Study 111-208). The cut-off dates for the safety data review for the ongoing Studies 111-302 and 111-205 are November 30, 2020 (data cut-off applied to the Addendum of the Study 111-205 Interim Clinical Study Report), and November 2, 2020 (data cut-off applied to the Addendum of the 111-302 Interim Clinical Study Report). Safety data included in the 120-safety update (cutoff date June 30, 2020) were reviewed as well. The cut-off

date for the safety data review for Study 111-206/208 is September 12, 2019 (data cut-off applied Interim Clinical Study Report at the time of the NDA submission), unless stated otherwise in the review.

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 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.

Several PTs were reclassified by the review team based upon review of verbatim term to preferred term mapping (Table 147, Appendix). Reclassification decisions were intended to capture an adverse event's underlying etiology, to improve specificity, or to avoid description of the same adverse event using different terminology and thus potentially diminishing a drug-attributable effect. The following PTs were recoded: 'otorrhea' and 'ear infection' to 'otitis', 'middle ear effusion' and 'otitis media acute' to 'otitis media', 'rhinitis allergic' and 'rhinorrhea' to 'rhinitis', 'body temperature increase' to 'pyrexia', 'injection site mass', 'injections site induration' and 'injection site inflammation' to 'injection site swelling', 'injection site rash' to 'injection site erythema'. With regards to injection site reactions recoding, if the verbatim term on the AE page included more than 1 reaction (e.g., red itchy patch), the medical reviewer used separate PTs describing individual signs or symptoms (e.g., injection site erythema and injection site pruritus).

The Applicant's strategy for injection site reaction (ISR) reporting was acceptable because it 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 by combining data from the ISR symptom page and AE page, referred to as ISR symptoms. Recoding was performed by the review team on the combined ADAE/ADCE dataset. Some preferred term recoding was based on verbatim terms (AETERM for ADAE data and CETERM for ADCE data) rather than preferred terms (AEDECOD for ADAE data and CEDECOD for ADCE data), and some verbatim terms

associated with the same preferred term were recoded differently or not recoded. For full details on the recoding of verbatim term/preferred term combinations, please see (Table 147).

Lastly, the review team conducted a separate analysis of adverse reactions (ARs) occurring during Study 111-301 with vosoritide or placebo using FDA MedDRA 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

The clinical reviewer used the safety data originating from the main phase of Study 111-301 as the primary source of safety assessment, as it was the only completed trial with a double-blind design that included a placebo arm. Supportive safety data were also obtained from Studies 111-202/205, which provided long-term safety data and from Studies 111-302 and 111-206/208. 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. A pooling strategy was applied for the subjects in cohorts 1, 2 and 3 (doses of 2.5, 7.5, 15 µg/kg, respectively) in Study 111-202/205, as these are the subjects who contributed to the long-term safety data. The limited exposure to doses lower than 15µg/kg daily during the first 12 months of Study 111-202 is not anticipated to change the long-term safety profile over the 60-month total period.

Clinical trial data were independently analyzed by clinical review team using Python 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 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 Harmonisation (ICH) 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 (e.g., Humatrope for pediatric short stature associated with patients with SHOX- 52, Norditropin for short stature associated with Turner syndrome- approximately 100 patients).

During the vosoritide clinical development program, 155 subjects were treated for ≥6 months and 154 subjects were treated for ≥1 year with any dose of vosoritide (see "All treated" column in Table 19), and 145 subjects were treated with a maximum dose of vosoritide 15 µg/kg for ≥1 year (See Table 19). Of the 155 subjects, 16 were treated with a maximum dose of vosoritide 15 µg/kg up to 6 years.

Table 19. Duration of Exposure to Vosoritide[a], Pooled Safety Population

	Only 15 µg/kg[b] (N=131)		Maximum 15 µg/kg[c] (N=148)		All Treated[d] (N=164)	
Duration of Exposure (At Least)	**No. of Subjects n (%)[e]**	**Person-Years**	**No. of Subjects n (%)[e]**	**Person-Years**	**No. of Subjects n (%)[e]**	**Person-Years**
≥6 months	129 (98.5)	277.01	145 (98.0)	352.62	155 (94.5)	396.11
≥1 year	129 (98.5)	277.01	145 (98.0)	352.62	154 (93.9)	395.43
≥2 years	71 (54.2)	200.49	83 (56.1)	271.53	91 (55.5)	313.32
≥3 years	12 (9.2)	62.74	24 (16.2)	133.79	32 (19.5)	175.57
≥4 years	9 (6.9)	52.79	21 (14.2)	123.83	29 (17.7)	165.62
≥5 years	9 (6.9)	52.79	19 (12.8)	115.27	27 (16.5)	157.06
≥6 years	7 (5.3)	42.38	16 (10.8)	99.45	16 (9.8)	99.45
Total	131 (100)	277.03	148 (100.0)	353.14	164 (100)	398.76

Source: Applicant's response to Agency's Information Request submitted June 8, 2021
[a] Duration of exposure includes subjects exposed to vosoritide in Studies 111-202, 111-205, 111-301 and 111-302, with exposure data up to November 30, 2020 for Study 111-205(the data cut-off applied to the 111-205 Interim CSR Addendum Report) and up to November 2, 2020 (the data cut-off applied to the 111-302 Interim CSR Addendum Report)
[b] The "Only 15 µg/kg" group includes subjects who exclusively took 15 µg/kg;
[c] The "Maximum 15 µg/kg" group includes subjects who took at least 1 dose of, and no dose higher than, 15 µg/kg.
[d] The "All Treated" group includes all subjects who took any active dose of vosoritide.
[e] Percentages were calculated using the total number of subjects in the safety population (N for each pooled group) as the denominator.
Randomized subjects in Study 111-206 are not included in any pooled groups.
Abbreviations: N, total number of subjects in pooled safety population; n, number of subjects.

The mean (SD) exposure to vosoritide in Study 111-301 is 50.4 weeks. Table 20 summarizes the exposure for Study 111-301.

Table 20. Duration of Exposure, Safety Population, Study 111-301

Variable	**15 µg/kg VOS N=60 n (%)**	**Placebo N=61 n (%)**
Duration of treatment (weeks)		
Mean (SD)	50.4 (9.4)	52.1 (0.7)
Median (min, max)	52.1 (0.3, 54.9)	52.1 (50.7, 54.3)
Subjects treated, by duration, n (%)		
<10 weeks	2 (3.3)	0
≥10 to <50 weeks	0	0
≥50 to <52 weeks	17 (28.3)	17 (27.9)
≥52 weeks	41 (68.3)	44 (72.1)

Source: adex.xpt; Software: Python
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation; VOS, vosoritide

The mean (SD) duration of exposure to vosoritide 15 µg/kg dose in all subjects enrolled in Studies 111-202 and 111-205 was 62 (11.99) months (Table 142, Appendix).

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Overall Adverse Event Summary

The demonstrated safety profile of vosoritide in pediatric population ages 5 to 18 years with ACH is acceptable at the proposed dosing regimen. There were no deaths in clinical program, and the incidence of study drug discontinuation due to AEs was low and mostly injection-related (e.g., anxiety, pain). The majority of AEs reported during clinical trial were nonserious, mild, or moderate.

In Study 111-301, the most frequent AEs were injection site reactions which are expected with an injectable drug. Arthralgia, low blood pressure (majority were asymptomatic events), infections, and gastrointestinal (GI) adverse events were reported more frequently with vosoritide than in the placebo group. Because of vosoritide's vasodilatory action low blood pressure is not unexpected. The other adverse events are commonly seen in the pediatric population in general (e.g., GI events, arthralgias, infections), and some of the infections, such as ear infections and upper respiratory tract infections, are more common in children with achondroplasia.

No safety signals were detected in Studies 111-202/205 that were not apparent in Study 111-301. Overall, the safety profile of vosoritide in Studies 111-202/205 was comparable with that observed in Study 111-301. Importantly, there was no evidence of abnormal skeletal growth, accelerated bone maturation, or abnormal bone morphology/morphometry with long-term exposure to vosoritide.

The AEs reported in the Addendum clinical study reports (CSRs) of Studies 111-302 and 111-205 were similar to those reported in Studies 111-301 and 111-202/205.

7.6.2. Deaths

No deaths were reported in the vosoritide clinical development program.

7.6.3. Serious Adverse Events

The incidence of SAEs in the clinical program was low ; all events occurred in 1 subject each. After reviewing the narratives for all the reported SAEs, the clinical team concluded that the majority of the events were unlikely related to study drug but rather represent expected comorbidities in children with ACH (e.g., obstructive sleep apnea, adenoidal hypertrophy, intracranial hypertension increased, spinal cord compression, dyspnea, syringomyelia) or common events seen in this age group (e.g., appendicitis, fracture after traumatic fall). These SAEs are not discussed further in this review. The narratives for SAEs that occurred during treatment with vosoritide, where a causal relationship between the event(s) and the study drug could not be ruled out completely, are briefly summarized below.

Study 111-301

In this study, few SAEs were reported, and the incidence was similar between vosoritide and placebo arms (Table 21). All events resolved and no SAE led to discontinuation. The clinical

team reviewed the narratives and does not consider any of the 4 SAEs in the drug group to be related to vosoritide.

Table 21. Serious Adverse Events, Safety Population, Study 111-301

Preferred Term	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Any SAE	3 (5.0)	4 (6.6)	-1.6 (-9.9, 6.7)
Influenza	1 (1.7)	0	1.7 (-1.5, 4.9)
Radius fracture	1 (1.7)	0	1.7 (-1.5, 4.9)
Sleep apnea syndrome	1 (1.7)	0	1.7 (-1.5, 4.9)
Adenoidal hypertrophy	1 (1.7)	1 (1.6)	0.1 (-4.4, 4.6)
Appendicitis	0	1 (1.6)	-1.6 (-4.8, 1.6)
Dyspnea	0	1 (1.6)	-1.6 (-4.8, 1.6)
Intracranial pressure increased	0	1 (1.6)	-1.6 (-4.8, 1.6)
Spinal cord compression	0	1 (1.6)	-1.6 (-4.8, 1.6)

Source: adae.xpt; Software: Python
[a] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; VOS, vosoritide

Studies 111-202/205

A total of 5 subjects reported 5 SAEs (Table 22). Three were reported within the first 2 years of treatment in Study 111-202, and 2 SAEs were reported during Year 5 of Study 111-205. The clinical team concludes that all but 1 SAE (spinal stenosis) were likely unrelated vosoritide (see discussion on spinal stenosis event below).

Table 22. Serious Adverse Events, Safety Population, Studies 111-202 and 111-205

Subject ID (Study No.)	Age (years/sex)	Adverse Event (PT)	Onset	Duration	Outcome
(b) (6)	(b) (6)	Sleep apnea syndrome	Day 224	3 days	Recovered/resolved
		Tonsillar hypertrophy	Day 446	1 day	Recovered/resolved
		Thyroglossal cyst	Day 651	1 day	Recovered/resolved
		Syringomyelia	Day 1467	ongoing	Not recovered/not resolved
[a]		Spinal stenosis	Day 1716 (approx.)	30 days	Recovered/resolved

Source: adae.xpt; Software: Python
[a] SAE reported with safety update addendums, after initial NDA submission
Abbreviations: approx, approximately; F, female; M, male; PT, preferred term

Spinal Stenosis

Subject (b) (6) is (b) (6) with ACH and unknown medical history (not reported). (b) (6) was on treatment with vosoritide 30 µg/kg/day and on an unspecified date (b) (6) developed neurological deterioration of the left lower limb with symptoms of tingling and unsteadiness, which gradually worsened over the last 3 to 4 weeks of reporting date. On Study Day 1744 magnetic resonance imaging (MRI) revealed T1-T2 spinal stenosis with cord compression. The subject was diagnosed with Grade 3 spinal stenosis. On Study Day 1746, the subject underwent decompression of spinal cord and T1-T2 laminectomy. The outcome of the

event of spinal stenosis was reported as recovered/resolved on Study Day 1746. Treatment with vosoritide was interrupted on Study Day 1744 and resumed on Study Day 1747. New-onset or worsening of a pre-existing spinal stenosis diagnosis as a result of vosoritide may be possible given the temporal relationship. However, a causal relationship between vosoritide and the event of spinal stenosis cannot be determined, due to lack of information on past medical history regarding diagnosis of spinal stenosis or other comorbidities prior to study drug initiation, and the fact that spinal stenosis is a common neurological complication in patients with ACH.

Study 111-302

Overall, there were 10 SAEs reported in Study 111-302 (Table 23).

Table 23. Serious Adverse Events, Safety Population, Study 111-302

Subject ID (Treatment Arm)	Age (Years/Sex)	Adverse Event (PT)	Onset Day	Duration	Outcome
(b) (6)	(b) (6)	Otitis media chronic	Day 71	2 days	Recovered/resolved
		Generalized tonic-clonic seizure	Day 397	<1 day (5 min)	Recovered/resolved
[a]		Sleep apnea syndrome	Day 506	1 day	Recovered/resolved
[a]		Worsening hip dysplasia	Day 476	5 days	Recovered/resolved
[a]		Lumbar spinal stenosis	Day 163	119 days	Recovered/resolved
[a]		Appendicitis	Day 522	3 days	Recovered/resolved
[a]		Syringomyelia / Spinal cord injury	Day 162/ Day 242	Ongoing/ 46 days	Recovering and Recovered/resolved
[a]		Knee deformity surgery	Day 739/ Day 741	3 days	Recovered/resolved
[a]		Knee deformity surgery	Day 682/ Day 684	3 days	Recovered/resolved

Source: adae.xpt; Software: Python
[a] SAE reported with safety update addendums, after initial NDA submission
Abbreviations: F, female; M, male; plc/vos, placebo/vosoritide; PT, preferred term; vov/vos, vosoritide/vosoritide

The narratives for all SAEs were reviewed by the team and the team concluded that the majority of the events were unrelated to the drug use (e.g., surgeries) and/or related to the underlying medical conditions (otitis, sleep apnea is commonly seen in patients with ACH) or trauma (spinal injury). The causal association between vosoritide and the events could not be ruled out completely in the following 2 cases, 1 of generalized tonic-clonic seizure and 1 of worsening of hip dysplasia.

Generalized Tonic-Clonic Seizure

Subject (b) (6) (vos/vos group) is (b) (6) with ACH and a medical history of pressure equalizing tube insertion, tibial bowing, hearing defect, speech delay, adenoidectomy, otitis media, moderate to severe obstructive sleep apnea, and tonsillectomy. The subject had no previous history of seizures. No concomitant medications were reported. On Study Day 397 of vosoritide 15 µg/kg/day treatment, (b) (6) experienced a Grade 2 generalized tonic-clonic seizure which lasted 5 mins and resolved without treatment. Subject was sleepy but neurologically

intact. (b) (6) was hospitalized for overnight observation. (b) (6) did not have any additional seizures overnight. The following day the subject's neurologic exam was intact, and (b) (6) was discharged home. Brain MRI (Study Day 398) and electroencephalography's (EEGs) (Study Days 401 and 438) were reported to be within normal limits. Unspecified laboratory tests collected revealed no signs of infection, electrolyte abnormalities, or dehydration. Treatment with vosoritide was held on Study Day 398 and resumed on Study Day 410. No additional events of seizures were reported in this subject.

A causal relationship between the event and study drug is unlikely but cannot be excluded completely because of the temporary relationship between the event and the drug. Confounding factors include history of chronic ear infections and negative rechallenge. Other possible etiology is a temporal lobe anomaly that is described in conditions related to FGFR3 abnormalities.

Worsening of Hip Dysplasia

Subject (b) (6) (vos/vos group) is (b) (6) with ACH and history of coxa vara. The subject's other medical history and concomitant medications were not reported. On Study Day 476 of vosoritide treatment, the subject experienced worsening of coxa vara. After starting treatment with vosoritide, the subject's growth rate increased, and (b) (6) proceeded to undergo eight-plate surgery based on the angle degree. No additional treatment information was provided, and no action was taken with vosoritide due to the event. The outcome of the event was reported as recovered/resolved on Study Day 481.

While hip deformity is a common condition in patients with ACH and it was present prior to initiation of treatment with vosoritide, the worsening of the coxa vara deformity may be a consequence of increased growth rate because of vosoritide treatment. However, the observed change from baseline in AGV after 1 year of treatment was 1.9 cm/year in this subject, which is similar to the mean treatment difference observed in Study 111-301, while the changes from baseline in the upper-to-lower body segment ratio and upper leg length to tibial length ratio were not clinically significant (<0.1). Therefore, a causal relationship between vosoritide and worsening hip deformity is unlikely but cannot be ruled out.

Studies 111-206 and 111-208

Four SAEs were reported during Study 111-206, 3 of which were included in the safety update report with a cut-off date of June 30, 2020. The events were 'grade 2 oxygen saturation decreased' after a preplanned adenotonsillectomy surgery, 'petit mal epilepsy' in a subject with history of birth asphyxia and seizure disorder, 'gastroenteritis' and 'vomiting'. All 4 events were reported as recovered/ resolved. The treatment assignments were not unblinded in any of these subjects which complicate the causality assessment of the events with vosoritide.

Two SAEs of 'intracranial pressure increased' and 'cervical cord compression' were reported in Study 111-208. The causality assessment is complicated since Study 111-206 is still ongoing and previous treatment assignments during Study 111-206 remain blinded.

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Drop-out rates in all studies were low. All AEs that led to treatment discontinuation were nonserious and mild. Only AEs of anxiety of injections led to discontinuation in more than 1 subject; however, this type of AE is expected in this age population. Overall, no signals were identified in clinical program to suggest a serious toxicity and/or tolerability concern associated with vosoritide.

In Study111-301, 2 subjects (1.7%) in the vosoritide group and none in placebo group discontinued. The reasons included nonserious AEs of anxiety (subject (b) (6)) and pain (subject (b) (6)) related to injections.

In Study 111-202, 5 out of 35 subjects (7%) discontinued vosoritide due to nonserious AEs, 3 subjects because of anxiety related to injections, 1 subject on Day 249 due to an erroneous diagnosis of growth plate closure, and 1 subject due to the AE Wolf Parkinson White syndrome (WPW). This medical reviewer reviewed all case narratives and concluded that WPW was unlikely related to the study drug (refer to Section 7.6.8 for details), and erroneous diagnosis of growth plate closure was unrelated to the study drug.

Of the 10 out of 30 subjects who discontinued vosoritide in Study 111-205 (refer to Section 6.2.3.3.1 for details), only 1 subject discontinued treatment due to nonserious AE of transaminase increase that was unrelated to the study drug (refer to Section 7.6.7 for details).

No subjects discontinued study drug in Studies 111-302 and 111-206/208 due to adverse events.

7.6.5. Treatment-Emergent Adverse Events

Data from Studies 111-301/302 and 111-202/205 were used to evaluate the overall safety profile of vosoritide. Although only data from the controlled Study 111-301 will be included in labeling, Studies 111-302 and 111-202/205 provided supportive and/or long-term safety data that is important for chronic use. Data from the ongoing Study 111-206/208 in younger children with achondroplasia are not discussed unless specified. The studies are still ongoing and blinded, and a small number of subjects were enrolled in these studies to date. Study 111-301 evaluated the safety of the study drug in a placebo-controlled setting over a 1-year duration, while Studies 111-202/205 evaluated the safety of drug in an uncontrolled setting for up to 6 years.

Study 111-301

Nearly all subjects in vosoritide and placebo arms experienced at least 1 AE during this study. AEs that occurred with a risk difference (RD) of ≥2% between vosoritide and placebo are listed in **Table 24** The AE profile observed in other supportive studies was consistent with that observed in Study 111-301.

Table 24. Adverse Events by PT Occurring With Higher Incidence in Vosoritide Arm and With a Risk Difference ≥2%, Safety Population, Study 111-301

Preferred Term	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Any AE	59 (98.3)	60 (98.4)	-0.1 (-4.6, 4.4)

Preferred Term	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Injection site reaction[b]	42 (70.0)	26 (42.6)	27.4 (10.4, 44.4)
Injection site swelling	26 (43.3)	10 (16.4)	26.9 (11.3, 42.5)
Injection site urticaria	8 (13.3)	2 (3.3)	10.0 (0.3, 19.7)
Arthralgia	9 (15.0)	4 (6.6)	8.4 (-2.6, 19.4)
Vomiting	16 (26.7)	12 (19.7)	7.0 (-8.0, 22.0)
Blood pressure decreased	7 (11.7)	3 (4.9)	6.8 (-3.0, 16.6)
Diarrhea	6 (10.0)	2 (3.3)	6.7 (-2.1, 15.5)
Fatigue	4 (6.7)	0	6.7 (0.4, 13.0)
Ear pain	6 (10.0)	3 (4.9)	5.1 (-4.2, 14.4)
Influenza	6 (10.0)	3 (4.9)	5.1 (-4.2, 14.4)
Dizziness	4 (6.7)	1 (1.6)	5.1 (-2.0, 12.2)
Gastroenteritis viral	4 (6.7)	1 (1.6)	5.1 (-2.0, 12.2)
Seasonal allergy	4 (6.7)	1 (1.6)	5.1 (-2.0, 12.2)
Dry skin	3 (5.0)	0	5.0 (-0.5, 10.5)
Oropharyngeal pain	6 (10.0)	4 (6.6)	3.4 (-6.4, 13.2)
Pain in extremity	6 (10.0)	4 (6.6)	3.4 (-6.4, 13.2)
Viral infection	5 (8.3)	3 (4.9)	3.4 (-5.5, 12.3)
Arthropod bite	4 (6.7)	2 (3.3)	3.4 (-4.3, 11.1)
Tonsillitis	3 (5.0)	1 (1.6)	3.4 (-3.0, 9.8)
Enterobiasis	2 (3.3)	0	3.3 (-1.2, 7.8)
Injection site discoloration	2 (3.3)	0	3.3 (-1.2, 7.8)
Injection site induration	2 (3.3)	0	3.3 (-1.2, 7.8)
Injection site rash	2 (3.3)	0	3.3 (-1.2, 7.8)
Presyncope	2 (3.3)	0	3.3 (-1.2, 7.8)
Procedural anxiety	2 (3.3)	0	3.3 (-1.2, 7.8)
Pruritus	2 (3.3)	0	3.3 (-1.2, 7.8)
Injection site erythema	41 (68.3)	40 (65.6)	2.7 (-14.1, 19.5)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as any AE with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included.
[a] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
[b] Injection site reactions that were associated with multiple signs or symptoms (refer to section 7.4.2 for details)
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; VOS, vosoritide

The results of the FMQ and GQ analyses that occurred with higher incidence in vosoritide arm and with a RD ≥2% are presented in Table 25. The adverse reactions based on FMQ and GQ analyses that rendered different results than Table 26 are marked in **bold** in Table 25 and included adverse reactions of "hypotension" (refer to Section 7.6.1 for details), "dizziness" and "fatigue" (see text below for details).

Table 25. Adverse Events by Narrow FDA Medical Query or Grouped Queries and Preferred Term Occurring With Higher Incidence in Vosoritide Arm and With a Risk Difference ≥2%, Safety Population, Study 111-301

FMQ (Narrow) Preferred Term	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Urticaria (narrow FMQ)	8 (13.3)	2 (3.3)	10.0 (0.3, 19.7)
Injection site urticaria	8 (13.3)	2 (3.3)	10.0 (0.3, 19.7)
Hypotension (narrow FMQ)	**8 (13.3)**	**3 (4.9)**	**8.4 (-1.8, 18.6)**
Blood pressure decreased	**7 (11.7)**	**3 (4.9)**	**6.8 (-3.0, 16.6)**
Hypotension	**1 (1.7)**	**0**	**1.7 (-1.5, 4.9)**

FMQ (Narrow) Preferred Term	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Vomiting (narrow FMQ)	16 (26.7)	12 (19.7)	7.0 (-8.0, 22.0)
Vomiting	16 (26.7)	12 (19.7)	7.0 (-8.0, 22.0)
Diarrhea (narrow FMQ)	6 (10.0)	2 (3.3)	6.7 (-2.1, 15.5)
Diarrhea	6 (10.0)	2 (3.3)	6.7 (-2.1, 15.5)
Dizziness (narrow FMQ)	**6 (10.0)**	**2 (3.3)**	**6.7 (-2.1, 15.5)**
Dizziness	**4 (6.7)**	**1 (1.6)**	**5.1 (-2.0, 12.2)**
Presyncope	**2 (3.3)**	**0**	**3.3 (-1.2, 7.8)**
Procedural dizziness	**1 (1.7)**	**0**	**1.7 (-1.5, 4.9)**
Vertigo	**0**	**1 (1.6)**	**-1.6 (-4.8, 1.6)**
Fatigue (narrow FMQ)	**5 (8.3)**	**2 (3.3)**	**5.0 (-3.3, 13.3)**
Fatigue	**4 (6.7)**	**0**	**6.7 (0.4, 13.0)**
Lethargy	**1 (1.7)**	**0**	**1.7 (-1.5, 4.9)**
Malaise	**1 (1.7)**	**2 (3.3)**	**-1.6 (-7.1, 3.9)**
Local administration reactions (narrow FMQ)	51 (85.0)	50 (82.0)	3.0 (-10.2, 16.2)
Injection site reaction[b]	42 (70.0)	26 (42.6)	27.4 (10.4, 44.4)
Injection site swelling	26 (43.3)	10 (16.4)	26.9 (11.3, 42.5)
Injection site urticaria	8 (13.3)	2 (3.3)	10.0 (0.3, 19.7)
Injection site induration	2 (3.3)	0	3.3 (-1.2, 7.8)
Injection site rash	2 (3.3)	0	3.3 (-1.2, 7.8)
Injection site erythema	41 (68.3)	40 (65.6)	2.7 (-14.1, 19.5)
Injection site inflammation	2 (3.3)	1 (1.6)	1.7 (-3.8, 7.2)
Injection site mass	1 (1.7)	0	1.7 (-1.5, 4.9)
Injection site vesicles	2 (3.3)	3 (4.9)	-1.6 (-8.7, 5.5)
Injection site discoloration	1 (1.7)	2 (3.3)	-1.6 (-7.1, 3.9)
Injection site hematoma	0	1 (1.6)	-1.6 (-4.8, 1.6)
Injection site pruritus	2 (3.3)	4 (6.6)	-3.3 (-11.0, 4.4)
Injection site bruising	5 (8.3)	8 (13.1)	-4.8 (-15.8, 6.2)
Injection site pain	2 (3.3)	5 (8.2)	-4.9 (-13.1, 3.3)
Injection site hemorrhage	2 (3.3)	7 (11.5)	-8.2 (-17.4, 1.0)
Gastroenteritis (GQ)	**8 (13.3)**	**5 (8.2)**	**5.1 (-5.9, 16.1)**
Gastroenteritis viral	**4 (6.7)**	**1 (1.6)**	**5.1 (-2.0, 12.2)**
Gastroenteritis	**4 (6.7)**	**4 (6.6)**	**0.1 (-8.8, 9.0)**

Source: adae.xpt; Software: Python
[a] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
[b] Injection site reactions that were associated with multiple signs or symptoms (refer to section 7.4.2 for details)
Abbreviations: CI, confidence interval; FMQ, FDA MedDRA query; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

The most common AEs were injection site reactions, arthralgia, vomiting, diarrhea, and blood pressure decrease. Certain AEs of infectious origin were also more frequently seen in subjects treated with vosoritide compared to placebo (Table 26). Blood pressure decrease-related safety issues are discussed in detail in Section 7.7.1. All other AEs that were seen more frequently in vosoritide group are briefly summarized.

AEs of Infectious Origin

The following AEs of infectious origin occurred more frequently in vosoritide arm compared to placebo arm: influenza (10% versus 4.9%, respectively), gastroenteritis viral (6.7% versus 1.6%), viral infection (8.3% versus 4.9%), tonsillitis (5.0% versus 1.6%), and enterobiasis (3.3% versus 0%) (Table 26). The incidence of infectious AEs was overall low, and they represent common infectious conditions in the pediatric population. The incidence of AE by System Organ

Class (SOC) Infections and Infestations in vosoritide group was overall lower (63.3%) compared to placebo (77%).

Arthralgia

The incidence of AE of arthralgia was low, at 15% of subjects in the vosoritide group and 6.6% of subjects in placebo group. The mean duration for arthralgia events was 4.6 days in vosoritide group versus 27 days in placebo group. Most (80%) of the events were mild (grade 1), resolved, and did not require dose interruption in any subject in vosoritide arm.

Vomiting

Vomiting was reported in 26.7% of subjects in the vosoritide arm versus 19.7% in placebo. The mean duration of the events was 1.2 days in vosoritide arm versus 1.6 days in placebo arm. The events were not linked to treatment initiation, as the mean time to onset of events was 146 days in vosoritide arm versus 161 days in placebo arm, and only 4 out of the 25 events (16%) in vosoritide arm occurred on Days 1 or 2 after treatment initiation All events in vosoritide arm were nonserious, of mild severity (e.g., grade 1), and resolved. Vosoritide was temporarily interrupted in 42% of the subjects experiencing vomiting compared to 25% in placebo. The events were generally not associated with other gastrointestinal symptoms, such as abdominal pain, nausea, fever, or diarrhea.

Diarrhea

Diarrhea was reported in 10% of subjects in the vosoritide arm versus 3.3% in placebo. The mean duration of AE of 'diarrhea' was 4.75 days in vosoritide arm versus 3 days in placebo arm. All events were nonserious and the majority were mild (grade 1) in severity, and only 1 subject in each arm required dose interruption as a result of the event. All diarrhea events resolved and the majority of cases did not require any treatment [88% (7 out of 8) in vosoritide arm). Most cases (63%) of diarrhea were not associated with other gastrointestinal symptoms.

Fatigue

The FMQ 'fatigue' (8.3% vosoritide versus 3.3% placebo) included the PTs of 'fatigue' (6.7% vosoritide versus 0% placebo), 'lethargy'(1.7% vosoritide versus 0% placebo), and 'malaise'(1.7% vosoritide versus 3.3% placebo) (Table 27). The mean duration of events was 1 day in vosoritide arm and 1.5 days in placebo arm. None of the events required dose interruption in vosoritide arm, while the study drug was interrupted for all events in placebo arm. All events were mild (grade 1) and nonserious. All events were reported as resolved. Of note, 1 AE of lethargy in vosoritide arm was reported in the same subject and on the same day as the event of fatigue. Since the PTs of 'fatigue', 'lethargy' and 'malaise' are synonymous terms, I recommend inclusion of the FMQ 'fatigue' (vosoritide 5 [8.3%] versus placebo 2 [3.3%]) in the Adverse Reactions section and table of the label, with a footnote describing the individual PTs that were included in the FMQ 'fatigue'.

Ear Pain

Six subjects (10%) in vosoritide arm and 3 (4.9%) subjects in placebo arm had an AE of 'ear pain'. Of these subjects, 2 out of 6 subjects in vosoritide arm versus 2 out of three subjects in

placebo arm had ear pain associated with other signs or symptoms, suggestive of an inflammatory/infectious process. The mean duration of events was 2.4 days in vosoritide versus 6 days in placebo arm, and none required study drug dose interruption. All events were graded as grade 1 and 2 in severity and all resolved.

Dizziness

The narrow FMQ term of 'dizziness' (10% vosoritide versus 3.3% placebo) included the PTs of 'dizziness' (6.7% vosoritide versus 1.6% placebo), 'presyncope' (3.3% vosoritide versus 0% placebo), 'procedural dizziness' (1.7% vosoritide versus 0% placebo), and 'vertigo'(1.7% vosoritide versus 3.3% placebo).

All events were mild in severity, all resolved, and study drug was not interrupted in any subject as a result of the event of dizziness. Four out of the 6 subjects with AEs of dizziness in vosoritide arm experienced the event at home, without a blood pressure measurement. Therefore a causal relationship between the events of dizziness and potential low blood pressure is unknown. Only 1 subject (b) (6)) in vosoritide arm had a reported adverse event of blood pressure decreased, when blood pressure decreased from a baseline of 109/58 to 83/50, 15 mins after study drug administration, and returned to normal values afterwards.

The mean duration of events was 6.7 days in vosoritide arm versus 1 day in placebo arm. The higher duration in vosoritide arm was driven by 1 subject ((b) (6)) who had dizziness reported for 41 days, from Day 145 to Day 185 of the study. There were no reported concomitant adverse events of decreased blood pressure in this subject during that time. The median duration of the AE 'dizziness' was 1 day in both treatment arms. The median time to onset of the events of dizziness was similar between treatment arms, with 18 days in vosoritide arm and 17 days in placebo arm.

Since the PTs of 'dizziness', 'presyncope', 'procedural dizziness,' and 'vertigo' are synonymous terms, I recommend inclusion of the FMQ 'dizziness' (vosoritide 6 [10%] versus placebo 2 [3.3%]) in the Adverse Reactions section of the label, with a footnote describing the individual PTs that were included in the FMQ 'dizziness'.

Injection Site Reactions

Vosoritide is an injectable drug and thus, injection site reactions are expected AEs. Thus, AEs of injection site reactions were evaluated as adverse events of special interest (AESIs) throughout the clinical program. Refer to Section 7.4.2 regarding the algorithm used by the Applicant for ISR reporting that was further verified by FDA's review team.

The incidence and exposure-adjusted event rates of each ISR sign, or symptom (regardless if occurring as a single type of reaction, or associated with other signs, or symptoms) are presented in Table 26. There was no overall imbalance in ISRs between treatment arms (85% vosoritide versus 82% placebo), but the number of events per subject was higher in vosoritide arm (6983 events) compared to placebo arm (1776 events). The most commonly reported ISRs in vosoritide arm were injection site erythema (6179 events in 45 [75%] subjects in vosoritide arm versus 1412 events in 42 [69%] subjects in placebo), injection site swelling (1862 events in 37 [61.7%] subjects in vosoritide arm versus 168 events in 22 [36.1%] subjects in placebo), injection site urticaria (443 events in 15 [25%] subjects in vosoritide arm versus 56 events in 6 [9.8%] subjects

in placebo) and injection site pruritus (236 events in 8 [13.3%] subjects in vosoritide arm versus 154 events in 6 [9.8%] subjects in placebo). For labeling purposes, this medical reviewer recommends reporting the frequency of injection site reactions occurring more frequently in vosoritide arm according to Table 26. Adverse Reactions table of the label (i.e., 'injection site erythema', 'injection site swelling,' and 'injection site urticaria'), since it represents a more accurate incidence of each ISR sign, or symptom, rather than reporting (b) (6) as proposed by the Applicant.

Table 26. Injection Site Reactions by Preferred Term, Any Grade, Safety Population, Study 111-301

	15 µg/kg VOS, N=60			Placebo, N=61				
Preferred Term	**n (%)**	**Events**	**Events per Person-Year**	**n (%)**	**Events**	**Events per Person-Year**	**Risk Difference (95% CI)**	**Event Rate Difference (95% CI)**
Any injection site reaction by symptom[1]	51 (85)	9274	159.9	50 (82)	2041	33.5	3.03 (-10.19, 16.25)	126.4 (122.8, 130)
Any injection site reaction by event[2]	51(85)	6938	120.4	50 (82)	1776	29.2	3.03 (-10.19, 16.25)	91.3 (88.1, 94.4)
Injection site erythema	45 (75)	6179	106.5	42 (68.9)	1412	23.2	6.15 (-9.82, 22.12)	83.3 (80.4, 86.2)
Injection site swelling	37 (61.7)	1862	32.1	22 (36.1)	168	2.8	25.6 (8.38, 42.82)	29.3 (27.8, 30.8)
Injection site urticaria	15 (25)	443	7.6	6 (9.8)	56	0.9	15.16 (1.9, 28.43)	6.7 (5.9, 7.5)
Injection site reaction	12 (20)	322	5.6	1 (1.6)	4	0.1	18.36 (7.75, 28.97)	5.5 (4.9, 6.1)
Injection site bruising	9 (15)	32	0.6	15 (24.6)	27	0.4	-9.59 (-23.68, 4.5)	0.2 (-0.1, 0.5)
Injection site pruritus	8 (13.3)	236	4.1	6 (9.8)	154	2.5	3.5 (-7.9, 14.89)	1.6 (0.9, 2.3)
Injection site pain	5 (8.3)	150	2.6	9 (14.8)	166	2.7	-6.42 (-17.74, 4.9)	-0.1 (-0.7, 0.5)
Injection site hemorrhage	3 (5)	10	0.2	12 (19.7)	30	0.5	-14.67 (-26.07, -3.27)	-0.3 (-0.5, -0.1)
Injection site vesicles	3 (5)	32	0.6	3 (4.9)	15	0.2	0.08 (-7.65, 7.82)	0.4 (0.2, 0.6)
Injection site discoloration	2 (3.3)	4	0.1	4 (6.6)	5	0.1	-3.22 (-10.92, 4.47)	0 (-0.1, 0.1)
Injection site discomfort	1 (1.7)	1	0	0	0	0	1.67 (-1.57, 4.91)	0 (0, 0)
Injection site hematoma	1 (1.7)	1	0	1 (1.6)	3	0	0.03 (-4.52, 4.57)	0 (-0.1, 0.1)
Injection site edema	1 (1.7)	2	0	1 (1.6)	1	0	0.03 (-4.52, 4.57)	0 (-0.1, 0.1)

Source: adae.xpt, adce.xpt; Software: Python
[1] Based on FDA analysis including recoding of individual injection site reactions symptoms (i.e., injection site erythema, injection site swelling) as separate events if occuring as a single injection site reaction event
[2] Based on Applicant analysis without recoding. If an injection site reaction event consisted of multiple symptoms (e.g., injection site erythema, injection site swelling and injection site urticaria), the event was counted only once.
Events per person-year is events divided by total exposure in group (VOS group, 57.99 person-years; placebo group, 60.93 person-years).
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

No ISRs were serious AEs. The majority were grade 1 (mild) (Table 137, Appendix). Seven events in 2 subjects, all in the vosoritide arm, were grade 2 in severity (4 events of injection site urticaria, 2 events of injection site erythema and 1 event of injection site vesicles) (Table 137, Appendix). All events resolved with intervention and the mean duration was relatively brief (mean [SD] 92.1 [623.5] mins in the vosoritide arm and 117.4 [823.9] mins in the placebo arm; median [min, max] 77 [1, 367] mins in the vosoritide arm and 7.5 [1, 355] in the placebo arm), and resolved without medical intervention (Table 139, Appendix).

Labeling Recommendations

For labeling purposes, this medical reviewer recommends inclusion of the adverse reactions based on PT and FMQs, or GQs (where appropriate) that occurred more frequently in vosoritide arm and with a risk difference of ≥5%, since a risk difference of <5% resulted in events occurring with a difference of ≤2 subjects between treatment arms, which are not considered clinically significant Table 27.

Table 27. Adverse Reactions That Occurred in ≥5% of Subjects Treated With Vosoritide and at a Rate Greater Than That of Placebo, Study 111-301

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

Source: adae.xpt; adce.xpt; Software: Python
[a] 2 out of 8 subjects in vosoritide arm had decreased blood pressure associated with symptoms
[b] includes the preferred terms: dizziness, presyncope, procedural dizziness, vertigo
[c] includes the preferred terms: fatigue, lethargy, malaise

Study 111-202/205

The incidence and type of AEs in Study 111-202/205 in the subjects exposed to vosoritide 15 µg/kg/day were similar to the AEs seen in Study 111-301. The most common AEs were injection site reactions and injection site erythema (80% each), pyrexia (61%), cough, hypotension, injection site swelling, and nasopharyngitis (53% each), headache and upper respiratory tract infection (46% each), nasal congestion, ear infection, oropharyngeal pain (38% each), vomiting, ear pain and viral infection (34% each), and arthralgia and back pain (30% each) (Table 143, Appendix). The observed AEs represent expected disease-related complications in children with ACH, as well as common illnesses of childhood. Conclusions regarding causality of events is limited by absence of a control group.

An analysis of incidence of AEs per year (Table 144, Appendix) demonstrated a general trend of decreasing frequency of AEs with time was noted in Study 111-202/205. The overall incidence of AEs reporting in 27 subjects exposed to vosoritide during the 6th year of exposure to the drug in Study 111-205 (submitted by Applicant on April 16, 2021 in response to FDA's Information Request) was low. The most frequent AEs of back pain, kyphosis, neck pain, pain in extremity and ear pain were reported in 2 subjects (7.4%) each. There were no new safety signals.

As expected, most subjects (28 out of 30 [93.3%]) experienced at least 1 ISR during Studies 111-202/205. Interestingly, the incidence of ISRs decreased after Year 2, as outlined in Table 28. The decrease in ISRs over time might be attributed to a difference in the reporting method of ISRs for Studies 111-202/205 and/or improvement in tolerability to study drug. In Study 111-202, any ISR regardless of its severity and duration was reported as an AE. In Study 111-205, an ISR was reported as an AE only if the event was a) of at least of grade 2 severity or higher, or b) deemed clinically significant in the opinion of the investigator considering (e.g., the ISR [excluding bruising] lasted >24 hours, or recurred/began >24 hours after the most recent injection; any change in duration or frequency was observed compared to previous ISRs).

Table 28. Injection Site Reactions by Year, Safety Population, Studies 111-202/205

Year	Incidence n (%)	Event Rate (Events/Person-Year)
Year 1 (N=30)	27 (90)	282
Year 2 (N=30)	24 (80)	218
Year 3 (N=30)	17 (56.7)	96
Year 4 (N=30)	5 (17.2)	9.6
Year 5 (N=29)	2 (6.9)	0.62

Source: adapted from Applicant's Table 14.3.1.1.2, 111-205 Interim CSR
Event rate is the number of events divided by total exposure.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; %, percentage

Study 111-302

The incidence and type of AEs in Study 111-302 was similar between the 2 treatment arms (vosoritide/vosoritide and placebo/vosoritide), with the most common reported AEs by PT being nasopharyngitis (19% versus 13%), headache (10% versus 13%), and upper respiratory tract infection (12% versus 11%) (Table 146, Appendix). There were no new safety signals identified for Study 111-302.

In conclusion, there were no AEs identified in the clinical program that raised significant safety concerns with the drug. The drug was overall well-tolerated. The majority of events were nonserious and mild, did not require drug discontinuation and resolved without treatment. The type and frequency of AEs were in general consistent between the trials, and no new safety signals were identified with longer treatment duration (up to 6 years in Study 111-205). Although an imbalance in frequency of AEs, such as arthralgia, vomiting, diarrhea, fatigue, ear pain, and dizziness, was noted between vosoritide and placebo treatment groups during the first year of treatment, this did not raise any worrisome safety concerns. All these events were transient, mild in severity, and the majority of them resolved with or without drug discontinuation. The AEs of arthralgia, vomiting, diarrhea, fatigue, ear pain also represent common events in the pediatric population, and some of them (e.g., arthralgia, ear pain) may be also related to the underlying disease itself. Overall, the observed imbalance in these events is most likely attributed to factors other than the interventional agent and/or to the play of chance.

Although events of dizziness may be due to the known effect of vosoritide on blood pressure (BP) lowering, they occurred infrequently, were nonserious, mild and resolved without treatment. The risk of these reactions will be communicated through the appropriate labeling; none of the above AEs require inclusion in Warning and Precaution section.

Lastly, vosoritide is an injectable drug and thus, injection site reactions are expected. All events were nonserious, mild, and of short duration. Only 5 subjects (2 subjects in Study 111-301 and 3 subjects in Study 111-202) discontinued treatment prematurely due injection site pain (1 subject) or anxiety of injections (4 subjects) (refer to Section 7.6.4). There was no association between presence of antidrug antibodies (ADAs) and injection site reactions that may be potentially associated with hypersensitivity (e.g., urticaria) (refer to Section 7.6.7 below). Overall, injection site reactions are expected and can be mitigated through appropriate labeling in Section 6.

7.6.6. Immunogenicity-Related Safety Issues

Refer to Section 14.2 for the discussion of the rate of positive antidrug antibodies and the potential effect of immunogenicity on efficacy. This section will focus on immunogenicity-related safety issues only.

In general, hypersensitivity reactions are not infrequent in this age group. Hypersensitivity reactions were seen in 30% of subjects in Study 111-301. In the entire clinical program, there were no severe and/or serious hypersensitivity reactions, and all reactions were mild and resolved without treatment discontinuation. No anaphylactic reactions were reported.

The majority of reported hypersensitivity reactions were “injections site urticaria” or “injection site rash.” Therefore, the medical reviewer analyzed whether there exists an association of ADAs with ISRs or overall hypersensitivity reactions; none was found in any study. In addition, there was no imbalance in frequency or severity of hypersensitivity reactions between ADA positive and ADA negative groups in any study. Overall, there are no clinical findings that suggest immunogenicity-related safety concerns with long-term vosoritide use.

Of note, the Applicant used the terms of ADAs and total anti-vosoritide antibodies (TAb) interchangeably during the submission, and herein, this medical reviewer will refer to them as ADA. The results of these analyses are briefly summarized below.

Hypersensitivity Adverse Reactions

Study 111-301

The overall incidence of hypersensitivity reactions was higher in the vosoritide arm (30%) compared to placebo (14.8%), primarily driven by a higher incidence of AEs of injection site urticaria in vosoritide arm (13.3%) versus placebo (3.3%) (Table 29). There was no imbalance in frequency of noninjection site hypersensitivity reactions in the 2 arms, and the majority of these reactions were reported in 1 subject each. Only rash and pruritus were reported in more than 1 subject. Rash was reported in 3 subjects in vosoritide group (as “rash” in 1 subject and “rash pruritic” in 2 subjects) and in 1 subject in placebo group, while pruritus was reported in 2 subjects in vosoritide group only. All events were nonserious AEs and the majority of the events were mild in severity. Only 1 subject in vosoritide treatment arm experienced 2 moderate (grade 2) events of “injection site urticaria.”

Table 29. Hypersensitivity Reactions, Any Grade, Safety Population, Study 111-301

Grouped Query Preferred Term	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)
Hypersensitivity (GQ)	18 (30.0)	9 (14.8)	15.2 (0.6, 29.9)
Injection site urticaria	8 (13.3)	2 (3.3)	10 (0.4, 19.7)
Injection site rash	2 (3.3)	0 (0)	3.3 (-1.2, 7.9)
Pruritus	2 (3.3)	0 (0)	3.3 (-1.2, 7.9)
Dermatitis allergic	1 (1.7)	0 (0)	1.7 (-1.6, 4.9)
Drug eruption	1 (1.7)	0 (0)	1.7 (-1.6, 4.9)
Lip swelling	1 (1.7)	0 (0)	1.7 (-1.6, 4.9)
Rash	2 (3.3)	1 (1.6)	1.7 (-3.9, 7.2)
Rash pruritic	1 (1.7)	0 (0)	1.7 (-1.6, 4.9)
Dermatitis atopic	0 (0)	1 (1.6)	-1.6 (-4.8, 1.5)
Dermatitis contact	0 (0)	1 (1.6)	-1.6 (-4.8, 1.5)
Hypersensitivity	0 (0)	1 (1.6)	-1.6 (-4.8, 1.5)
Injection site pruritus	2 (3.3)	4 (6.6)	-3.3 (-10.9, 4.5)

Source: adae.xpt; Software: R
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

There was a slightly higher incidence of ISR in ADA positive group (23 out of 25 [92%]) compared to ADA negative group (28 out of 35 [80%]). Placebo-treated subjects had similar frequency of ISRs (82%) compared to vosoritide-treated subjects with negative ADA. The mean duration of ISR in ADA-positive vosoritide-treated subjects was slightly higher (40 hours) compared to ADA-negative vosoritide-treated subjects (25 hours), but similar to the duration of these events in placebo subjects (35 hours) (Figure 86, Appendix). Most ISRs were Grade 1 (mild) and self-limiting.

Studies 111-202/205

The profile of hypersensitivity reactions in Studies 111-202/205 was similar to Study 111-301 with most commonly reported AEs of injection site urticaria (23%), rash (6%), and hypersensitivity (10%; the type of reactions was not specified). All AEs reactions were mild (grade 1 or 2), did not lead to the drug discontinuation, and the incidence declined after Year 2.

Similar to Study 111-301, there was no association between the frequency of ISRs and presence of ADA (Figure 87, Appendix).

7.6.7. Laboratory Findings

Overall, there were no clinically meaningful changes in any laboratory parameter in the clinical program.

All reported shifts in laboratory values in Studies 111-301 and 111-202/205 were of small magnitude; the majority of shifts were grade 0 to grade 1 (NCI-CTCAE), transient, and were not associated with any symptoms. No SAEs associated with laboratory abnormalities were reported in the clinical program. None of the observed changes require labeling (Table 140 and Table 145, Appendix).

One subject in the clinical program, [redacted] (b) (6) who completed Study 111-202 (treated with vosoritide for 744 days) and was enrolled in Study 111-205, discontinued

treatment with vosoritide because of elevated transaminases. The clinical reviewer deemed the event as unlikely to be related to study drug (see detailed narrative and assessment in Section 17).

7.6.8. Electrocardiograms

As noted in the Regulatory History, Section 12, FDA agreed with the Applicant's plan to not conduct a thorough QT study based on the following:

- The sequence homology between vosoritide and endogenous CNP
- Vosoritide is a large biologic peptide, such that an effect on cardiac ion channels is very unlikely
- The nonclinical program characterizes a low QT prolongation potential; no statistically significant hERG current inhibition was observed at a concentration of vosoritide that is 8620-fold greater than the C_{max} in subjects treated with 15 µg/kg vosoritide; and 5) lack of any signal in early phase clinical development (in Studies 111-101 and 111-202) (refer to IRT consult from January 21, 2021, in DARRTS).

However, FDA requested to evaluate the cardiac safety of vosoritide by collecting electrocardiogram (ECG) data in the phase 3 trial. Consistent with FDA's request, ECG was performed at baseline (predose) and at the following study visits (postdose around C_{max}): Day 10, Week 13, Week 26, Week 39, and Week 52. This medical reviewer reviewed all available information and concluded that there were no observed meaningful changes in ECG findings during the 52-week pivotal study, and no difference between treatment arms were noted. No subject in the study had an abnormal QTc prolongation (e.g., >450 msec).

No SAEs related to ECG abnormalities were reported in the clinical program. One subject discontinued Study 111-202 preliminary due to nonserious AEs of WPW. Briefly, (b) (6) initiated treatment with a daily SC injection of vosoritide at 30 µg/kg (Cohort 4) in Study 111-202. On Study Day 10, the subject was diagnosed with nonserious, Grade 1 AE of intermittent WPW syndrome during routine per-protocol ECG monitoring. The subject was asymptomatic. The subject discontinued study drug with the last dose administered on Study Day 10.

> ***Medical reviewer's comments:*** *A causal relationship between study drug and WPW syndrome cannot be ruled out completely due to the temporal relationship of the events; however, a clear mechanistic rationale is not obvious. The most common etiology of WPW is a congenital heart disease. This case and ECG findings were previously reviewed in detail by QT-IRT reviewer, Dr. Christine Garnett, on March 5, 2017, who did not raise any concerns that the event was associated with use of the drug (refer to QT-IRT consult in DARRTS). No other AE of WPW syndrome were reported during the clinical development program to date.*

The ECG data were also reviewed by IRT team (refer to IRT consult in DARRTS, dated January 21, 2021). IRT reviewer concluded that no significant QTc prolongation effect of vosoritide was detected in the integrated nonclinical and clinical QT assessment and no labeling is required.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Blood Pressure Decrease / Hypotension

Issue

Effect of vosoritide on blood pressure.

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. Thus, vosoritide carries a risk of hypotension that may be symptomatic in severe cases (e.g., syncope, dizziness).

Assessment

BP and heart rate (HR) were monitored in the clinical program at prespecified time points after injections. The Applicant included the evaluation of AEs of hypotension and AEs that may potentially be related to hypotension as adverse events of special interest in the safety assessments in all trials. The medical reviewer analyzed independently the vital signs reported in the clinical program as well as all AEs that were reported as hypotension or BP decrease, or may have potentially been related to decrease in BP (e.g., dizziness, fatigue, syncope, presyncope, and vomiting). The results of these analyses are briefly detailed below. In summary, changes in the mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR observed in the clinical program over time, as well as from predose to postdose, were small and of no clinical significance. No difference between vosoritide and placebo arms was noted in decrease in postdose SBP according to prespecified threshold criteria, while a higher percentage of subjects in vosoritide arm compared to placebo had decrease in DBP according to various prespecified threshold criteria. All events were transient, the majority were asymptomatic, and were of no obvious clinical significance. Of the few subjects who had symptomatic hypotension and/or were reported to have AEs suggestive of low BP, such as dizziness or syncope, all had AEs that were mild, resolved quickly, 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 a monitorable event (e.g., majority [73%] of the AEs of low BP were reported within 60 mins of injection) and can be mitigated through appropriate labeling. Although the events of symptomatic hypotension were uncommon and nonserious in the clinical program (2 of 60 [3.3%] of subjects in Study 111-301 over a 1-year period, 2 of 121 [2.5%] subjects in Study 111-302 over a 1-year period, and 4 of 22 [18%] subjects in Studies 111-202/205 over a 5-year period), the review team recommends the risk of symptomatic hypotension to be included in the label under section 5. Warning & Precautions and section 6. Adverse Reactions, to adequately inform the public of this potential risk in light of drug's mechanism of action and appropriate risk mitigation strategies.

Study 111-301

In Study 111-301, BP and HR were monitored for 2 hours postdose during the first 4 study visits (Day 1: every 15 mins for the 1st hour, then every 30 mins for the 2nd hour; Day 2, 3 and 10: every 30 mins for the first 2 hours) and for 1 hour on subsequent visits (every 30 mins).

Changes in Mean BP and HR values

SBP, DBP and HR were similar in both treatment groups at baseline; there were no meaningful differences between group in postbaseline changes (Table 30).

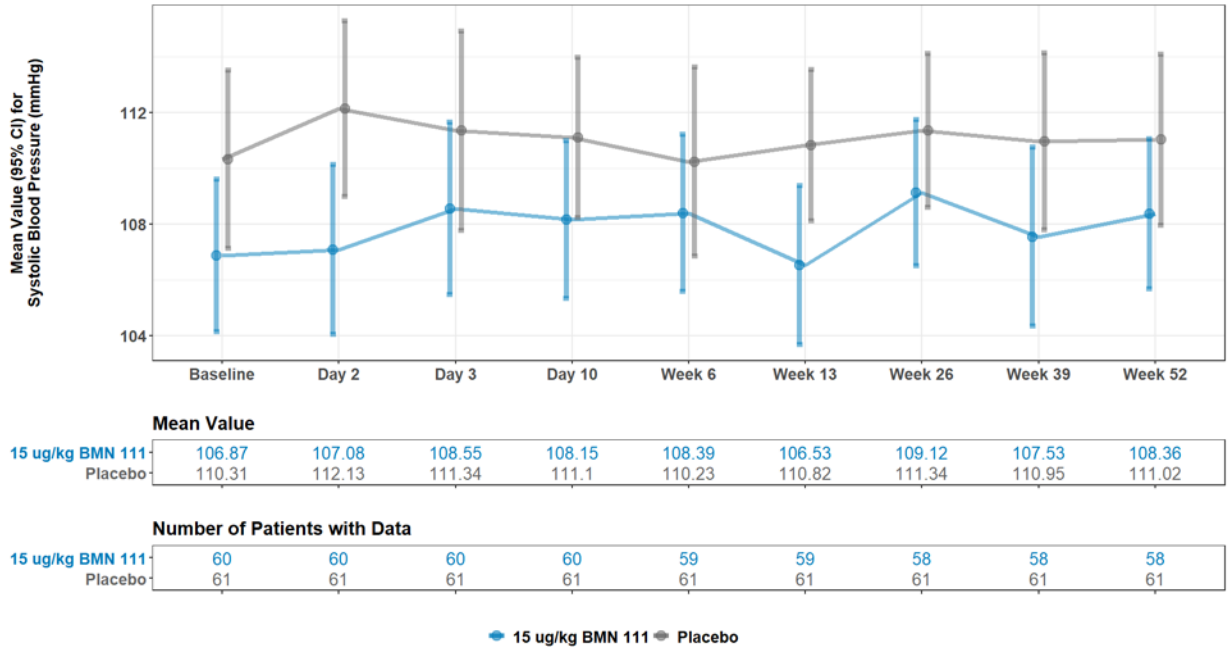
Table 30. Postdose Changes in DBP (mmHg), SBP (mmHg) and HR (beats/mins) From Predose Values, Safety Population, Study 111-301

Predose Value and Postdose Change From Baseline Value [Mean (SD)]	DBP		SBP		HR	
	15 µg/kg VOS N=60	Placebo N=61	15 µg/kg VOS N=60	Placebo N=61	15 µg/kg VOS N=60	Placebo N=61
Day 1						
Predose	61.1 (10.1)	62.6 (9.3)	106.9 (10.8)	110.3 (12.7)	94.7 (13.7)	89.7 (14)
15 min postdose	1 (12.2)	2.9 (12.8)	3.7 (12.8)	0.4 (14.6)	3.7 (11.9)	-0.1 (12.4)
30 min postdose	0.7 (11.7)	2 (9.6)	2.9 (13.3)	0.5 (16)	3.2 (13.2)	-0.8 (11.7)
60 min postdose	0.6 (10.4)	3.7 (9.8)	2.5 (11.6)	3.1 (14.5)	4.8 (13.6)	-1.4 (13)
90 min postdose	0.2 (12.2)	2.4 (9.1)	1.8 (12.7)	1.5 (12.7)	0.5 (12.7)	2.1 (11.9)
120 min postdose	-0.1 (10.4)	3.2 (11.5)	1.6 (13)	3.5 (13.9)	-0.7 (14.8)	-0.8 (13.3)
Day 2						
Predose	62 (10)	64.2 (8.7)	107.1 (12)	112.1 (12.5)	95.6 (13.4)	94.3 (15.7)
30 min postdose	-1.9 (12.5)	-0.3 (11.4)	-0.4 (12.6)	-1.5 (11.6)	4.1 (11.1)	-3.1 (14.9)
60 min postdose	-2.4 (11.4)	0 (10)	0.3 (11.6)	-1.8 (11.7)	0.1 (12.8)	-4.1 (14.8)
90 min postdose	-2.4 (11.1)	0.6 (10.6)	0.8 (12.1)	-2.5 (9.8)	-1.1 (11.1)	-3.9 (15)
120 min postdose	-2.1 (14)	-0.4 (10.6)	0.5 (12.7)	0.2 (10.2)	-1.8 (11.6)	-5.3 (15.6)
Day 10						
Predose	61.8 (9.7)	64.7 (8.7)	108.2 (11.2)	111.1 (11.4)	95.7 (13.8)	94.3 (13.6)
30 min postdose	-1.3 (9.9)	-2.1 (8.7)	-0.4 (11.7)	-1.5 (9.5)	0.1 (12.5)	-3.3 (11.1)
60 min postdose	1 (10)	0.3 (10.4)	0 (11.2)	-2.4 (9.6)	0.6 (13.3)	-4.2 (12.4)
Week 26						
Predose	63.2 (9.3)	63.6 (11.3)	109.1 (10.2)	111.3 (11)	90.3 (12.4)	89.7 (14.4)
30 min postdose	-1.3 (8.5)	1 (12.8)	-1.1 (9.6)	-0.4 (12.3)	5 (11.7)	-1.7 (11.1)
60 min postdose	-3.3 (9.8)	0.8 (13.8)	-2.2 (9.9)	1 (11.2)	2.7 (10.7)	-1.2 (12.7)
Week 52						
Predose	62.8 (8.9)	64.5 (8.4)	108.4 (10.5)	111 (12.3)	90.4 (11.8)	87.1 (12.5)
30 min postdose	-2.7 (7)	-0.1 (10.5)	-1.6 (9.6)	1.2 (12.5)	3.9 (11.5)	-1.7 (9.6)
60 min postdose	-1.1 (8.5)	2.2 (9.2)	-0.7 (10.4)	2.7 (11.4)	3.3 (13.1)	0 (11.7)

Source: advs.xpt; Software: R
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; min, mins; SBP, Systolic blood pressure; SD, standard deviation

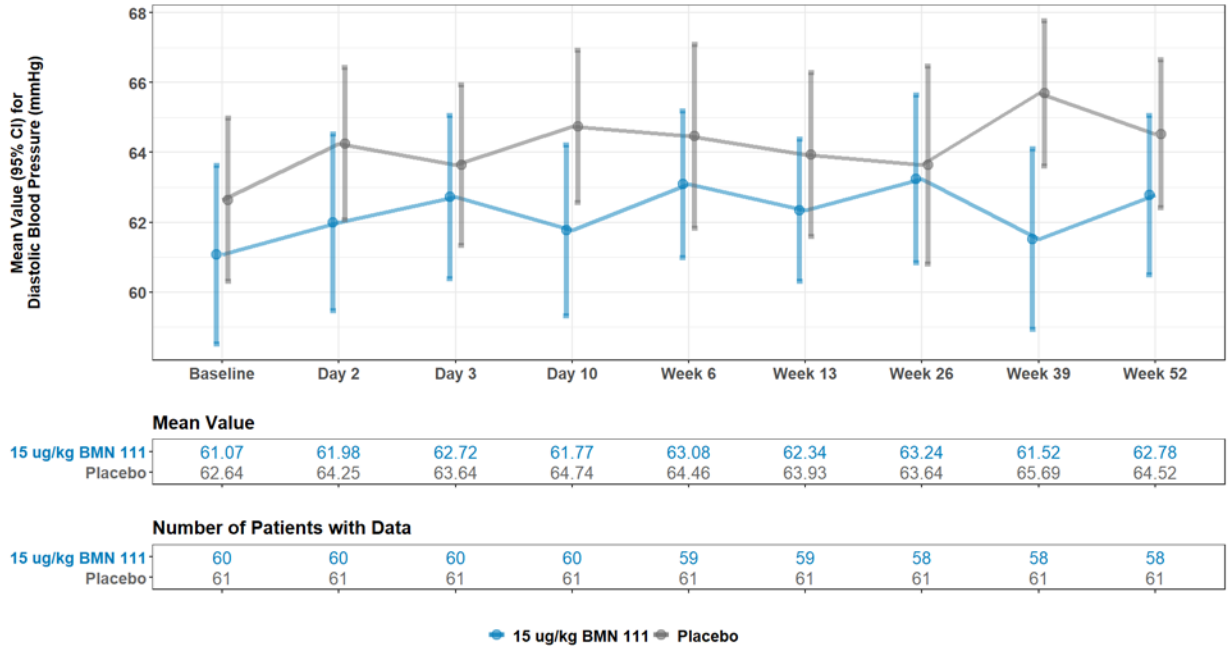
Analysis of these assessments over the 52-week study period does not raise additional concerns. There were no concerning changes in any of the mean postdose SBP, DBP, or HR changes from baseline over time in both treatment groups (Figure 16, Figure 17, and Figure 18).

Figure 16. Mean Values for Systolic Blood Pressure Over the 52-Week Study Period, Safety Population, Study 111-301



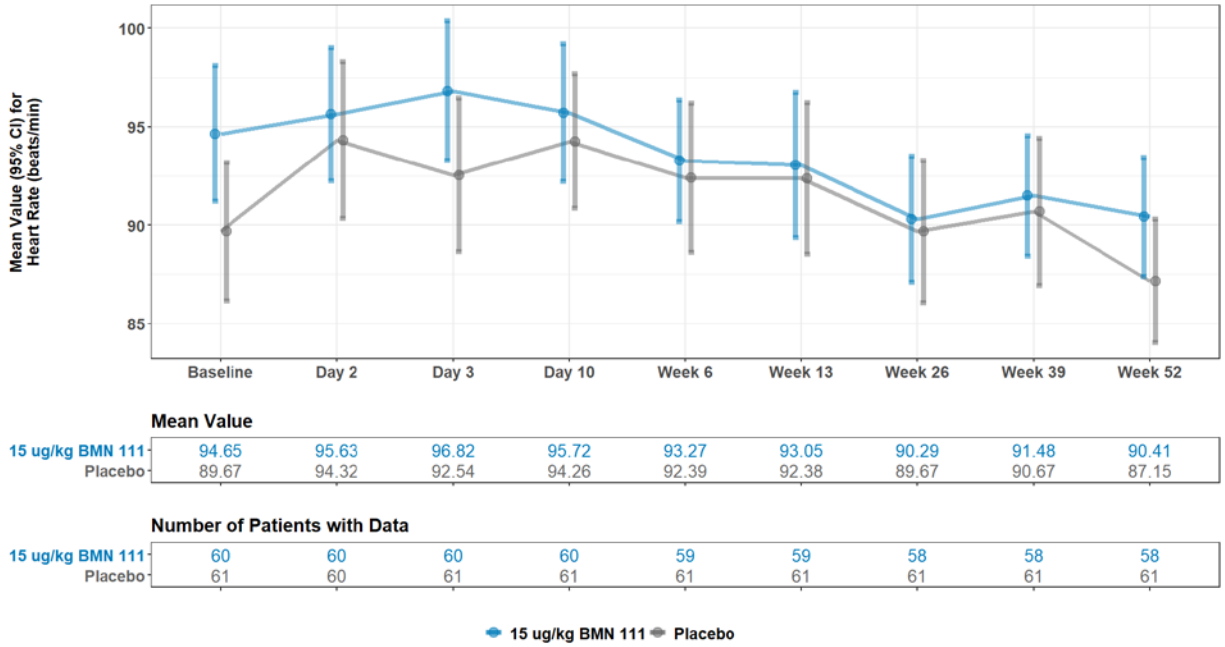
Source: advs.xpt; Software: R; FDA's analysis
Abbreviations: BMN 111, vosoritide; CI, confidence interval

Figure 17. Mean and Confidence Interval for Diastolic Blood Pressure Over Time, Safety Population, Study 111-301



Source: advs.xpt; Software: R; FDA's analysis
Abbreviations: BMN 111, vosoritide; CI, confidence interval

Figure 18. Mean and Confidence Interval for Heart Rate Over Time, Safety Population, Study 111-301



Source: advs.xpt; Software: R; FDA's analysis
Abbreviations: BMN 111, vosoritide; CI, confidence interval

Proportion of Subjects With Potentially "Clinically Meaningful" BP Changes

The Applicant further analyzed blood pressure changes that might be of clinical significance using the following criteria:

(1) SBP: For ages 1 to 10 years, a postdose decrease in SBP from ≥70 mm Hg (plus 2x age) to <70 mm Hg (plus 2x age) and for ages >10 years, a decrease in SBP from ≥90 mm Hg to <90 mm Hg, according to NIH Guidelines, Pediatric Basic and Advanced Life Support defining criteria for hypotension (Chemical Hazards Emergency Medical Management (CHEMM) 2010).

AND/OR

(2) DBP: a postdose decrease of a) ≥20% of predose value, b) <45 mm Hg and c) <40 mm Hg. As per Applicant, these thresholds were chosen based on prior regulatory precedence for DBP thresholds accepted by FDA as holding clinical significance in another BioMarin pediatric program (Brineura®, BLA 761052, approved April 27, 2017) with subjects of similar age as the vosoritide study population.

As per Applicant's analyses, there was no imbalance in the proportion of subjects experiencing prespecified changes in SBP (20% vosoritide versus 23% placebo) between treatment arms. A greater proportion of subjects in vosoritide group experienced a decrease in DBP that met prespecified threshold at any time during the study compared to placebo group (Table 31). It should be also noted that the majority of events of DBP <40 mm Hg, or <45 mm Hg overlapped with the events that met the criteria of DBP decrease of ≥20% predose value.

Table 31. Proportion of Subjects With Decrease in Postdose Blood Pressure According to Predefined Criteria, Safety Population, Study 111-301

Decrease in Postdose Blood Pressure Variable, n (%)	Vosoritide 15 µg/kg (N=60)	Placebo (N=61)
SBP <70 mm Hg +2x age (age 1-10 years), or <90 mm Hg (>10 years old)	12 (20)	14 (23)
DBP ≥20% of predose value	52 (86)	43 (70.5)
DBP <45 mm Hg	27 (45.0)	20 (32.8)
DBP <40 mm Hg	10 (16.7)	6 (9.8)

Source: Table 14.3.6.1.7.1.1, ISS and Tables 14.3.6.1.3., 14.3.6.1.5.2 and 14.3.6.1.4.2, CSR 111-301; modified.
Abbreviations: DBP, diastolic blood pressure; ISS, integrated summary of safety; n, number of subjects with event; % percent of subject with event; N, total number of subjects per treatment arm; SBP, systolic blood pressure

To better characterize the observed changes in BP parameters, this medical reviewer conducted additional analysis of pre- and postdose blood pressure values at each study visit in all subjects experiencing at least 1 event of decrease in SBP or DBP according to above mentioned threshold criteria and based on the data provided by the Applicant in response to Agency's information request from December 18, 2020. The results of this analysis are summarized below:

- Overall, there were no clear patterns in terms of timing for decreases in SBP or DBP meeting the prespecified thresholds. The more frequent events of prespecified decreases in blood pressure noted within the first 2 days of the study were likely a result of more frequent measurements according to the protocol requirements.
- Most events of decline in DBP were accompanied by either a simultaneous increase, or stable SBP, or a rebound in DBP value with the next measurement. Eight out of 60

(13.3%) subjects in vosoritide arm had simultaneous decline in SBP and DBP; BP normalized in all cases with the next evaluation and without any intervention.

The review team consulted the Division of Cardiology and Nephrology (DCN) regarding the clinical relevance of reporting the changes in SBP and DBP according to the above-mentioned pre-established thresholds in the label. The DCN consultant concluded that inclusion of data regarding postdose changes in BP according to prespecified threshold criteria are not clinically relevant and should therefore not be included in the label.

Analysis of BP-Related AEs

A total of 8 (13.3%) subjects in the vosoritide arm and 3 (4.9%) subjects in the placebo arm had AEs of BP decrease or hypotension (Table 32). These AEs were noted during the 2-hour observation time period of the protocol-specified clinic visits only, as home BP monitoring was not required during the study. It should be noted that as per protocol, AE of 'BP decrease' did not require presence of symptoms and it was done at Investigator's discretion as no threshold criteria for "BP decreased" exist, while AE of 'hypotension' required presence of symptoms in the setting of a decrease in BP. Six out of the 8 subjects in vosoritide arm and all 3 subjects in placebo arm with a reported AE of "BP decrease" or "hypotension" met at least 1 of the threshold criteria for SBP or DBP decrease described above.

As per Applicant's analysis of 8 subjects in vosoritide group, 1 subject ([redacted] (b) (6)) had AE of 'hypotension', and 7 subjects had AE of 'BP decrease'. This medical reviewer identified 1 additional subject ([redacted] (b) (6)) who had reported AEs of 'dizziness' and 'blood pressure decreased' simultaneously on Day 1 (see Section 6, above, for details), which renders the subject as experiencing symptomatic blood pressure decreased, or "hypotension." Subject [redacted] (b) (6) developed symptoms of dizziness, pallor, nausea, and vomiting 30 mins post drug administration. Blood pressure decreased from a predose value of 108/65 mm Hg to 90/57 mm Hg at the time of event. The symptoms resolved within 5 mins of the event and blood pressure normalized at 103/67 mm Hg without medical intervention. All events of "BP decreased" and 'hypotension' were transient, mild in severity (Grade 1), and resolved within 1 hour without any intervention. Thus, of the 8 subjects in vosoritide group who had AEs of BP decrease or hypotension, 2 (3.3%) subjects had symptomatic BP decreased (e.g., hypotension), and 6 subjects had BP decrease without associated symptoms. Majority (8 out of 11) of the AEs of BP decrease or hypotension in vosoritide arm lasted ≤60 mins and there were no SAEs associated with BP decrease were reported in the study. No subject discontinued study drug due to event of decreased blood pressure or hypotension (Table 32).

Table 32. Blood Pressure Decreased and Hypotension Adverse Events, Study 111-301

Parameter	Vosoritide (N=60)	Placebo (N=61)
Number of subjects with adverse events	8 (13.3)	3 (4.9)
Total number of events	11	3
Time from first dose to first event onset, days		
Median (min, max)	7.0 (1, 184)	3.0 (1, 3)
Time from last dose to first event onset, mins		
Median (min, max)	31.2 (18, 120)	93 (18, 1410)
Duration of events, mins		
Median (min, max)	31.0 (5, 90)	128.0 (43, 61922)
≤15 min	2	0
>15 min to ≤60 min	6	1
>60 min to ≤120 min	1	0
>120 min to 24 hours	0	1
>24 hours	0	1
Not available	2	0
Outcome of events, n		
Recovered/resolved	11	3
Severity		
Grade 1	11	3
Events leading to study drug discontinuation, n	0	0

Source: adapted from Applicant's Table 14.3.1.7.6, 111-301 CSR and ISS ISE
Abbreviations: N, number of subjects; n, subjects with event.

In addition, the medical reviewer searched the safety database for AEs by PTs that could potentially be associated with blood pressure decreases (e.g., dizziness, presyncope, syncope, vertigo, fatigue, lethargy, malaise, nausea, blurred vision, and cold sweats). The result of this search identified only AEs under the FMQ 'dizziness' (that includes PTs of dizziness, presyncope, syncope, vertigo) (6 [10%] vosoritide versus 2 [3.3%] placebo), FMQ 'fatigue' (that includes PTs of fatigue, lethargy, malaise) (5 [8.3%] vosoritide versus 2 [3.3%] placebo), and nausea (3 [5%] vosoritide versus 4 [6.6%] placebo). Although, FMQs 'fatigue' and 'dizziness' were reported more frequently in vosoritide arm compared to placebo arm, the majority of subjects did not have recorded BP measurements during the events, which complicates the causality assessment of the drug with these events. Only 2 subjects with the AEs of dizziness had BP measurements at time of the event, and 1 of these 2 subjects had reported low BP that resolved without treatment (refer to Section 7.6.5, for details). The frequency of nausea was lower in vosoritide group compared to placebo group and nausea is not an uncommon event in this age group, however, due to the absence of BP values during the event no definite conclusion can be made at this time. The most important is that these AEs were infrequent, all events were mild, resolved without treatment and within short period of time and did not require drug discontinuation.

Studies 111-202/205

There were no clinically significant changes in mean SBP, DBP, and HR from predose to postdose values at any time during the Studies 111-202/205.

Similar to Study 111-301, the Applicant provided data on blood pressure changes that meet prespecified criteria (see above) in all age groups. Overall, 66.7% subjects experienced a decrease in SBP to below 70 mm Hg plus 2x age at any time during Studies 111-202/205, 96.7% experienced a decrease in DBP >20% form predose value, 80% experienced a decrease in DBP

to <45 mm Hg, and 46.7% experienced a decrease in DBP <40 mm Hg at any time during the study. The higher proportion of subjects with prespecified BP decreases for both SBP and DBP values compared to proportion of subjects in Study 111-301 is expected, given the longer duration of Studies 111-202/205. All but 1 subject (see below) with decrease in BP below prespecified thresholds were asymptomatic, and all events were self-limiting, transient, and without pattern with regards to the timing of the study.

No SAEs or hypotension-related AEs that led to preliminary drug discontinuation were reported in the study. Fourteen (53.8%) subjects experienced at least 1 AE of blood pressure decrease/ hypotension (Table 143, Appendix). Of note the AE reporting the PT 'hypotension' in Studies 111-202/205 did not require presence of symptomatic blood pressure decrease (as in Study 111-301), thus both AEs of symptomatic, or asymptomatic BP decrease were reported within the PT of "hypotension." This medical reviewer evaluated further all 14 case reports and identified 4 subjects with 4 events of symptomatic hypotension. These events are briefly summarized below:

- Subjec (b) (6) (Cohort 2), (b) (6) experienced 1 AEs of hypotension associated with syncopal symptoms. The syncopal episode occurred on Study Day 246 (first day of vosoritide 15 µg/kg/day dose escalation from 7.5 µg/kg/day), 45 mins after study drug administration, while sitting up and watching nurse preparing the injection site for intravenous access. Predose BP was within normal limits. The event resolved within 1 min. The BP during the event decreased to 60/37 mm Hg and 1 min later was 103/47 mm Hg and further increased to normal levels. BP remained normal during the next 3 hours of monitoring.
  - This subject experienced another episode of syncope on Day 366 after the injection of that was not associated with low BP. No other events of syncope, presyncope or hypotension were reported in this subject to date.
- Subject (b) (6) (Cohort 2), (b) (6), experienced an AE of hypotension on Study Day 451 (while on vosoritide 15 µg/kg/day) associated with presyncope symptoms after micturition. BP decreased to 91/63 mm Hg from 117/68 mm Hg prior to the event. She lied down and was treated with oral fluids and food. The symptoms resolved and BP returned to baseline, 23 mins after the event. She had no recurrent events of presyncope.
- Subject (b) (6) 2 (Cohort 1), (b) (6), experienced a symptomatic hypotension AE (grade 2) on Day 1017 manifested as dizziness 30 mins after study drug administration. The predose BP was 122/73 mm Hg, decreased to 88/54 mm Hg 30 mins postdose and returned to 111/60 mm Hg, 45 mins postdose without medical intervention. No recurrence of the event was reported throughout the study.
- Subject (b) (6) 0 (Cohort 3), (b) (6), experienced AE of hypotension associated with dizziness, nausea and pallor on Study Day 1088, approximately 2 hours post vosoritide administration, while standing for anthropometric measurements. The predose BP values were within normal limits 115/67 mm Hg and decreased to 90/60 mm Hg during the event; BP returned normal (BP 115/58 mm Hg) 5 mins later and was normal with subsequent measurements.

Given the temporal relationship and the effect of vosoritide on vascular tone, it is possible that these syncopal and presyncopal events were caused by vosoritide, although other confounding factors may have played a role in some cases (e.g., situational syncope, anxiety, micturition).

However, all events were nonserious, mild, self-limiting, nonrecurrent, and did not require study drug discontinuation.

Study 111-302

Applicant reported 3 nonserious AEs in 3 (2.5%) subjects in Study 111-302 with symptomatic decrease in blood pressure. All cases were mild (Grade 1, or 2), self-limiting, nonrecurrent and not resulting in study drug discontinuation.

7.7.2. Abnormal Skeletal Growth

Issue

Effect of vosoritide and/or accelerated vosoritide-induced growth on bone abnormalities/morphology.

Background

The clinical signs of bone overgrowth, expected from the effect of vosoritide on growth plates, include valgus deformity, swollen limbs, degeneration, and dysfunction of joints and microscopic changes in bone tissue were noted in healthy animals.

The pharmacology/toxicology team do not consider these exaggerated pharmacologic effects as a safety concern in the targeted population where enhanced bone growth is the desired outcome, and no signs were reported in ACH models (refer to Section 7.1.2). However, the potential effect of vosoritide on bone deformities/bone morphology in humans is unknown clinically and therefore remains a concern.

Assessment

Skeletal deformities were monitored in the clinical studies by X-ray of limbs, hip, and spine. The Applicant also conducted evaluation of bone morphology by dual energy X-ray absorptiometry (DEXA) scans. Lastly, the AEs that are known to be related to acceleration of growth induced by growth-promoting therapies, including slipped capital femoral epiphysis, avascular necrosis, and osteonecrosis, were evaluated as AESIs throughout the studies. The clinical findings are discussed below.

X-Ray Findings

No significant bone abnormalities were found on X-ray of limbs, hip, spine or chest. All changes were small and of unknown clinical significance.

Lower Limbs

In the clinical program, there was no reported increase in disproportionality between tibial and fibular length as demonstrated by absence of change in the distance between the ankle joint and the distal growth plate of the fibula on both sides (left and right) from baseline. There was no worsening in tibia bowing angle.

In Study 111-301/302 there was no imbalance in growth rate between tibia and fibula at Week 52.

In Studies 111-202/205, a proportional (1:1 ratio) increase in tibial and fibula length was observed. At baseline, the tibia bowing angle was approximately 180 degrees, suggesting no bowing in the age categories of ≥5 to <8 and ≥8 to <11 years, and a mean (SD) change from baseline to Week 48 of -5.20 (4.97) and -6.67 (8.86), respectively, were noted, suggesting a worsening with slight bowing. However, the interpretation of these changes is difficult in the absence of a control arm. In addition, tibial bowing is a common bone deformity in patients with ACH and it is reported to progress through childhood as a result of the standing position, with approximately 40% of adults affected (Ireland et al. 2014).

Lumbar Spine

There were small proportional increases in the height of vertebral bodies in all studies. There were no concerning changes in the vertebral height ratios, interpedile distances, or width of the spinal canal from baseline to Week 52 in Study 111-301 or with longer treatment duration (up to Month 48 in Study 111-202/205). No worsening in mean sacral tilt, lumbar lordosis and lumbar spine kyphosis angles were noted in clinical program. All changes were small, similar between treatment arms (in Study 111-301), age groups and with longer treatment duration.

Hip

There were no hip deformities detected on X-Ray in any subjects.

Dual Energy X-ray Absorptiometry

DEXA scans of the whole body, except head, and lumbar spine were performed in Study 111-301 only. There were no notable changes in 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

Most subjects did not have symptoms or signs that may be associated with vosoritide-related abnormal bone growth. Four subjects in the clinical program had bone-related SAEs (refer to Section 7.6.3).

In Study 111-302, 2 subjects had 3 bone-related SAEs: hip deformity (1 subject), and syringomyelia and spinal cord injury (1 subject). Syringomyelia and spinal cord injury were most likely due to an underlying medical history of myelomalacia and trauma rather than drug. For the subject with the SAE of hip deformity, which could be associated with accelerated linear growth, causal assessment is challenging, as this subject had a baseline hip deformity, and the observed change from baseline in AGV after 1 year of treatment was 1.9 cm/year, which was similar to the mean treatment difference observed in Study 111-301, while the changes from baseline in the upper-to-lower body segment ratio and upper leg length to tibial length ratio were not clinically significant (<0.1) (refer to Section 7.6.3 for additional details).

In Study 111-205, 1 subject had an SAE of spinal stenosis with cord compression on Study Day 1744 that resolved on Study Day 1746 after surgery. New onset or worsening of a pre-existing spinal stenosis diagnosis caused by vosoritide may be possible given the temporal relationship. However, a causal relationship between vosoritide and the event of spinal stenosis cannot be determined because of lack of information regarding the subject's past medical history prior to study drug initiation and the fact that spinal stenosis is a common neurological complication in

ACH. In Study 111-208, 1 subject [redacted] (b) (6) had an SAE of cervical cord compression for which [redacted] (b) (6) underwent surgery that is most likely not related to the drug, as the subject had a medical history of "significant narrowing at the foramen magnum, spinal decompression surgery, chondrodystrophy and central sleep apnea"; however, the study is still blinded.

In the age group studied, arthralgia is not uncommon sand may also represent "growing pain" that is the most common cause of musculoskeletal pain in children during period of growth or is secondary to frequent activity-related accidents seen in this age group. Nevertheless, in Study 111-301, more subjects in the vosoritide group compared to placebo (15 versus 6.6%) group had a nonserious AE of arthralgia that could be caused by accelerated growth. Notably, all AEs of "arthralgia" were mild and resolved without treatment/drug discontinuation. Additionally, there was 1 nonserious adverse event of fracture reported in Study 111-301 in a vosoritide arm, which was likely unrelated to study drug (traumatic distal radial fracture after fall from a scooter).

No events of slipped capital femoral epiphyses, or avascular necrosis and osteonecrosis were reported during vosoritide clinical development program to date.

In conclusion, there were no findings on X-ray suggestive of worsening of preexisting or appearance of new bone abnormalities. No subjects reported AEs that are related to abnormal bone growth with short-term or long-term (up to 6 years) treatment with vosoritide. However, some AEs that may be associated with disproportional growth, such as spinal stenosis, imbalance, and limping, were not evaluated in the clinical program (e.g.,). At this time no additional labeling is required based on the available data, except the reporting of the most frequent AEs in Section 6. However, the long-term risk of AEs related to disproportionality should be further monitored in postmarketing settings.

7.7.3. Bone Age

Issue

Effect of vosoritide on bone age.

Background

Although patients with ACH have a delay in bone age relative to chronological age and the bone age is expected to improve with treatment, there is a potential risk of undue acceleration in bone age with all growth-promoting products. Although there were no concerning findings of accelerated bone age in Study 111-301, there was a trend with longer treatment in Study 111-202/205 toward positive values in differences between bone age and chronological age. An acceleration in bone age may lead to the premature closure of growth plates and ultimately shorter-than-expected final height.

Assessment

The bone age was evaluated in clinical studies by using a widely accepted method based on Greulich and Pyle Atlas on X-rays of the left hand.

The medical reviewer conducted additional analyses of bone age versus chronological age observed in the program. An FDA pediatric endocrinologist, Dr. Ovidiu Galescu, with expertise

in bone age, was also consulted (refer to consult in DARRTS, dated 04/08/2021). The results of these analyses are presented below.

Study 111-301

Assessment of bone age was conducted at baseline, Week 26, and Week 52. (Table 33). As expected, the mean (SD) bone age at baseline was similar and below chronological age in both treatment arms: 7.62 (2.93) years vosoritide versus 8.13 (3.03) placebo (Lee et al. 2009; Pannier et al. 2010). The change in mean (SD) bone age from baseline after 1 year of treatment was similar in both treatment arms and is consistent with chronological age progression: 1.02 (0.83) vosoritide versus 1.14 (0.82) placebo. The changes were similar in females and males.

Table 33. Bone Age and Chronological Age, Safety Population, Study 111-301

Parameter	Vosoritide 15ug/kg (N=61)	Placebo (N=60)
Bone age (years), mean (SD)		
Baseline	7.62 (2.93)	8.13 (3.03)
Week 52	8.49 (2.88)	9.37 (3.2)
Δ B to Week 52	1.02 (0.83)	1.14 (0.82)
Chronological age (years), mean (SD)		
Baseline	8.35 (2.43)	9.06 (2.47)
Bone age – chronological age at baseline	-0.73	-0.93

Source: Table 14.3.6.4.1.1, CSR 111-301, modified
Abbreviations: SD, standard deviation

Study 111-302

Review of additional 1-year data from subjects exposed to vosoritide in the phase 3 trial did not suggest accelerated bone maturation after 2 years of treatment. In the 33 subjects in the vos/vos treatment arm in whom the bone age was assessed at Week 104 of total treatment in Studies 111-301 and 111-302, the mean (SD) change from baseline to Week 104 in the difference in bone age and chronological age (years) was -0.05 (1.46).

Study 111-202/205

As in Study 111-301, subjects at baseline had delayed bone age compared to chronological age (Table 34). The medical reviewer analyzed bone age data and noted a decrease in the difference between bone age and chronological age over time, as suggested by a trend from negative values at baseline towards positive values, with most notable changes for subjects in Cohorts 2 and 3, which raises concerns of accelerated bone maturation with vosoritide treatment and subsequent premature final height achievement.

Table 34. Difference Between Mean Bone Age and Mean Chronological Age (Mean [SD]), Safety Population, Study 111-202/205

Mean (SD)	Cohort 1 (2.5 µg/kg) (N=6)	Cohort 2 (7.5 µg/kg) (N=6)	Cohort 3 (15 µg/kg) (N=10)	Cohort 4 (30 µg/kg) (N=8)	Overall
Baseline, n	6	6	10	8	30
Baseline diff.	0.14 (1.95)	-0.43 (1.82)	0.75 (1.85)	-0.13 (1.03)	0.16 (1.66)
Month 6, n	6	6	10	8	30
M 6 diff.	-0.05 (1.78)	-0.79 (1.88)	0.85 (1.65)	0.62 (1.54)	0.28 (1.73)
CFB to M 6	-0.19 (0.73)	-0.36 (0.88)	0.10 (1.07)	0.75 (0.79)	0.12 (0.95)

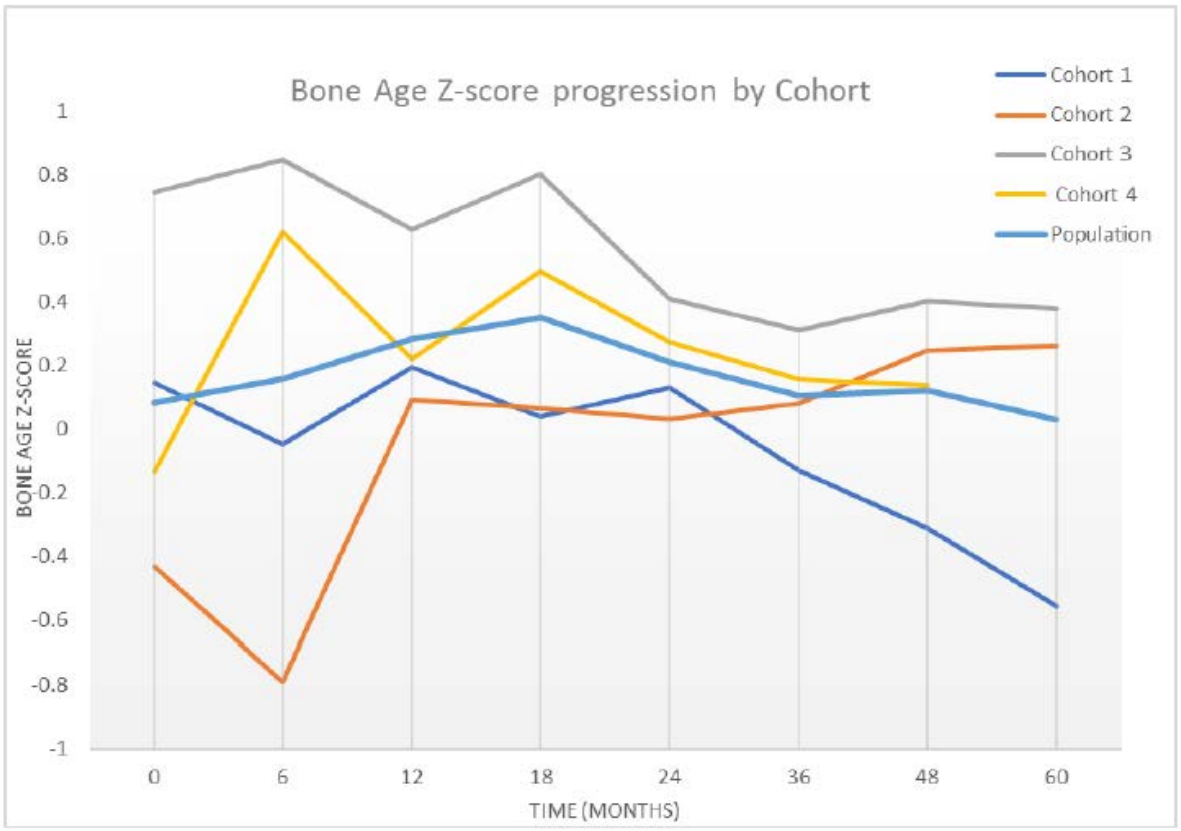
Mean (SD)	Cohort 1 (2.5 µg/kg) (N=6)	Cohort 2 (7.5 µg/kg) (N=6)	Cohort 3 (15 µg/kg) (N=10)	Cohort 4 (30 µg/kg) (N=8)	Overall
Month 12, n	5	6	10	8	29
M 12 diff.	0.35 (1.90)	0.09 (1.18)	0.63 (1.73)	0.22 (1.27)	0.35 (1.48)
CFB to M 12	0.19 (1.04)	0.52 (0.94)	-0.12 (1.05)	0.35 (0.34)	0.20 (0.87)
Month 18, n	6	6	8	8	28
M18 diff.	0.04 (2.14)	0.07 (1.38)	0.81 (1.66)	0.50 (1.45)	0.39 (1.60)
CFB to M 18	-0.11 (1.04)	0.50 (1.28)	-0.15 (1.07)	0.63 (0.57)	0.22 (1.01)
Month 24, n	6	5	10	8	29
M 24 diff.	0.13 (1.74)	0.64 (0.86)	0.54 (1.64)	0.27 (1.08)	0.40 (1.36)
CFB to M 24	-0.01 (0.79)	0.58 (1.26)	-0.20 (1.09)	0.40 (0.48)	0.14 (0.94)
Month 36, n	6	5	7	8	26
M36 diff.	-0.13 (1.42)	0.37 (0.65)	0.01 (1.86)	0.16 (0.72)	0.09 (1.21)
CFB to M 36	-0.28 (1.21)	0.31 (1.39)	0.11 (1.1)	0.29 (0.67)	0.11 (1.04)
Month 48, n	6	5	8	8	27
M 48 diff.	-0.31 (1.25)	0.47 (0.40)	0.32 (1.50)	0.14 (0.67)	0.15 (1.06)
CFB to M 48	-0.45 (1.47)	0.41 (1.77)	0.24 (0.91)	0.27 (1.01)	0.12 (1.22)
Month 60, n	4	5	8	0	17
M 60 diff.	-0.56 (1.13)	0.43 (0.80)	0.38 (1.32)		0.17 (1.16)
CFB to M 60	-0.28 (1.65)	(2.21)	0.29 (0.73)		0.18 (1.43)

Source: adapted from Applicant's Table 14.3.6.4.1, Study 111-202/205
Abbreviations: B, baseline; CFB, change from baseline; diff, difference; M, month; SD, standard deviation

Dr. Galescu conducted additional analyses evaluating the progression of bone age by using Z-scores for analysis. Z-score is a more reliable parameter as compared to the absolute difference between bone and chronological ages i.e., (bone age-chronological age) since it accounts for both the age and the sex of the subject. Dr. Galescu concluded that based on the results of these analyses, an accelerated bone growth resulting in premature final adult height achievement as a result of vosoritide treatment is unlikely. The results of these analyses are briefly summarized below.

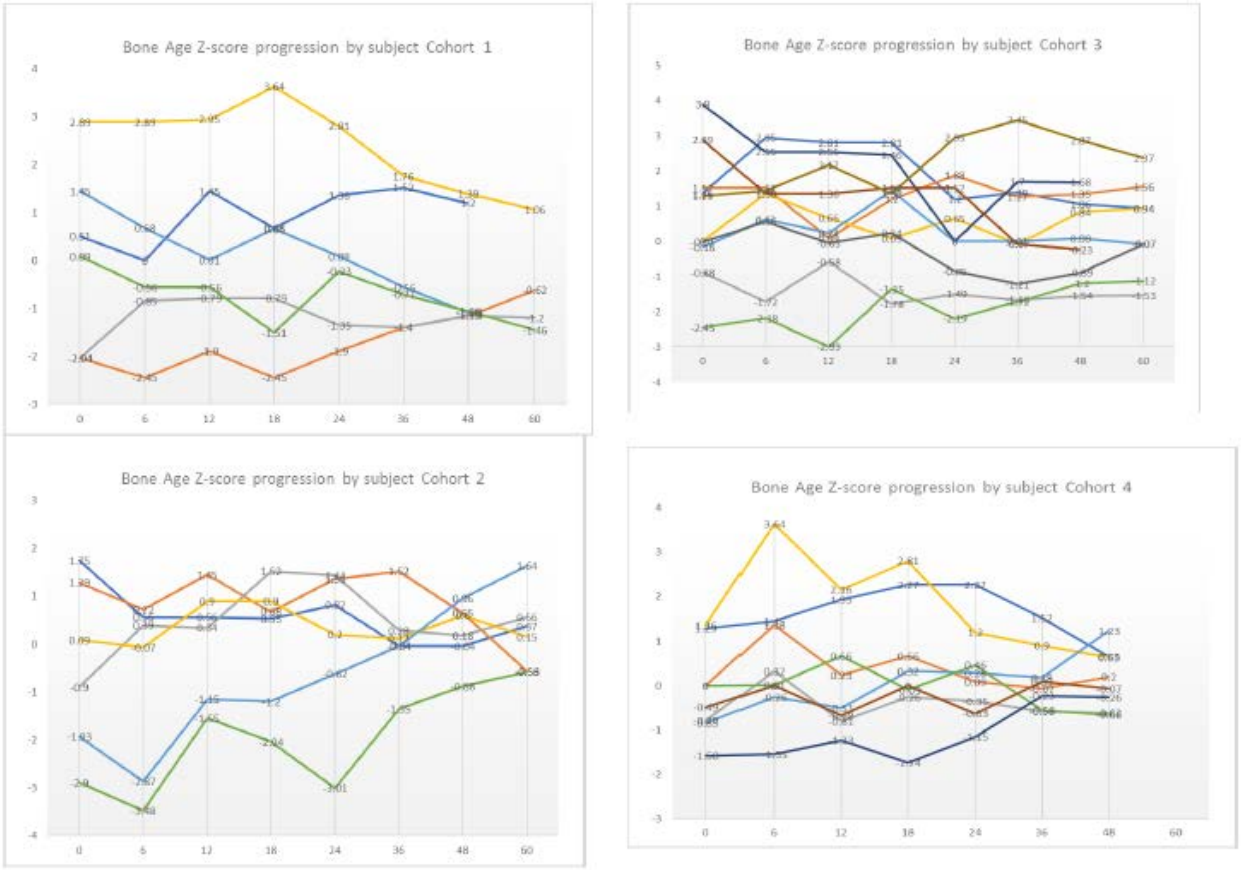
There was no discernable pattern of bone age progression based on Z-scores parameters either by cohort or in the overall study population (Figure 19) although individual variability in Z-scores was observed (Figure 20).

Figure 19. Progression of Mean Bone Age Z-Score Over Time by Cohort and Overall, Study 111-202/205



Source: Dr. Galescu's analysis

Figure 20. Progression of Bone Age Z-Score Over Time by Subjects, by Cohort, Study 111-202/205

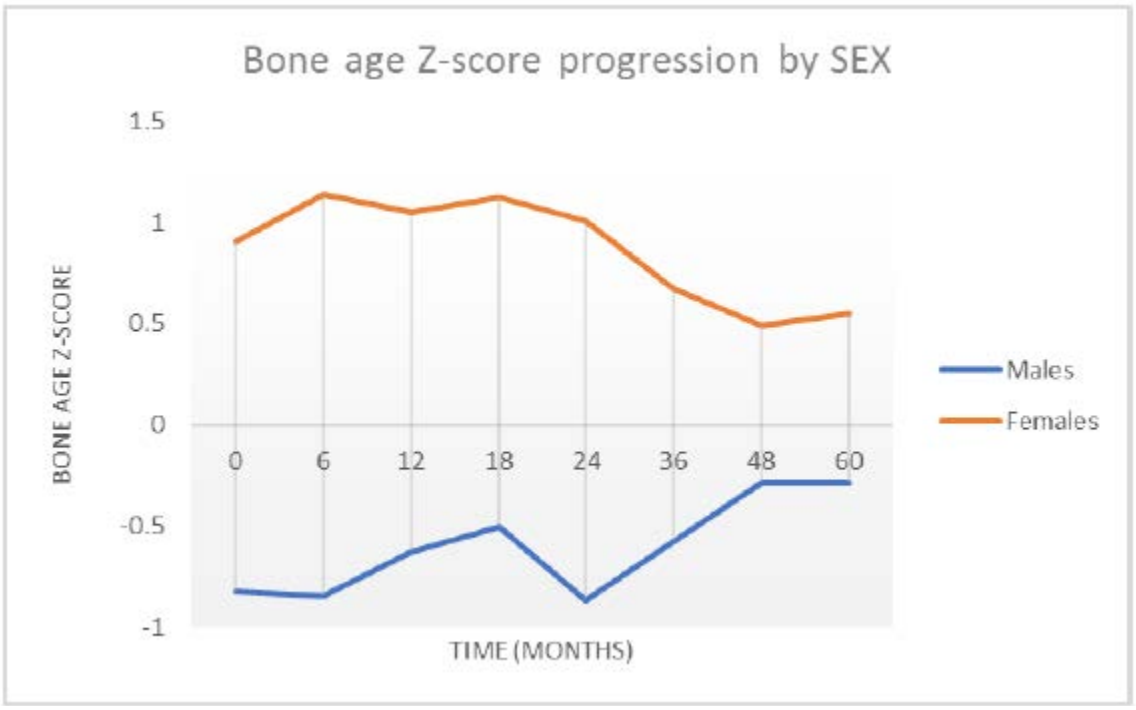


Source: Dr. Galescu's analysis

When the changes in bone age Z-scores were evaluated by sex, it was noted that females tended to have a slightly advanced mean (95% CI) bone age Z-score of 0.9 (-0.49 to 2.89) compared to chronological age at baseline. Males had a slightly delayed mean (95% CI) bone age Z-score of -0.82 (-2.9 to 3.9) at baseline when compared to chronological age, consistent with the epidemiological data. Both females and males tended to normalize their bone age Z-score, suggesting a potential reversal of pathophysiological changes in the bone with vosoritide treatment (Figure 21).

Of note, this analysis has limitations since only 60-month nonmissing values were included (from 9 of 13 boys and 9 of 17 girls); the assessment of subjects who already had discontinued treatment at each time point were not imputed in this analysis.

Figure 21. Mean Bone Age Z-Score Progression by Sex, Study 111-202/205



Source: FDA's pediatric endocrinologist analysis

Lastly, the analysis of individual bone age Z-scores in the 7 subjects with an increase or decrease in bone age Z-score from baseline by >2 at any time during the study (as presented in CSR 111-205, Listing 16.2.8.8.1.3) did not identify any concerns with accelerated bone age. The bone age Z-score changes from baseline were highly variable, with values ranging from -3.12 to +3.57. Some changes were transient, and only 1 subject had a bone age Z-score at last assessment of >2: This was (b) (6) who had a bone age Z-score of 1.29 at baseline and bone age of 2.37 at Month 60, with highest bone age Z-score of 3.45 noted at Month 36, then declined, demonstrating the variable and transient changes in bone age Z-score throughout the study and likely the lack of reliable measurement of bone age in ACH subjects, given their abnormal skeleton.

One subject ((b) (6)) in Study 111-202 discontinued the study due to the AE of "erroneous diagnosis of growth plate closure" that is further summarized here:

- Subject (b) (6) with ACH and a medical history of upper respiratory tract infection, urinary tract infection, elbow deformity, limb deformity, sleep apnea syndrome, and adenotonsillectomy. This subject initiated treatment with vosoritide at 7.5 µg/kg daily. The protocol-scheduled hand X-ray on Day 183 was assessed by central reading laboratory as uninterpretable, and an unscheduled scan was performed on Study Day 232. The bone age was estimated to be 10.5 years (by Greulich and Pyle method), which was concordant with chronological age, and the image showed a growth plate closure in 1 phalanx. Following this finding, on Study Day 249, the subject was withdrawn from treatment due to growth plate closure, according to protocol stopping criteria at that time (which was later amended to include evidence of AGV of <1.5 cm/year as well). At the time of treatment withdrawal, the subject was Tanner stage 1. Her AGV at baseline was 0.36 cm/year, and her AGV on Study Day 183 (Month 6) was

4.1 cm/year. Although the subject discontinued study treatment, she remained in the study and completed the Month 24 visit, with AGV values as follows: Month 12: 3.6 cm/year, Month 18: 3.4 cm/year, Month 24: 3.1 cm/year, which demonstrate continuous growth and erroneous diagnosis of growth plate closure.

The medical reviewer agrees with the Applicant's assessment of erroneous diagnosis of growth plate closure, considering the location and limitations associated with bone morphology interpretation in achondroplasia, as well as evidence of age-appropriate growth rates following vosoritide discontinuation.

Conclusion

As expected, bone age was delayed at baseline in all subjects and improved with vosoritide. There were no clinically meaningful changes in bone age/chronological age ratio to suggest that vosoritide treatment advances bone age relative to chronological age.

There were initial concerns regarding accelerated changes in bone age based on the absolute difference between bone age and chronological age seen in Studies 111-202/205. The interpretation of these findings is complicated because of multiple study limitations, including small size of the study, absence of a control group, and relative heterogeneous baseline bone age Z-scores with outliers from -2.9 to +3.9. The reliability and validity of the Greulich and Pyle atlas in determining the bone age in children with achondroplasia who have various anatomic bone deformities is unknown; the atlas uses a pool of healthy children as reference. In addition, no acceleration of bone age was detected when data were re-analyzed using Z-score that is a better parameter than absolute difference for the evaluation of bone age changes over time.

Overall, the data do not suggest a concerning pattern of changes in bone age relative to chronological age. Therefore, the medical reviewer does not recommend including a description of a hypothetical risk of bone age acceleration in the labeling.

7.7.4. Use Errors and Use Difficulties Associated With Use of the Proposed User Interface

Issue

Errors and difficulties associated with administration of the drug using the to-be-marketed syringe were identified during the review of the results of Human Factor (HF) studies.

Background

Vosoritide injection product consists of vosoritide lyophilized powder, prefilled diluent syringes (0.5 mL, 0.6 mL or 0.7 mL), diluent syringe needles and administration syringes.

The Applicant conducted and included in the NDA the results from 2 HF validation studies to support the vosoritide user interface design.

Assessment

The Division of Medication Error Prevention and Analysis reviewed the results of the submitted studies (refer to the review in DARRTS from August 9, 2021). The reviewers concluded that the

results of the HF validation studies demonstrate that trained and untrained participants experience use errors and use difficulties with this product, indicating that the user interface is not optimized for safe and effective use.

For example, with respect to the syringe, participants had difficulty activating the needle guard, which led to a small underdose due to the syringe design. Additionally, there is a protrusion on the syringe plunger that activates the needle guard, and users measured their doses using that protrusion instead of the syringe plunger, which could lead to overdose. Refer to the HF validation study reports review for the other examples of use errors and use difficulties encountered with use of the proposed product. Furthermore, the reviewer also noted that in the HF validation study, trained participants experienced similar use errors as untrained participants. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) is concerned that use errors will occur with the introduction of this product to the market. At this time in the review cycle, changes to the labels and labeling alone are unlikely to meaningfully further reduce the residual risk associated with the observed use errors and use difficulties. Overall, to mitigate the identified risks, it would require changing the product design that may not be practicable at this point in time. The reviewer also indicated that this patient population may have the benefit of closer patient interaction with health care providers, so that they receive more training, skill verification, and more frequent monitoring; however, the Applicant has not developed specific training materials for validation to date.

Clinical Pharmacology reviewers concluded that the risk associated with underdose is not critical and most likely will not affect the efficacy of the product, since the dose response curve is flat. In Study 111-202, vosoritide exhibited similar efficacy in the dosing range of 11.7 to 30 µg/kg for 6 months. In a worst-case scenario of underdose (i.e., 15% dose loss) the range of the expected doses is as follows: (b) (4) Thus, the expected are still within the dose range of a flat exposure-response curve and 15% underdose is not expected to affect efficacy. The clinical reviewers agreed with Clinical Pharmacology reviewers and concluded that the risk of adverse events with overdose is also minimal. The doses of up to 30 µg/kg were used in Study 111-202/205 and no dose-dependent adverse events were identified to date with high doses.

DMEPA evaluation of the proposed packaging, label and labeling identified other areas of vulnerability that may lead to medication errors and should be addressed during this review cycle.

Conclusion

The current user interface is acceptable to support the safe and effective use of the product because the consequences of the user errors are of low clinical impact. Nevertheless, DMEPA recommends that the Applicant consider optimizing the user interface to avoid these use errors. If the Applicant changes the user interface then a new HF validation study would be useful to determine if the design changes were successful in reducing the use errors.. DMEPA provided additional recommendations to the Applicant that should be implemented prior to approval of the NDA (refer to the full list of recommendations in Table 5 of DMEPA review).

8. Therapeutic Individualization

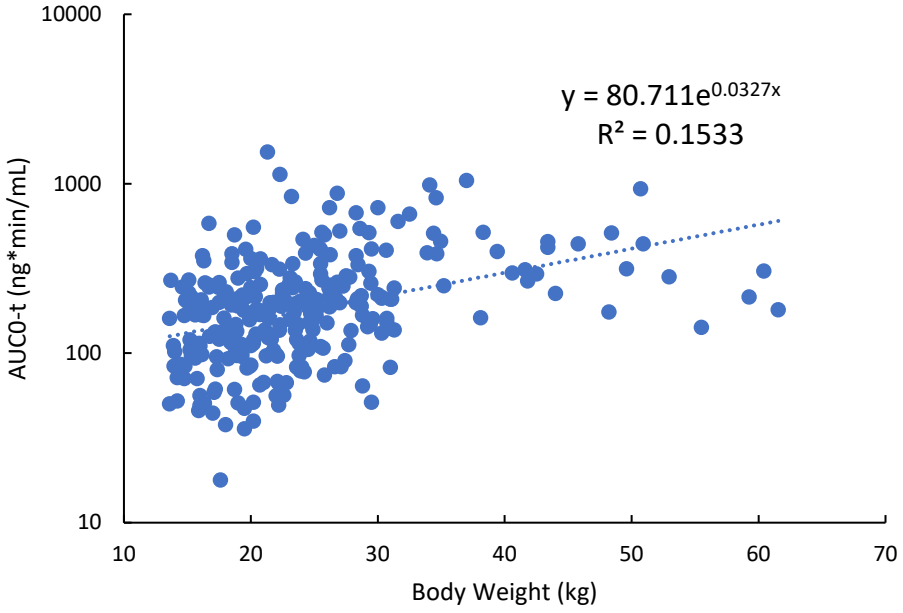
PopPK analyses were conducted by pooling data from 5 phase 2 and phase 3 Studies (111-202, 111-205, 111-301, 111-302, and 111-206). PopPK analyses show that body weight is a significant covariate for vosoritide apparent clearance (CL/F) and volume of distribution (Vd/F) and extrinsic factors such as injection solution concentration and treatment duration affected the relative bioavailability (F) of vosoritide. No other intrinsic or extrinsic factors were found to be predictive for CL/F, Vd/F, or F in popPK analyses.

8.1. Intrinsic Factors

Body Weight

PopPK analyses indicated that CL/F and Vd/F of vosoritide increases with increasing body weight in subjects with achondroplasia. A body weight-based dosing scheme is expected to generate a higher drug exposure (AUC and C_{max}) in patients with higher body weight. An increasing trend in AUC_{0-t} with increasing body weight was observed in subjects receiving 15 µg/kg QD dose in Study 111-301 (Figure 22).

Figure 22. The Correlation Between Individual Subject's AUC_{0-t} at 15 µg/kg and Body Weight, Study 111-301



Source: Clinical pharmacology reviewer's analysis.

(b) (4)

n October 22nd of 2021, in the Applicant's response to the Agency's

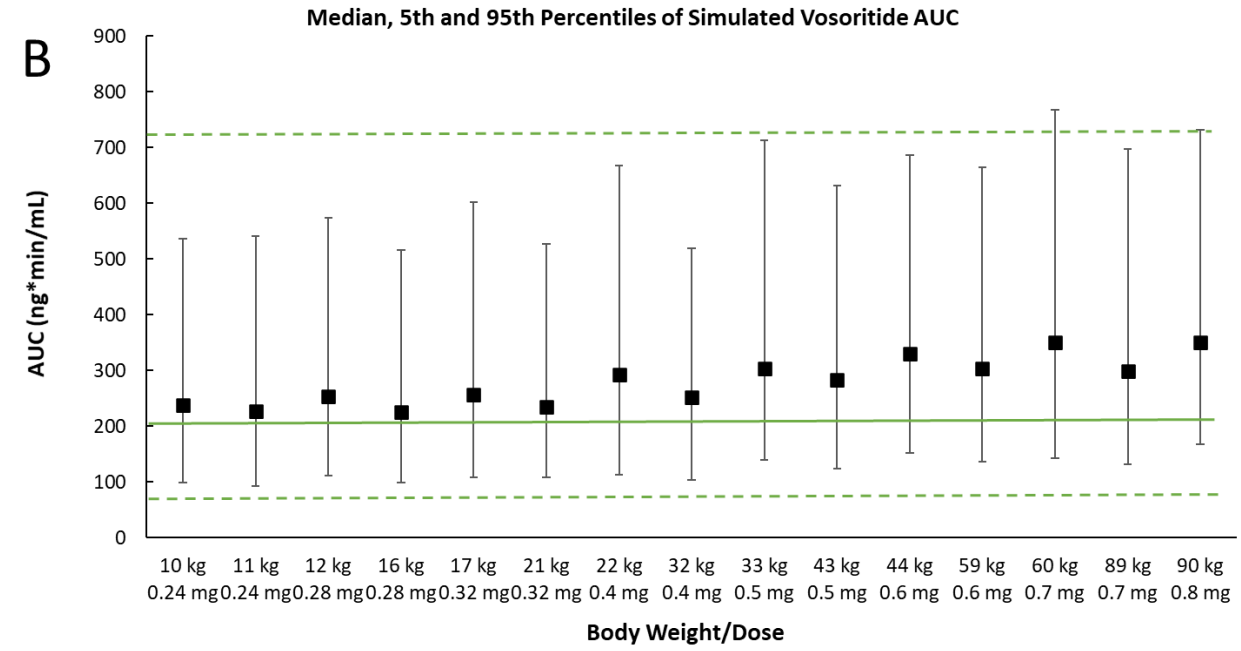
information request, the Applicant submitted an eight-weight-band dosing approach (b) (4) (0.24 mg for 10-12 kg subjects, 0.28 mg for 12-16 kg subjects, 0.32 mg for 17-21 kg subjects, 0.4 mg for 22-32 kg subjects, 0.5 mg for 33-43 kg subjects, 0.6 mg for 44-59 kg subjects, 0.7 mg for 60-89 kg subjects, and 0.8 mg for subjects weighing 90 kg or higher). (b) (4)

Compared with the 15 µg/kg dose used in Study 111-301, the eight-weight-band dosing would increase the dose in patients with body weight ≤26 kg while it would reduce the dose in patients with body weight approximately 27 kg and higher (with the exception of 33 kg where the dose is 15.2 µg/kg). (b) (4) the simulated median AUC values of vosoritide in different weight bands for the eight-band dosing regimen are more consistent with the median AUC at 15 µg/kg observed in Study 111-301 (Figure 23). With the eight-band dosing regimen, the simulated median AUCs in subject ≥ 22 kg are slightly higher than the median AUC observed in Study 111-301 (Figure 23B). However, this is within the observed variability in the study as shown by the lower 5th and upper 95th percentiles of simulated AUC values for the eight-band dosing regimen which are either within the range or slightly exceeding the upper 95th percentile of AUC observed in Study 111-301 (Figure 23B).

Similarly, (b) (4) the simulated median C_{max} values of vosoritide in subjects ≤ 59 kg for the proposed eight-band dosing regimen are more consistent with the median C_{max} at 15 µg/kg observed in Study 111-301 (Figure 24). A direct comparison between simulated and observed C_{max} values in subjects >59 kg is inappropriate because no subjects in vosoritide group in Study 111-301 had body weight >53 kg.At the worst-case scenario, in subjects with body weight of 10 kg receiving 0.24 mg QD vosoritide (24 µg/kg dose), the simulated C_{max} values are within the 5^{th} and 95^{th} values of observed C_{max} at 15 µg/kg in Study 111-301. On the other hand, the simulated median C_{max} of a subject with body weight of 89 kg or 90 kg is approximately 40% lower than the observed median C_{max} in Study 111-301. The lower C_{max} in subjects ≥89 kg are not expected to affect the efficacy of vosoritide because vosoritide showed flat exposure-response relationships for efficacy and safety in the dose range of 7.5 to 30 µg/kg QD in Study 111-202 and a 40% decrease in C_{max} from the observed median C_{max} at 15 µg/kg is unlikely to have a clinically meaningful impact on efficacy. Overall, the proposed eight-weight-band-based dosing regimen is acceptable.

Figure 23. Simulated Vosoritide AUC Values for [redacted] (b) (4) Eight-Weight-Band (B) Dosing Regimens as Compared to Observed AUC Values at 15 µg/kg, Study 111-301

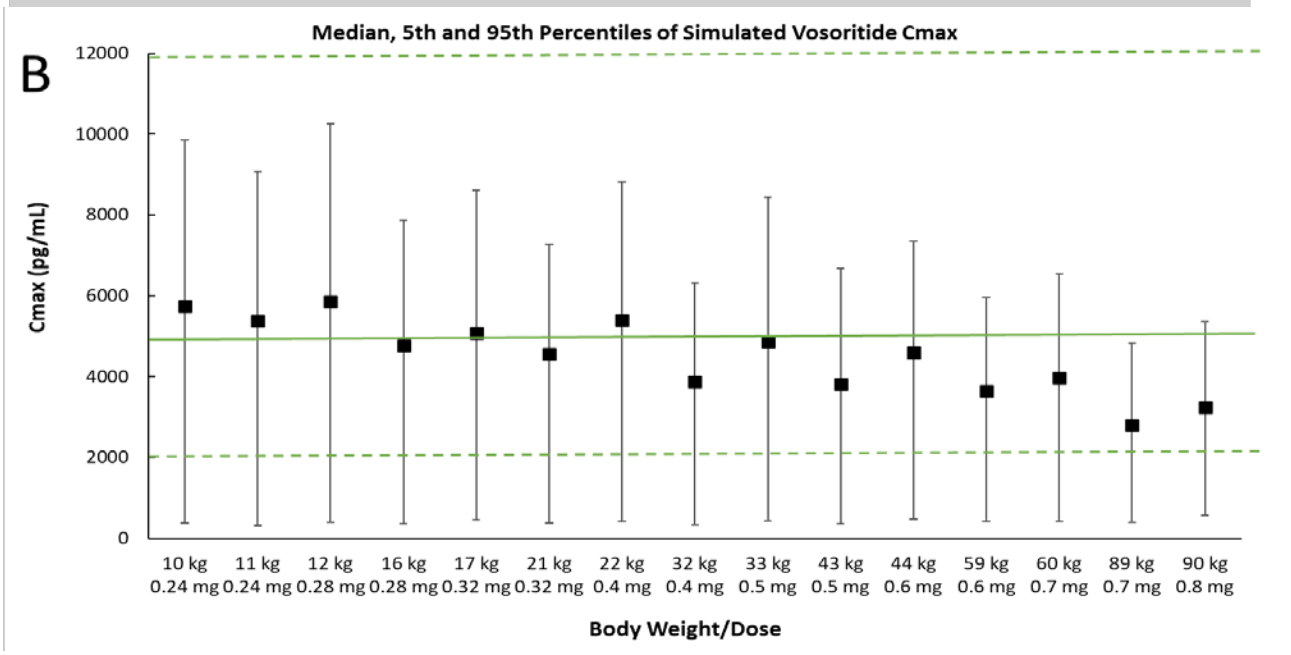
[redacted] (b) (4)



Source: Clinical pharmacology reviewer's analysis.
Note: Black squares represent the simulated median AUC for each weight, the upper and lower whiskers represent the simulated lower 5th and upper 95th percentiles of AUC. The green dashed lines and solid line represent the lower 5th and upper 95th percentiles, and median of observed AUC at 15 µg/kg in Study 111-301..
Abbreviations: AUC, area under the curve

Figure 24. Simulated Vosoritide C_{max} Values for (b) (4) and Eight-Weight-Band (B) Dosing Regimens as Compared to Observed C_{max} Values at 15 µg/kg, Study 111-301

(b) (4)



Source: Clinical pharmacology reviewer's analysis.
Note: Black squares represent the simulated median C_{max} for each weight, the upper and lower whiskers represent the simulated lower 5th and upper 95th percentiles C_{max}. The green dashed lines and solid line represent the lower 5th and upper 95th percentiles, and median of observed C_{max} at 15 µg/kg in Study 111-301.

Renal Impairment

No dedicated PK study was conducted in subjects with renal impairment. Subjects with moderate-to-severe renal impairment (serum creatinine >2 mg/dL) were excluded in clinical studies and 10 subjects with creatinine CL of 60 to 90 mL/min (mild renal impairment) were

enrolled in Study 111-301. The exposure of vosoritide did not increase in subjects with ACH with mild renal impairment. PopPK analysis showed that creatinine CL or eGFR was not a significant covariate for vosoritide CL/F or Vd/F. No dose adjustment is needed for patients with mild renal impairment. Due to lack of data in subjects with moderate-severe renal impairment, vosoritide is not recommended for use in patients with eGFR <60 mL/min/1.73 m^2.

Hepatic Impairment

Vosoritide is mainly eliminated by protease-mediated catabolism and natriuretic peptide receptor-C receptor mediated cellular uptake. Hepatic impairment is not expected to alter the PK of vosoritide. No dedicated PK study was conducted in subjects with hepatic impairment. Subjects with moderate-to-severe hepatic impairment were excluded from clinical studies. PopPK analysis showed that hepatic function (serum level of alanine aminotransferase, aspartate aminotransferase, or bilirubin) was not a significant covariate for vosoritide CL/F or V_d/F. No dose adjustment is needed for patients with any degree of hepatic impairment.

Age, Race, Sex

PopPK analysis indicated that age (2 to 18 years) and sex have no apparent impact on plasma exposure of vosoritide (see Appendix Section 14.3). In Study 111-301, the mean AUC_{0-t} of African American or black subjects (N=3) was approximately 50% higher than that of other races. However, a higher vosoritide exposure was not observed in African American or black subjects in Study 111-202 or Study 111-101. The final popPK data had PK data from 6 African American or black subjects only. The popPK analyses showed slightly lower CL/F in African American or black subjects than other races. The small sample size of African American or black subjects in popPK analysis precluded a meaningful conclusion.

Immunogenicity

In Study 111-301, the plasma exposure (AUC and C_{max}) of vosoritide was comparable between visits where there was detectable ADAs titer and where there was no detectable ADA titer, suggesting ADAs did not affect plasma exposure of vosoritide. PopPK analysis showed that ADA titer or neutralizing antibody (NAb) titer was not a significant covariate for vosoritide CL/F or relative bioavailability. No dose adjustment is needed for patients with positive ADA or NAb status. Refer to Sections 6.2.1.4.2 and 7.3 for the effects of immunogenicity on efficacy and safety.

8.2. Drug Interactions

8.2.1. Drug Interactions

No clinical drug interaction studies were conducted with vosoritide. In vitro microsome stability studies showed that cytochrome P450 (CYP) enzymes were not involved in the elimination of vosoritide. In vitro CYP inhibition and induction studies indicated that vosoritide did not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, nor induce CYP 1A2, 2B6, or 3A4/5 at clinically relevant concentrations. In vivo CYP mediated drug-drug interactions for vosoritide are unlikely. Transporter inhibition or induction studies were not conducted with vosoritide.

Considering the rapid hydrolysis of vosoritide (T1/2<30 min) and once daily dose regimen, vosoritide is unlikely to affect the PK of concomitantly used transporter substrates.

8.2.2. Duration of Treatment

The treatment duration appeared to have a positive effect on relative bioavailability. PopPK analyses showed that after receiving 15 µg/kg QD dosing for 2.3 years and 4.6 years, the relative bioavailability of vosoritide in subjects with ACH increased 1.52 and 2-fold, respectively. The mechanism causing the time effect on vosoritide relative bioavailability is not clear. No drug accumulation was observed in Study 111-101 following vosoritide 5 µg/kg QD dosing for 10 days, indicating the time effect was not due to drug accumulation. In the clinical studies, subjects with ACH received body weight-based doses of vosoritide. The total dose increased as subjects grew and gained weight over time. In the dose range of 7.5 to 30 µg/kg, vosoritide shows greater than dose proportional PK. For example, the mean single-dose AUC increased 21-fold when the dose increased from 7.5 µg/kg to 30 µg/kg. The increasing body weight of subjects with ACH and nonlinear PK may partially explain the effect of long-term treatment on the relative bioavailability of vosoritide. In the proposed new weight-band-based dosing regimen, patients with a higher body weight receive a lower weight-based dose (µg/kg), which can reduce the treatment duration effect on vosoritide. No further dose adjustment is needed for long-term treatment.

8.2.3. Solution Concentration

Injection solutions at 3 concentrations (0.2, 0.8, and 2.0 mg/mL) were used in Study 111-202. The 0.2 mg/mL solution was only used for 2.5 and 7.5 µg/kg dose groups in Study 111-202. PopPK analyses showed the relative bioavailability of 0.2 mg/mL vosoritide solution was 56% higher than that of 0.8 mg/mL or 2 mg/mL vosoritide solutions. The plasma concentrations of vosoritide in subjects receiving 2.5 µg/kg were generally below the limit of quantitation. The PK data of 0.2 mg/mL vosoritide solution was mainly derived from 8 subjects receiving 7.5 µg/kg in Study 111-202. Among the 8 subjects, subject (b) (6) (outlier) had a >50-fold higher exposure than other subjects at Day 29 visit. The large variability and small sample size of the PK data of 0.2 mg/mL vosoritide solution led to uncertainties in the 56% higher relative bioavailability predicted by popPK analyses. In addition, the 0.2 mg/mL solution was not used in Study 111-301 and will not be available commercially. In clinical use, vosoritide lyophilized powder will be reconstituted into 0.8 mg/mL and 2.0 mg/mL solution before SC administration. No vosoritide concentration-dependent dose adjustment is needed.

8.3. Plans for Pediatric Drug Development

To support use in pediatric patients, studies were conducted in juvenile rats and juvenile/adolescent NHP's to assess BMN-111's pharmacologic and toxicologic effects on skeletal tissues. In these nonclinical studies, radiologic, histomorphometric, gross, and/or microscopic observations of various bones and alterations in the levels of biomarkers of bone turnover were consistent with bone growth. Observed effects included (but were not limited to) increased thickness of the proliferative and hypertrophic/calcified zones of physeal cartilage, physeal persistence, increased thickness in the primary spongiosa, disorganization of the columnar arrangement in the proliferative and in hypertrophic/calcified zones of chondrocytes, etc. The proliferative effects correlated with increases in bone length (humerus, femur, tibia and

lumbar spine). Decreases in BMC/BMD, associated with decreases in cancellous bone, and reductions in bone strength parameters (femur 3-point bending, femoral neck shear, and L4 vertebral compression), were evident in the rat but not in the NHP; these effects were considered to reflect the ongoing bone growth related to the pharmacology of BMN-111 in growing animals. The effects on skeletal tissues were generally dose-dependent (in incidence and severity) and many were reversible. However, the excessive growth of skeletal tissues in these normal animals was associated with macroscopic and microscopic alterations that correlated with limited use of hindlimbs, valgus, kinks in the tail/hunched posture, and other signs observed clinically. The excessive bone growth occurring in 'normal' animals resulted in adverse clinical signs that formed the basis for identifying the NOAEL of 10 µg/kg in juvenile rats (<0.1x the MRHD based on AUC; 0.2x the MRHD based on BSA) and 90 µg/kg in juvenile/adolescent NHPs (2x the MRHD based on AUC; 3x the MRHD based on BSA). As the effects on bone growth are the desired pharmacologic outcome, the effects observed in these studies are not considered to be suggestive of a safety concern for the indicated population.

Subsequently, the Applicant relied upon clinical information from 2 clinical studies discussed elsewhere in this review to support the proposed indication. Consultants from DPMH agree that products indicated for increased linear growth in patients with achondroplasia with open epiphyses would provide a public health benefit. DPMH labeling recommendations are incorporated into labeling. Specifically, section 8.4 of labeling describes the basis of approval, specifically, a summary of the clinical studies performed in the affected population.

8.4. Pregnancy and Lactation

Review of Nonclinical Data

The reproductive and developmental toxicity of BMN-111 was evaluated in fertility, embryofetal development, and pre- and post-natal toxicity studies (Refer to Section 13.1.3.4 for details). Effects on reproductive endpoints were also evaluated as a component of repeat-dose toxicity studies.

In a rat fertility study, slight non-dose-related decreases in testicular spermatid count/density (within historical range) and slight increases in the time to mating were observed, but there were no effects on epididymal sperm count/density or motility or on the ability of males to impregnate females. There was no effect of drug treatment on female estrous cyclicity, fertility, or ability to maintain a pregnancy at the highest dosage tested. As there was no overall effect on fertility, the NOAEL was considered the highest dose administered to each sex. The effects on male rats were consistent, but not identical, with decreases in sperm count (~30%) observed in the 26-week adult rat study at doses ≥150 µg/kg (4.7x the exposure at the MRHD, 2.4x based on BSA). Lower fertility rates (but within historical range) were also observed at the highest dose administered in the 26-week juvenile rat study, but these effects were inter-related with significant clinical signs affecting movement associated with exaggerated pharmacologic bone growth.

Potential effects of BMN-111 on embryofetal development were evaluated in both the rat and rabbit. There were no effects on maternal animals or on embryofetal development in either species and the NOAEL was the highest dose administered in each study. Similarly, in the pre- and postnatal toxicity study, there were no effects on parental females or on offspring survival,

growth and development, learning and memory, or reproductive capability, leading to identification of the high dose as the NOAEL.

Data supporting the labeling statements are summarized in Table 35 while the safety multiples are summarized in Table 36.

Table 35. Nonclinical Data Supporting Labelling for Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	No adverse effects on maternal animals or on embryofetal development in rats or rabbits at the highest dosages evaluated (540 and 240 µg/kg, respectively).
8.2 Lactation	No effects on parturition or offspring survival, growth, and development at the highest dosage evaluated (540 µg/kg). BMN-111 was detected in maternal milk.
8.3 Females and Males of Reproductive Potential	No effects were observed that warrant precautionary statements in the label.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	There were no effects on fertility parameters.

Source: Reviewer generated table
Abbreviations: BMN-111, vosoritide

Table 36. Reproductive Toxicology Safety Margins

		NOAEL			Safety Multiples[a]	
Study	Basis for NOAEL	µg/kg	µg/m^2	Exposure (AUC_{0-t}) pg·min/mL	Exposure (AUC)-Based	BSA (mg/m^2) Based
Clinical exposure						
301	-	15	375[b]	290000	-	-
Reproductive and developmental toxicity						
Fertility rat	Highest dose administered	540	3240	M: 4250000 F: 3000000	14.6x 10.3x	8.6x 8.6x
EFD rat	Highest dose administered	540	3240	3950000	13.6x	8.6x
PPND rat	Highest dose administered	540	3240	3950000[c]	13.6x	8.6x
EFD rabbit	Highest dose administered	240	2880	57967000	200x	7.7x

Source: Reviewer generated table:
[a] BSA margins were also included given the short half-life of the drug
[b] Based on a 20-kg child; km =20
[c] TK profiles not established. Data are from EFD rat study at the same dose
Abbreviations: AUC, area under the curve; BSA, body surface area; EFD, embryo-fetal development; NOAEL, no-observed-adverse-effect level; PPND, prenatal and postnatal development; TK, toxicokinetic

Proposed labeling text is addressed separately from this review.

Review of Human Data

Pregnancy

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

The incidence of achondroplasia is about 1 in every 25,000 to 30,000 people, which represents about 13,178 people in the United States (calculated from U.S. Census 2019 which estimates the U.S. population to be 329.45 million). Vosoritide is not recommended to be used in patients whose epiphyses are closed. Since complete bone fusion happens on average between ages 12 and 18 for girls, vosoritide use during pregnancy is likely to be rare. For these reasons, a postmarking pregnancy safety study is unlikely to be feasible; therefore, DPMH does not currently recommend a postmarketing pregnancy safety study.

Lactation

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

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

Females and Males of Reproductive Potential

There are no known clinical data indicative of an effect on fertility. There is no known drug-drug interaction between vosoritide and hormonal birth control. DPMH recommends omitting subsection 8.3.

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) Review team has assessed NDA 214938 with respect to Chemistry, Manufacturing, and Controls (CMC) 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 NDA from a quality perspective.

The drug substance, vosoritide, is a 39 amino acid peptide. It contains 1 disulfide bridge between cysteines (Cys23 and Cys39), which forms a 17 membered cyclic peptide ring. (b) (4) Based on stability data, a retest period of (b) (4) month is granted for (b) (4) when stored (b) (4)

The drug product, Voxzogo (vosoritide) for injection, is a single-dose, sterile, white to yellow, lyophilized powder provided as 0.4 mg/vial, 0.56 mg/vial, and 1.2 mg/vial in a 2mL glass vial sealed with rubber stopper. The drug product in single-dose vial is co-packaged with a prefilled diluent syringe, a diluent needle, and a dose administration syringe. Prior to use, the drug product is reconstituted with sterile water for injection provided in a diluent syringe. The reconstituted product is intended for subcutaneous administration using a dose administration syringe.

Based on stability data, an expiration period of 24 months for the drug product when stored at 2°C to 8°C (36°F to 46°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 a room temperature of 20°C to 25°C (68°F to 77°F) for a maximum of 3 hours.

9.1. Device or Combination Product Considerations

The proposed product is a co-packaged combination product (see above). Center for Device and Radiological Health (CDRH) reviewed the device constituent parts of this co-packaged combination product. The CDRH final recommendation for the device constituent parts of this co-packaged combination product is approvable (refer to CDRH consult from 1/8/2021).

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

The inspection for this NDA consisted of 4 domestic sites representing 10 clinical study sites in addition to the Applicant. Based on the inspections of the 4 clinical sites and the Applicant, the Office of Scientific Investigation (OSI) concluded that the inspectional findings support validity of data as reported by the Applicant under this NDA.

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

Refer to Section 20.1. Clinical Sites Inspection Summary and Section 23. Financial Disclosure.

11. Advisory Committee Summary

Joint public advisory committee meeting of the PAC and EMDAC was held on July 30, 2018, to discuss therapeutic goals for the ACH community and the appropriate elements of the clinical development program for vosoritide (during closed session) and for other drugs seeking indication for the treatment of achondroplasia (during the open session).

Briefly, the Advisory Committee members agreed that the AGV can be used as a primary endpoint; however, final height is a key goal of treatment in the intended population. In addition, improvement in disease complications should be evaluated as key secondary endpoints.

All Committee members agreed that a randomized, placebo-controlled study design is optimal to provide statistically and clinically significant efficacy data and sufficient safety data in the intended population to support the drug's approval. The Committee noted that if placebo cannot be used in the planned study(s) due to the small number of potential participants and potential unwillingness of patients and/or caregivers to take the 'risk' of being randomized to the placebo treatment arm, another option is to use historical control data as a comparator. In addition, Committee members stated that a trial length of at least 2 years is most appropriate for evaluation

of primary efficacy endpoint of change in growth velocity, since shorter trials may miss growth velocity attenuation over a relatively short time frame should it occur.

The above AC recommendations were communicated to the Applicant by the Agency on July 30, 2018. Refer to Regulatory History in Appendix (Section 12).

A second AC meeting was not convened during this marketing application review cycle because the previous AC meeting adequately addressed the important elements of the clinical development program.

III. Appendices

12. Summary of Regulatory History

- Pre-investigational new drug (IND) meetings on May 13, 2011, (written response only [WRO] and October 6, 2011 (tele-conference (T-con)): The FDA provided overall recommendations on clinical and nonclinical development program of vosoritide for treatment of children with achondroplasia (ACH), including selection of appropriate endpoints (e.g., growth parameters, bone-related complications, final adult height), age of enrolled subjects, and duration of phase 1/2 studies, among others.
- IND 111299 for vosoritide (BMN-111) was submitted on November 30, 2011, for a phase 1, first in human, single- and multiple-dose study in healthy adult volunteers (Study 111-101). The Applicant was allowed to proceed with this study.
- Orphan drug designation for vosoritide was granted on January 17, 2013, for the treatment of ACH.
- The IND was placed on partial clinical hold (PCH) on June 4, 2013, for clinical trials in pediatric subjects with doses that exceeded an exposure greater than 554,000 pg.min/mL (corresponding to the highest single dose of 15 µg/kg used in adults) and treatment duration longer than 10 days.
  - (b) (4) FDA requested the Applicant conduct a phase 1 trial in children with ACH to characterize safety and pharmacokinetics (PK) of the drug.
  - In response to the PCH, the Applicant withdrew protocol 111-201 and submitted a new protocol 111-202 titled, "A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN-111 in Children with Achondroplasia," that incorporated FDA's recommendations. The PCH was removed on November 27, 2013.
- On November 9, 2015, BioMarin submitted a new protocol for Study 111-205 entitled, "A Phase 2, Open-Label, Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of BMN-111 in Children with Achondroplasia (who completed Study 111-202)."
- On February 29, 2016, the Office of Pharmaceutical Quality (OPQ) provided recommendations regarding the proposed drug substance and drug product specifications and test methods for BMN-111.
- Fast Track designation for vosoritide for the treatment of ACH was submitted on November 8, 2016. FDA denied the Fast Track designation on January 3, 2017, because the clinical data generated to date did not demonstrate that BMN-111 had the potential to address an important unmet need in this condition. FDA concluded the data collected to date did not clearly establish that the growth was purely attributable to the effect of the drug itself and that the observed small changes will result in the improvement in final height or the functional or psychological well-being of these patients.
- Type C meeting, January 26, 2017: This meeting was requested by the Applicant as an end-of-phase 2 (EOP2) meeting. However, FDA reviewed the data submitted in the

meeting package and concluded that they were insufficient to grant the EOP2 meeting. Of note, the Applicant previously requested EOP2 meetings on September 16, 2015, and December 9, 2015. These meetings were denied because the submitted data were inconclusive regarding the magnitude and persistence of growth and because the phase 2 Study 111-202 was ongoing at the time.

- The overall development plan for BMN-111 was discussed during a Type C meeting. FDA also provided general recommendations regarding phase 3 study entitled, "Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN-111 in Children with Achondroplasia (111-301)," that was included in the submission. Overall, FDA agreed that a randomized, double-blind, placebo-controlled phase 3 study design in children ages 5 and older was acceptable. However, FDA continued to express concern that short-term annualized growth velocity (AGV) might be insufficient to establish a clinical benefit without additional long-term data evaluating the effect of treatment on final height or improvement in comorbidities. FDA recommend conducting a longer study of at least a 2-year duration. (b) (4)
- FDA recommended conducting at least 2 randomized, placebo-controlled studies to establish the efficacy and safety of the drug in the different age groups (infants and toddlers and older patients). The Applicant agreed with FDA recommendations and indicated the intent to initiate a new Study 111-206 in infants and toddlers (b) (4)
- FDA also commented on the ongoing observational natural history (NH) study (Study 111-901) that was included in the package. Of note, the protocol for this study has 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 Applicant develop and submit for review a new dedicated historical study protocol with the primary objective to obtain valid, contemporary, retrospective, and prospective information on growth (including final height).

- On May 5, 2017, the Applicant submitted the revised protocol for Study 111-301.The Applicant included the clinical outcome assessment tools (that measured quality of life (QoL) and activities of daily living). However, no changes were made to the proposed primary endpoint (AGV) or duration of the pivotal study. The Applicant indicated that the 2-year duration of the study will impact its feasibility.
- On March 5, 2018, FDA provided further comments on the clinical outcome assessment (COA) tools proposed in Study 111-301.
  - Based on the data submitted, FDA concluded that the proposed assessment was not fit for purpose in the context of the drug development program; however, it may provide some insight into clinical benefit.
- On June 7, 2017, the Office of Pharmaceutical Quality provided further recommendations on the proposed commercial packaging presentation and the adequacy of the proposed drug substance and drug product process performance qualification plans.

- On March 7, 2018, the Applicant submitted 3 new clinical protocols and an overall update to the clinical development program for BMN-111.
  - The clinical development program updates included the Applicant's plan for the new national history registries (Kaiser's Study, 111-501 European cross-sectional and retrospective study, and prospective/retrospective study at Johns Hopkins University), among others. The new protocols included:
    - Study 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"
    - Study 111-302, entitled, "A Phase 3, Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of BMN-111 in Children with Achondroplasia"
    - Ongoing Study 111-901, entitled, "A multicenter, Multinational Clinical Assessments Study for Pediatric Patients with Achondroplasia"
- 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 appropriate drug development programs for 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 agreed that the primary endpoint can be growth velocity. However, they indicated that an improvement in the final height remains the ultimate goal of the treatment. The improvement in compilations should be evaluated as secondary endpoints.
  - The AC members agreed that for drug approval, a randomized, placebo-controlled study design is optimal to provide efficacy and safety data in the intended population. The AC members also noted that if the use of placebo is not feasible, the other option would be to use historical control data as a comparator. However, the committee also concluded that the existing natural history data to date are not sufficient for use as a reliable comparator.
  - The AC members recommended including as many young patients as possible in the development program but to do so after efficacy and safety profile of the drug was characterized in older children.
  - The AC members also indicated that the study should be at least 2 years in duration.
- The AC recommendations and the overall development program based on AC recommendations were further discussed between the Applicant and FDA on July 30, 2018 (Advice/Information Request letter), and October 17, 2018 (T-con).
  - FDA recommended conducting at least 2 randomized, placebo-controlled trials in 2 different age groups.
  - FDA also concluded that without validated prediction model that may help extrapolate final height from short-term height changes, the study should be at least of a 2-year duration and should include at least a subset of children followed prospectively to final height. In addition, FDA recommended including evaluations of other clinically meaningful endpoints, including effects of the drug on complications.

  - The Applicant agreed with a majority of FDA's recommendations and indicated that they plan to have at least 30 subjects from a phase 2 study with final height data at the planned time of new drug application (NDA) submission. The Applicant also agreed to amend protocols for Studies 111-301 and 111-206 to include evaluation of the impact of treatment on important complications as secondary endpoints. However, the Applicant reiterated that a 2-year study has significant challenges with enrolling and retaining of subjects.
  - 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, and on January 23, 2020).

- Type C meeting on December 6, 2018 (written response only)
  - FDA agreed with the Applicant's plan to request a waiver for conducting a thorough QT (TQT) study.
  - FDA indicated that (b) (4) the available data from Studies 111-202 and 111-101 and the adequately planned concertation-QT analysis in Study 111-301 may potentially serve as an alternative to the TQT study".

- On January 9, 2019, BioMarin submitted the new protocol for Study 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 Study 111-206) to evaluate long-term safety and efficacy of BMN-111 until subjects reach near-final adult height.
- On May 31, 2019, FDA provided further chemistry, manufacturing, and controls (CMC) recommendations addressing specific drug development elements to be included in a marketing application.
- On October 25, 2019, the Applicant submitted a human factor (HF) validation study protocol for FDA review. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the submitted protocol and provided further recommendations on December 21, 2019.
- On January 21, 2020, FDA notified the Applicant that no additional nonclinical studies were required to define the carcinogenic risk related to vosoritide treatment. The Executive Carcinogenicity Assessment Committee was consulted and concurred that the approval of a carcinogenicity waiver was warranted for vosoritide (refer to Dr. Minck's review in DARRTS from January 13, 2020).
- The pre-NDA meeting between BioMarin and FDA took place on March 4, 2020.
  - The content and structure of the proposed NDA was discussed during the meeting.
  - However, FDA noted that the vosoritide clinical development plan that included a 1-year pivotal study was not in agreement with previous FDA recommendations to conduct 2 randomized, placebo-controlled studies in 2 different age groups.
  - FDA also indicated that the proposed use of retrospective natural history database for the comparison may be acceptable provided the data were properly collected, analyzed, and matched to study subjects' characteristics.

  - [redacted] (b) (4) FDA reiterated the importance in bridging of the improvement in short-term linear height to final adult height. [redacted] (b) (4) planned to collect FAH in the postmarketing settings. Lastly, there were no agreements for late submission of application components within 30 days after submission of the original application; therefore, the application was expected to be complete at the time of submission.

- On April 27, 2020, OPQ issued written responses to a February 12, 2020, pre-NDA meeting request to discuss the overall CMC data to be provided in the NDA.
- BioMarin submitted NDA 214938 for vosoritide (BMN-111) on August 20, 2020.
- Priority review status was granted for NDA 214938 on January 25, 2021, based on the proposed indication (serious disease) and absence of alternative treatment for the proposed indication. However, the review timeline was not changed because the review designation was assigned after the time of filing.

13. Pharmacology Toxicology: Additional Information and Assessment

Vosoritide (identified as BMN111 in all nonclinical study summaries) has been characterized in a series of nonclinical pharmacology, pharmacokinetic, and toxicology studies. In vitro studies were conducted to demonstrate target binding, receptor affinity, cross-species activity, and pharmacologic activity. Multiple in vivo studies were performed to evaluate pharmacologic activity in both normal animals (rodents and nonhuman primates [NHPs]) and in achondroplastic mutant strains of animals (rodents). Receptor-binding activity was evaluated in a secondary pharmacology study while central nervous system (CNS), respiratory, and cardiovascular safety pharmacology studies were evaluated in cell lines and/or various nonclinical test species.

The absorption, distribution, metabolism, excretion (ADME) profile was primarily characterized as a component of the repeat-dose toxicity studies. Additionally, a series of single-dose studies was also performed in rats at various ages, in achondroplastic and wild-type mice, and by various routes of administration.

The toxicology program for BMN111 was primarily conducted in rats and NHPs. Both species have high amino acid sequence homology with human C-type natriuretic peptide (CNP) and the natriuretic peptide receptors (NPRs), thereby supporting use of these species. The NHP was selected as the nonrodent model based on similarities in foramen magnum placement and weight-bearing hind limbs as in humans and cardiovascular effect predictability relative to humans. Toxicity was evaluated in single-dose studies in both species, in repeat-dose studies of up to 26-weeks (rat) or 44-weeks (NHP) duration in juvenile and/or adolescent/adult animals, and in reproductive and developmental toxicity studies in rats and/or rabbits. Genotoxicity and carcinogenicity studies were not warranted for this compound. The subcutaneous (SC) route of administration was used for all studies, though intravenous (IV) dosing was included in the single-dose studies to support the determination of bioavailability.

Normal animals were used in these studies. As a result of the pharmacologic activity, exaggerated bone growth was a common observation that resulted in clinical signs of gait disturbances, postural changes, etc., that in some cases were dose-limiting. Dose and safety multiples at the no observed adverse effect levels (NOAELs) for the pivotal nonclinical, repeat-dose toxicity studies are summarized in Table 37:

Table 37. Repeat-Dose Toxicity Study Safety Margins

		NOAEL			Safety Multiples[b]	
Study	**Basis for NOAEL[a]**	**µg/kg**	**µg/m²**	**Exposure (AUC_{0-t}) pg·min/mL**	**Exposure (AUC) based**	**BSA (mg/m²) based**
Clinical exposure						
Study 301	-	15	375[c]	290000	-	-
Repeat dose toxicity - rat						
28 day (adult)	Swollen hind-paws/joints limiting hindlimb use resulting from bone overgrowth at 500 µg/kg	150	900	2230417	7.7x	2.4x
26 week (adult)	Altered ambulation and valgus resulting from excessive bone overgrowth (e.g., abnormal shape of the stifle, carpal joints, long bones, and vertebrae, increased bone growth plate thickness and/or growth plate dysplasia, etc.) at ≥150 µg/kg	50	300	614401	2.1x	0.8x
26 week (juvenile)	Effects on the hindlimbs affecting ambulation, motor activity, and maze solving times, microscopic and histomorphometric alterations at growth plates, degenerative changes at the joints, etc., resulting from bone overgrowth ≥30 µg/kg	10	60	M: 22842 F: 10133 16488 (mean)	0.08x 0.03x 0.06x	0.2x 0.2x 0.2x
Repeat dose toxicity - NHP						
28 day (adolescent)	Highest dose evaluated	300	3600	11143786	38x	9.6x
26 week (adolescent)	Limited use of hips and/or decreased range of motion of the hind legs associated with abnormal shape of femur secondary to bone overgrowth at 300 µg/kg	90	1080	489884	1.7x	2.9x
44 week (adult)	Limited hindlimb use secondary to pharmacologic effects on growth plate thickness, bone length, chondrocyte proliferation, etc., at ≥75 µg/kg	25	300	57960[d]	0.2x	0.8x

Source: Reviewer generated table:
[a] Refer to Section 13.1.3 for details of study observations
[b] BSA margins were also included given the short half-life of the drug
[c] Based on a 20 kg child
[d] Based on Week 4 data as levels were only detected in a single animal at later timepoints
Abbreviations: AUC, area under the curve; BSA, body surface area; NHP, nonhuman primate; NOAEL, no-observed-adverse-effect level

Summaries of key nonclinical studies supporting the NDA are provided in Section 13.1. For those few studies that were submitted with the NDA, but not to the IND, detailed reviews are in Section 13.2.

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Pharmacology and Safety Pharmacology

In vitro pharmacology studies demonstrated that BMN-111 preferentially binds to NPR-B (3.5nM) over NPR-A and NPR-C, has similar potency to native CNP in murine fibroblast cells, activates human NPR-B receptors in human chondrocytes, and attenuates FGF-mediated increases in mitogen-activated protein kinase (MAPK) phosphorylation. Increases in cultured bone lengths and expansion of the growth plates were noted in tissues from achondroplastic mutant mice.

In vivo pharmacology studies were performed in normal mice, rats, and NHPs. The lengths of the body, tail, or various bones were increased by up to 15%, 7%, and 19% (depending on the bone) in mice, rats, and NHPs, respectively. In general, the growth effects were proportional for the bones evaluated, and effects on both the magnitude and number of structures were dependent on dose and treatment duration. Microscopic examination revealed alterations to regions involved in longitudinal growth (e.g., the physis [growth plate], trabecular bone [primary spongiosa], and metaphysis of the femur) and included increased thickness of the proliferative and hypertrophic/calcified zones (increases in growth plate width), and/or the number and size of chondrocytes. Exaggerated pharmacology (bone overgrowth) was also noted in all species which resulted in mobility issues and adverse clinical signs, particularly in rodents. Pharmacologic activity was also evaluated in 2 fibroblast growth factor receptor 3 (FGFR3) achondroplastic mutant mouse strains ($FGFR3^{G380R}$ and $FGFR3^{Y367C/+}$). In both strains, treatment with BMN-111 resulted in a more phenotypically 'normal' appearance compared to the appearance of untreated mutant animals.

Safety pharmacology studies evaluating effects on the CNS, cardiovascular, and respiratory systems were performed. In separate good laboratory practice (GLP)-compliant CNS and respiratory safety pharmacology studies, rats were administered single doses of 30, 100, or 300 µg/kg of BMN-111 by SC injection. No effects were noted on nervous or respiratory system functioning at the doses evaluated.

Multiple cardiovascular safety pharmacology studies were performed since CNP is found in vascular endothelium and the heart where it is expected to induce smooth muscle relaxation. These studies are summarized below:

- In a GLP-compliant hERG assay conducted in HEK293 cells, the half maximal inhibitory concentration (IC_{50}) was >50 µg/mL, more than 8600-fold the human exposure at the maximum recommended human dose (MRHD).
- In a non-GLP study in wild-type Friend Virus B (FVB) mice, SC doses of 20, 70, 200, 2000 nmol/kg (88, 280, 800, 8000 µg/kg) were administered. Dosages <280 µg/kg (approximately 12x the clinical maximum plasma concentration (C_{max}) at the MRHD, based on data from juvenile animals) were associated with minimal decreases in blood

pressure and increases in heart rate. At dosages >800 µg/kg (approximately 20x the clinical C_{max} at the MRHD, extrapolated from 600 µg/kg in a single-dose study), blood pressure was reduced by >17% and heart rate was increase by up to ~11%.

- In non-GLP studies in telemeterized NHPs (anesthetized or conscious), BMN-111 was administered SC as single or multiple doses. In anesthetized animals, decreases in heart rate with associated increases in pressure were observed in animals at dosages >7 µg/kg. Decreases of up to 41% in mean arterial pressure were seen that peaked within 20 to 60 mins postdosing followed by recovery by 90 mins postdosing at 70 µg/kg. The decreases in blood pressure were associated with increases in heart rate by up to 50%. The observed effects on both blood pressure and heart rate increased with dose. Following repeated dosing, the magnitude of effects were progressively less. There were no effects on electrocardiogram (ECG) waveforms. In conscious animals, dosages up to 70 µg/kg were also associated with decreased pressure (reduced up to 15%) and increased heart rates (up to 40%). These effects generally peaked within 30 mins and declined thereafter, with the magnitude of effects decreasing with subsequent dose administration.
- In a GLP study in telemeterized NHPs, BMN-111 was administered SC at doses of 10, 50, or 200 µg/kg (administered 3 days apart) or multiple doses (7 days) of 200 µg/kg. At a dose of 50 µg/kg (equivalent to the clinical C_{max} at the MRHD, extrapolated from data at 60 µg/kg in a single-dose study), decreases in systolic (-16%) and diastolic (-7%) pressure were noted with a compensatory 37% increase in heart rate. At 200 µg/kg (approximately 11x the clinical C_{max} at the MRHD, extrapolated from data at 250 µg/kg in the 44-week study), mean systolic, diastolic, and arterial pulse blood pressures was reduced by 16%, 9%, 12%, respectively (across all timepoints), with compensatory increases of up to 49% in heart rate. Associated with the increased heart rates at these doses were dose- and time-dependent shortening of the PR (maximum -15%), QT (maximum -23%), and heart rate-corrected QT (QTcB) (maximum -8%) intervals, although QRS duration was not affected. These effects peaked within 2 hours before normalizing. Upon repeated dosing, the magnitude of blood pressure effects, but not heart rate, appeared to attenuate.

A secondary pharmacology study evaluating potential off-target effects revealed that BMN-111 inhibits 8 receptors/channels by more than 50%, summarized in Table 38:

Table 38. Receptors/Channels Inhibited More Than 50% by BMN-111

Receptor/Channel	Species	Inhibition (%)[a]	IC_{50} (µM)
APJ (apelin receptor)	Human	78	3.15
Potassium Channel (SK_{CA})	Rat	85	2.1
Somatostatin sst3	Human	53	10.2
NPR-A[b]	Guinea Pig	70	4.39
Neuromedin U NMU_2	Human	60	6.56
Progesterone PR-B	Human	50	11.4
NPBW2/*GPR8*	Human	54	9.84
Calcium Channel N-Type	Rat	60	7.53

[a] Values for 11.44 µM vosoritide reported from IC_{50} experiment.

[b] NPR-A is the receptor for the Atrial Natriuretic Factor (old nomenclature).

Source: Applicant table (Table 2.6.2.3.1.1 (page 71) from Pharmacology Written Summary; based on data from report BMN-111-11-026)
Abbreviations: BMN-111; vosoritide

The IC_{50} values ranged from 2.1 µM to 11.4 µM (~8 to 46 µg/mL), well in excess of the C_{max} of 5800 pg/mL at the MRHD.

13.1.2. Pharmacokinetics / ADME

The nonclinical pharmacokinetic profile of BMN-111 was determined as part of the repeat-dose and reproductive toxicology studies. Summary information is provided in Section 13.1.2. More detailed exposure data are provided with the individual toxicology study reports summarized in Section 13.1.3.

Absorption

Following the SC administration of BMN-111 across nonclinical species, t_{max} was typically reached by 15 to 30 mins. The $t_{1/2}$ was short (<30 mins) and bioavailability was in the range of 1% to 11%. Exposure increased with dose in a proportional to greater than proportional manner in both sexes. In mice, exposures tended to be higher in females than in males at the lower range of doses evaluated but were higher in males at the higher doses evaluated. There were no meaningful differences in exposure between $FGFR3^{ACH}$ and wild-type FVB mice. In rats, exposure was comparable between the sexes at low doses but was up to 2-fold higher in males as the doses were increased. Exposures did not differ dramatically in rats of different ages following a single dose. In the NHP, exposures were comparable between the sexes at the lower dosages evaluated while at higher dosages the exposure in females was up to 2-fold higher than in males following a single dose. In both the rat and the NHP, exposures were generally higher in males than in females upon repeated dosing. Based on single-dose studies in rats and NHPs in which SC and IV doses were administered, the SC bioavailability ranged from 5% to 7% in rats and 1% to 11% in NHPs, with bioavailability increasing with dose in both species. Accumulation ratios of up to 9-fold and 4-fold were observed in rodents and NHPs, respectively, following repeated dosing. However, the increased exposure following multiple dose administrations is unlikely due to accumulation as BMN-111 has a relatively short $t_{1/2}$ compared to the dosing interval. Furthermore, predose levels on the subsequent days of dosing were below the limit of quantitation (BLQ).

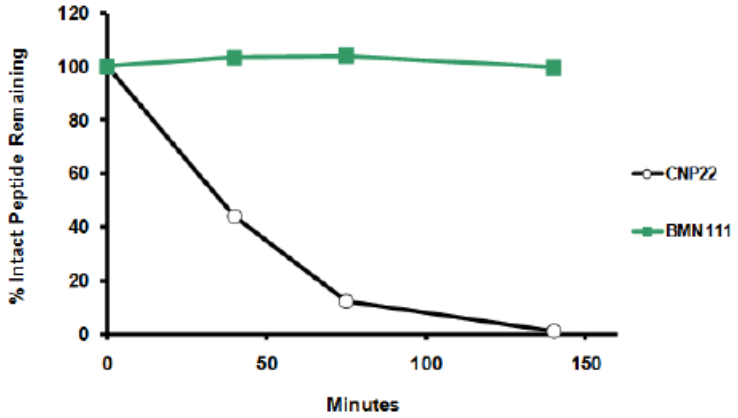
Distribution

Tissue distribution of BMN-111 was evaluated in mice and rats following single- and/or repeated-dose administration (800 µg/kg). In mice, distribution was ascertained by measuring cyclic guanosine monophosphate (cGMP) activation in various tissues. Peak levels of cGMP were seen 15 mins after treatment. Following a single SC dose, cGMP was noted in plasma, growth plate and articular cartilage (distal femur and tibia), cortical bone (tibia), kidneys, and lungs. There was no increase in cGMP in the brain beyond that seen in controls, demonstrating that BMN-111 does not cross the blood-brain barrier. Following multiple-dose administration, cGMP was noted in the distal femur and kidney. In the femur, an increase in cGMP signal was seen with repeated dosing while in the kidney the cGMP response decreased over time, suggesting NPR-B desensitization. CNP immunoreactivity revealed increased immunofluorescence at the growth plates that persisted beyond the treatment period, indicating that the half-life in the growth plate may be longer than that in plasma. However, the cGMP signal was not sustained. Positron emission tomography (PET) imaging was used to evaluate the distribution of ^{124}I-BMN-111 following SC and IV dosing in rats. Following SC treatment, the highest levels were detected in the stomach and injection site. Levels in all evaluated tissues declined rapidly thereafter. In another biodistribution study in rats, SC administration of 90 µg/kg of ^{124}I-BMN-111 revealed that most radioactivity was at the injection site, in the plasma, and in highly perfused organs. Levels were detected at the first post-injection time point (15 min) and were highest at 0.5 to 1 hour after treatment. At 0.5 hours post-treatment, the highest concentrations were detected at the injection site > kidneys > plasma > stomach > lungs > heart > spleen > small intestine > liver. The tissue:plasma ratios were <1 for the majority of tissues at all time points; the only exceptions were the injection site and stomach.

Metabolism

BMN-111 is metabolized by neutral endopeptidase (NEP), one of the main clearance pathways responsible for the short half-life of these peptides. The resistance of BMN-111 to NEP (human) degradation was evaluated. In the presence of NEP, a time-dependent disappearance of native CNP22 was observed while BMN-111 remained intact. Data are summarized in Figure 25 below:

Figure 25. BMN-111 Resistance to NEP Degradation



In vitro NEP resistance assay using purified recombinant human neutral endopeptidase in PBS buffer at 37oC. Plot shows the time-dependent disappearance of CNP22 in the presence of NEP, while vosoritide remains intact throughout the incubation.

Source: Applicant figure (figure 2.6.4.5.1.1 from Pharmacokinetics Written Summary)
Abbreviations: BMN-111, vosoritide; NEP, neutral endopeptidase; CNP22, C-type natriuretic peptde-22; PBS, phosphate buffer saline

Excretion

No specific excretion studies were performed.

Antidrug Antibody Formation

Antidrug antibodies (ADA) formed in both rats and NHPs. There were no significant sex-related differences in incidence or mean and median titers identified. There also was no evidence that the presence of ADA reduced exposure to BMN-111. Refer to the toxicokinetic summaries below.

Toxicokinetics

Toxicokinetic data were obtained as a component of the pivotal repeat-dose and reproductive studies. Detailed summaries of the exposure data are provided in Section 13.1.3.

13.1.3. Toxicology

The primary drug-related observations in the repeat-dose toxicity study were related to the pharmacologic activity of the drug on the skeletal system. In these normal animals, the pharmacologic effects often resulted in bone overgrowth that impeded movement. This was the basis for the identification of the NOAEL for the study.

13.1.3.1. General Toxicology

13.1.3.1.1. Single Dose Toxicity

In the single-dose rat study, SC doses up to 800 mg/kg and IV doses up to 150 mg/kg were administered to male and female Sprague Dawley rats that were 8 to 10 weeks old. No toxicity was observed, and the high dose administered by each route was considered the NOAEL.

In a single-dose study in NHPs, doses up to 200 mg/kg SC and 20 mg/kg IV were administered to animals that were ages 2 to 3.5 years. No adverse effects were noted and the high dose for each route was considered the NOAEL.

13.1.3.1.2. Multiple Dose Toxicity

All repeat-dose toxicity studies have previously been submitted and reviewed under the IND with the exception of a 7-day feasibility study in juvenile rats. This study was performed to evaluate the feasibility of treating juvenile animals. Observations from the pivotal repeat-dose toxicity studies in the rat and NHP are summarized.

13.1.3.1.2.1. 28-Day Repeat-Dose Subcutaneous Injection Toxicity and Toxicokinetic Study of BMN-111 in Sprague Dawley Rats With a 7-Day Recovery

Dosages of 50, 150, or 500 µg/kg were administered to adult rats (ages 6 to 8 weeks) for 28 days followed by a 7-day recovery period. The primary observations in this study were related to the pharmacologic activity of BMN-111 on the tarsal joints and bones. Clinical signs of swollen hind-paws/joints limiting hindlimb use were observed in 18/20 males and 9/20 females at the high dose (HD) with associated microscopic changes related to the pharmacology of the compound. Microscopic observations were limited to the injection sites and effects on bones, growth plate, and joints. The mid dose (MD) of 150 µg/kg (7.7x the exposure at the MRHD; 2.4x the body surface area (BSA)-based dose at the MRHD) was identified as the NOAEL based on the immobility evident at the HD (500 µg/kg). Although this dosage (150 µg/kg) can be considered the NOAEL in a 28-day study, animals administered this dosage had similar microscopic effects as those at the higher dosage but at a lower severity.

13.1.3.1.2.2. 26-Week Repeat-Dose Toxicity and Toxicokinetic Study by Subcutaneous Administration of BMN-111 in Sprague Dawley Rats With a 28-Day Recovery

Adult rats (>35 weeks at initiation) were administered BMN-111 at 0, 50, 150, or 500 µg/kg for 26 weeks followed by a 4-week recovery period (Study overview presented in Table 39 and results summarized in Table 40 and following text). Effects on hindlimbs, tail kinks, altered ambulation, and valgus were observed at the MD/HD with the effects persisting through the recovery period at the HD. Other minor antemortem effects were also noted. Pathologic examination revealed macroscopic and microscopic alterations to various bones. Macroscopic findings at the end of dosing were observed in all male drug-treated groups and in MD/HD females and included abnormal shape of the stifle and carpal joints, tail (coccygeal vertebra), sternum, femur, and in a few other bones (e.g., radius, tibia, thoracic vertebra, and spinal vertebrae). Microscopic observations included increased bone growth plate thickness and/or growth plate dysplasia in the affected bones (femur, tibia, ulna, radius, vertebrae, and sternum). The macroscopic and microscopic effects were also evident at the end of the recovery period at the HD (not known at the MD) in both sexes. In addition to these structures, the skull was also noted to have an abnormal shape in a small number of MD/HD males at the end of treatment and in a single HD male at the end of recovery; there were no microscopic correlates. Sperm counts were ~30% lower at the MD/HD and were not reversed by the end of recovery (only HD evaluated) but they remained within the historical range and there were no effects on sperm

motility, sperm morphology, or microscopic correlates. As the effects on bone and sperm were still evident at the completion of the recovery period, the LD of 50 µg/kg/day (2.1x the exposure at the MRHD; 0.8x the BSA at the MRHD) was identified as the NOAEL.

Table 39. 26-Week Study in Adult Rats, Study Overview

Study Features and Methods	Details
Study Number	BMN-111-11-036
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 50, 150, or 500 µg/kg; once daily
Route of administration:	SC injection
Formulation/vehicle:	(b) (4) mol/L citrate buffer (b) (4), pH 5.5, containing (b) (4) w/v) trehalose dihydrate, (b) (4) % (w/v) mannitol, (b) (4) mg/mL methionine, and (b) (4) % (w/v) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Hsd: Sprague-Dawley SD rats
Number/sex/group:	15
Age:	Male: 35-39 weeks; Female: 39 weeks
Satellite groups/unique design:	Additional 5/sex at C and HD for recovery assessments and 6 (control) or 9 (drug treated)/sex for TK
Deviation from study protocol affecting interpretation of results:	Minor not affecting study integrity

Source: Reviewer generated table
Abbreviations: BMN-111, vosoritide; C, control; GLP, good laboratory practice; HD, high dose; SC, subcutaneous; SD, Sprague Dawley; TK, toxicokinetics

Table 40. 26-Week Adult Rat Study Observations

Parameters	Major Findings
Mortality	Deaths occurred in all groups, but none considered drug-related
Clinical signs	Increases in the incidence of kinked tails were observed at all doses, with the severity increasing with dose. Limited use of the hindlimbs and altered gait observed at the MD/HD and valgus at the HD that persisted through recovery.
Body weights/feed consumption	No adverse effects noted
Ophthalmoscopy	NA
Hematology	No significant effects on hematology or coagulation parameters
Clinical chemistry	There were statistically significant alterations noted for a number of clinical chemistry parameters in MD/HD males and/or females but none of these effects were toxicologically significant given the small magnitude of difference from control, lack of a dose response, absence of correlative histopathology observations, and/or absence of corresponding effects on opposite sex. There were no differences for any of these parameters at the end of recovery. The only notable effect was a reduction in troponin 1 levels to less than 50% of control levels in MD and HD males for which there was minimal recovery
Urinalysis	Increased uGGT to creatinine ratio were seen in MD/HD females that persisted through recovery (<2-fold) that were related to a reduction in creatinine levels. There were no effects on serum urea nitrogen or microscopic correlates
Male reproductive assessment	There were reductions in sperm counts (density) at all dosages, with the reductions reaching statistical significance in MD (decreased ~31%) and HD (decreased ~27%) males. Decreased sperm counts were still evident following the reversal period at the HD (decreased ~43%). No effects on motility or morphology, histopathology of testes and epididymis, or on sperm staging
Vaginal cytology	No effects observed
ANP/BNP levels	No effects noted
BMC/BMD – in vivo	No drug-related effects were noted
Organ weights	Increased lung (up to 12%) and adrenal weights (up to 17%) persisting through recovery seen in HD males. Increased lung weights (up to 15%) at all dosages in females at end of treatment.

Source: Reviewer generated table
Abbreviations: ANP, atrial natriuretic peptide; BMC, bone mineral content; BMD, bone mineral density; BNP, B-type natriuretic peptide; HD, high dose; MD, medium dose; uGGT, urinary gamma glutamyl transferase

Gross Pathology: Multiple effects were noted on the shape of various structures, including joints (stifle and carpal joints), tail, sternum, legs (femur and tibia), and vertebra (thoracic and spinal) in males at all dosages and in MD/HD females. The incidence is summarized in Table 41 (note that some structures are grouped together under bone).

Table 41. 26-Week Adult Rat Study, Macroscopic Observations of Joints and Bones

Sex	Males				Females			
BMN 111 µg/kg	0	50	150	500	0	50	150	500
No. Animals Examined	15	15	15	15	15	15	15	15
Joint, Other								
Abnormal Shape	0	3	11	13	0	0	6	14
Tail								
Abnormal Shape	0	13	12	14	0	0	9	11
Bone, Other								
Abnormal Shape	0	3	6	6	0	0	0	2
Femur Bone								
Abnormal Shape	0	0	5	3	0	0	0	2
Sternum Bone								
Abnormal Shape	0	0	0	2	0	0	2	3

Note: Toxicokinetic animals excluded.
Source: Applicant table (Table 2 of the Anatomic Pathology report (page 1391) of report BMN-111-11-036)
Abbreviations: BMN-111, vosoritide

The macroscopic findings were also evident in recovery group animals.

Histopathology: Microscopic examinations were only performed on tissues for which there were macroscopic observations and on animals found dead or subjected to unscheduled euthanasia.

Treatment-related microscopic findings were present in the femur, tibia, sternum, vertebrae [thoracic and coccygeal (tail)], and various joints (stifle and/or carpal joint bones). Effects observed in LD males included increased growth plate thickness and dysplasia in joints and/or tail. The effects included increased growth plate thickness and dysplasia. The increased growth plate thickness was primarily characterized by increased layers of chondrocytes in the zones of multiplication, maturation, and hypertrophy. In affected animals, the chondrocytes appeared as oval to circular clusters of varying sizes with irregular contours sometimes separated by a cellular cartilage matrix. The growth plate dysplasia was characterized by disorganized chondrocytes forming variably sized, irregularly shaped aggregates of cells in the shaft of long bones forming a continuous band of cartilage across the subphyseal bone, increases in endochondral ossification, increased subphyseal trabecular bone, and increased numbers of retained cartilage cores in subphyseal trabecular bone. Although the overgrowth was related to the pharmacology of BMN-111, the alterations in long bones (femur; tibia; and less frequently, radius), resulted in an abnormal angle of the distal bone that correlated to the in-life observations of valgus deformity, swollen limbs, and limited use/altered ambulation. Because these effects impeded ambulation, they were considered adverse at the MD/HD. The treatment-related microscopic findings are summarized in Table 42.

Table 42. 26-Week Adult Rat Study, Drug-Related Microscopic Observations

	Sex	Males				Females			
	BMN 111 µg/kg	0	50	150	500	0	50	150	500
Joint, Other									
	No. Examined	1	4	11	13	0	0	6	14
Growth Plate Thickness, Increased									
	Not Present	1	0	0	0	0	0	1	0
	Minimal	0	1	4	1	0	0	3	4
	Slight	0	2	7	6	0	0	2	9
	Moderate	0	1	0	6	0	0	0	1
	Total Findings	0	4	11	13	0	0	5	14
Growth Plate Dysplasia									
	Not Present	1	0	0	1	0	0	0	0
	Minimal	0	0	1	3	0	0	3	2
	Slight	0	3	10	6	0	0	3	12
	Moderate	0	1	0	3	0	0	0	0
	Total Findings	0	4	11	12	0	0	6	14
Tail									
	No. Examined	1	13	12	14	0	0	9	11
Growth Plate Thickness, Increased									
	Not Present	1	0	1	0	0	0	0	0
	Minimal	0	12	8	5	0	0	9	7
	Slight	0	1	3	6	0	0	0	4
	Moderate	0	0	0	3	0	0	0	0
	Total Findings	0	13	11	14	0	0	9	11
Growth Plate Dysplasia									
	Not Present	1	13	12	13	0	0	9	9
	Minimal	0	0	0	0	0	0	0	2
	Slight	0	0	0	1	0	0	0	0
	Total Findings	0	0	0	1	0	0	0	2
Femur									
	No. Examined	1	0	5	3	1	0	0	2
Growth Plate Thickness, Increased									
	Not Present	1	0	1	0	1	0	0	0
	Minimal	0	0	2	1	0	0	0	1
	Slight	0	0	2	1	0	0	0	1
	Moderate	0	0	0	1	0	0	0	0
	Total Findings	0	0	4	3	0	0	0	2
Growth Plate Dysplasia									
	Not Present	1	0	2	3	1	0	0	0
	Minimal	0	0	1	0	0	0	0	0
	Slight	0	0	1	0	0	0	0	2
	Moderate	0	0	1	0	0	0	0	0
	Total Findings	0	0	3	0	0	0	0	2
Sternum									
	No. Examined	0	0	0	2	0	0	2	3
Growth Plate Thickness, Increased									
	Minimal	0	0	0	0	0	0	2	2
	Slight	0	0	0	0	0	0	0	1
	Moderate	0	0	0	2	0	0	0	0
	Total Findings	0	0	0	2	0	0	2	3
Growth Plate Dysplasia									
	Not Present	0	0	0	0	0	0	2	1
	Minimal	0	0	0	1	0	0	0	1
	Slight	0	0	0	1	0	0	0	1
	Total Findings	0	0	0	2	0	0	0	2
Bone, Other									
	No. Examined	0	0	2	2	0	0	0	0
Growth Plate Thickness, Increased									
	Not Present	0	0	2	1	0	0	0	0
	Minimal	0	0	0	1	0	0	0	0
	Total Findings	0	0	0	1	0	0	0	0
Growth Plate Dysplasia									
	Not Present	0	0	1	1	0	0	0	0
	Minimal	0	0	1	1	0	0	0	0
	Total Findings	0	0	1	1	0	0	0	0

Note: Toxicokinetic animals excluded.

Source: Applicant table (Table 3 of the Anatomic Pathology report (pages 1392-1393) of report BMN-111-11-036)

Following recovery, increased growth plate thickness and/or dysplasia were still evident in joints (stifle and carpus), tail, femur, sternum, and bone (other – thoracic vertebra).

Toxicokinetics: BMN-111 was rapidly absorbed with t_{max} ranging from 5 to 15 mins postdosing. Exposure did increase with dose in both males and females, with exposures higher at Day 85 sampling as compared to that seen on Days 1 and 176, and males were generally exposed to higher levels than females. The increases in exposure were approximately dose-proportional between the LD and MD and greater than proportional from the MD to HD. After reaching peak levels, BMN-111 concentrations rapidly declined, although the decline appeared to be more gradual with duration of dosing. Selected data are tabulated in Table 43 (table modified by reviewer to show selected columns).

Table 43. 26-Week Adult Rat Study, Toxicokinetics

	Group	Dose Level (µg/kg/day)	Gender	C_{max} (pg/mL)	T_{max} (min)	AUC_{0-t} (pg•min/mL)	$AUC_{0-\infty}$ (pg•min/mL)	$t_{1/2}$ (min)	CL/F (mL/min/kg)	V_z/F (mL/kg)
1	6	50	M	12667	5.00	404204	416903	17.5	120	026
			F	6063	15.0	145417	150536	20.9	332	9002
			Combined	8455	5.00	274810	283616	18.1	176	611
	7	150	M	22060	5.00	762758	NC	NC	NC	NC
			F	32600	5.00	682408	712601	18.3	210	559
			Combined	27330	5.00	722583	NC	NC	NC	NC
	8	500	M	101167	15.0	4780983	NC	NC	NC	NC
			F	99500	5.00	2634433	2645646	15.1	189	128
			Combined	93917	5.00	3715408	3735365	22.6	134	367
85	6	50	M	50433	15.0	1851217		NC	56.4	NC
			F	18917	15.0	783308		38.5	158	8800
			Combined	34675	15.0	1336913		33.7	80.7	3929
	7	150	M	99400	15.0	4464550		NC	76.9	NC
			F	54667	15.0	2673133		28.8	160	6667
			Combined	77033	15.0	3568842		NC	104	NC
	8	500	M	555000	5.00	29684542		NC	45.4	NC
			F	133933	15.0	8580967		19.2	184	5113
			Combined	340083	5.00	18848404		43.4	72.9	4559
176	6	50	M	19830	15.0	592675		27.6	83.4	3318
			F	16800	15.0	635775		72.3	73.6	7675
			Combined	18315	15.0	614401		43.8	79.2	4997
	7	150	M	38067	15.0	1436808		NC	NC	NC
			F	27817	15.0	1317208		21.7	113	3550
			Combined	32942	15.0	1377008		NC	NC	NC
	8	500	M	495667	15.0	25410983		NC	NC	NC
			F	163333	5.00	8715225		24.4	56.9	2000
			Combined	356300	15.0	18369410		NC	NC	NC

Source: Applicant table (Derived from Table 1 of the Toxicokinetic report (pages 1258-1260) of report BMN-111-11-036)
Abbreviations: Cl, clearance; F, fraction absorbed; NC, not calculated

Antidrug Antibodies: Multiple animals were ADA positive on Day 176 and/or 211. The incidences are tabulated in the reviewer created Table 44.

Table 44. 26-Week Adult Rat Study, ADA Incidence

	Dosage Level (µg/kg)					
Parameter	**50**		**150**		**500**	
Sex	M	F	M	F	M	F
Day 176	10/13	9/14	11/15	11/15	5/19	12/24
Day 211					1/5	3/5

Source: Data derived from text in report BMN-111-11-036
Abbreviations: ADA, antidrug antibodies

Toxicokinetic data were not collected from these animals so it is unknown if there was an effect on exposure.

13.1.3.1.2.3. A 26-Week Subcutaneous Injection Toxicity Study of BMN-111 in Juvenile Rats Followed by a 6-Week Recovery

In this 26-week study, juvenile rats (1 week old at treatment initiation) were administered dosages of 0, 10, 30, or 90 µg/kg (Study overview presented in Table 45 and results summarized in Table 46 and following text). . Effects on the hindlimbs affecting ambulation, motor activity, and maze solving times were evident at the MD and HD. Microscopic and histomorphometric effects were observed on bone, growth plates, and/or bone lengths. Additional observations included degenerative changes at the joints resulting from bone overgrowth and effects on bone mineral content (BMC)/bone mineral density (BMD). Few effects were reversible. As compared to adults, treatment with BMN-111 to young animals affected the same target tissues at lower dosages and exposures. For this juvenile animal study, the LD of 10 µg/kg/day (0.06x the exposure at the MRHD; 0.2x the BSA-based dose at the MRHD) was identified as the NOAEL, although it could also be considered a NOEL dosage as there was no indication of either pharmacologic or toxicologic effects at this dosage.

Table 45. 26-Week Study in Juvenile Rats, Study Overview

Study Features and Methods	**Details**
Study Number	BMN-111-11-052
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 10, 30, 90 µg/kg; once daily
Route of administration:	SC injection
Formulation/vehicle:	(b) (4) mol/L citrate buffer (b) (4), pH 5.5, containing (b) (4)% (w/v) trehalose dihydrate, (b) (4)% (w/v) mannitol, (b) (4) mg/mL methionine, and (b) (4)% (w/v) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Rat / Crl:CD(SD)
Number/sex/group:	10 tox +16 recovery
Age:	7 days at initiation
Satellite groups/unique design:	For TK: 9/sex (control) or 27/sex (treated). This study was a comprehensive evaluation of BMN-111 on growth and development in growing rats. As a result, multiple parameters were evaluated that are not typically included in a chronic toxicity study.
Deviation from study protocol affecting interpretation of results:	Minor not affecting study integrity

Source: Reviewer generated table
Abbreviations: BMN-111, vosoritide; GLP, good laboratory practices; SC, subcutaneous; SD, Sprague Dawley; TK, toxicokinetics

Table 46. 26-Week Juvenile Rat Study, Observations

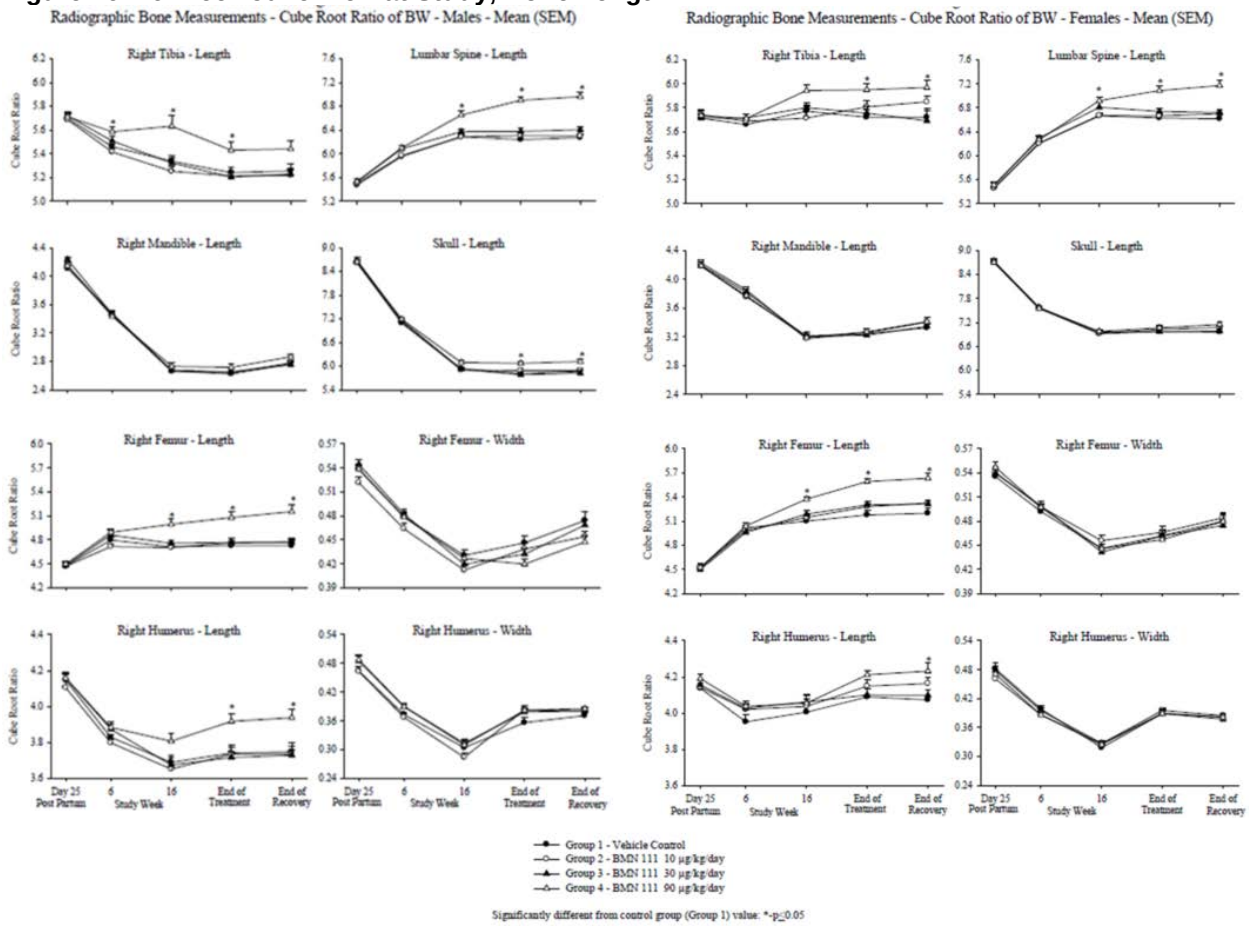
Parameters	Major Findings
Mortality	Evident in all groups. None considered drug-related
Clinical signs	Observations consisted of swelling, stiffness, limited use, and abnormal appearance to hindlimbs/hindpaws, abnormal gait, prominent backbone, thin body appearance, hunched posture, and kinked tail. These effects were noted in HD animals beginning at Week 12 and persisted through the recovery period.
Body weights/feed consumption	No adverse effects
Growth	Increases in crown-rump length were noted at the HD (~7%) and MD males (~3%). Tail lengths were increased up to ~15% at the MD/HD of both sexes
Ophthalmoscopy	No effects
Sexual maturation	No effects
Functional observation battery	Treatment-related changes in FOB measures were noted in HD males and females, with the number of parameters affected, incidence, and/or magnitude of effect reaching statistical significance (males more affected than females). Observations involved alterations in ambulatory function (e.g., gait, locomotor activity, body position, rearing, hindlimb grip strength, and toe pinch) and were attributed to bone overgrowth affecting the hind limbs/paws/joints of these animals resulting from exaggerated pharmacology. Effects were also evident during the recovery period.
Motor activity	Reduced activity in HD animals persisting through recovery, attributed to the ambulatory disturbances
Learning/memory testing	Longer times were required to complete the tasks as a result of the limb dysfunction. Not all animals could be evaluated as a result of the limb dysfunction.
ECG	NA
Hematology	No effects
Clinical chemistry	Slight increases in ALP (↑36%) and Phos (↑16%) and a decrease in Creat (↓19%) in HD males that were reversible. No effects in females.
Urinalysis	No effects
Reproductive capability	No adverse effects on estrous cyclicity or sperm parameters
Bone/cartilage turnover markers	The level of the bone formation biomarker procollagen 1 N-terminal propeptide (P1NP) was lower in HD males (↓18%) and females (↓13%) at Day 21, with the effect in females reaching statistical significance. At all other time points, there were no differences between treated groups and controls. The level of the bone resorption marker tartrate resistant acid phosphatase 5b (Tracp-5b) was increased in HD males (↑1.9-fold) and females (↑1.3-fold) at the end of treatment, although the effects attained statistical significance only for the males. No effects were observed for the bone resorption marker C-terminal telopeptide (CTx1).

Parameters	Major Findings
Radiolucency	Increased radiolucency (an indication of the presence of less dense material where bone is growing) was seen in HD males and females beginning at Week 16, with the number of animals and structures affected increasing with longer treatment. Effects on various structures were also noted at the MD. The radiolucency was observed at the physis and/or metaphysis of multiple sites (e.g., proximal calcaneum, caudal vertebrae, distal and proximal femur, humerus, proximal metatarsal, distal and proximal tibia, and others) and was generally bilateral. Many of the effects persisted through recovery at the HD. Other effects observed included displacements and /or fractures and minimal periosteal reaction of various structures, and abnormal shapes to various structures (e.g., calcaneum, femur neck, tibia). These changes were consistent with gross and/or microscopic findings of physeal persistence and proliferation and degenerative changes at these sites. These proliferative effects on the physis correlated to an increase in length of the long bones and were an expected pharmacological effect of BMN-111.
BMC/BMD – In vivo	DEXA scans revealed reductions in BMC and BMD in the tibia, femur, and spine, primarily at the HD. The reductions started to appear by Weeks 14/15 in the tibia (later at the other sites) and reached as high as 19%. These effects were associated with increases in area of up to 21% in affected structures. Effects were still evident during the recovery period. Similar patterns were observed using pQCT which also revealed decreased cortical area and thickness at the tibia metaphysis.
BMC/BMD – Ex vivo	Scans obtained of the femur at the end of treatment were consistent with the in vivo data. Reductions in BMC/BMD were noted for all areas of the femur were noted for both sexes at the HD, with the effects in males being larger (↓ up to 28%) than in females (↓ up to 11%) that were still evident following recovery. The ex vivo pQCT analysis of the femur revealed decreases in total and cortical area, BMC/BMD, and thickness that lasted through the recovery period. Reductions at various sites were as much as -28% in males and -12% in females, with the effects at most sites in males reaching statistical significance. Similar effects were seen in the lumbar vertebra although the magnitudes of the reductions were less than that seen in the femur.

Source: Reviewer generated table
Abbreviations: ALP, alkaline phosphatase; BMC; bone mineral content; BMD, bone mineral density; BMN-111, vosoritide; creat, creatinine; DEXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; FOB, functional observation battery; HD, high dose; MD, mid dose; Phos, phosphorous; pQCT, peripheral Quantitative Computed Tomography

Radiographic measurements: As early as Week 6, increases in tibial length were evident. As treatment progressed, increases in the length of the femur, lumbar spine, humerus, and skull were noted in HD males and/or females, with many of the effects reaching statistical significance for value or trend. The increases in length were in the range of 3% to 11% and persisted through the end of recovery. Data are shown in Figure 26.

Figure 26. 26-Week Juvenile Rat Study, Bone Length



Source: Applicant figure (Derived from Figures 8 and 9 of Bone report (pages 5001-5002) of report BMN-111-11-052)

Gross pathology: Gross macroscopic examination revealed depressed, raised and/or dark areas, pale discoloration, fracture, and/or small size of the femur, acetabulum, femoroacetabular joint and/or tibia of HD males and/or females. Discoloration and depressed area of the femur were also observed in single MD animals. These effects often correlated to degeneration, bone necrosis, periosteal fibrosis, and articular cartilage hyperplasia and/or hypertrophy observed microscopically on the head and neck of the femur at the HD. Enlargement and/or raised areas noted on the tibia and tibiotarsal joint correlated to disorganized cartilage and/or bone growth observed at the distal physis/metaphysis, and bent tibia correlated to the disorganized cartilage/bone growth observed at the distal physis/metaphysis of the tibia. Thickening of the acetabulum and enlargement of the femoroacetebular joint in HD males and females was correlated with tissue degeneration of these structures. Correlative microscopic effects were not seen at the MD.

Organ weights: There were no statistically significant effects on organ weights, although the thymus weights of HD males were approximately 24% lower and correlated with minimal to slight decreased lymphoid cellularity.

Bone measurements: At the end of treatment, increases in the length and a decrease in the width of the femur and tibia were observed in HD males while increases in the length of the femur, tibia, and radius were seen in HD females. Results are summarized in Table .

Table 47. 26-Week Juvenile Rat Study, Bone Measurements at Treatment Termination

Summary of Bone Measurement – Scheduled Euthanasia (Day 189 pp)

Difference to Control	Males						Females					
	Right Femur		Right Tibia		Right Radius		Right Femur		Right Tibia		Right Radius	
	L	W	L	W	L	W	L	W	L	W	L	W
	%	%	%	%	%	%	%	%	%	%	%	%
2 vs 1	0.89	-0.68	-0.14	-1.56	-2.52	-2.89	0.95	3.30	0.14	-4.90	1.67	-2.71
3 vs 1	1.81	-3.16	2.72	-5.10	1.22	-7.84	0.42	-1.10	0.84	-5.83	1.02	0.00
4 vs 1	**6.29**	**-13.91**	**9.46**	**-10.96**	3.75	-3.64	**4.42**	-4.84	**8.59**	-6.61	**5.10**	0.35

Values represent % difference compared to vehicle control group and those in bold attained statistical significance p <=0.05

Source: Applicant table (Table 6 from pathology report (page 5813) of report BMN-111-11-052)
Note: Groups 1, 2, 3, 4 are control, LD, MD, HD, respectively
Abbreviations: HD, high dose; LD, low dose; L, length; MD, medium dose; W, width

Following the 6-week recovery period, BMN-111-related increase in bone length was seen in all 3 structures of both males and females as were decreases in femur width (both sexes) and tibia width (males). Results are summarized in Table 48.

Table 48. 26-Week Juvenile Rat Study, Bone Measurement at Recovery

Summary of Bone Measurement – Scheduled Euthanasia (Day 231 pp)

Difference to Control	Males						Females					
	Right Femur		Right Tibia		Right Radius		Right Femur		Right Tibia		Right Radius	
	L	W	L	W	L	W	L	W	L	W	L	W
	%	%	%	%	%	%	%	%	%	%	%	%
2 vs 1	0.87	-0.48	-0.76	0.94	0.51	-1.53	-0.12	-0.06	-0.26	0.24	-0.02	-5.99
3 vs 1	1.36	-0.06	0.99	0.24	0.85	0.48	0.35	-1.98	0.74	-2.25	1.11	-5.13
4 vs 1	**5.74**	**-10.33**	**6.86**	**-5.89**	**4.18**	-0.33	**4.44**	**-7.13**	**6.53**	-3.36	**3.72**	-5.97

Values represent % difference compared to vehicle control group and those in bold attained statistical significance p <=0.05

Source: Applicant table (Table 7 from Pathology report (page 5814) of report BMN-111-11-052)
Note: Groups 1, 2, 3, 4 are control, LD, MD, HD, respectively
Abbreviations: HD, high dose; LD, low dose; L, length; MD, medium dose; W, width

Histopathology: The administration of BMN-111 was associated with changes in bones at the MD and HD that were attributed to the pharmacologic, or exaggerated pharmacologic, activity of the drug. The effects were observed at the growth plate and associated metaphysis, adjacent cancellous bone, articular cartilage, and/or joints and affected bones of the appendicular skeleton (femur, tibia, calcaneum, metatarsus), the anterior appendicular skeleton (humerus, radius and ulna), axial bones (acetabulum, sternum, and caudal vertebrae), and joints (femoroacetabular and tibiotarsal). The observations primarily consisted of enlargement and/or persistence of the growth plate related to effects on chondrocyte proliferation, or to degeneration/necrosis, disorganization, and/or inflammation that was considered reflective of the exaggerated growth of bones causing mechincal dysfunction or possibly vascular disruptions. The observations included the following:

- Femur: degeneration/necrosis/fissure of the physeal/epiphyseal femoral head, necrosis, fibrosis periosteal of the neck, hypertrophy/hyperplasis of articular cartilage, decreased metaphyseal/epiphyseal cancellous bone, physeal persistance at the trochanter, increased hypertrophic zone./primary spongiosa of the physis, osteod accumulation of woven bone, endosteal fibrosis, and persistence/hypertrophy of cartilage

- Acetabulum: degeneration/necrosis of cartilage, persistence of physeal cartilage, periosteal bone formation
- Femoacetabular joint: chronic degeneration/fibrosis
- Tibia: disorganized cartilage/bone growth at distal physis/metaphysis, distal physeal persistence/thickening, distal periosteal bone formation, decreased metaphyseal/epiphyseal cancellous bone proximal, increased hypertrophic zone of the physis
- Calcaneum: physeal persistence/thickening, decreased metaphyseal cancellous bone
- Metatarsus: physeal persistence/thickening, decreased cancellous/cortical bone
- Tibiotarsal joint: articular/periarticular inflammation, tenosynovial inflammation
- Humerus: decreased metaphyseal/epiphyseal cancellous bone, increased hypertrophic zone at the physis
- Humeroscapular joint: physeal persistence/thickening
- Radius: increased hypertrophic zone/primary spongiosa, physeal persistence/thickening, decreased metaphyseal cancellous bone
- Ulna: increased hypertrophic zone, decreased metaphyseal cancellous bone
- Sternum: increased hypertrophic zone of the physis
- Caudal vertebrae: thickening of the physis

These effects were observed in HD males and females although some effects were also noted in a small number of MD males.

Following recovery, microscopic findings noted at the end of dosing were still present in most of the bones and joints they were seen in at the end of dosing but at a slightly lower incidence. The degenerative/necrotic changes in the proximal femur, acetabulum, and joint were slightly reduced in severity and the disorganized cartilage/bone growth in the distal tibia was slightly increased in severity compared to that seen at the end of dosing. Findings in most other bones were either reduced in incidence and/or severity or occurred in fewer bone. No BMN-111-related microscopic findings were seen in the radius and ulna following recovery.

There were no soft tissue effects noted considered treatment-related although there was a slightly higher incidence in HD males of progressive cardiomyopathy (observed in 6, 3, 3, and 10 males at the C, LD, MD, and HD, respectively), acinar cell atrophy in the pancreas (observed in 2, 0, 1, and 6 males at the C, LD, MD, and HD, respectively), and decreases in lymphoid cellularity associated with slight decreases in thymus weights (observed in 0, 0, 0, and 3 males at the C, LD, MD, and HD, respectively). Similar increases in the incidence of these effects were not seen in females.

Histomorphometry: Histomorphometric examination revealed BMN-111-related effects on multiple parameters. At the end of dosing, drug-related and statistically significant effects were evident in HD males for the following static bone parameters: bone volume variables (BV/TV ↓71% and Md.V/TV ↓72% correlated to decreases in cancellous bone noted on microscopic evaluation; OV/BV ↑9.7-fold and OS/BS ↑1.6-fold with no change in osteoid thickness), bone microarchitecture variables (Tb.Sp ↑2.7-fold, Tb.Th ↓22%, and Tb.N ↓64%) and osteoblast surface variable (Ob.S/BS ↑1.5-fold). The increases in OV/BV, OS/BS and Ob.S/BS suggest osteoblast function in depositing osteoid. There were no changes in osteoclast surface (Oc.S/BS) at this time point. However, osteoclast-related loss could have occurred earlier during treatment.

Moreover, the increase in OV/BV, OS/BS and Ob.S/BS could also be an indication of decreased, delayed, or defective mineralization. Analogous changes were seen in HD females, but the magnitudes were minimal (≤25%) and none of the effects reached statistical significance.

At the necropsy following the reversal period, statistically significant effects on bone volume (BV/TV ↓51% and Md.V/TV ↓51%) and osteoid volume (OV/BV ↑4.3-fold) were still evident. Effects were still seen on osteoblast surface (Ob.S/BS ↑1.2-fold) and bone microarchitecture parameters (Tb.Sp ↑2.3-fold, Tb.Th ↓16% and Tb.N ↓42%), although the effects were no longer statistically significant.

Biomechanical Testing: In 3-point bend testing, decreases in peak load, stress, stiffness, and/or area under the curve (AUC) were seen in HD males and/or females; decreases in peak load were also evident in MD males. These effects were consistent with the reductions in BMC/BMD and microscopic changes. Data are shown in Table 49.

Table 49. 26-Week Juvenile Rat Study, 3-Point Bending

Mean and Percent Difference of Biomechanics Parameters - Femur 3-point Bending - Treatment Period - Males and Females

	Units	Group	Vehicle Control	BMN 111 10 µg/kg/day		BMN 111 30 µg/kg/day		BMN 111 90 µg/kg/day	
			Value	Value	%	Value	%	Value	%
Males									
Peak Load	N	Mean	202.41	193.19	-4.6	**178.47**	-11.8	**127.02**	-37.2
		SD	22.04	20.44		15.41		23.29	
Ultimate Stress	MPa	Mean	206.38	207.57	0.6	213.41	3.4	208.69	1.1
		SD	24.70	15.92		19.11		31.48	
Stiffness	N/mm	Mean	409.41	398.38	-2.7	368.29	-10.0	**265.57**	-35.1
		SD	49.34	33.27		37.63		68.39	
Modulus	MPa	Mean	6525.34	6749.22	3.4	7194.08	10.2	**8034.15**	23.1
		SD	1167.39	792.27		1206.13		1030.37	
AUC	N-mm	Mean	169.11	161.65	-4.4	135.61	-19.8	**99.66**	-41.1
		SD	66.13	34.04		52.57		39.97	
Toughness	MPa	Mean	10.95	10.99	0.4	10.04	-8.3	8.60	-21.4
		SD	3.54	1.56		3.75		2.56	
Females									
Peak Load	N	Mean	160.40	158.07	-1.5	156.36	-2.5	**128.44**	-19.9
		SD	14.48	13.35		16.58		20.96	
Ultimate Stress	MPa	Mean	230.76	219.06	-5.1	221.85	-3.9	214.33	-7.1
		SD	17.74	17.82		17.69		23.54	
Stiffness	N/mm	Mean	453.00	450.87	-0.5	437.25	-3.5	**372.04**	-17.9
		SD	54.03	48.07		56.63		57.56	
Modulus	MPa	Mean	7274.69	6809.63	-6.4	6882.26	-5.4	7317.78	0.6
		SD	959.86	1163.97		896.02		1199.04	
AUC	N-mm	Mean	72.85	72.88	0.0	82.23	12.9	**55.67**	-23.6
		SD	10.96	16.98		13.81		14.90	
Toughness	MPa	Mean	9.43	9.36	-0.7	10.50	11.4	7.89	-16.3
		SD	1.42	2.22		1.20		1.68	

% percent difference from Vehicle Control

Values in bold are significantly different from Vehicle Control

Source: Applicant table (Table 28 from Bone report (page 5032) of report BMN-111-11-052)
Abbreviations: AUC, area under the curve; BMN 111, vosoritide

Effects were still present in HD animals at the end of recovery.

Femoral neck shear testing could not be performed on HD animals at the end of treatment based on the abnormal aspect of the proximal femur, lack of mineralization, and evidence of fracture and/or damage noted at collection. Reductions were noted in various endpoints at the MD as summarized in Table 50.

Table 50. 26-Week Juvenile Rat Study, Femoral Neck Shear

Mean and Percent Difference of Biomechanics Parameters - Femoral Neck Shear - Treatment Period - Males and Females

		Group	Vehicle Control	BMN 111 10 µg/kg/day		BMN 111 30 µg/kg/day	
	Units		Value	Value	%	Value	%
Males							
Peak Load	N	Mean	175.68	170.81	-2.8	163.96	-6.7
		SD	24.98	22.19		18.15	
Stiffness	N/mm	Mean	523.35	447.65	-14.5	412.46	-21.2
		SD	136.21	95.53		93.51	
AUC	N-mm	Mean	56.32	57.90	2.8	80.54	43.0
		SD	18.38	20.73		38.77	
Females							
Peak Load	N	Mean	142.86	145.43	1.8	**119.47**	-16.4
		SD	14.03	14.95		15.05	
Stiffness	N/mm	Mean	525.55	556.35	5.9	**445.64**	-15.2
		SD	96.51	49.96		59.47	
AUC	N-mm	Mean	41.89	42.31	1.0	33.10	-21.0
		SD	12.99	16.37		9.52	

% percent difference from Vehicle Control

Values in bold are significantly different from Vehicle Control

Source: Applicant table (Table 30 from Bone report (page 5042) of report BMN-111-11-052)
Abbreviations: AUC, area under the curve; BMN 111, vosoritide

Following recovery, there were no statistically significant differences between control and MD animals. A few HD females were able to be evaluated, and reductions in peak load and stiffness of a larger magnitude than that occurring at the MD were seen.

Vertebral compression testing of the L4 vertebra revealed decreases in peak load, apparent stress, yield load, yield stress, stiffness, modulus, AUC, and toughness, with many of the observed effects attaining statistical significance in HD males and/or females. Data are shown in Table 51.

Table 51. 26-Week Juvenile Rat, Vertebral Compression

Mean and Percent Difference of Biomechanics Parameters - L4 Vertebral Body - Treatment Period - Males and Female

		Group	Vehicle Control	BMN 111 10 µg/kg/day		BMN 111 30 µg/kg/day		BMN 111 90 µg/kg/day	
	Units		Value	Value	% vs 1	Value	% vs 1	Value	% vs 1
Males									
Height	mm	Mean	3.58	3.56	-0.5	3.54	-1.3	3.54	-1.1
		SD	0.15	0.11		0.09		0.07	
Peak Load	N	Mean	481.24	476.96	-0.9	445.86	-7.4	**304.74**	-36.7
		SD	87.00	91.11		94.32		34.76	
Apparent Strength	MPa	Mean	45.88	43.41	-5.4	43.81	-4.5	**31.66**	-31.0
		SD	5.80	7.47		7.54		2.43	
Yield Load	N	Mean	435.01	439.46	1.0	409.80	-5.8	**290.50**	-33.2
		SD	101.23	72.22		89.99		31.48	
Yield Stress	MPa	Mean	41.42	40.07	-3.3	40.25	-2.8	**30.22**	-27.0
		SD	7.68	6.28		7.33		2.57	
Stiffness	N/mm	Mean	4832.62	4723.69	-2.3	4724.72	-2.2	**3466.88**	-28.3
		SD	874.40	1112.39		1239.43		533.68	
Modulus	MPa	Mean	1657.26	1528.10	-7.8	1653.38	-0.2	**1273.44**	-23.2
		SD	273.03	322.01		438.09		129.20	
AUC	N-mm	Mean	43.05	42.24	-1.9	37.61	-12.7	**23.18**	-46.2
		SD	11.27	12.19		10.07		4.54	
Toughness	MPa	Mean	1.14	1.07	-5.9	1.04	-8.8	**0.68**	-40.4
		SD	0.23	0.26		0.19		0.11	
Females									
Height	mm	Mean	3.47	3.44	-0.9	3.59	3.3	3.54	1.9
		SD	0.12	0.09		0.15		0.08	
Peak Load	N	Mean	430.43	440.91	2.4	386.21	-10.3	**353.88**	-17.8
		SD	72.68	38.22		64.40		77.01	
Apparent Strength	MPa	Mean	49.48	50.44	1.9	43.57	-12.0	**39.82**	-19.5
		SD	7.11	3.55		6.26		6.00	
Yield Load	N	Mean	412.60	413.62	0.2	366.72	-11.1	**333.84**	-19.1
		SD	75.48	41.13		65.33		69.34	
Yield Stress	MPa	Mean	47.44	47.32	-0.3	41.33	-12.9	**37.64**	-20.7
		SD	7.54	3.98		6.17		5.71	
Stiffness	N/mm	Mean	4760.20	5053.38	6.2	4144.11	-12.9	3802.38	-20.1
		SD	1039.25	590.17		1128.42		783.42	
Modulus	MPa	Mean	1907.08	1989.73	4.3	1669.79	-12.4	1527.82	-19.9
		SD	433.62	230.58		408.98		296.89	
AUC	N-mm	Mean	31.04	33.09	6.6	29.91	-3.6	26.07	-16.0
		SD	6.48	4.46		6.12		7.63	
Toughness	MPa	Mean	1.02	1.11	8.2	0.94	-7.9	**0.82**	-19.6
		SD	0.16	0.17		0.17		0.18	

% percent difference from Vehicle Control

Values in bold are significantly different from Vehicle Control

Source: Applicant table (Table 32 from Bone report (page 5050) of report BMN-111-11-052)
Abbreviations: AUC, area under the curve; BMN 111, vosoritide

Reductions were still evident following recovery.

Toxicokinetics: Exposure to BMN-111 was higher following multiple dosing as compared to that occurring after a single dose. Following multiple dosing, exposure increased with dose in a greater than proportional manner. Exposure in males was higher than in females, likely contributing to the increased toxicity seen in males. BMN-111 was rapidly absorbed with t_{max} occurring between 5 and 30 mins. The $t_{1/2}$ was ~45 mins when it was able to be calculated. Data are summarized in Table 52.

Table 52. 26-Week Juvenile Rat Study, Exposure Summary

Group	Dose Level	Dose Day	Gender	Cmax	Tmax	T 1/2	AUC0-t	AUC0-inf	CL/F	Vz/F
	µg/kg			pg/mL	min	min	pg*min/mL	pg*min/mL	mL/min*kg	mL/kg
2	10	1	F	0	NA	NC	0	NC	NC	NC
2	10	1	M	3290	5.0	NC	NC	NC	NC	NC
mean				**1645**						
2	10	182	F	527	15	NC	10133	NC	NC	NC
2	10	182	M	680	30	NC	22842	NC	NC	NC
mean				**603**	**22.5**		**16488**			
3	30	1	F	240	5.0	NC	NC	NC	NC	NC
3	30	1	M	2953	5.0	NC	NC	NC	NC	NC
mean				**1597**	**5.0**					
3	30	182	F	1987	15	NC	84208	NC	NC	NC
3	30	182	M	3857	15	NC	140208	NC	NC	NC
mean				**2922**	**15.0**		**112208**			
4	90	1	F	3210	5.0	NC	NC	NC	NC	NC
4	90	1	M	2803	5.0	NC	NC	NC	NC	NC
mean				**3007**	**5.0**					
4	90	182	F	16900	5.0	44.1	459917	512291	176	11176
4	90	182	M	26150	15	40.1	734877	807642	111	6453
mean				**21525**	**10.0**	**42.1**	**597397**	**659967**	**144**	**8814**

NC : Not Calculated
Source: Applicant table (Table 9.1 from Toxicokinetic report (page 4683) of report BMN-111-11-052)
Abbreviations: Cl/F; apparent clearance; NC, not calculated; Vz/F, apparent volume of distr bution during terminal elimination

Antibody Evaluation: The incidence of ADA at the end of dosing was comparable between the 3 drug treated groups, ranging from 56% to 67% (not dose-related) although there was a dose-related increase in mean titers 138, 767, and 1368 at the LD, MD, and HD, respectively. The incidence (39% to 56%) and titers (74, 322, 234 at the LD, MD, and HD, respectively) were lower at the end of recovery.

13.1.3.1.2.4. 28-Day Repeat-Dose Subcutaneous Injection Toxicity and Toxicokinetic Study of BMN-111 in Cynomolgus Monkeys With 7-Day Recovery

In this study, young (ages 2 to 3 years) NHPs were administered BMN-111 at dosages of 0, 20, 90, or 300 µg/kg for 28 days followed by a 7-day recovery period. The primary observations in this study were related to the pharmacology of the compound. Microscopic effects observed included dose-related widening of the growth plate of the sternum and femur due to increased chondrocyte proliferation and differentiation. The degree of proliferation in the physeal cartilage in this study appears to have exceeded the rate of vascular invasion, osteoid formation, and remodeling. For this reason, the observations in the primary spongiosa and trabecular bone, including necrosis, degeneration, and disorganization, were considered to be secondary to physeal cartilage proliferation. These effects were present at all dosages in the sternum and at the

MD and HD in the femur. Corresponding to the increased size of the growth plates were increases in the levels of CTX-II. The observed effects were partially reversed by the end of the 7-day recovery period. Additional pharmacologic effects included increases in cGMP levels at the MD and HD and increased heart rate from 2 to 5 hours post dosing in HD animals with associated shortening of ECG waveforms. There was no change in blood pressure noted. None of these effects were considered toxicologically limiting or adverse. As a result, the NOAEL in this study was the HD of 300 µg/kg (38.5x the exposure at the MRHD; 9.6x the BSA-based at the MRHD).

13.1.3.1.2.5. 26-Week Repeat-Dose Toxicity and Toxicokinetic Study of Subcutaneous Administration of BMN-111 in Cynomolgus Monkeys With a 28-Day Recovery

BMN-111 was administered at dosages of 0, 20, 90, or 300 µg/kg to young (ages 2 to 3 years) monkeys for 26 weeks followed by a 4-week recovery period (Study overview presented in Table 53 and results summarized in Table 54 and following text). . The primary observations in this study were related to the pharmacology of the test article and included increases in cGMP, P1ND, bone-specific alkaline phosphatase (BSAP), NTx, and CtxII levels at the MD and HD, expected effects based on the test article target. Additional pharmacologic effects on bone included increases in bone length and growth plate width at all dosages, particularly the MD and HD, while increases in the levels of various biomarkers of bone activity occurred at the MD and HD. As the effects were consistent with the pharmacology of the compound, they were considered treatment related although they did not necessarily attain statistical significance. At the HD, limited use of hips and hindlimbs were evident in a number of animals that were associated with abnormal femur heads noted macroscopically in some affected animals. As a result, the MD of 90 µg/kg/day (1.7x the exposure at the MRHD; 2.9x the BSA-based dose at the MRHD) was identified as the NOAEL.

Table 53. 26-Week Juvenile NHP Study, Study Overview

Study Features and Methods	Details
Study Number	BMN-111-11-035
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 20, 90, 300 µg/kg; once daily
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) mol/L citrate buffer (b) (4), pH 5.5, containing (b) (4)% (w/v) trehalose dihydrate (b) (4)% (w/v) mannitol (b) (4) mg/mL methionine, and (b) (4) (w/v) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Cynomolgus monkeys
Number/sex/group:	4
Age:	2-3 years
Satellite groups/unique design:	3 at C and HD for recovery
Deviation from study protocol affecting interpretation of results:	None affecting study integrity

Source: Reviewer generated table
Abbreviations: C, control; GLP, good laboratory practice; HD, high dose; NHP, nonhuman primate;

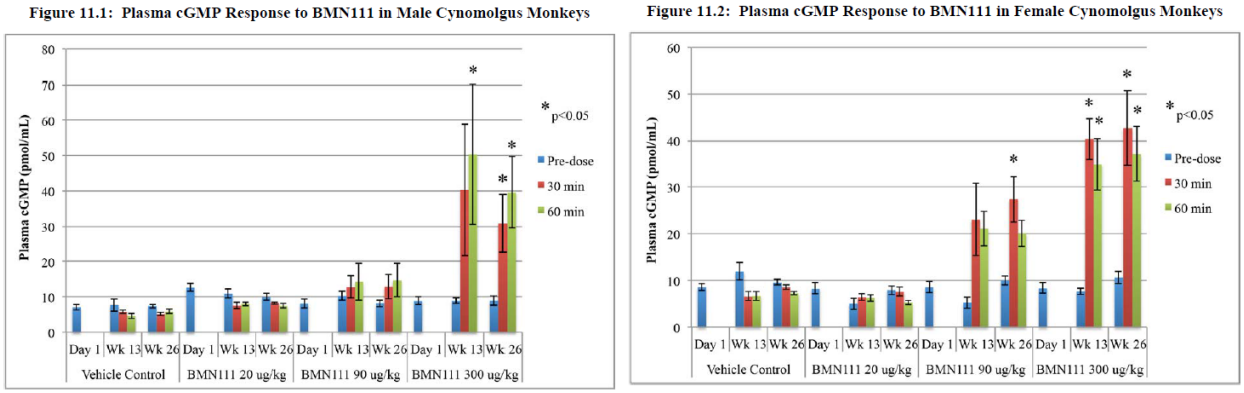
Table 54. 26-Week Juvenile NHP Study, Observations

Parameters	Major Findings
Mortality	None
Clinical signs	Adverse treatment-related clinical signs consisting of limited use of hips and/or decreased range of motion of the hind legs was evident in HD animals (4 males and 1 female), appearing between approximately Week 13 and 21 for all animals except for 1 male in which these effects appeared during the recovery period. These observations were noted throughout the reversal period.
Body weight/food consumption	No effects
Ophthalmoscopy	NA
ECG	Heart rates were increased slightly (up to ~40 bpm, ~26%) during the first 1 to 4 hours postdosing at the HD on dosing Day 2 and on subsequent days through approximately Day 122 before the effect attenuated, but none of the increases attained statistical significance. There were no effects on blood pressure (measured via tail cuff on conscious animals) nor were there any effects on PR interval, QRS duration, QT interval, or corrected QT (QTc) interval. Qualitative review of ECGs did not reveal rhythm abnormalities.
Hematology	No toxicologically significant effects
Clinical chemistry	No toxicologically significant effects
Urinalysis	No effects
Atrial and brain natriuretic peptide	ANP levels were increased up to 7-fold on Day 85 (MD and/or HD at 30 min) and Day 176 (all groups at 30 min); these effects were statistically significant. Increases of a larger magnitude (up to 13-fold) were seen at all doses on Day 85 at 90 min postdose, but the variability was excessive and none of the effects were statistically significant. There were no effects on BNP.
BMC/BMD (in vivo)	BMC and BMD were evaluated via DEXA analysis for the tibia/fibula, femur, and whole body at predose, Week 13, Week 25, and recovery. For both males and females, BMC increased as the animals grew, but there were no statistically significant differences between the groups. BMD remained relatively constant throughout the study.

Source: Reviewer generated table
Abbreviations: ANP, atrial natriuretic peptide; BMC, bone mineral content, BMD, bone mineral density; BNP, B-type natriuretic peptide; C, control; DEXA, dual energy X-ray absorptiometry; ECG, electrocardiogram; HD, high dose; MD, medium dose; NHP, nonhuman primate

cGMP levels: Treatment and dose-related increases in plasma cGMP levels (versus predose levels on the same day of collection) were evident in HD males and MD/HD females at Weeks 13 and 26. The increases were of similar magnitudes at these 2 timepoints and often reached statistical significance. Data are shown in Figure 27.

Figure 27. 26-Week Juvenile NHP Study, cGMP Levels



Source: Applicant figures (Figures 11.1 and 11.2 from Cyclic Guanosine Monophosphate report (pages 1532-1533) of report BMN-111-11-035)
Abbreviations: NHP, nonhuman primate; cGMP, cyclic guanosine monophosphate; BMN-111, vosoritide

Bone growth: Tibial growth plate height and lengths of the tibia, femur, and humerus were measured predose, Week 13, Week 25, and recovery. Absolute and normalized tibial growth plate height and length were increased in both sexes by Week 13, with some of the effects reaching statistical significance. By Week 25, tibial growth plate height was increased at the MD/HD for both sexes, with some of the effects in MD/HD males and HD females reaching statistical significance. Tibial lengths were also increased, but only the effects in HD males achieved statistical significance. The lengths of the femur and humerus were also increased in males but only some of the measures in the humerus were statistically significant. Bone lengths were still longer at the end of recovery, but the differences were not statistically significant. In females, minimal increases in bone lengths were evident. Week 25 data are shown in Table 55.

Table 55. 26-Week Juvenile NHP Study, Differences in Bone Length Compared to Controls

	Bone Length Summary Data, Week 25 (Day 171)							
	Males				Females			
Bone Type	**0 µg/kg**	**20 µg/kg**	**90 µg/kg**	**300 µg/kg**	**0 µg/kg**	**20 µg/kg**	**90 µg/kg**	**300 µg/kg**
Tibia growth plate height								
Medial	1.17	1.00 (-15)	1.38 (18)	1.20 (3)	0.84	1.05 (25)	1.15 (37)	1.03 (23)
Central	0.17	0.23 (35)	0.83 (388)[a]	0.87 (412)[a]	0.24	0.48 (100)	0.43 (79)	0.76 (217)[a]
Lateral	0.81	0.93 (15)	1.13 (40)	1.31 (62)[a]	0.73	0.73 (-)	0.83 (14)	0.8 (10)
Tibia								
Medial	102.90	107.15 (4)	106.62 (4)	110.16 (7)[a]	104.63	106.93 (2)	104.5 (-)	110.5 (6)
Central	104.81	108.78 (4)	107.78 (3)	111.86 (7)[a]	106.03	108.38 (2)	105.78 (-)	111.83 (5)
Lateral	103.41	107.63 (7)	105.7 (7)	109.49 (6)[a]	104.51	107.43 (3)	104.1 (-)	109.83 (5)
Femur								
Medial	116.84	121.78 (4)	120.43 (3)	119.86 (3)	123.04	125.15 (2)	119.25 (-3)	121.8 (-1)
Central	114.26	119.05 (4)	117.93 (3)	116.47 (2)	120.09	122.58 (2)	115.83 (-4)	119.29 (-1)
Lateral	117.17	121.43 (4)	120.68 (3)	119.96 (2)	122.2	125.03 (2)	118.7 (-3)	122.5 (-)
Humerus								
Medial	102.24	105.88 (4)	108.55 (6)	108.20 (6)[a]	103.74	105.43 (2)	104.08 (-)	107.71 (4)
Central	106.77	110.00 (3)	112.78 (6)	112.40 (5)	107.86	109.65 (2)	107.83 (-)	111.93 (4)
Lateral	105.33	108.93 (3)	111.45 (6)	111.47 (6)[a]	107.21	108.73 (1)	106.93 (-)	110.49 (93)

Source: Data compiled from Table 2.3 of Bone Analysis report (pages 1623-1624) of report BMN-111-11-035
Data expressed in mm (% change)
[a] $p<0.05$ compared to control
Abbreviations: NHP, nonhuman primate

Analogous patterns were seen for the differences in growth velocity from predose to Week 13 or 25. Summary data for changes in growth velocity through these periods are shown in Table 56.

Table 56. 26-Week Juvenile NHP Study, Growth Velocity Summary

Summary of Long Bone Growth Absolute Difference in Mean Growth Velocity (mm/year)

	Tibia			Femur			Humerus		
	medial	central	lateral	medial	central	lateral	medial	central	lateral
Week 13 to pre-dose phase									
G1 M (n=7)	21.38	19.70	17.01	9.38	7.95	9.90	9.85	16.59	11.96
G2 M (n=4)	24.61	22.67	20.92	8.48	8.76	10.32	13.55	17.14	16.04
G3 M (n=4)	32.26	28.85*	26.18*	18.62	15.95	18.62	19.91*	26.55*	22.67*
G4 M (n=7)	36.18*	33.55*	29.92*	18.38	15.80	18.43	25.70*	32.97*	29.49*
G1 F (n=7)	5.32	7.26	8.28	17.74	15.95	16.41	11.96	13.75	12.01
G2 F (n=4)	11.63	15.92	14.76	21.83	21.20	23.08	14.13	16.37	15.30
G3 F (n=4)	20.75*	23.71*	22.81*	30.77	27.02	27.38	21.38	22.90*	21.29
G4 F(n=7)	21.73*	23.82*	22.19*	37.27*	33.74	32.82	20.04	22.75*	19.37
Week 25 to pre-dose phase									
G1 M (n=7)	16.16	16.87	16.13	12.27	10.89	12.58	9.02	13.92	12.85
G2 M (n=4)	15.79	16.24	15.74	14.59	14.54	14.34	12.53	15.29	16.50
G3 M (n=4)	23.56	21.91	20.51	20.86	19.40	20.51	18.60*	23.26*	22.11*
G4 M (n=7)	29.76*	29.66*	26.87*	17.65	15.55	18.57	21.93*	26.70*	27.25*
G1 F (n=7)	7.85	9.54	9.66	21.09	19.48	18.25	12.32	13.47	12.92
G2 F (n=4)	14.84	16.19	16.04	24.87	24.32	24.07	13.74	16.04	15.99
G3 F (n=4)	18.15*	20.11*	19.45*	26.32	23.87	23.77	19.95	19.90	19.15
G4 F(n=7)	23.18*	23.32*	21.60*	27.82	26.93	26.27	17.91	20.17	18.65

G = Group; M: Male; F: Female; n: number of animals in the group.
* = Statistically significant, P<0.05 when compared to control.

Source: Applicant table (Text Table 2 (page 63) of report BMN-111-11-035)
Abbreviations: F, female; G, group; M, male; n, number of animals in the group; NHP, nonhuman primate

There were no significant effects on the length between L1 and L4 vertebrae or in the dimensions of the foramen magnum or skull.

Bone biomarkers: Markers of bone formation (N-terminal propeptide of procollagen I [P1NP], osteocalcin, and BSAP), bone resorption (C-telopeptides of type I collagen [sCTx or CtxI] and N-telopeptides of type I collagen [NTx]), and collagen degradation (C-telopeptides of type II collagen [CtxII]) were measured predose, Weeks 13 and 25, and at the end of the dosing (Week 26) and recovery (~Week 30) periods.

There were no consistent drug-related effects on bone formation markers P1NP and osteocalcin. In males, the levels of P1NP tended to be higher than controls at Weeks 13 and 26 (termination) but were lower at Week 25 and recovery across dosages. In females, the levels were generally higher in all drug-treated groups. For osteocalcin, the levels were generally higher for males and lower for females relative to their respective controls. None of the effects for these 2 parameters, with the exception of the reduction in osteocalcin in HD females at the end of dosing (Week 26), were statistically significant.

For BSAP, dose-related increases were seen for most drug-treated groups throughout the study, but the effects did not reach statistical significance with the exception of males at the HD at the end of the recovery period.

There were no statistically significant effects on the bone resorption marker CtxI. For NTx, levels were higher than controls at all dosages in males (up to 1.5x; statistically significant at Week 13 in all groups). There were no effects in females.

Levels of the collagen degradation marker CtxII were increased up to 1.8x (across sexes), primarily at the MD/HD, with some of the effects attaining statistical significance for both sexes on Day 85 of the study.

Bone biomarker data during the treatment period are summarized in Table 57.

Table 57. 26-Week Juvenile NHP Study, Bone Biomarker Levels Percent Change From Control

Gender	Male	Female	Male	Female	Male	Female	Male	Female
Daily Dose (µg/kg)	**0 (Control)**	**0 (Control)**	**20**	**20**	**90**	**90**	**300**	**300**
Number of Animals	7	7	4	4	4	4	7	7
Number of Recovery Animals	3	3	0	0	0	0	3	3
PINP (µg/L) – Day 85	1690.12	1531.01	-	-	+19.4%	+18.6%	+34.9%	+40.7%
PINP (µg/L) – Day 176	-	1254.84	-	-	-	+19.7%	-	+57.6%
PINP (µg/L) – Day 183	-	1081.25	-	-	-	+25.5%	-	+62.1%*
BSAP (UL) - Day 85	379.13	322.49	-	-	-	+36.9%	+35.2%	+38.2%
BSAP (UL) - Day 176	448.08	-	-	-	-	-	+35.2%	-
BSAP (UL) - Day 183	-	299.96	-	-	-	+20.7%	-	+27.6%
Osteocalcin (ng/mL)	-	-	-	-	-	-	-	-
CTXII (pg/mL) – Day 85	156.24	130.57	-	-	+52.8%	+82.4%*	+88.3%*	+62.1%*
CTXII (pg/mL) – Day 176	182.55	127.07	-	-	-	+29.4%	+41.5%	+29.3%
CTXII (pg/mL) – Day 183	-	104.93	-	-	-	+31.0%	-	+46.4%
NTX (nM BCE) – Day 85	144.09	-	+48.2%*	-	+40.6%*	-	+46.5%*	-

Source: Data pulled from Applicant table in Bone Analysis report (pages 1595 and 1599) of report BMN-111-11-035
Abbreviations: BCE, bone collagen equivalents; BSAP, bone-specific alkaline phosphatase; CTXII, C-terminal telopeptides of type II collagen; NHP, nonhuman primate; NTX, N-telopeptides of type I collagen; PINP, N-terminal propeptide of procollagen I

Gross pathology: The only effects noted macroscopically considered treatment-related were abnormal shapes to the proximal end of the femur, observed in 1 HD male at the end of treatment and in 1 HD female at the recovery necropsy. These observations were considered BMN-111-related since they correlated with the clinical observation of limited use of hips in these animals.

Organ weights: There were no effects on organ weights considered drug-related.

Histopathology: Treatment-related microscopic alterations in nonbone structures were limited to observations at the injection site. Observations included perivascular leukocyte infiltrates (lymphocytes/macrophages and/or eosinophils), fibrosis, hair shaft granulomas, hemorrhage, acute inflammation, and degeneration and/or regeneration of the panniculus muscle were present in the injection sites of animals. When present, the severity of these findings was generally minimal or slight. Although these effects were noted in all groups, including controls, treated animals tended to exhibit more observations, a slightly higher incidence, and/or increase in severity as compared to that seen in controls. Following the reversal period, the incidence and severity of the injection site lesions were reduced from those observed at the end of dosing, suggesting reversibility. In the HD male with a macroscopically observed abnormal shape to the head of the femur, microscopic examination revealed disorganized and enlarged hyaline growth centers of the bones in the acetabulum and degenerate articular cartilage of the acetabula. Similar

sections were not collected from recovery animals. There were no effects on spermatogenic staging or on histology of the male reproductive organs. The majority of animals were immature.

Microscopic effects were evident in the sternal growth plates where thickening of the growth plate characterized by increased layers of chondrocytes in the zones of multiplication and hypertrophy. The incidence and severity of these observations are summarized in Table 58.

Table 58. Microscopic Observations in Sternum

Incidence and Severity of Test Article-Related Microscopic Findings - Dosing Phase

	BMN 111					
Sex	Males			Females		
Dose Level (µg/kg)	20	90	300	20	90	300
Sternum Bone						
Number Examined	4	4	4	4	4	4
Increased Thickness, Growth Plate						
Unremarkable	2	0	0	3	0	0
Minimal	2	3	2	1	4	4
Slight	0	1	2	0	0	0
Average Severity[a]	1.0	1.3	1.5	1.0	1.0	1.0

Severity scale: 1 = minimal and 2 = slight.
a Average severity based on the number of animals affected.

Source: Applicant table (Text Table 1 of Anatomic Pathology report (page 1839) of report BMN-111-11-035)

Sternal growth plates were of normal thickness following recovery.

Histologic examinations of the midpoint of the distal femur, parietal bone from the calvarium cap, and bone marrow from these 2 structures were evaluated. In the femurs of both males and females, increased thickness of the proliferative and hypertrophic/calcified zones of physeal cartilage was observed at all dosages, generally of minimal to minor severity. Disorganization of chondrocytes in the proliferative zone was minimal in males and minimal to mild in females at the various dosages. In the primary spongiosa, increased thickness was also of minimal to mild severity across dosages. Following recovery, minimally increased thickness of the proliferative zone of physeal cartilage was still present in HD males but not in females. There were no effects noted on parietal bone or bone marrow from either source. Although effects were observed in the femur at all dosages, these histologic findings were consistent with exaggeration of the process of normal endochondral bone growth and were not considered adverse.

Histomorphometry: Histomorphometry was performed on the femurs and parietal (calvarium). There were no significant effects on the parietal bone. For the femur, increases in the area (up to 2.5x across sexes) and height (up to 2.3x across sexes) of the various zones (reserve cartilage, multiplication, hypertrophy) of the growth plate were revealed, but the increases were not necessarily dose-related and did not reach statistical significance.

Following recovery, the area and height of these areas were no different from controls for males. In females, the areas and heights of the various zones were lower than those of controls, particularly at the MD and/or HD, with the effects at the HD reaching statistical significance for the area of the zone of hypertrophy (-59%), height of the zone of reserve cartilage (-23%), and height of the zone of hypertrophy (-53%).

A sum of the 3 growth plate zones in femurs was also calculated, and a similar pattern was noted. Increases in area and height were observed in both sexes at all dosages, although the only

increases attaining statistical significance were for the height in MD and HD males (both ~1.3x). Following reversal, slight non-statistically significant increases in area and height were observed in males while statistically significant decreases were seen in the summation of both area (-37%) and height (-35%) for females. Data are summarized in Table 59.

Table 59. Femur Growth Plate Histomorphometry, Summation of 3 Zones (Dosing and Recovery)

Table 13a. Femur Growth Plate Histomorphometry (Sum of Three Zones) – Dosing Phase (Day 183)

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Group	Gender	Data	Summation of Zones Area (mm^2)	Summation of Zones Height (µm)
1 Vehicle	Male	Mean	10.91	490.07
		SD	1.59	60.59
		n	4	4
		stat	n.a.	n.a.
2 Low Dose BMN 111 20 µg/kg	Male	Mean	12.37	506.55
		SD	2.16	55.94
		n	4	4
		stat	n.s.	n.s.
3 Mid Dose BMN 111 90 µg/kg	Male	Mean	14.42	539.35
		SD	1.25	47.72
		n	4	4
		stat	*	n.s.
4 High Dose BMN 111 300 µg/kg	Male	Mean	14.11	531.28
		SD	0.47	60.24
		n	4	4
		stat	*	n.s.
1 Vehicle	Female	Mean	8.32	372.60
		SD	0.50	24.39
		n	4	4
		stat	n.a.	n.a.
2 Low Dose BMN 111 20 µg/kg	Female	Mean	10.34	423.32
		SD	2.09	73.34
		n	4	4
		stat	n.s.	n.s.
3 Mid Dose BMN 111 90 µg/kg	Female	Mean	13.48	581.07
		SD	8.18	376.12
		n	4	4
		stat	n.s.	n.s.
4 High Dose BMN 111 300 µg/kg	Female	Mean	11.78	490.92
		SD	3.32	124.89
		n	4	4
		stat	n.s.	n.s.

n.a.: not applicable
n.s.: not significant
*: p <0.05 when compared to Group 1

Table 13b. Femur Growth Plate Histomorphometry (Sum of Three Zones) – Recovery Phase (Day 211)

Group	Gender	Data	Summation of Zones Area (mm^2)	Summation of Zones Height (µm)
1 Vehicle	Male	Mean	10.56	455.16
		SD	2.52	95.63
		n	3	3
		stat	n.a.	n.a.
4 High Dose BMN 111 300 µg/kg	Male	Mean	13.74	499.02
		SD	3.20	100.30
		n	3	3
		stat	n.s.	n.s.
1 Vehicle	Female	Mean	9.36	410.00
		SD	1.00	32.58
		n	3	3
		stat	n.a.	n.a.
4 High Dose BMN 111 300 µg/kg	Female	Mean	6.66	297.50
		SD	0.99	44.45
		n	3	3
		stat	*	*

n.a.: not applicable
n.s.: not significant
*: p <0.05 when compared to Group 1

Source: Applicant tables (Table 13a and 13b of Anatomic Pathology report (page 1680-1681) of report BMN-111-11-035)

Bone measurements: Measurements of the foramen magnum, skull, and spine were obtained at necropsy. Slight changes in dimension were noted, but the effects did not follow a dose-response, were not statistically significant, and were not considered treatment related. No drug-related effects were seen at the recovery measurements either.

Biomechanical testing: Biomechanical testing revealed no drug-related effects on femur or vertebral strength based on mechanical compression and/or 3-point bend data.

Toxicokinetics: Exposure to BMN-111 increased with dose in a slightly greater than proportional manner. BMN-111 was rapidly absorbed, with t_{max} being achieved within 6 to 9 mins on Day 1 and increasing to 15 to 32 mins by Day 176. After reaching C_{max}, concentrations quickly declined with the mean $t_{1/2}$ ranging from approximately 30 mins to 2 hours. There were no consistent sex-related effects. Data (selected) are summarized in Table 60 (table modified by reviewer to show selected data for sexes combined).

Table 60. Mean Toxicokinetic Data

Mean Toxicokinetic Parameters for BMN 111 in Monkey Plasma

Interval	Group	Dose Level (µg/kg)	Sex	Animal Number	C_{max} (pg/mL)	T_{max} (min)	AUC_{0-t} (pg·min/mL)	AUC_{0-600m} (pg·min/mL)	$t_{1/2}$ (min)	V_z/F (mL/kg)	CL/F (mL/min/kg)	AR AUC_{0-600m}
Day 1	2	20	MF	Mean	1868	6.25	177306	220019	38.6	4831	259	
				SD	1259	3.54	NA	NA	NA	NA	NA	
				CV%	67	57	NA	NA	NA	NA	NA	
				N	8	8	2	2	2	2	2	
	3	90	MF	Mean	19778	8.75	1029969	1070263	28.6	5865	167	
				SD	8355	5.18	1060222	1075869	9.5	4293	135	
				CV%	42	59	103	101	33	73	81	
				N	8	8	8	8	8	8	8	
	4	300	MF	Mean	83575	8.57	4284934	4325905	35.3	4575	118	
				SD	57865	4.97	4746472	4732680	22.9	1716	73	
				CV%	69	58	111	109	65	38	62	
				N	14	14	14	14	14	14	14	
Day 85	2	20	MF	Mean	497	30.0	31138	44150	NA	NA	NA	NA
				SD	97	26.0	NA	NA	NA	NA	NA	NA
				CV%	19	87	NA	NA	NA	NA	NA	NA
				N	3	3	2	2	0	0	0	1
	3	90	MF	Mean	22656	14.6	1291108	1329246	48.7	10190	161	0.944
				SD	25308	7.4	2273603	2291071	45.4	10550	148	0.562
				CV%	112	51	176	172	93	104	92	60
				N	8	8	8	8	6	6	6	8
	4	300	MF	Mean	179700	31.4	18689811	18704639	126	12050	60.9	5.03
				SD	133641	30.5	22058410	22047743	55	16696	69.3	4.78
				CV%	74	97	118	118	43	139	114	95
				N	14	14	14	14	6	6	6	14
Day 176	2	20	MF	Mean	NA	NA	NA	NA	NA	NA	NA	NA
				SD	NA	NA	NA	NA	NA	NA	NA	NA
				CV%	NA	NA	NA	NA	NA	NA	NA	NA
				N	1	1	1	1	0	0	0	1
	3	90	MF	Mean	10984	22.1	489884	523098	39.6	8036	182	0.508
				SD	5510	18.2	395371	400769	35.6	4418	115	0.248
				CV%	50	82	81	77	90	55	63	49
				N	7	7	7	7	4	4	4	7
	4	300	MF	Mean	109393	21.5	9474541	9538698	54.7	4740	83.3	2.81
				SD	98522	17.3	16312616	16295681	25.6	3605	92.7	3.64
				CV%	90	81	172	171	47	76	111	129
				N	14	14	14	14	12	12	12	14

AR Accumulation ratio (AUC_{0-600m}) versus Day 1.
DN Dose normalized.
NA Not applicable.

Source: Applicant table (Material pulled from Table 1 of Toxicokinetic report (page 1459) of report BMN-111-11-035)

Antidrug antibodies: Positive ADAs were detected in several animals during weeks 13 and/or 26. The incidence was 7/8 (88%), 2/8 (25%), and 5/14 (36%) for the LD, MD, and HD groups, respectively. All animals with positive ADA titers on week 13 remained positive at week 26. Plots of the concentration time data for the ADA-positive animals were visually inspected, but no definitive effect on toxicokinetic parameters as a result of ADA positive titer could be ascertained. The higher ADA incidence in the LD group may have been the result of drug interference in the antibody detection assay for animals dosed at the higher dose levels or may indicate an immune-tolerizing effect at the MD/HD.

13.1.3.1.2.6. 44-Week Repeat-Dose Toxicity and Toxicokinetic Study Following Daily Subcutaneous Administration of BMN-111 in Cynomolgus Monkeys With a 13-Week Recovery

Dosages of 0, 25, 75, or 250 µg/kg were administered for 44 weeks to adult (ages 4 to 5 years) animals followed by a 13-week recovery period (Study overview presented in Table 63 and results summarized in Table 64 and following text). The primary findings in this study were exaggerated effects on the skeletal system related to the mechanism of action. Key findings included limited use of hips and hindlimbs at ≥75 µg/kg that were correlated with macroscopic and microscopic alterations to the bones and joints. These effects, along with alterations in growth plate thickness and length of bones, delayed growth plate closure, and increased CTxII and cGMP levels were related to the pharmacology of the drug. Additional effects included increased atrial natriuretic peptide (ANP) levels with associated increases in heart rate and apparent increase in irritation and/or immune response at the injection site. Based on the persistent bone effects that impeded movement at dosages ≥75 µg/kg, the low dose of 25 µg/kg (0.2x (based on week 4 data) the exposure at the MRHD; 0.8x the BSA-based dosed at the MRHD) was considered the NOAEL in this study.

Table 61. 44-Week Study in Adult NHPs, Study Overview

Study Features and Methods	Details
Study Number	BMN-111-11-043
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 25, 75, 250 µg/kg; once daily
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) citrate buffer (b) (4), pH 5.5, containing (b) (4) (w/v) trehalose dihydrate, (b) (4) (w/v) mannitol, (b) (4) mg/mL methionine, and (b) (4) % (w/v) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Cynomolgus monkeys
Number/sex/group:	4
Age:	4-5 years
Satellite groups/unique design:	3 at C and HD for recovery
Deviation from study protocol affecting interpretation of results:	None affecting integrity

Source: Reviewer generated table
Abbreviations: C, control; GLP, good laboratory practice; HD, high dose; NHP, nonhuman primate

Table 62. 44-Week Study in Adult NHPs, Observations

Parameters	Major findings
Mortality	None
Clinical signs	Limited use of the hindlimbs was noted in 5 HD males and 1 HD female, resulting from decreased range of motion in the hip joint (males) or from inflammation of the knee (female). Limited motion was also seen in 1 MD male. These effects appeared as early as Week 21 in several animals while in others it appeared toward the end of the dosing phase and persisted into the recovery period. In animals in which these effects appeared earlier in the dosing phase, the severity tended to increase with dosing duration. Hypoactivity and lateral recumbency were noted for a number of HD males that was attributed to discomfort resulting from the impaired limb mobility.
Body weights/food consumption	No drug-related effects
Ophthalmoscopy	No effects
ECG	No effects on blood pressure. Heart rates were statistically increased (↑ 27%) in HD males only at the end of treatment and in HD females through most of the treatment period (↑ 27%-32%). Statistically significant effects were also noted in MD females (↑ 22% to 28%) through approximately the first 10 weeks of treatment. Recovery was evident by the end of the reversal period. Slightly shorter QT intervals (not statistically significant) were associated with the increased heart rate, but there were no effects on QTc, PR, QRS durations or qualitative ECGs.
Hematology	No adverse effects
Clinical chemistry	No adverse effects
Urinalysis	No effects
Reproductive assessment	No effect on menstrual cyclicity or spermatogenic parameters.
Atrial and brain natriuretic peptide	The levels of ANP were increased as much as 1.5-fold in males and 16-fold in HD females at various time points (statistically significant), but the excessive variability confounds data interpretability. There were no meaningful changes on BNP levels.
BMC/BMD (in vivo)	DEXA scanning for whole body, femur, and tibia/fibular revealed no effects during treatment or recovery.

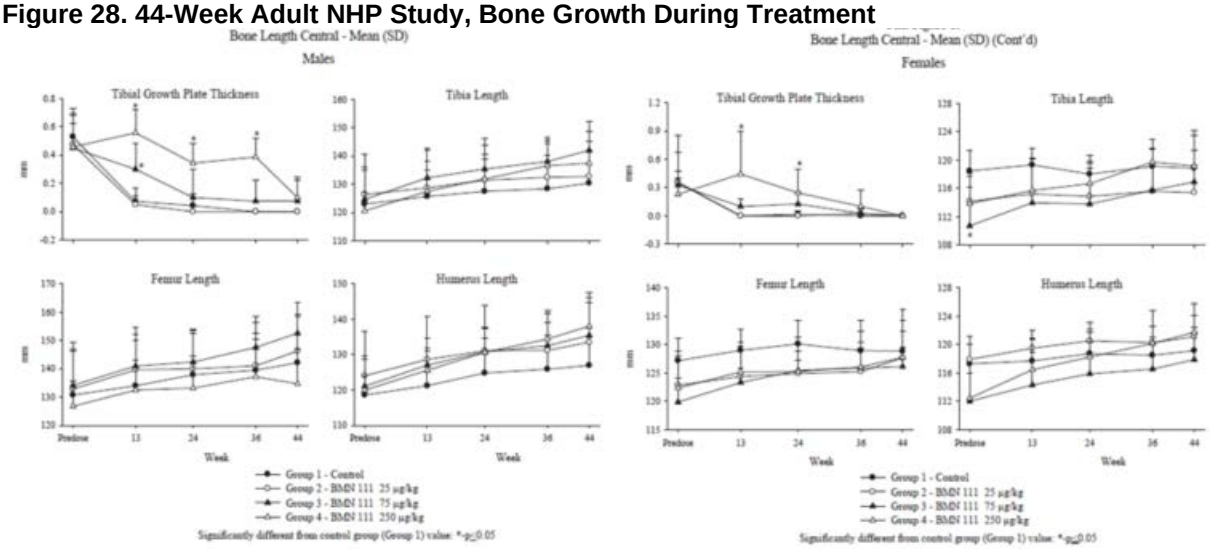
Source: Reviewer generated table
Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; DEXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; HD, high dose; MD, medium dose; NHP, nonhuman primate

cGMP levels: cGMP levels were increased in a dose-related manner at all dosages. Over time, the magnitude of the response decreased at the LD and MD, but remained elevated at the HD. High variability was evident at most time points, particularly at the MD and HD. There was no difference in response between the sexes.

Bone growth: In vivo, proximal tibia growth plate thickness was increased at the MD and HD in both sexes. These effects were associated with a delay in growth plate closure and slight lengthening of the long bones from baseline. Increased thickness was generally greatest at Week 13 before tapering down with continued treatment. By Week 44, there were no differences in growth plate thickness compared to control, although the growth plates remained open for some MD and HD animals. Tibial growth plates were closed for most controls by Week 13. In drug-treated groups, growth plate closure occurred quickly once treatment ended, and all were closed by the end of recovery. The lengths of the femur, tibia, and humerus increased in all groups over the course of the study. For both sexes, increased growth (statistically significant compared to

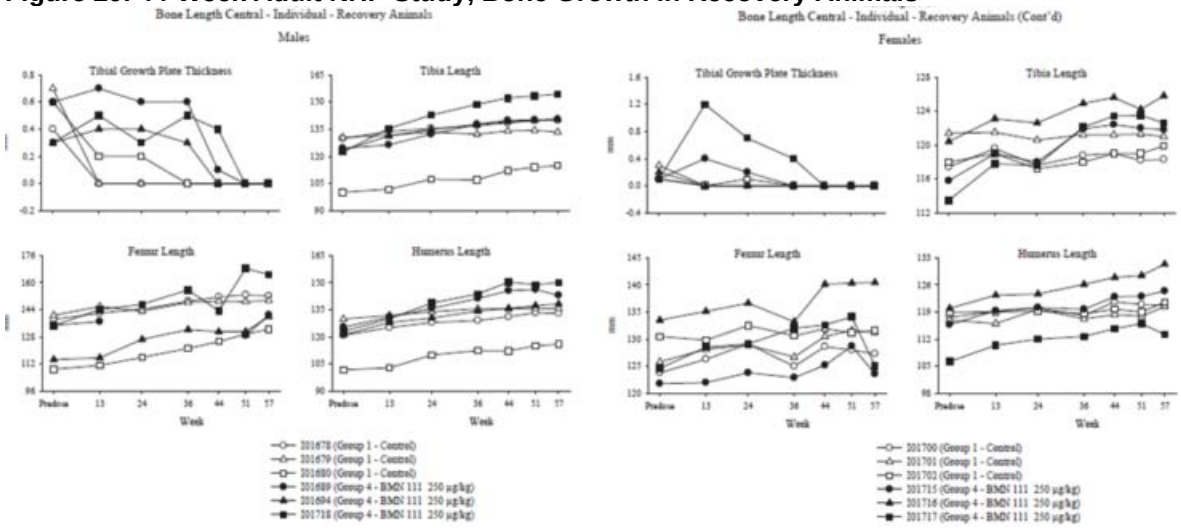
predose lengths) was seen as compared to that occurring in controls. During recovery, changes in HD animals during the treatment period were sustained. Data are summarized in Figure 28 and Figure 29.

Figure 28. 44-Week Adult NHP Study, Bone Growth During Treatment



Source: Applicant figure (Text Figure 19 of Bone Interpretation report (page 3069-3070) of report BMN-111-11-043)
Abbreviations: NHP, nonhuman primate

Figure 29. 44-Week Adult NHP Study, Bone Growth in Recovery Animals



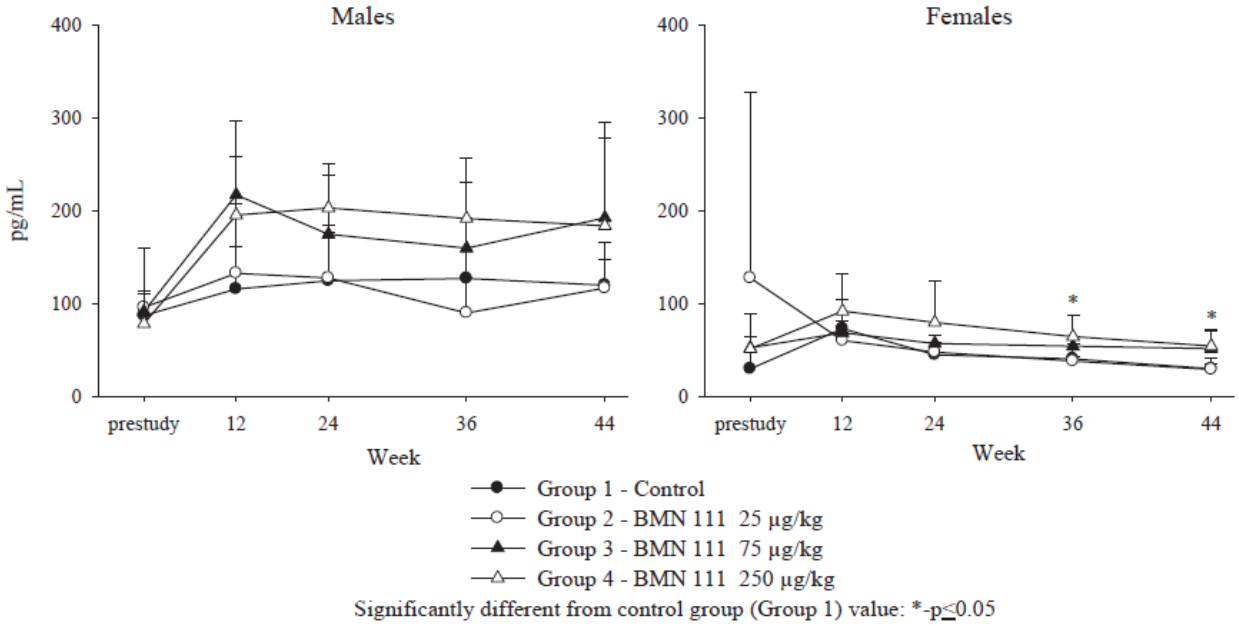
Source: Applicant figure (Text Figure 20 of Bone Interpretation report (page 3071-3072) of report BMN-111-11-043)
Abbreviations: NHP, nonhuman primate

There were no effects considered drug-related on spine length, skull width/length, or on foramen magnum width/length.

Bone biomarkers: Markers of bone formation (P1NP, osteocalcin (OC), and BSAP) were similar to controls throughout the treatment and recovery periods. Bone resorption markers [C-telopeptides of type I collagen (CTx1) and N-telopeptides of type I collagen (NTx)] were also not affected by treatment. The level of the cartilage degradation marker C-telopeptides of type II collagen (CTxII) was slightly increased at the MD and HD of both sexes, although it attained

statistical significance only at the HD in females at Weeks 36 (1.6x) and 44 (1.8x) and remained increased in HD females during recovery. These data are summarized in Figure 30.

Figure 30. 44-Week Adult NHP Study, CTxII Levels



Source: Applicant figure (Text Figure 11 of Bone Interpretation report (page 3060) of report BMN-111-11-043)
Abbreviations: NHP, nonhuman primate; CTxII, C-telopeptides of type II collagen

Gross pathology: Macroscopic observations considered BMN-111 related were noted on the femur, pelvic acetabulum, tibia, patella, humerus, scapula, and ulna of 1 MD male and HD animals of both sexes (4 males, 3 females). The effects on femurs and pelvic acetabula correlated with limited use of hindlimbs observed clinically for most animals, and most observations had microscopic correlates. Drug-related observations are summarized in Table 63.

Table 63. 44-Week Adult NHP Study, Gross Postmortem Observations

Test Article-Related Macroscopic Observations - Terminal Necropsy

	BMN 111							
Sex	Males				Females			
Dose Level (µg/kg)	0	25	75	250	0	25	75	250
Number Examined	4	4	4	4	4	4	4	4
Femur								
Abnormal shape[a]	0	0	0	1	0	0	0	1
Depressed area	0	0	1	2	0	0	0	0
Raised area	0	0	1	3	0	0	0	2
Fracture	0	0	0	2	0	0	0	0
Thickened joint capsule[a]	0	0	0	1	0	0	0	0
Bone, Other[b]								
Abnormal shape[a]	0	0	0	1	0	0	0	0
Depressed area	0	0	1	2	0	0	0	0
Raised area	0	0	0	0	0	0	0	1
Shallow acetabulum[a]	0	0	0	2	0	0	0	0
Luxation[a]	0	0	0	0	0	0	0	1

a All or some recorded as a tissue comment or an observation comment.
b Pelvis (acetabulum), tibia, patella, humerus, scapula, and/or ulna.

Source: Applicant table (Text Table 1 of Anatomic Pathology report (page 3139) of report BMN-111-11-043)
Abbreviations: NHP, nonhuman primate

The depressed areas in affected bones was typically described as articular cartilage erosion (seen on femurs, humerus, acetabular rim, tibia, and ulna, and/or scapula) while the raised area comprised periarticular bone growth (seen on the femur). The abnormal shape was due to bone curvature (femur and tibia). Shallow acetabulum was sometimes associated with a thickened joint capsule, and fractures were seen at the femoral neck. The luxation seen in the HD female was described as a nonreducible patella lateral luxation. Following recovery, effects were evident in the femur (depressed area, raised area) and pelvis acetabulum and/or tibia depressed area) of 2 HD males.

Organ weights: No drug-related effects noted.

Histopathology: Treatment-related microscopic observations were seen at the injection site and on bones.

Effects were seen at the injection site of animals in all groups. However, BMN-111 appeared to be slightly more irritating and/or immunogenic as there was a dose-related increase in the incidence and severity of fibrosis and perivascular infiltrates of mononuclear cells, especially in females, as compared to the effects seen in controls. Other injection site observations included hemorrhage, perivascular infiltrates of eosinophils, and/or small foci of granulomatous inflammation on hair shafts. The severity of the findings was generally minimal, although in some cases they were slight to moderate in severity. At recovery, reversal of effects was ongoing but full recovery was not seen; mononuclear infiltrates (minimal severity) were still evident in some animals and fibrosis (minimal severity) was also evident in a single HD male.

Microscopic effects were note at various sites in multiple bones, primarily at the HD, that correlated with the macroscopic observations; these findings were generally considered secondary to the exaggerated pharmacology of the drug. The most notable effect was an increase in growth plate thickness in the sternum that was observed in all drug-treated females related to the pharmacologic activity of the drug. The observations are summarized in Table 64.

Table 64. 44-Week Adult NHP Study, Drug-Related Microscopic Observations

	BMN 111							
Sex	Males				Females			
Dose Level (µg/kg)	0	25	75	250	0	25	75	250
Bone, Other[a]								
Number Examined	1	0	1	2	1	0	0	1
Increased Thickness, Growth Plate								
Slight	0	0	0	2	0	0	0	0
Moderate	0	0	0	0	0	0	0	1
Erosion, Articular Cartilage								
Minimal	0	0	0	0	0	0	0	1
Moderate	0	0	1	2	0	0	0	0
Exostosis								
Minimal	0	0	0	0	0	0	0	1
Fracture								
Minimal	0	0	0	1	0	0	0	0
Fibrosis, Joint Capsule								
Moderate	0	0	1	1	0	0	0	0
Marked	0	0	0	1	0	0	0	0
Hyperplasia, Synovium								
Slight	0	0	1	0	0	0	0	0
Sternum								
Number Examined	4	4	4	4	4	4	4	4
Increased Thickness, Growth Plate								
Minimal	0	0	0	0	0	4	4	4

a Pelvis (acetabulum), tibia, humerus, scapula, and/or ulna.

Source: Applicant table (Text Table 3 of Anatomic Pathology report (page 3141) of report BMN-111-11-043)
Abbreviations: BMN-111, vosoritide; NHP, nonhuman primate

Evaluation of the femur at the end of treatment revealed complete or partial closure of the growth plate in 3, 3, 1, and 2 females in the control, LD, MD, and HD groups (n=4/sex/group), respectively. No closure was seen in males or the remaining females. At the end of recovery, complete closure was seen in 1 male and 3 females controls while partial closure was seen in 1 male and 2 females HD animals (n=3/sex/group). Taken together, these data suggest that BMN-111 treatment at the MD and HD leads to delayed closure of the physis, although the preponderance of closure in the females may also be indicative of the effect of estrogens on long bone growth.

Additional histologic findings in the femur included proliferation of chondrocytes in the proliferative zone of the physis in HD animals, and increased thickness of trabecular bone in the epiphysis at the HD of both sexes and metaphysis of HD females. The proliferation of chondrocytes is consistent with bone growth and increased thickness of trabecular bone is consistent with closure of the physis. Taken together, the proliferation of chondrocytes at the MD and HD was considered drug-related, but the relationship of trabecular thickness to drug treatment was concluded to be uncertain by the Applicant. The incidence and severity are summarized in Table 65.

Table 65. 44-Week Adult NHP Study, Femur Observations

Summary of Selected Histologic Findings in the Epiphysis, Metaphysis and Physis: Dosing Phase, Day 309									
Histologic Finding, Incidence and Incidence by Severity		Males				*Females*			
		BMN111 (µg/kg)				*BMN111 (µg/kg)*			
		0	25	75	250	*0*	*25*	*75*	*250*
Femur, Epiphysis									
Thickness Increased, trabecular bone	Incidence	2/4	4/4	3/4	3/4	*0/4*	*2/4*	*2/4*	*2/4*
	minimal	1/4	2/4	1/4	0/4	*0/4*	*1/4*	*1/4*	*2/4*
	mild	1/4	2/4	2/4	2/4	*0/4*	*1/4*	*1/4*	*0/4*
	moderate	0/4	0/4	0/4	1/4	*0/4*	*0/4*	*0/4*	*0/4*
	Sum of Severity Scores	3	6	5	7	*0*	*3*	*3*	*2*
Femur, Metaphysis									
Thickness Increased, trabecular bone	Incidence	1/4	1/4	3/4	2/4	*0/4*	*0/4*	*1/4*	*3/4*
	minimal	0/4	0/4	2/4	1/4	*0/4*	*0/4*	*0/4*	*3/4*
	mild	1/4	1/4	1/4	1/4	*0/4*	*0/4*	*1/4*	*0/4*
	Sum of Severity Scores	2	2	4	3	*0*	*0*	*2*	*3*
Femur, Physis									
Proliferation, Chondrocyte, proliferative zone	Incidence	2/4	1/4	4/4	4/4	*0/4*	*1/4*	*2/4*	*3/4*
	minimal	2/4	1/4	3/4	2/4	*0/4*	*1/4*	*2/4*	*2/4*
	mild	0/4	0/4	1/4	2/4	*0/4*	*0/4*	*0/4*	*1/4*
	Sum of Severity Scores	2	1	5	6	*0*	*1*	*2*	*4*
Sum of Severity Scores: Combined		7	9	14	16	*0*	*4*	*7*	*9*
Mean Group Severity Scores: Combined		1.8	2.3	3.5	4.0	*0.0*	*1.0*	*1.8*	*2.3*

Incidence = Number Affected / Number Evaluated; Sum of Severity Scores = the sum of the incidence of each finding at each severity for males and females X the numerical score for that severity; Mean Group Severity Score = The sum of severity scores for each group divided by the number of animals evaluated in each group.

Source: Applicant table (Text Table 2 (page 56) of report BMN-111-11-043)
Abbreviations: BMN-111, vosoritide; NHP, nonhuman primate

Following recovery, chondrocyte proliferation and increased trabecular thickness were still seen in HD animals

Histomorphometry (femur and parietal bone): The area and height of the zones of reserve cartilage, multiplication, and hypertrophy were increased in HD males. At the end of treatment, the areas of these zones were increased 1.5- to 1.7-fold and the heights were increased 1.2- to 1.6-fold. With the effects in the zone of multiplication reaching statistical significance. There were no effects evident at the end of recovery or in females at any timepoint. For parietal bone, no drug-related effects were seen.

Biomechanical testing: There were no drug-related effects on femur or vertebral strength based on mechanical compression and/or 3-point bend data.

Toxicokinetics: Exposure to BMN-111 increased with dose in a greater than proportional manner. Mean exposures tended to be higher following multiple dosing as compared to following a single dose at the MD and HD but not at the LD; the increase in exposure with dose generally correlated with a modest decrease in clearance. Plasma concentrations tended to be highly variable within each dose group, with CVs greater than 30%. Following administration, BMN-111 was rapidly absorbed with a t_{max} typically achieved within 20 mins. The $t_{1/2}$ was also short, generally less than 1 hour. There were no sex-related effects at the LD and MD; at the HD the mean C_{max} in females were greater than in males at the corresponding time points on all

sampling days. Data at the various time points are shown in Table 66 (modified by reviewer to only present mean data for sexes combined).

Table 66. 44-Week Adult NHP Study, Exposure Summary

Summary of the Mean Toxicokinetic Parameters for BMN 111 in Monkey Plasma: Day 2

Dose Group	Dose Level (µg/kg)	Sex		C_{max} (pg/mL)	DN C_{max} [(pg/mL)/(µg/kg)]	T_{max} (hr)	AUC_{0-6} (pg·hr/mL)	DN AUC_{0-6} [(pg·hr/mL)/(µg/kg)]	AUC_{0-t} (pg·hr/mL)	$t_{1/2}$ (hr)	CL/F (mL/hr/kg)	V_z/F (mL/kg)
2	25											
	Combined M and F		Mean	2890	116	0.0830	1380	55.2	1130	NA	NA	NA
			SD	1680	67.2	0	NA	NA	NA	NA	NA	NA
			N	6	6	6	1	1	1	0	0	0
3	75											
	Combined M and F		Mean	13700	183	0.167	12300	163	10700	0.512	5780	3500
			SD	8110	108	0.0893	9670	129	8330	0.297	2900	1080
			N	8	8	8	7	7	7	5	5	5
4	250											
	Combined M and F		Mean	79400	318	0.208	91000	364	88900	0.510	5110	2840
			SD	40500	162	0.117	90600	363	91700	0.244	3450	1300
			N	14	14	14	14	14	14	13	13	13

Summary of the Mean Toxicokinetic Parameters for BMN 111 in Monkey Plasma: Week 4

Dose Group	Dose Level (µg/kg)	Sex		C_{max} (pg/mL)	DN C_{max} [(pg/mL)/(µg/kg)]	T_{max} (hr)	AUC_{0-6} (pg·hr/mL)	DN AUC_{0-6} [(pg·hr/mL)/(µg/kg)]	AUC_{0-t} (pg·hr/mL)	$t_{1/2}$ (hr)	CL/F (mL/hr/kg)	V_z/F (mL/kg)
2	25											
	Combined M and F		Mean	2390	95.5	0.107	1230	49.1	966	NA	NA	NA
			SD	909	36.4	0.0631	282	11.3	199	NA	NA	NA
			N	7	7	7	3	3	3	0	0	0
3	75											
	Combined M and F		Mean	20100	267	0.208	17400	232	15400	0.462	4920	2960
			SD	6490	86.6	0.0773	8830	118	8110	0.197	2440	1560
			N	8	8	8	8	8	8	6	6	6
4	250											
	Combined M and F		Mean	113000	451	0.256	164000	656	162000	0.696	2970	2500
			SD	47000	188	0.0832	125000	498	125000	0.221	3840	2490
			N	14	14	14	14	14	14	14	14	14

Summary of the Mean Toxicokinetic Parameters for BMN 111 in Monkey Plasma: Week 12

Dose Group	Dose Level (µg/kg)	Sex		C_{max} (pg/mL)	DN C_{max} [(pg/mL)/(µg/kg)]	T_{max} (hr)	AUC_{0-t} (pg·hr/mL)	DN AUC_{0-t} [(pg·hr/mL)/(µg/kg)]	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)	CL/F (mL/hr/kg)	V_z/F (mL/kg)
2	25											
	Combined M and F		Mean	1900	76.0	0.150	1270	50.7	1060	NA	NA	NA
			SD	1120	45.0	0.0915	NA	NA	NA	NA	NA	NA
			N	5	5	5	1	1	1	0	0	0
3	75											
	Combined M and F		Mean	18300	245	0.262	17900	239	16300	0.716	7540	8220
			SD	20800	277	0.122	16400	219	15500	0.210	4810	6740
			N	7	7	7	7	7	7	5	5	5
4	250											
	Combined M and F		Mean	187000	748	0.321	243000	972	241000	0.718	3480	3570
			SD	181000	723	0.206	214000	854	215000	0.247	5930	7700
			N	14	14	14	14	14	14	14	14	14

Summary of the Mean Toxicokinetic Parameters for BMN 111 in Monkey Plasma: Week 44

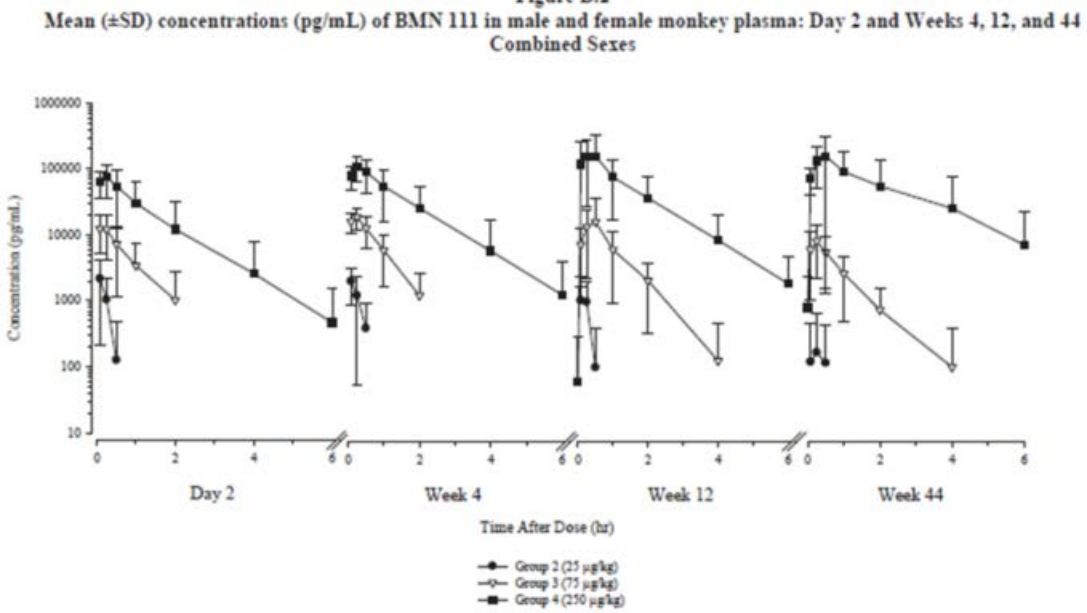
Dose Group	Dose Level (µg/kg)	Sex		C_{max} (pg/mL)	DN C_{max} [(pg/mL)/(µg/kg)]	T_{max} (hr)	AUC_{0-t} (pg·hr/mL)	DN AUC_{0-t} [(pg·hr/mL)/(µg/kg)]	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)	CL/F (mL/hr/kg)	V_z/F (mL/kg)
2	25	M	Mean	1170	46.8	0.167	NA	NA	NA	NA	NA	NA
			SD	NA	NA	NA	NA	NA	NA	NA	NA	NA
			N	2	2	2	0	0	0	0	0	0
3	75											
	Combined M and F		Mean	8490	113	0.302	9130	122	7990	0.582	6050	5040
			SD	5810	77.4	0.292	4600	61.3	4070	0.0575	1260	890
			N	8	8	8	7	7	7	3	3	3
4	250											
	Combined M and F		Mean	178000	711	0.345	311000	1240	310000	1.02	2380	3250
			SD	147000	588	0.221	377000	1510	378000	0.468	2100	3980
			N	14	14	14	14	14	14	14	14	14

Note All Group 2 Females had concentration values that were below the limit of quantitation; therefore, no toxicokinetic analysis was performed.

Source: Applicant tables (Material pulled from Tables 1-4 of Toxicokinetic report (pages 2470-2477) of report BMN-111-11-043)
Abbreviations: BMN-111, vosoritide; NHP, nonhuman primate

Data are shown graphically in Figure 31.

Figure 31. 44-Week Adult NHP Study, Exposure at Various Timepoints



Source: Applicant figure (Figure B2 of Toxicokinetic report (page 2509) of report BMN-111-11-043)
Abbreviations: NHP, nonhuman primate; SD, standard deviation

Antidrug antibodies: The incidence of animals testing positive for anti BMN-111 antibodies increased with study duration. ADA appeared in more animals at the LD and MD early in the study, with the majority of BMN-111 treated animals having ADA detected by Week 44. ADA was still detectable in most males at the end of the reversal period. Data are shown in Table 67.

Table 67. 44-Week Adult NHP Study, ADA Incidence

	Number of Animals With ADA Detected (Based on Screen)					
Dosage (µg/kg)	# of animals (M/F)	Week 4	Week 12	Week 24	Week 44	Recovery Week 13[a]
0	7/7	0/0	0/0	0/0	0/0	0/0
25	4/4	1/0	3/2	4/3	4/4	-
75	4/4	1/1	3/2	3/4	3/4	-
250	7/7	0/1	1/2	2/2	4/7	2/0

Source: Data compiled from Tables C1-C5 of the Toxicokinetic report (pages 2513-2517) of report BMN-111-11-043
[a] n=3/sex evaluated
Abbreviations: ADA, antidrug antibodies; NHP, nonhuman primate

A direct correlation between ADA incidence or titer values and exposure was not possible, but the ADA may have contributed to the observed variability in exposure.

13.1.3.2. Genetic Toxicology

BMN-111 is a peptide and genetic toxicology studies are not warranted. No genetic toxicology studies were conducted.

13.1.3.3. Carcinogenicity

Carcinogenicity studies were not performed. In vivo carcinogenicity studies were considered highly likely to be infeasible and/or uninterpretable. Based on the mechanism of action, however, vosoritide is not expected to be tumorigenic.

13.1.3.4. Reproductive Toxicology

13.1.3.4.1. Study of Fertility and Early Embryonic Development to Implantation of BMN-111 Administered by Subcutaneous Injection in Rats

Key Study Findings: BMN-111 at dosages of 0, 90, 270, or 540 µg/kg were administered (Study overview presented in Table 70 and results summarized in Table 71 and following text). Males were treated for 4 weeks prior to cohabitation with females that were treated for 2 weeks prior to cohabitation. Treatment continued through mating until termination (after 50 to 52 days) for males and until gestation Day 7 in females (anywhere from 23 to 44 days). Clinical signs of altered gait, limited use of the hindlimbs, vocalization when touched, and hunched posture were observed at all dosages in males and at the MD/HD in females. Kinking of the tail was also observed at the HD. Regarding reproductive endpoints, seminal vesicle weights and spermatid counts/density in the testes (but not in epididymal sperm count/density) were reduced at all dosages, although the reductions did not necessarily reach statistical significance and the counts were within the historical range. There was no effect on sperm motility. An increase in the time to mate was evident at the MD and HD; this was likely secondary to the ongoing clinical effects on mobility resulting from bone overgrowth although a direct effect on male reproductive tissues cannot be completely ruled out. No effects were seen on estrous cyclicity or other female reproductive parameters evaluated. The effects observed in males had no overall effect on fertility as the number of animals mating or the ensuing number of implantations was similar between groups. The effects seen in the fertility study were consistent with the decreased sperm density and reduced motility reported at dosages $\geq$150 µg/kg in adult rats following 26 weeks of treatment. In contrast, there were no effects on the number of animals mating or number of implants in a juvenile animal study following 26 weeks of treatment at dosages up to 90 µg/kg. Regarding females, no effects on estrous cyclicity have been reported in the previously conducted repeat dose studies.

In summary, the data from the fertility and repeat dose toxicity studies suggest that BMN-111 exerts effects on male reproductive tissues. However, there were no overall effects on the ability of animals to initiate or maintain a pregnancy. The clinical signs were a result of exaggerated pharmacology and were considered adverse since they had a severe impact on the animals. As a result, a NOAEL was not identified for males and was considered the LD for females. However, there were no effects on endpoints related to fertility endpoints and the HD (540 µg/kg) was considered the NOAEL (14.6 (male) and 10.3x (female) the exposure at the MRHD; 8.6x the BSA-based dose at the MRHD).

Table 68. Rat Fertility Study, Overview

Study Features and Methods	Details
Study number	BMN-111-14-060
GLP compliance:	Yes
Dose and frequency of dosing:	0, 90, 270, 540 µg/kg; once daily
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) citrate buffer (b) (4), pH 5.5, containing (b) (4) trehalose dihydrate, (b) (4) mannitol, (b) (4) methionine, and (b) (4) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Rat / Crl:CD(SD)
Number/sex/group:	25
Satellite groups/unique design:	3 (C) or 6 (drug treated)/sex for TK
Deviation from study protocol affecting interpretation of results:	None affecting study integrity

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; SD, Sprague Dawley; TK, toxicokinetics

Table 69. Rat Fertility Study, Observations

Parameters	Major Findings
Mortality	None
Clinical signs	Hunched posture and irregular gait were observed at an increased incidence in all drug-treated male groups and in MD/HD females. These effects were also associated with limited use of hindlimbs at the MD/HD. Additional effects observed in males at the MD/HD included increased incidences of bent/kinked tail, vocalization to the touch, and chromorhinorrhea
Body weights/food consumption	Reductions in weight gain in excess of 20% were observed in both sexes, but effects on absolute weights were minimal (<5%)
Mating/fertility	Time to mate was increased at the HD as reflected by a reduced number of animals mating during the first week of cohabitation and an increased number mating during the second week. There were no effects on the ensuing number of pregnancies.
Estrous cyclicity	No effects noted
Necropsy findings	In males, effects were noted on seminal vesicle weights in all groups (reduced by <22%). There were no effects on the weights of other reproductive tissues. Testicular sperm counts (↓ 29%) and density (↓ 30%) were considered reduced at the HD (but within the historical range). Lesser effects were seen at the LD and MD. In females, there were no effects on the numbers of corpora lutea, implantations, or embryo/fetal viability.

Source: Reviewer generated table
Abbreviations: HD, high dose; LD, low dose; MD, medium dose

Toxicokinetics: Peak plasma levels occurred 5 to 15 mins after dose administration, and levels remained quantifiable for up to 2 hours following dosing on Day 1 and for up to 3 hours following dosing at the later time points evaluated. Exposure increased with dose, although not necessarily in a dose-proportional manner. Drug levels tended to be slightly higher in males as compared to females. Evidence of accumulation was seen with repeated dosing and clearance decreased with increasing dose levels and dosing duration. Data are summarized in Table 70.

Table 70. Rat Fertility Study, Exposure Data

Gender	Day	Dose (µg/kg)	Tmax (min)	Cmax (ng/mL)	AUC(0-t) (min*ng/mL)	AUC(0-inf) (min*ng/mL)	T1/2 (min)	Vz/F (mL/kg)	CL/F (mL/min/kg)
Female	1	90	5.00	5.06	91.7	92.9	9.36	13100	969
	1	270	5.00	17.0	352	355	12.0	13200	761
	1	540	5.00	38.3	1280	1290	14.8	8990	420
	GD 7	90*	15.0	8.46	617	628	34.1	7040	143
	GD 7	270	15.0	16.3	854	864	27.2	12300	313
	GD 7	540	5.00	45.0	3000	3280	45.9	10900	165
Male	1	90	5.00	10.0	196	196	10.8	7140	458
	1	270	15.0	44.5	1490	1500	19.1	4970	180
	1	540	15.0	82.1	2620	2630	17.0	5040	206
	50	90	5.00	13.6	406	411	35.9	11300	219
	50	270*	5.00	72.8	2660	2710	28.5	4090	99.7
	50	540	15.0	86.1	4250	4510	46.0	7940	120

*Fails the Rsq<0.800 criteria, therefore AUC(0-inf), T1/2, Vz/F and CL/F listed for this group are for information purposes only and are not reportable.
Source: Applicant table (Tables 2.1 of Toxicokinetic report (page 439) of report BMN-111-14-060)

ADA titers were observed in the majority of drug-treated animals, but a formal assessment of the effect on exposure was not performed as part of the study.

13.1.3.4.2. An Embryo-Fetal Development Study of BMN-111 Administered by Subcutaneous Injection in Rats

Key Study Findings: BMN-111 was administered from GD 6 to 17 to presumed gravid rats at dosages of 0, 90, 270, or 540 µg/kg (Study overview presented in Table 71 and results summarized in Table 72 and following text). No drug-related adverse effects on fetal development were noted. The HD (540 µg/kg) was identified as the NOAEL (13.6x the exposure at the MRHD; 8.6x the BSA-based dose at the MRHD).

Table 71. Rat EFD Study, Overview

Study Features and Methods	Details
Study Number	BMN-111-14-061
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 90, 270, 540 µg/kg; once daily
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) citrate buffer (b) (4), pH 5.5, containing (b) (4) trehalose dihydrate, (b) (4) mannitol, (b) (4) methionine, and (b) (4) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Rat / Crl:CD(SD)
Number/group:	25
Satellite groups/unique design:	3 (C) or 6 (drug treated) for TK
Deviation from study protocol affecting interpretation of results:	None affecting study integrity

Source: Reviewer generated table
Abbreviations: EFD, embryo-fetal development; GLP, good laboratory practice; SD, Sprague Dawley; TK, toxicokinetics

Table 72. Rat EFD Study, Observations

Parameters	Major Findings
Mortality	None
Clinical signs	No adverse effects reported
Body weights/food consumption	No adverse effects noted
Cesarean Section Observations	There were no effects on the numbers of corpora lutea, implantations, pre- or post-implantation loss, or embryo/fetal viability.
Fetal Observations	There were no effects on sex ratio or body weights. Fetal gross, visceral, and skeletal examinations revealed no drug-related effects.

Source: Reviewer generated table
Abbreviations: EFD, embryo-fetal development

Toxicokinetics: The t_{max} occurred between 5 and 15 mins after dose administration. Drug levels increased with dose in an approximately proportional manner. There was slight accumulation with repeated dosing; clearance also decreased with repeated dosing. Data are summarized in Table 73.

Table 73. Rat EFD Study, Exposure Data

Gender	Day	Dose (µg/kg)	Tmax (min)	Cmax (ng/mL)	AUC(0-t) (min*ng/mL)	AUC(0-inf) (min*ng/mL)	T1/2 (min)	Vz/F (mL/kg)	CL/F (mL/min/kg)
Female	DG 6	90	5	10.9	216	226	13.8	7930	398
		270*	15	37.3	1170	1180	18.2	5990	228
		540	5	47.5	1520	1530	13.6	6940	354
	DG 17	90	5	10.8	530	534	25.0	6070	169
		270	15	35.5	1750	1750	19.7	4390	154
		540	15	64.5	3950	3970	20.8	4080	136

* Fails the Rsq<0.800 criteria, therefore the $AUC_{(0\text{-inf})}$, $T_{1/2}$, Vz/F and CL/F parameters listed in this row are for information purposes only and are not reportable.

Source: Applicant table (Tables 2.1 of Toxicokinetic report (page 313) of report BMN-111-14-061)
Abbreviations: EFD, embryo-fetal development

13.1.3.4.3. An Embryo-Fetal Development Study of BMN-111 by Subcutaneous Injection in Rabbits

Key Study Findings: BMN-111 was administered from GD 7 to 19 to presumed gravid rabbits at dosages of 0, 45, 135, or 240 µg/kg (Study overview presented in Table 74 and results summarized in Table 75 and following text). No drug-related adverse effects on fetal development were observed and the HD (240 µg/kg) was considered the NOAEL (200x the exposure at the MRHD; 7.7x the BSA-based dose at the MRHD).

Table 74. Rabbit EFD Study, Overview

Study Features and Methods	Details
Study Number	BMN-111-14-081
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 45, 135, 240 µg/kg; once daily
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) citrate buffer (b) (4), pH 5.5, containing (b) (4)) trehalose dihydrate, (b) (4) mannitol, (b) (4) methionine, and (b) (4) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Rabbit / New Zealand White [Hra:(NZW)SPF]
Number/group:	20
Satellite groups/unique design:	2 (C) or 3 (drug treated) for TK
Deviation from study protocol affecting interpretation of results:	None affecting study integrity

Source: Reviewer generated table
Abbreviations: EFD, embryo-fetal development; GLP, good laboratory practice; TK, toxicokinetics

Table 75. Rabbit EFD Study, Observations

Parameters	Major findings
Mortality	None
Clinical signs	No adverse effects reported
Body weights/food consumption	No adverse effects noted
Cesarean Section Observations	The numbers of pregnant animals, corpora lutea, implantations, pre- or postimplantation loss, litter size, and total number of fetuses were comparable between groups.
Fetal Observations	There were no effects on sex ratio or body weights. Fetal gross, visceral, and skeletal development was not altered by drug treatment.

Source: Reviewer generated table
Abbreviations: EFD, embryo-fetal development

Toxicokinetics: The t_{max} occurred between 60 and 110 mins after dose administration. Drug levels increased in a greater than proportional manner over the doses evaluated. There was no accumulation as exposure decreased slightly with repeated dosing. Applicant data are summarized in Table 76 (Applicant tables modified by reviewer to only present mean and standard deviation (SD) for each dose level).

Table 76. Rabbit EFD Study, Exposure Data

Dose (µg/kg)	Day		Tmax (min)	Cmax (ng/mL)	AUC(0-t) (min*ng/mL)	AUC(0-inf) (min*ng/mL)	T1/2 (min)	Vz/F (mL/kg)	CL/F (mL/min/kg)
45	7	N	3	3	3	3	3	3	3
		Mean	110	42.5	7920	8070	46.3	376	5.59
		SD	17	2.57	441	358	10.6	99.1	0.242
	19	N	3	3	3	3	3	3	3
		Mean	70	38.5	5950	5970	33.2	362	7.54
		SD	35	9.54	236	221	3.41	50.0	0.276
135	7	N	3	3	3	3	3	3	3
		Mean	60	149	27100	27800	53.8	380	4.95
		SD	30	22.1	4500	4950	10.7	70.7	0.833
	19	N	3	3	3	3	3	3	3
		Mean	70	155	24900	24900	31.4	255	5.58
		SD	17	40.1	5390	5380	6.23	77.7	1.20
240	7	N	3	3	3	3	3	3	3
		Mean	80	351	60300	62500	60.7	337	3.90
		SD	17	53.3	8280	9210	13.0	50.9	0.628
	19	N	3	3	3	3	3	3	3
		Mean	80	379	58000	58800	48.2	288	4.10
		SD	17	88.2	5260	4990	15.6	106	0.366

Source: Applicant table (Material pulled from Tables 2.3, 2.5, 2.7, 2.9, 2.11, and 2.13 of Toxicokinetic report (pages 340-345) of report BMN-111-14-081)
Abbreviations: EFD, embryo-fetal development

13.1.3.4.4. A Subcutaneous Developmental and Perinatal/Postnatal Reproduction Toxicity Study of BMN-111 in Rats, Including Postnatal Behavioral/Functional Evaluation

Key Study Findings: BMN-111 was administered at dosages of 0, 90, 270, and 540 µg/kg once daily from gestation Day 6 through postpartum Day 20 (Study overview presented in Table 77 and results summarized in Table 78 and following text). There were no effects on maternal animals or their ability to maintain a pregnancy, parturition, or care of the litter. No effects were noted on offspring growth or development or on their ability to reproduce. The NOAEL was considered the HD of 540 µg/kg (13.6 the exposure at the MRHD; 8.6x the BSA-based dose at the MRHD (based on the embryo-fetal development study data)).

Table 77. Rat PPND Study, Overview

Study Features and Methods	Details
Study Number	BMN-111-18-103
GLP Compliance:	Yes
Conducting laboratory	(b) (4)
Dose and frequency of dosing:	0, 90, 270, 540 µg/kg; once daily
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) citrate buffer (b) (4) pH 5.5, containing (b) (4) trehalose dihydrate, (b) (4) mannitol, (b) (4) methionine, and (b) (4) polysorbate 80 prepared in Sterile Water for Injection, USP.
Species/strain:	Rat / Crl:CD(SD)
Number/group:	24
Deviation from study protocol affecting interpretation of results:	None affecting study integrity

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; PPN, prenatal and postnatal development; SD, Sprague Dawley

Table 78. Rat PPND Study, Observations

Parameters	Major Findings
Mortality	No deaths considered drug-related. A single LD animal was electively euthanized on GD 22 after delivery of a single stillborn pup. This animal showed signs of dystocia (e.g., ungroomed fur, pale ears/extremities, decreased activity, cold to the touch, bradypnea, etc.). Upon necropsy, there were an additional 15 dead fetuses found in-utero. The other tissues appeared normal. This observation was not considered drug-related based on the absence of similar findings at higher dosage levels.
Clinical signs	No adverse effects reported
Body weights/food consumption	No adverse effects
Maternal parturition and littering observations	There were no effects on the proportion pregnant, gestation length, or the numbers of females delivering. The number of pups/litter and liveborn were considered comparable between groups; the number dams with stillborn pups was increased in controls.
Maternal necropsy observations	There were no effects observed considered drug-related. Organ weights were comparable between groups, with the exception of lung weights that were heavier (<8%) in all drug-treated groups
Plasma and milk drug levels	Plasma and milk concentrations increased with dose. Drug levels in milk were less than 5% of the levels in maternal plasma. In pups, drug was detected in a single HD female only on postpartum Day 1.
Pup survival, clinical observations, body weight, and food consumption	No adverse drug-related effects were noted
Reflex and physical development	No effects observed on markers of reflex of physical development or on the age at which preputial fold separation or vaginal patency occurred at
Neurological functioning and learning/memory assessments	No effects were noted in an FOB or on tests of learning/memory using passive avoidance and the Morris water maze

Parameters	Major Findings
Reproductive performance	Estrous cyclicity, the number of animals that mated, and the ensuing pregnancy rates were similar between groups. C-section revealed no effect on the numbers of corpora lutea, implantations, pre- or post-implantation loss, viable embryos, and nonviable embryos.
Postmortem observations	There were no drug-related gross postmortem alterations or effects on organ weights

Source: Reviewer generated table
Abbreviations: FOB, Functional observational battery; GD, gestational day; HD, high dose; LD, low dose; PPND, prenatal and postnatal development

Toxicokinetics: Drug levels were determined in plasma from maternal animals at pretreatment and on lactation day (LD) 14 (predose and 30 min postdose), from maternal milk on LD 14 (30 min postdose), in pup plasma on postpartum Day (PPD) 1 prior to nursing, and from pups on PPD 14.

Drug levels were BQL in all animals prior to treatment. On LD 14, mean maternal plasma drug levels increased with dose but not dose-proportionally. Drug was detected in maternal milk from 1/5, 3/5, and 5/5 animals evaluated in the LD, MD, and HD, respectively. The level detected in the milk from a single LD animal was approximately 5% of the level in maternal plasm while the levels in milk at the MD and HD mean levels at the MD and HD were <3% of the level in maternal plasma (ranging in individual animals from 1.3% to 4.7% at the MD and 1.6% to 5.0% at the HD). Drug levels in pup plasma were BQL at both PPD 1 and 14, with the exception of a single pup on PPD 1 at the HD that had a level of ~0.14 ng/mL. This level was considerably lower than that measured on the same day in maternal plasma (23.1 ng/mL) and milk (1.16 ng/mL) obtained from the dam this pup belonged to. Data are summarized in Table 79.

Table 79. Maternal Plasma and Milk Drug Concentrations

	Dosage (µg/kg)			
Analyte	**0**	**90**	**270**	**540**
Mean maternal concentrations (ng/mL)				
Plasma	BQL	1.52	16.9	28.2
Milk	BQL	0.090	0.299	0.896
Milk:Plasma ratio range	-	NA	0.013-0.047	0.016-0.050

Source: Reviewer generated table based on data from report BMN-111-18-103
Abbreviations: BQL, below the quantification limit

13.2. Individual Reviews of Studies Submitted to the NDA

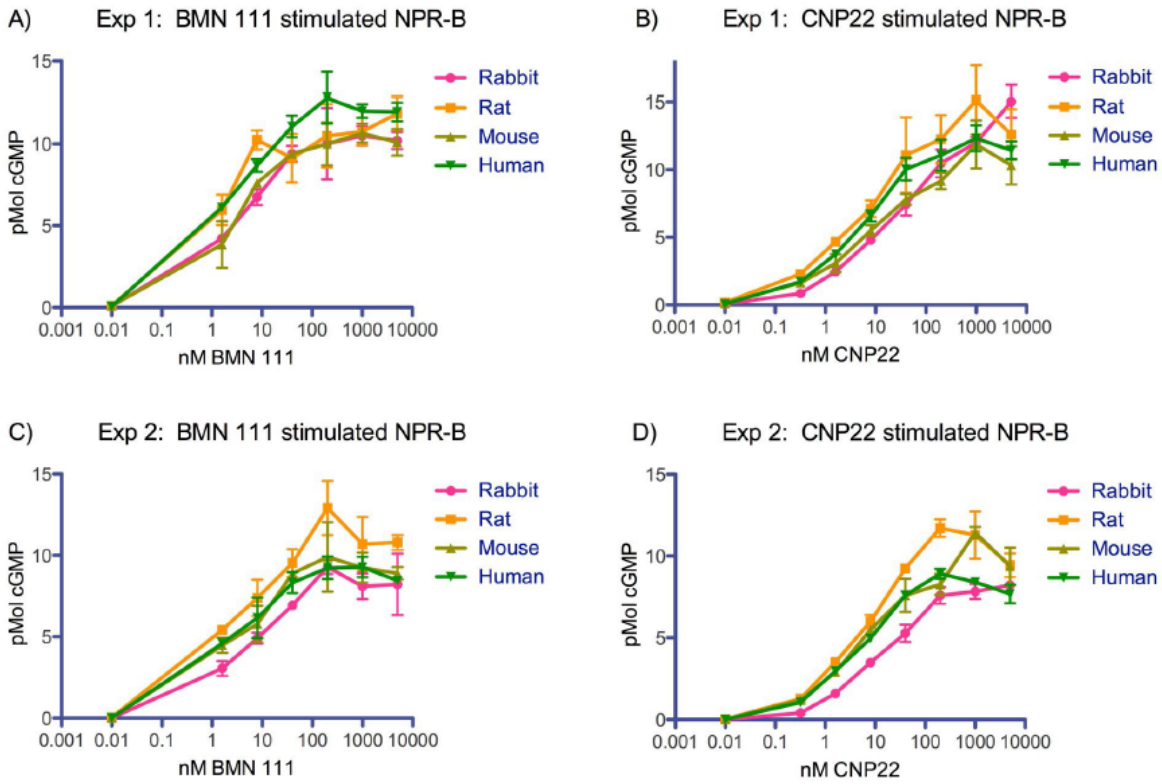
Pertinent studies submitted with the NDA that had not been submitted or reviewed under the IND are summarized in this section.

13.2.1. Pharmacology

13.2.1.1. Relative Affinity Determination and Potency of BMN-111 With NPR-B Derived From Rat, Mouse, Rabbit and Cynomolgus Monkey/Human (Study BMN-111-18-002)

The purpose of this study was to compare the binding to NPR-B between BMN-111 and native CNP22. NPR-B from various species was expressed on HEK293T cells and potency for inducing cGMP was evaluated. In independent experiments, the potency of BMN-111 was comparable to that of CNP22 across species, as summarized in Figure 32 and Table 80.

Figure 32. NPR-B Signaling/Potency by BMN-111 and CNP22



Two independent experiments were performed with BMN 111 (A & C,1.6 nM – 5 µM) and CNP22 (B & D, 0.32 nM – 5 µM) for each species of NPR-B. Error bars represent SEM, n=3 wells assayed per concentration.
Source: Applicant figure (Figure 4.3.2 (page 13) of report BMN-111-18-002)
Abbreviations: BMN-111, vosoritide; CNP22, c-type natriuretic peptde-22; cGMP, cyclic guanosine monophosphate; NPR-B, natriuretic peptide receptor-B

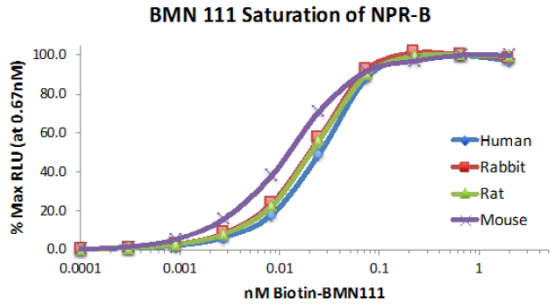
Table 80. NPR-B Potency (EC_{50}) Values for CNP22 and BMN-111 Signaling

NPR-B Species	EC_{50} (nM CNP22)	EC_{50} (nM BMN 111)	n
Rabbit	75.4, 24.1	2.9, 4.4	2
Rat	5.6, 5.2	1.4, 2.2	2
Mouse	9.3, 7.0	2.8, 2.4	2
Human	5.3, 4.1	1.7, 1.7	2

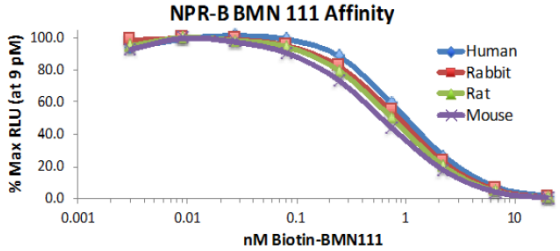
The EC_{50} values for CNP22 and BMN 111 signaling for each species of NPR-B were determined by a non-linear regression calculation with SoftMaxPro.
Source: Applicant table (Table 4.3.1 (page 13) of report BMN-111-18-002)
Abbreviations: BMN-111, vosoritide; CNP22, c-type natriuretic peptde-22; NPR-B, natriuretic peptide receptor-B

Saturation and dissociation of binding to NPR-B was also evaluated and found to be similar between the various species. The binding/dissociation curves and calculated half maximal effective concentration (EC_{50}) values are summarized in Figure 33 and Table 81.

Figure 33. Saturation and Dissociation Curves for BMN-111



Data are plotted as a % max RLU at the saturated 0.67 nM concentration. This normalization was necessitated due to the variability in the amount of functional NPR-B-Fc bound on the plate.



Based on the saturation curve, 0.1 nM biotin-BMN 111 was bound to immobilized NPR-B-Fc and dissociated with increasing concentrations of BMN 111 (3 pM – 20 nM).

Source: Applicant figures (Figures 4.4.1 and 4.4.2 (pages 14-15) of report BMN-111-18-002)
Abbreviations: BMN-111, vosoritide; NPR-B, natriuretic peptide receptor-B; RLU, relative light units

Table 81. Calculated Saturation and Dissociation EC50 Values

NPR-B (Species)	Saturation EC_{50} (pM Biotin-BMN111)	Dissociation EC_{50} (nM BMN111)	Signal Intensity at Saturation (RLU)
Rabbit	20	0.894	144,852
Rat	21	0.820	153,838
Mouse	12	0.702	49,077
Human	24	1.081	237,853

Source: Applicant table (Table 4.4.1 (page 15) of report BMN-111-18-002)
Abbreviations: BMN-111, vosoritide; NPR-B, natriuretic peptide receptor-B; RLU, relative light units

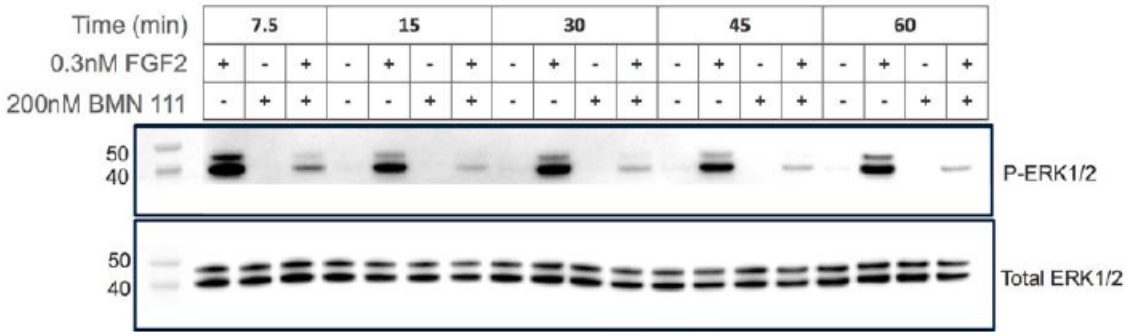
These data demonstrate that the signaling s of BMN-111 is comparable to that of CNP22 across the species evaluated. The binding and dissociation of BMN-111 was also similar between the species evaluated, indicating comparable affinities.

13.2.1.2. Evaluation of Dosing Frequency on Suppression of FGF2-Signaling and Restoration of Proliferation and Matrix Deposition by BMN-111 (Study RS19-001)

FGF-2 signaling leads to suppression of proliferation and matrix deposition through the Raf/MAK kinase pathway in rat chondrosarcoma (RCS) cells. These events are the same as seen in achondroplastic chondrocytes. Therefore, this system was used to evaluate the effect BMN-111 dosing frequency has on the suppression of FGF2 signaling.

RCS cells were treated with FGF2 and BMN-111, alone or in combination, and phosphorylation of ERK1/2 was evaluated. Addition of FGFR2 led to the phosphorylation of ERK1/2 while the presence of BMN-111 reduced its expression. This effect was evident throughout the testing period, as shown in Figure 34.

Figure 34. BMN-111Suppression of ERK1/2 Phosphorylation



Source: Applicant figure (Figure 4.1.2 (page 9) of report RS19-001)
Abbreviations: ERK1/2, extracellular signal-regulated kinases 1 and 2

The ability of BMN-111 to reverse the suppression of proliferation and matrix deposition was also evaluated in RCS cells. BMN-111 was found to reverse growth and matrix suppression of RCS cells following continuous or pulsatile exposure. Data are summarized in Figure 35 and Figure 36.

Figure 35. Effect of BMN-111 on FGFR2-Induced Suppression of Cell Proliferation

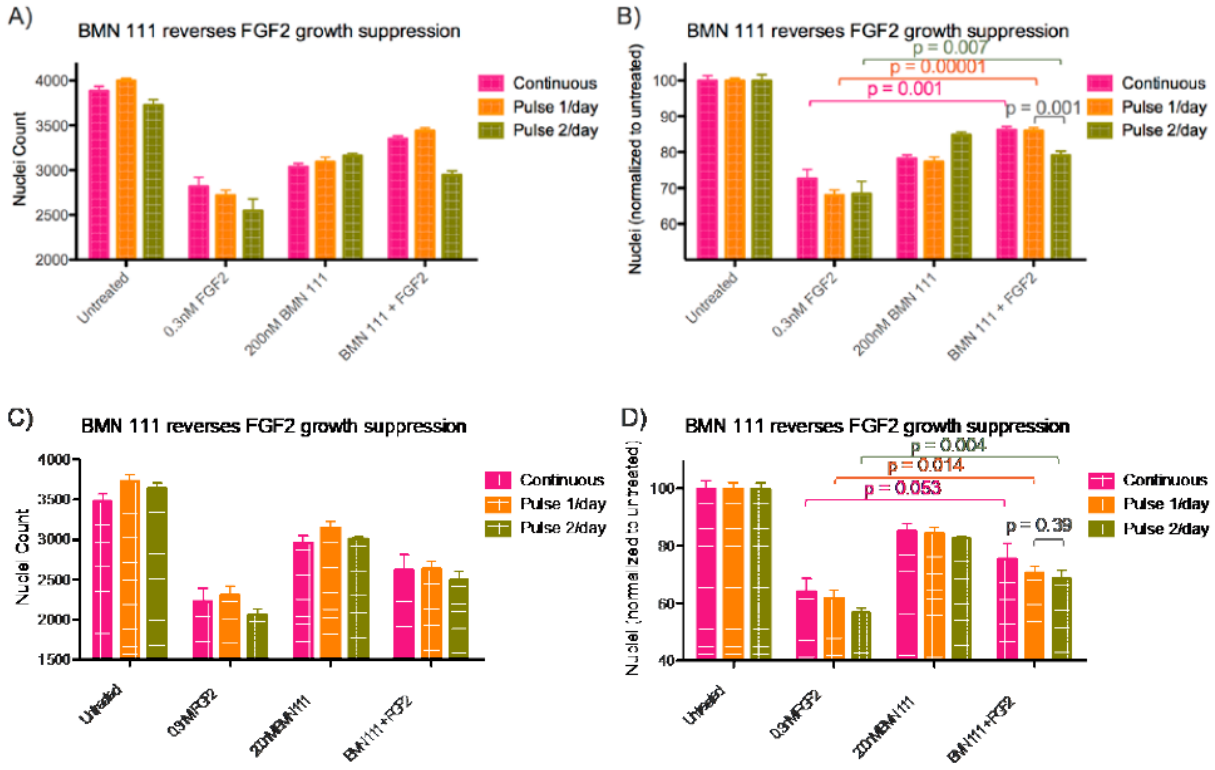
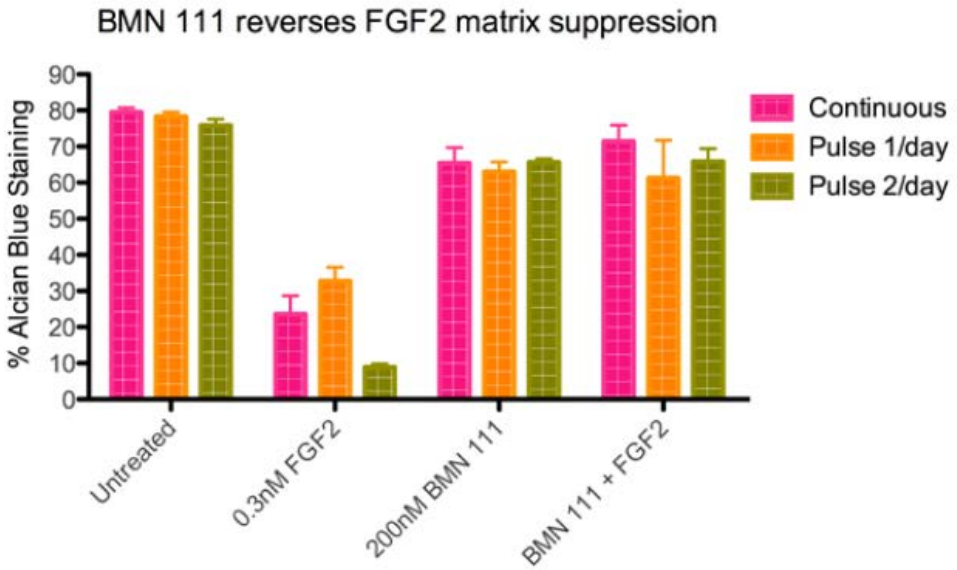


Figure 3.2.3: A, C) Nuclei from four fields representing 3 treated wells from 2 independent experiments were counted, averaged and graphed. B, D) Nuclear/cellular counts were normalized to each plate's untreated control to allow for plate-to-plate variability. Paired T-test statistical analysis was performed in Excel.

Source: Applicant figure (Figure 4.2.3 (page 11) of report RS19-001)
Abbreviations: BMN 111; vosoritide; FGFR2, Fibroblast growth factor receptor 2

Figure 36. Effect of BMN-111 on FGFR2-Induced Suppression of Matrix Deposition



Source: Applicant figure (Figure 4.3.1 (page 12) of report RS19-001)
Abbreviations: BMN 111; vosoritide; FGF2, f broblast growth factor 2

13.2.2. ADME Studies

A series of nonpivotal ADME studies was submitted with the NDA. These included single-dose studies following SC administration in juvenile (BMN-111-15-072) and adult rats BMN-111-15-076), SC and intramuscular (IM) administration in adult rats (BMN-111-17-048), and in $FGFR3^{ACH}$ and wild-type mice (BMN-111-15-100). Collectively, these studies demonstrated increases in exposure with dose and age in rats, that IM administration results in higher exposure compared to SC administration, and that exposure in mutant mice was similar to that observed in wild-type mice.

The biodistribution was also evaluated using PET imaging over a 90-min observation window (BMN-111-17-027). Following a single dose, levels were highest at the injection site. As the injection site levels declined, the levels in the stomach and bladder increased. In a tissue distribution study (BMN-111-18-004), levels increased in all tissues peaking at 30 to 60 mins after dosing, with the exception of the injection site where levels declined over time. The levels were highest at the injection site, kidney, and plasma at 15 and 30 mins after administration. By 60 mins after treatment, the highest level was still at the injection site, followed by levels in the stomach, plasma, and kidney. Tissue:plasma ratios were generally <1 over the 60-min assessment period with the exception of the injection site at all time points, the kidney at the 15- and 30-min time points, and the stomach at 1 hour.

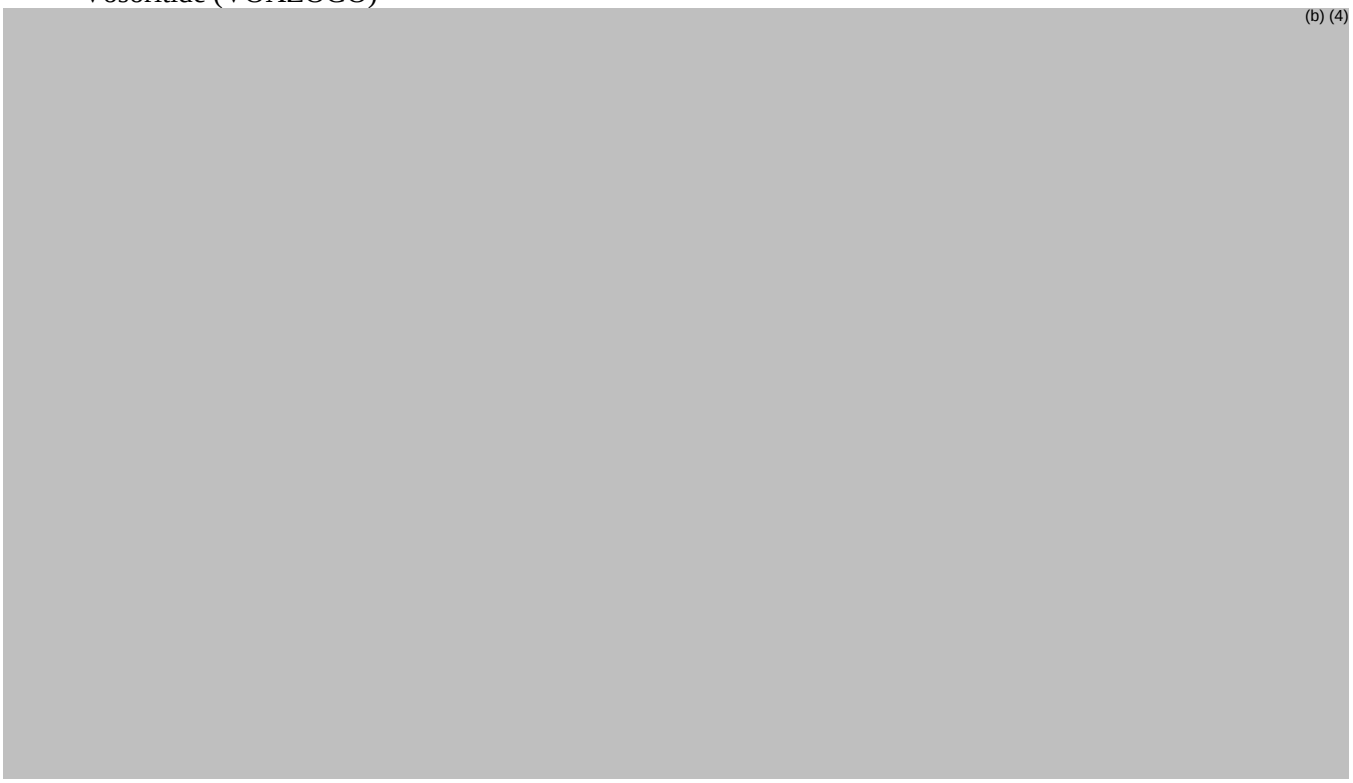
13.3. Impurities/Degradants

Multiple product- and process-related impurities were identified in the drug substance that were derived as part of the (b) (4) process or from the cell substrates or culture.

The product-related impurities were qualified based on their presence at higher levels in drug batches used for nonclinical toxicology studies or the levels administered being higher at the NOAEL dose than those administered at the clinical dose. All process-related impurities are removed during the manufacturing process and are below the limit of detection/limit of quantification (b) (4)

The levels of the process-related impurities fall below the threshold of toxicological concern (TTC) limit of 1.5 µg/kg per day identified in the International Council for Harmonisation (ICH) M7 guidance or the permissible daily exposure (PDE) identified in the ICH Q3D guidance.

An extractable and leachable study (STUQL19AA0345-1) was performed to identify and estimate the amounts of impurities/degradants that may be extracted from the container closure system and syringes that may leach into drug product during use. This study revealed 4 organic and 4 elemental compounds. The levels detected and the maximum possible daily exposure (based on the maximum daily dose volume of (b) (4) mL/day) in drug product and diluent (sterile water for injection) are summarized in Table 82 and Table 83.



The maximum daily exposure to the 4 organic impurities are at levels below the safety concern threshold of 1.5 µg/day. Three of the elemental impurities also fall below the 1.5 µg/day exposure. These elements are present in humans and all 4 also fall within the "other" classification in ICHQ3D as they are considered to be of inherently low toxicity for which a PDE has not been determined. Consequently, the risks posed by these substances is considered negligible.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Vosoritide, also known as BMN-111, is a modified recombinant human CNP. Compared to endogenous CNP, vosoritide has a prolonged elimination half-life because the addition of 2 amino acids (Pro and Gly) on the N terminus improves resistance to NEP degradation. One in vitro metabolism and 2 in vitro drug interaction study reports were provided in the current NDA.

14.1.1. Metabolic Stability (BMN-111-18-093)

The metabolic stability of vosoritide was evaluated in pooled human liver microsomes (HLM). In the absence of HLM, vosoritide 40 µg/mL was stable in the buffer alone during 120 mins of incubation. The concentration of vosoritide declined with incubation time in both the presence of active nicotinamide adenine dinucleotide phosphate (NADPH), and the absence of reduced NADPH. The addition of NADPH did not affect the metabolism of vosoritide in human liver

microsomes, suggesting that cytochrome P450 (CYP) enzymes were not involved in the elimination of vosoritide.

14.1.2. Cytochrome P450 Inhibition (BMN-111-18-093)

Pooled HLM were utilized to evaluate the CYP enzyme inhibition (reversible and time-dependent inhibitory effect) potential of vosoritide. Vosoritide (0 to 1 µg/mL) effects on the activities of CYP1A2 (phenacetin O-dealkylation), CYP2B6 (bupropion hydroxylation), CYP2C8 (amodiaquine N-dealkylation), CYP2C9 (diclofenac 4'-hydroxylation), CYP2C19 (S-mephenytoin 4'-hydroxylation), CYP2D6 (dextromethorphan O-demethylation), and CYP3A4/5 (midazolam 1'-hydroxylation and testosterone 6β-hydroxylation) were measured.

The results showed that vosoritide at 1 µg/mL did not inhibit the CYP enzymes in a reversible manner. Vosoritide up to 1 µg/mL also did not inhibit CYP enzymes in a time-dependent manner. Due to the lack of inhibition, an IC_{50} value could not be calculated for any condition and consequently, an NADPH- and time-dependent shift in the IC_{50} could not be determined.

14.1.3. Cytochrome P450 Induction (BMN-111-18-102)

Cryopreserved human hepatocytes from 3 donors were cultured in sandwich configuration to assess the induction effect of vosoritide (0.01, 0.1 and 1 µg/mL) on CYP enzymes. To measure induction, gene expression of all the targets was quantified by using TaqMan®. Additionally, enzyme activity of the target CYPs (CYP1A2, 2B6 and 3A4/5) was determined using phenacetin, bupropion, and midazolam as the substrates, respectively, to confirm the results of the gene expression analysis. The mRNA measurements showed that vosoritide at the concentrations of 0.01, 0.1 and 1 µg/mL did not induce CYP1A2, 2B6, or 3A4/5 in hepatocytes from any donor. Consistently, vosoritide at the concentrations of 0.01, 0.1 and 1 µg/mL did not cause induction of CYP1A2, 2B6, or 3A4/5 activity in the hepatocytes from any donor. According to the FDA in vitro drug interaction guidance, since vosoritide does not induce CYP3A4, further evaluation of the induction potential of CYP2C enzymes is not needed.

14.2. In Vivo Studies

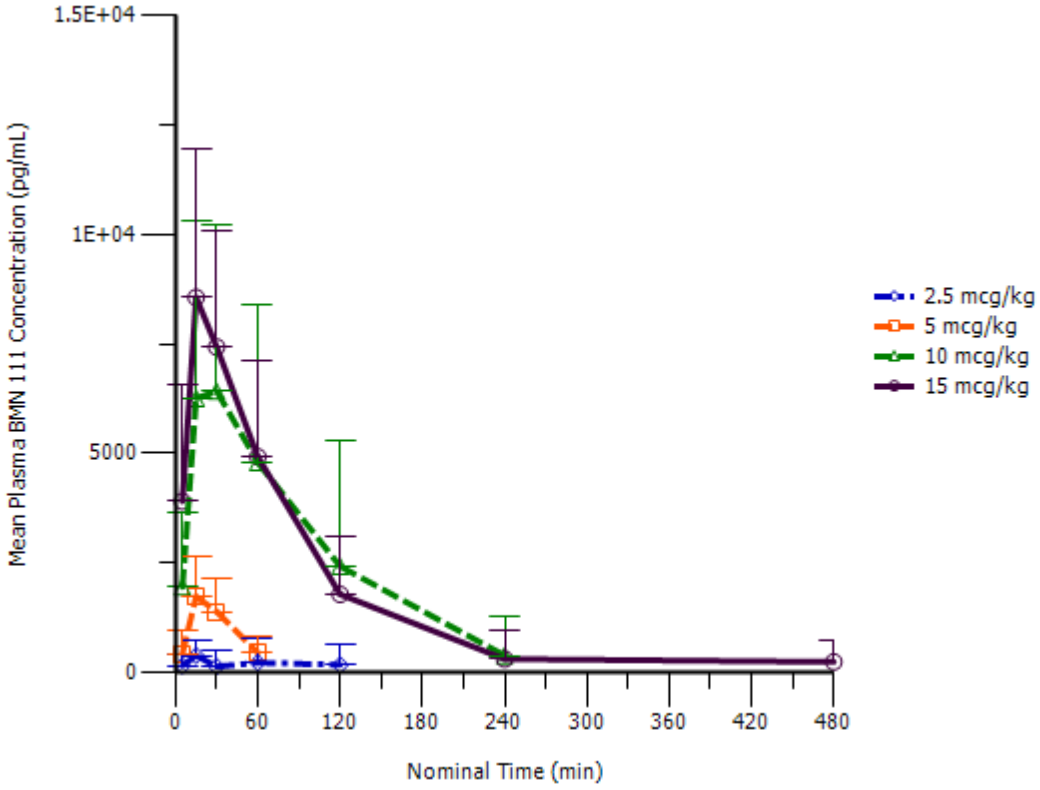
14.2.1. A Phase 1, Two Part, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of BMN-111 Administered to Healthy Adult Male Volunteers (Study 111-101)

Study Design: Study 111-101 was a phase 1, 2-part (Part 1: single ascending dose [5, 10, 15 µg/kg] and Part 2: multiple-ascending dose [2.5, 5 µg/kg daily, 0.5 to 8.0 µg/kg daily]), double-blind, placebo-controlled study of 48 healthy adult male volunteers ages 22 to 45 years, inclusive. Vosoritide was SC administered. Blood samples for PK analysis (including cGMP and ANP biomarker analysis) were obtained at predose and at 5, 15, 30, 60, 120, 240, and 480 mins postdose following dosing on Day 1 in Part 1, following dosing on Day 1, 6, and 10 for Cohorts

1 and 2 in Part 2, and following dosing of Day 4, 6, and 10 for Cohorts 3A and 3B in Part 2 of the study.

PK Results: Mean single-dose vosoritide plasma concentration-time profiles in healthy adult males by dose are shown in Figure 37. The PK parameters are summarized in Table 84. A large intersubject variability in AUC and C_{max} values was observed with the majority of CVs >40%. After subcutaneous injection of single doses of 2.5 to 15.0 µg/kg, vosoritide was rapidly absorbed, with median time to maximum concentration (T_{max}) ranging from 15 to 30 mins. Within the dose range of 2.5 to 15.0 µg/kg, the corresponding PK exposure parameters C_{max} and AUC_{0-t} generally increased with dose (Table 85).

Figure 37. Mean (±SD) Plasma Concentration-Time Profiles Following Single Doses of Vosoritide From 2.5 to 15 µg/kg in Adult Male Subjects



Source: Figure 9.1.1.1 in Study 111-101 Clinical Pharmacology Report
Abbreviations: SD, standard deviation

Table 84. Mean ± SD PK Parameters for Vosoritide Following Single Dose Administration to Healthy Adult Male Subjects

	Dose			
PK Parameter	**2.5 µg/kg**	**5 µg/kg**	**10 µg/kg**	**15 µg/kg**
$AUC_{0\text{-}t}$ (ng*min/mL)	129 (n=1)	83.2±15.5 (n=7)	607±562 (n=5)	687±424 (n=4)
$AUC_{0\text{-}inf}$ (ng*min/mL)	N.A.	N.A.	1200±759 (n=2)	921±515 (n=3)
C_{max} (pg/mL)	749±435 (n=4)	1820±923 (n=11)	6750±4080 (n=5)	8830±2880 (n=4)
T_{max} (min)	26.0±22.7 (n=4)	16.5±4.5 (n=11)	24.0±8.2 (n=5)	21.0±7.4 (n=4)
T1/2 (min)	N.A.	N.A.	53.8±31.4 (n=2)	69.5±61.2 (n=3)
CL/F (mL/min/kg)	N.A.	N.A.	10.4±6.6 (n=2)	20.3±11.3 (n=3)

Source: Table 9.1.1.1 in Study 111-101 Clinical Pharmacology Report
Abbreviations: CL/F, apparent clearance; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration

Table 85. Dose Proportionality-Based C_{max} and $AUC_{0\text{-}t}$ Following Single Dosing in Human Adult Male Subjects

Dose µg/kg	**Dose Proportionality**	**C_{max} pg/mL**	**C_{max} Proportionality**	**$AUC_{0\text{-}t}$ ng/mL/min**	**$AUC_{0\text{-}t}$ Proportionality**
2.5	1.0	749	1.0	129	1.0
5.0	2.0	1815	2.42	82.1	0.636
10	4.0	6752	9.01	607.5	4.71
15	6.0	8828	11.8	687.2	5.33

Source: Table 9.1.1.2 in Study 111-101 Clinical Pharmacology Report

Mean ± SD PK parameters following multiple doses of vosoritide (2.5 µg/kg once daily [QD] and 5 µg/kg QD) are summarized in Table 86. In 5.0 µg/kg dose group, comparison of PK exposure parameters on Day 10 and Day 6 with Day 1 indicate that both C_{max} and $AUC_{0\text{-}t}$ showed limited changes. Vosoritide did not show drug accumulation with once daily dosing for up to 10 days.

Table 86. Mean ± SD PK Parameters for Vosoritide Following Multiple Dose Administration to Healthy Adult Male Subjects

	Dose					
	2.5 µg/kg			**5 µg/kg**		
PK Parameter	**Day 1**	**Day 6**	**Day 10**	**Day 1**	**Day 6**	**Day 10**
$AUC_{0\text{-}t}$ (ng*min/mL)	129 (n=1)	63.8 (n=1)	110 (n=1)	74.2±12.5 (n=3)	83.0±41.2 (n=4)	69.5±20.7 (n=4)
C_{max} (pg/mL)	749±435 (n=4)	804±410 (n=5)	736±313 (n=6)	1410±604 (n=6)	1420±716 (n=6)	1400±688 (n=5)
T_{max} (min)	26.0±22.7 (n=4)	15.0±0.0 (n=5)	25.0±18.2 (n=6)	15.2±0.41 (n=6)	29.8±14.8 (n=6)	21.0±8.2 (n=5)

Source: Table 9.1.2.1 in Study 111-101 Clinical Pharmacology Report
Abbreviations: PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration

All subjects in both Part 1 and Part 2 of the study tested negative for total anti-vosoritide antibodies (TAbs) at all time points tested. Vosoritide demonstrated a dose-related increase in cGMP concentrations in plasma and urine following single and multiple daily doses. With multiple daily dosing, the observed cGMP response was similar on Days 6 and 10 compared to Day 1.

14.2.2. A Phase 2, Open-label, Sequential Cohort Dose-Escalation Study of BMN-111 in Children With Achondroplasia (Study 111-202)

Study Design: Study 111-202 was a pediatric, phase 2, open-label dose-escalation study to assess the PK/pharmacodynamic (PD), safety and tolerability of daily vosoritide administered to 35 subjects with a clinical diagnosis of ACH. The 2-year study period comprised an initial 6-month dose-finding phase and an optional, open-label, 18-month extension phase to commence at the end of the initial phase of the study. In the initial 6-month period of the study, vosoritide was administered SC daily in one of the following dosing regimens:

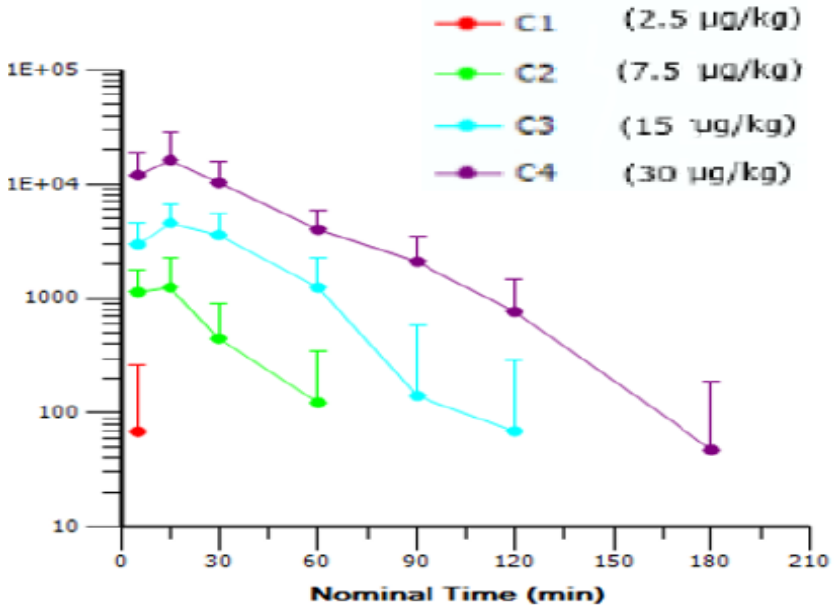
- Cohort 1 (n=8 subjects): daily dose of 2.5 µg/kg
- Cohort 2 (n=8 subjects): daily dose of 7.5 µg/kg
- Cohort 3 (n=10 subjects): daily dose of 15.0 µg/kg
- Cohort 3 (n=9 subjects): daily dose of 30.0 µg/kg

In the initial 6-month period of the study, on Days 1, 10, 29, 85, and 183, full PK samples were collected predose and at 5, 15, 30, 60, 90, 120, and 180 mins postdose.

In the 18-month extension phase, Cohort 1 subjects were escalated from 2.5 µg/kg to 7.5 µg/kg (7 subjects) and then to 15 µg/kg (6 subjects); Cohort 2 subjects were escalated from 7.5 µg/kg to 15 µg/kg (6 subjects). Full PK samples were drawn at the dose adjustment visit and partial PK sampling 4 weeks after the adjustment during follow-up visits. Cohorts 3 and 4 remained on the 15 and 30 µg/kg doses, respectively. Full PK samples were taken at Months 12 and 24, while partial PK samples were taken at 4 time points (predose, 15, 30, and 60 mins post dose) at Months 8, 10, 15, 18, and 21.

PK Results: As shown in Figure 38 and Table 87, Cohort 1 (2.5 µg/kg) provided limited PK data due to concentrations of vosoritide in the majority of plasma samples being BLQ (<391 pg/mL). For Cohorts 2, 3 and 4, vosoritide was rapidly absorbed with median T_{max} values between 15.0 and 16.0 mins across dose levels and rapidly eliminated with mean $T_{1/2}$ of 24 to 27 mins. Single-dose vosoritide exhibited more than proportional increase in both C_{max} and AUC within the dose range of 7.5 to 30 µg/kg (Table 87).

Figure 38. Mean (+SD) Single-Dose Plasma Concentration-Time Profiles of Vosoritide



Source: Figure 9.1.1.1.1 in Study 111-202 Clinical Pharmacology Report
Abbreviations: SD, standard deviation

Table 87. Single-Dose Plasma Pharmacokinetic Parameters of Vosoritide

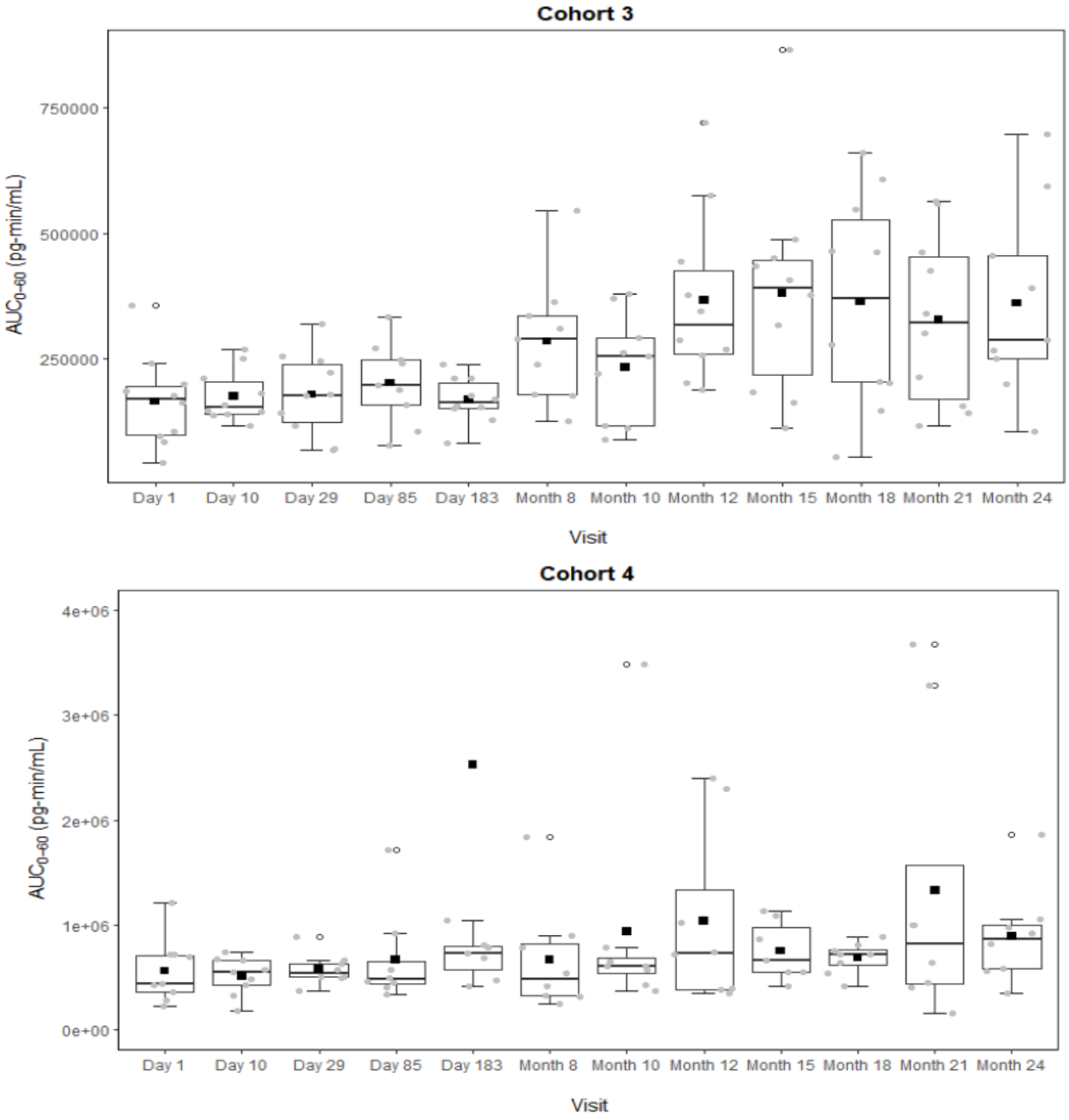
	Dose			
PK Parameter	**2.5 µg/kg**	**7.5 µg/kg**	**15 µg/kg**	**30 µg/kg**
AUC_{0-t} (ng*min/mL)	1.37 (n=1)	32.2±28.1 (n=7)	175±113 (n=10)	689±383 (n=9)
AUC_{0-inf} (ng*min/mL)	N.A.	N.A.	293±258 (n=2)	779±393 (n=8)
C_{max} (pg/mL)	549 (n=1)	1360±901 (n=7)	4750±1990 (n=10)	16800±11500 (n=9)
T_{max} (min)	5.0 (n=1)	13.7±6.3 (n=7)	15.8±6.0 (n=10)	14.4±7.3 (n=9)
T1/2 (min)	N.A.	N.A.	24.4±7.2 (n=2)	27.0±7.7 (n=8)
CL/F (mL/min/kg)	N.A.	N.A.	83.7±73.8 (n=2)	49.2±28.4 (n=8)
Vz/F (mL/kg)	N.A.	N.A.	2560±1730 (n=2)	1830±1020 (n=8)

Source: Table 9.1.1.1.1 in Study 111-202 Clinical Pharmacology Report
Abbreviations: CL/F, apparent clearance; PK, pharmacokinetic; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal elimination

The multidose PK parameters of vosoritide in subjects from Cohorts 3 and 4, who received the same dose through 24 months, were analyzed across the entire study period. Median T_{max} and mean $T_{1/2}$ ranged from 15.0 to 30.0 min, and 21.2 to 42.7 min, respectively. For Cohort 3, both mean C_{max} and AUC_{0-60} increased over time. Mean C_{max} increased from 4.75 ng/mL (Day 1) to 8.73 ng/mL (Month 24) and AUC_{0-60} increased from 165 ng*min/mL (Day 1) to 361 ng*min/mL (Month 24) (Figure 39). For Cohort 4, only a slight increase in vosoritide exposure was observed over 24 months (Figure 39). Mean C_{max} slightly increased from 16.8 ng/mL (Day 1) to 20.5 ng/mL (Month 24) and AUC_{0-60} increased from 559 ng*min/mL (Day 1) to 888 ng*min/mL (Month 24).

***Reviewer's comment**: Due to the short $T_{1/2}$ of vosoritide, all predose C_{trough} values after daily dosing were <BLQ. The increased vosoritide exposure over 24 months was not caused by drug accumulation but was likely due to increased total daily dose over 24 months (pediatric subject's body weight gain over 24 months) and more than proportional PK of vosoritide.*

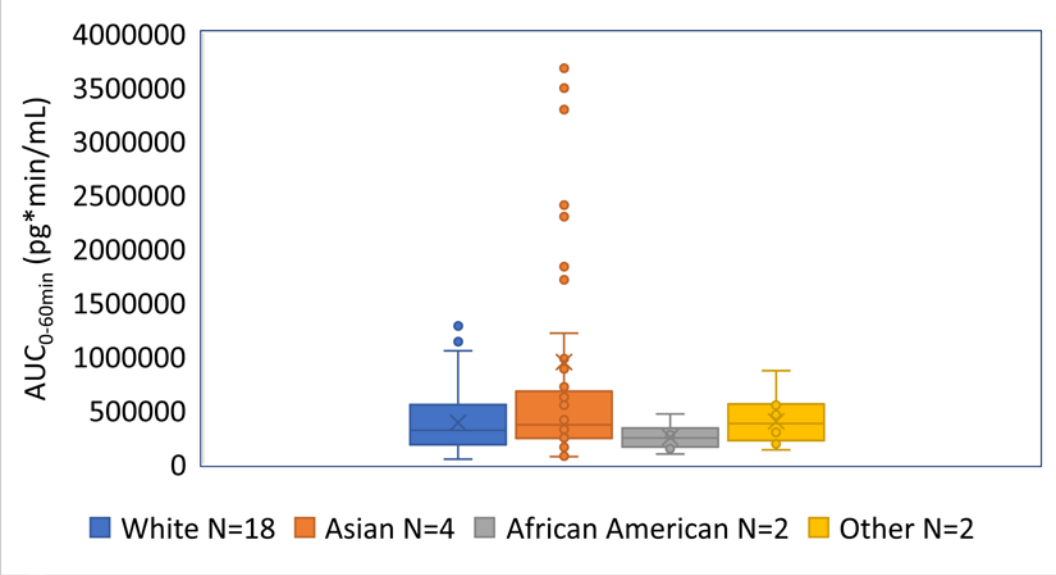
Figure 39. Distribution of Vosoritide AUC_{0-60} in Cohorts 3 and 4 Through 24 Months



Source: Figure 9.1.2.1.1 in Study 111-202 Clinical Pharmacology Report
Note: 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 standard span of the data is defined within the range from Q1-1.5*IQR to Q3+1.5*IQR. Whiskers are drawn to the nearest value not beyond the range of the standard span; points beyond are drawn as individual open circles. The exposure of each subject measured at a particular visit is shown as gray circles, and the mean exposure of the subjects at that visit is shown as a black square.

Effect of Race on the PK of Vosoritide: In Cohorts 1, 2 and 3, 18 Whites, 4 Asians, 2 African Americans or Blacks, and 2 other races received at least 1 dose of 15 µg/kg vosoritide. The AUC_{0-60} values of the 18 subjects at 15 µg/kg dose are summurized in Figure 40. No obvious difference in AUC of vosoritide was observed among Whites, Asians, African Americans or Blacks, or others.

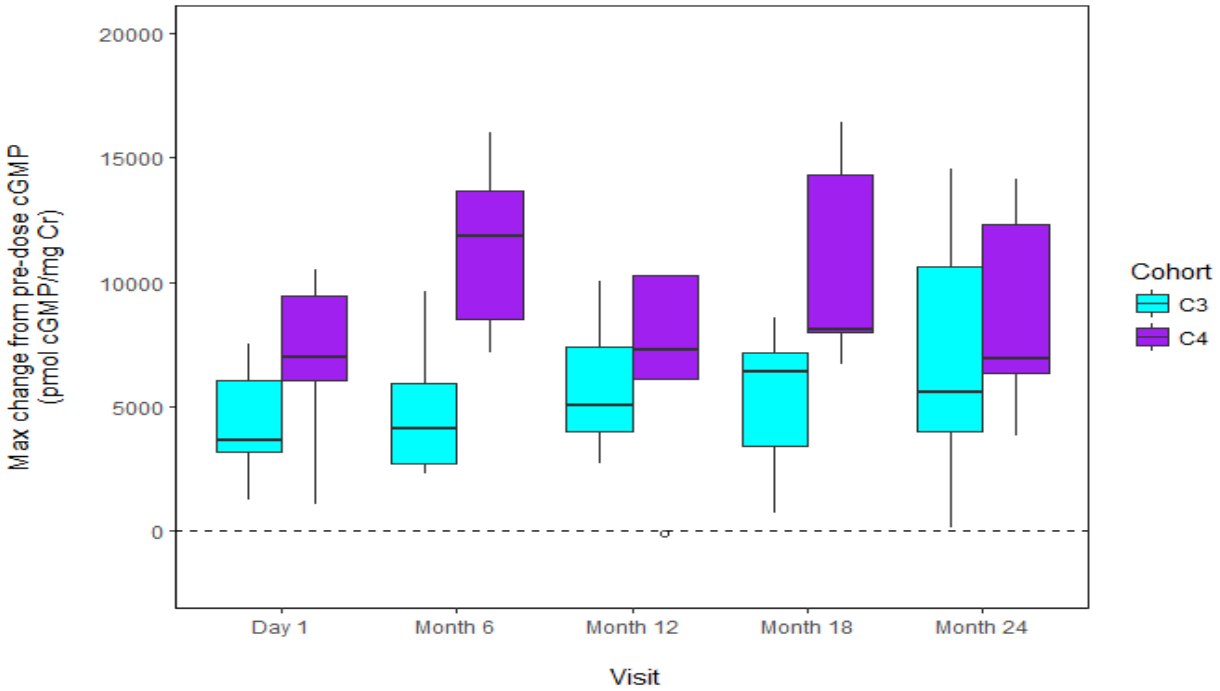
Figure 40. Distribution of Vosoritide Exposure by Race in Study 111-202



Source: Clinical Pharmacology reviewer's analysis

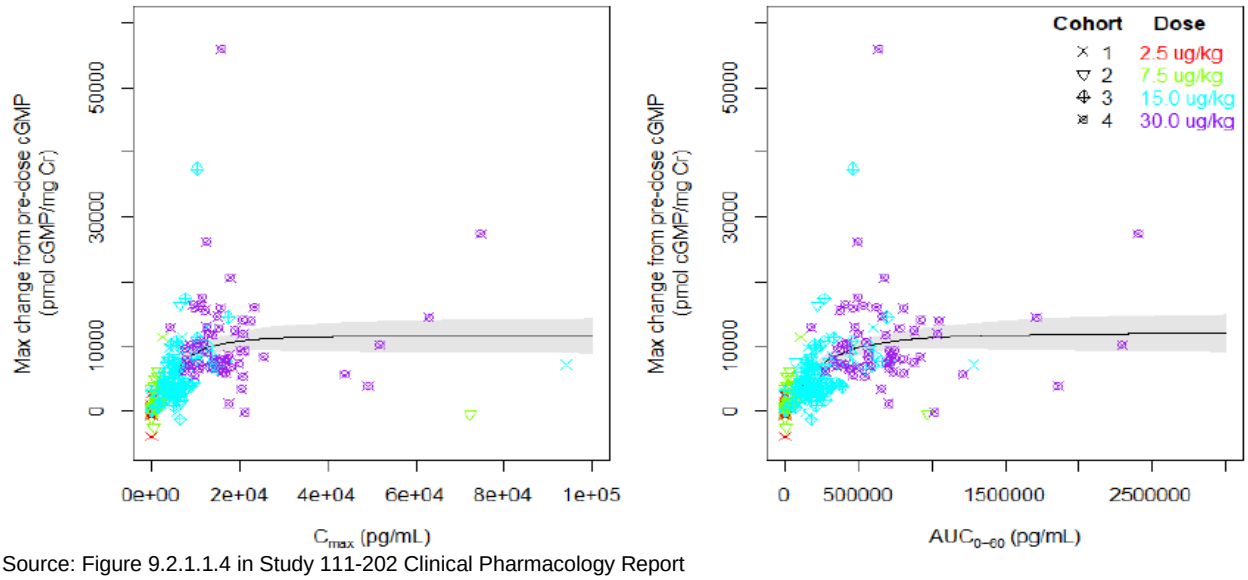
PK/PD Relationships: Serum collagen type X biomarker (CXM), serum BSAP, and urine cGMP were measured as bone growth biomarkers. Following once daily dosing of vosoritide, dose-dependent increases in urine cyclic guanosine monophosphate (cGMP, normalized to creatinine) were observed over 24 months (Figure 41). A sigmoid E_{max} model was used to fit the correlations between visit-matched maximum postdose increases from predose urine cGMP concentrations and vosoritide C_{max} and AUC_{0-t} for the 24-month period (Figure 42). Based on the model fitting, the EC_{50} values for C_{max} and AUC_{0-t} of vosoritide were 5570 pg/mL and 215 ng*min/mL, respectively. The mean AUC_{0-t} following a single dose of 30 µg/kg vosoritide (689 ng*min/mL) was >3-fold greater than the estimated EC_{50}. The results suggest that at 30 µg/kg dose, vosoritide activity as assessed by urine cGMP is saturated.

Figure 41. Maximum Increase in Urine cGMP in Cohorts 3 and 4 over 24 Months



Source: Figure 9.2.1.1.2 in Study 111-202 Clinical Pharmacology Report
Note: 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 standard span of the data is defined within the range from Q1-1.5*IQR to Q3+1.5*IQR.
Abbreviations: cGMP, cyclic guanosine monophosphate

Figure 42. Visit-Matched Maximum Increase in Urine cGMP and Vosoritide C_{max} and AUC_{0-t} (0-24 Months)

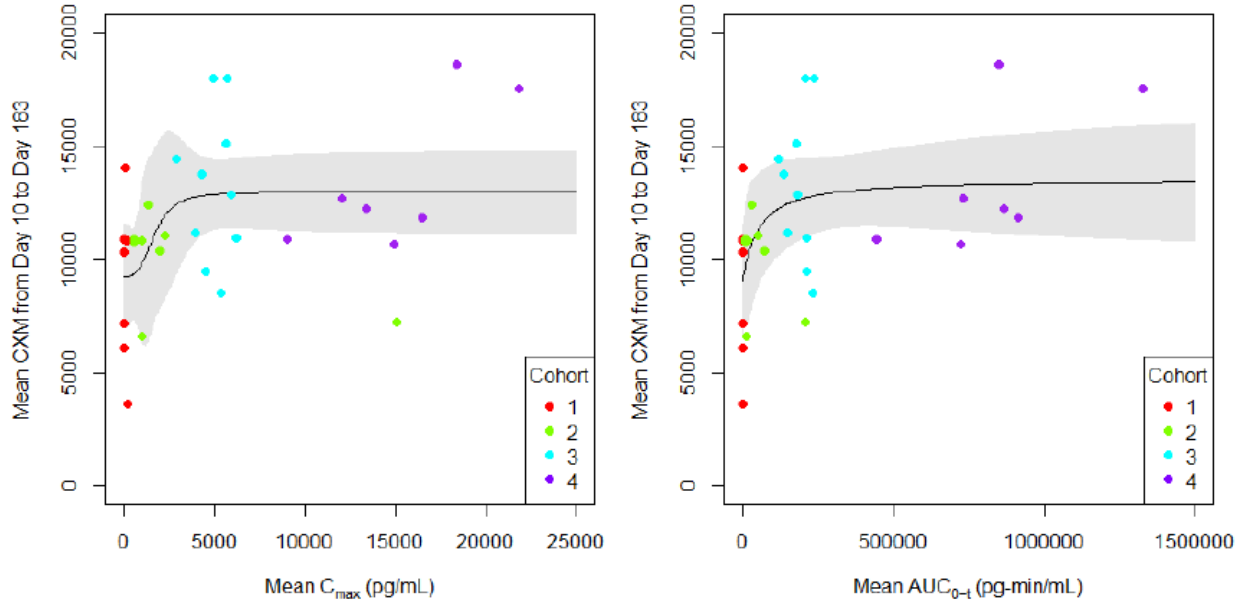


Source: Figure 9.2.1.1.4 in Study 111-202 Clinical Pharmacology Report
Note: Solid line represents sigmoid Emax model fit through the data and the shaded region represents the 95% confidence interval.
Abbreviations: cGMP, cyclic guanosine monophosphate

Potential correlations between vosoritide PK and mean serum CXM from Day 10 to Day 183 were explored using a sigmoid E_{max} model. This analysis included data from 33 subjects with available CXM and vosoritide PK data. The results of the 6-month analysis demonstrate a steep

exposure-response relationship across the exposure observed with 2.5 µg/kg and 7.5 µg/kg dose levels and an upper plateau of mean CXM at exposure observed at 15 µg/kg and 30 µg/kg dose levels (Figure 43).

Figure 43. Mean of CXM of Individual Subjects From Day 10 to Day 183 by Individual Mean Vosoritide C_{max} and AUC_{0-t} (Initial 6 Months)

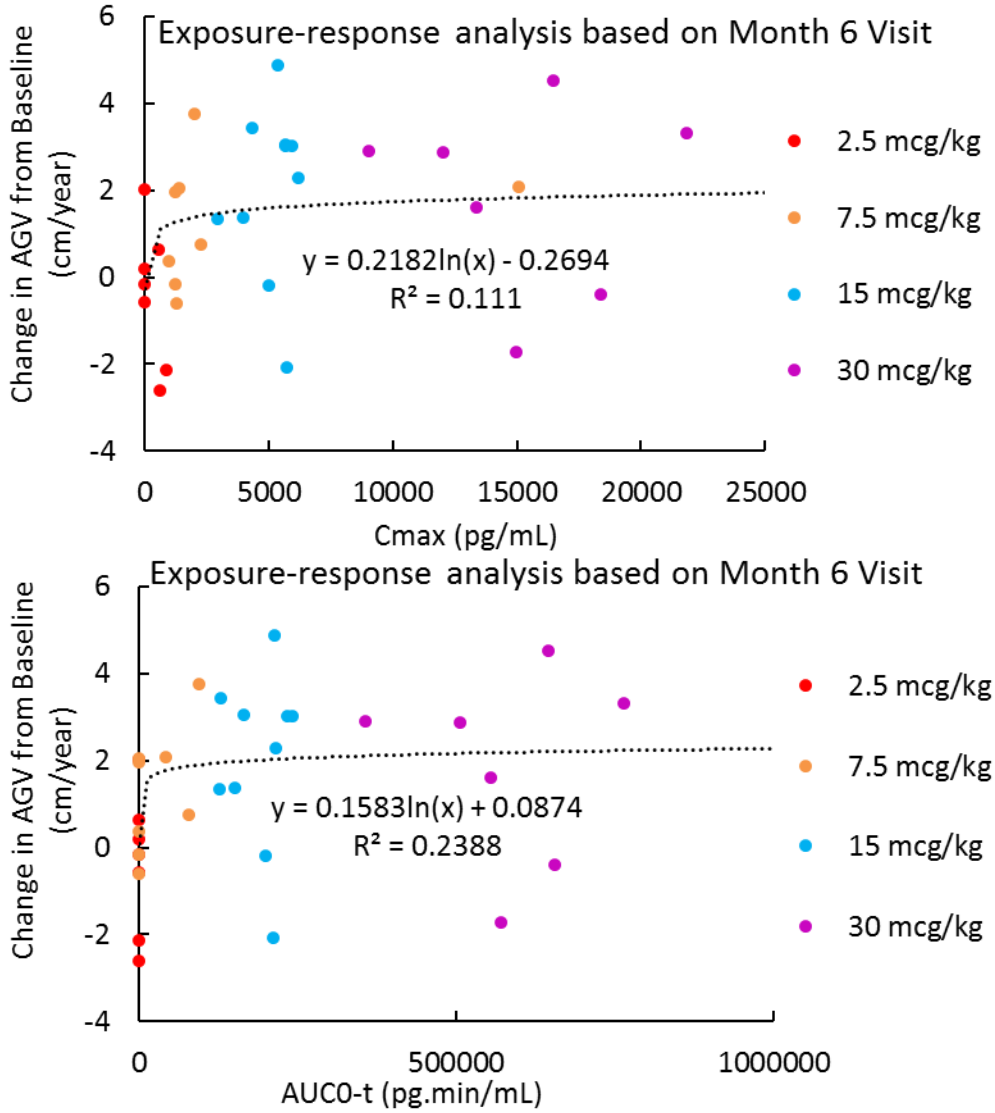


Source: Figure 9.2.1.3.3 in Study 111-202 Clinical Pharmacology Report
Note: Points represent mean of CXM of individual subjects from Day 10 to Day 183 and individual mean BMN-111 C_{max} (left) and AUC_{0-t} (right), color coded by study cohort (C1 = Cohort 1 [2.5 µg/kg]; C2 = Cohort 2 [7.5 µg/kg]; C3 = Cohort 3 [15 µg/kg]; C4 = Cohort 4 [30 µg/kg]). Solid line represents the Emax model fit through the data and the shaded region represents the 95% confidence interval.
Abbreviations: CXM, collagen type X biomarker

Potential correlations between vosoritide PK and mean serum BSAP were explored, but no significant correlation between vosoritide plasma exposure and change in predose BSAP concentrations was observed across the exposure obtained from 2.5 to 30 µg/kg dose levels.

Exposure-Response Relationship for Efficacy: Potential correlations between the change in AGV from baseline to Day 183 and vosoritide PK were explored using a logarithmic regression analysis. The results of the 6-month analysis demonstrate a steep exposure-response relationship across the exposure observed with 2.5 µg/kg and 7.5 µg/kg dose levels, and an upper plateau of growth velocity increases at exposure observed at 15 µg/kg and 30 µg/kg dose levels (Figure 44). Similarly, the results of the 24-month analysis demonstrate a flat exposure-response (E-R) relationship at the dose range of 15 to 30 µg/kg.

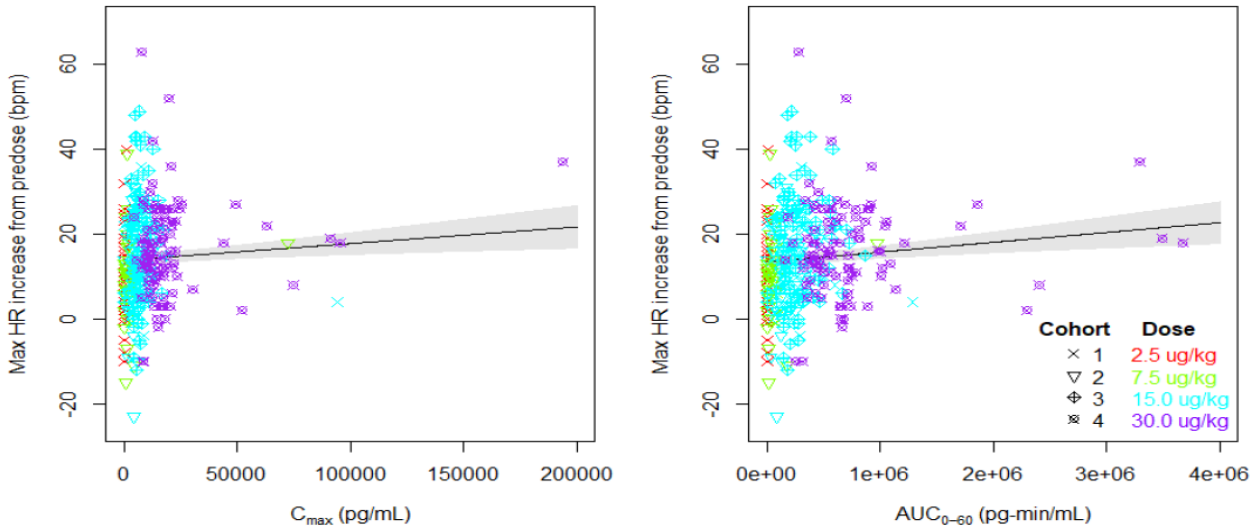
Figure 44. Relationship Between Change in Annualized Growth Velocity From Baseline and Individual Mean C_{max} and AUC_{0-t}



Source: Clinical Pharmacology reviewer's analysis
Abbreviations: AGV, annualized growth velocity

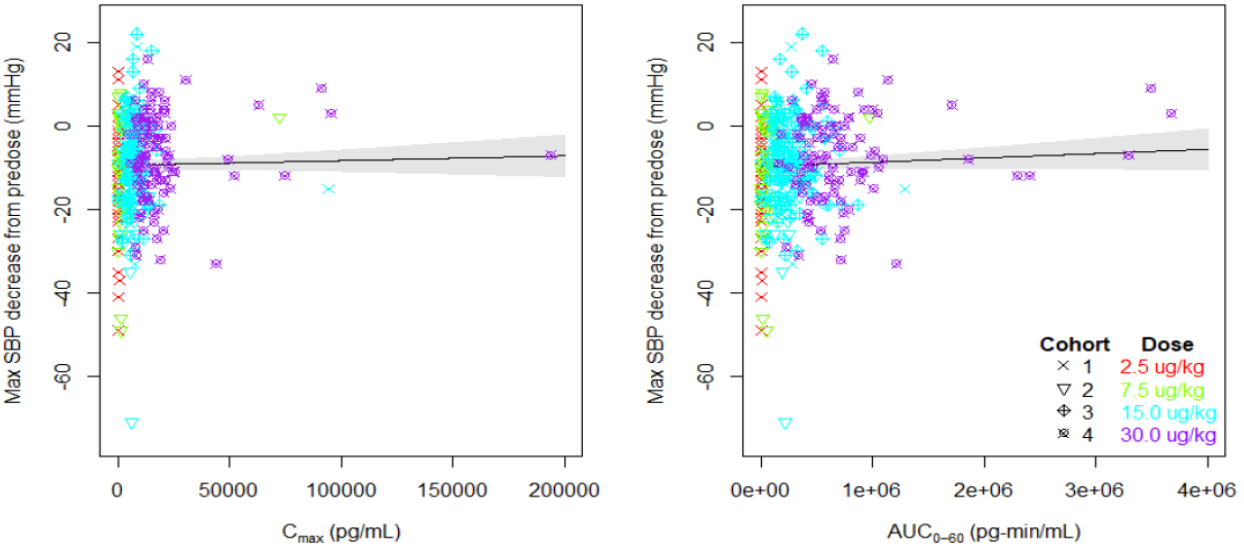
Exposure-Response Relationship for Safety: E-R analyses for safety were conducted in R (version 3.4.1) using the increases in heart rate (HR) and decreases in blood pressure (BP) as the safety endpoints. The predose HR or BP assessment at a given visit was used as the baseline value to calculate the maximum postdose change at that visit. The relationships between HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) and C_{max} or AUC_{0-60} were modeled using a linear model. The model parameter estimates and 95% confidence intervals for C_{max} and AUC_{0-60} are summarized in Table 88. E-R analysis using HR data collected over 24 months suggests a potential weak correlation between vosoritide exposure and increase in HR with a positive slope in subjects given daily doses between 2.5 µg/kg and 30 µg/kg (Figure 45). E-R analysis for the decrease in SBP or DBP indicates no obvious correlation between vosoritide exposure and decrease in SBP (Figure 46) or DBP (Figure 47) through 24 months of daily dosing at the dose range of 2.5 to 30 µg/kg.

Figure 45. Visit-Matched Vosoritide C_{max} and AUC_{0-60} and Maximum Increase in Heart Rate From Predose (0-24 Months)



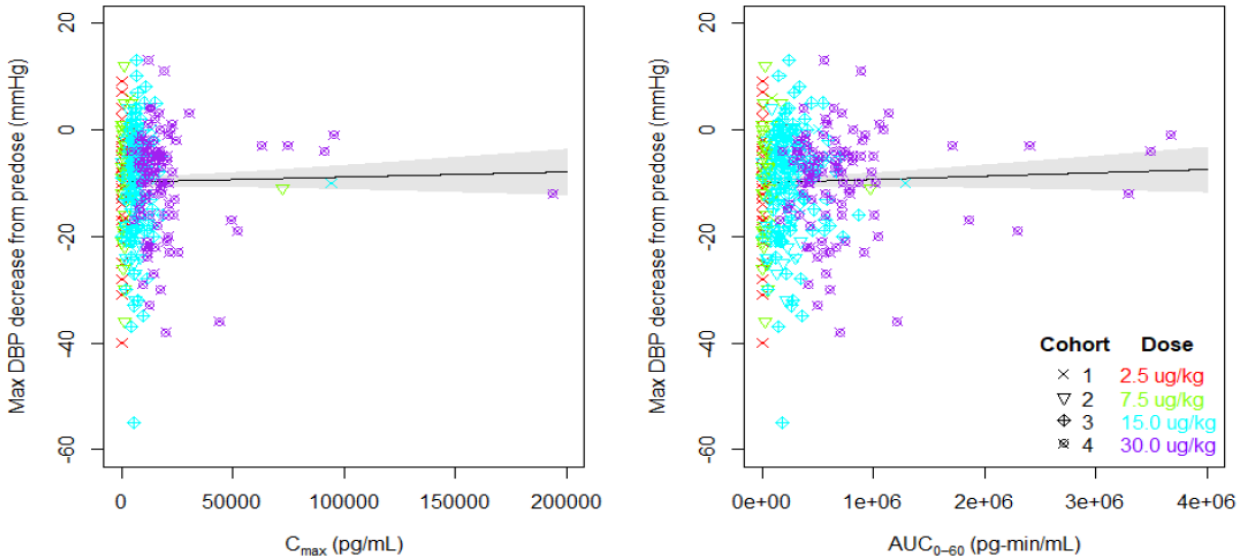
Source: Figure 9.2.3.2 in Study 111-202 Clinical Pharmacology Report
Abbreviations: HR, heart rate

Figure 46. Visit-Matched Vosoritide C_{max} and AUC_{0-60} and Maximum Decrease in Systolic Blood Pressure (0-24 Months)



Source: Figure 9.2.3.4 in Study 111-202 Clinical Pharmacology Report
Abbreviations: SBP, systolic blood pressure

Figure 47. Visit-Matched Vosoritide C_{max} and AUC_{0-60} and Maximum Decrease in Diastolic Blood Pressure (0-24 Months)



Source: Figure 9.2.3.6 in Study 111-202 Clinical Pharmacology Report
Note: Solid line represents the linear fit through the data and the shaded region represents the 95% confidence interval.
Abbreviations: DBP, diastolic blood pressure

Table 88. Linear Model Parameter Estimates for Heart Rate, Systolic Blood Pressure, and Diastolic Blood Pressure (Entire Study Period)

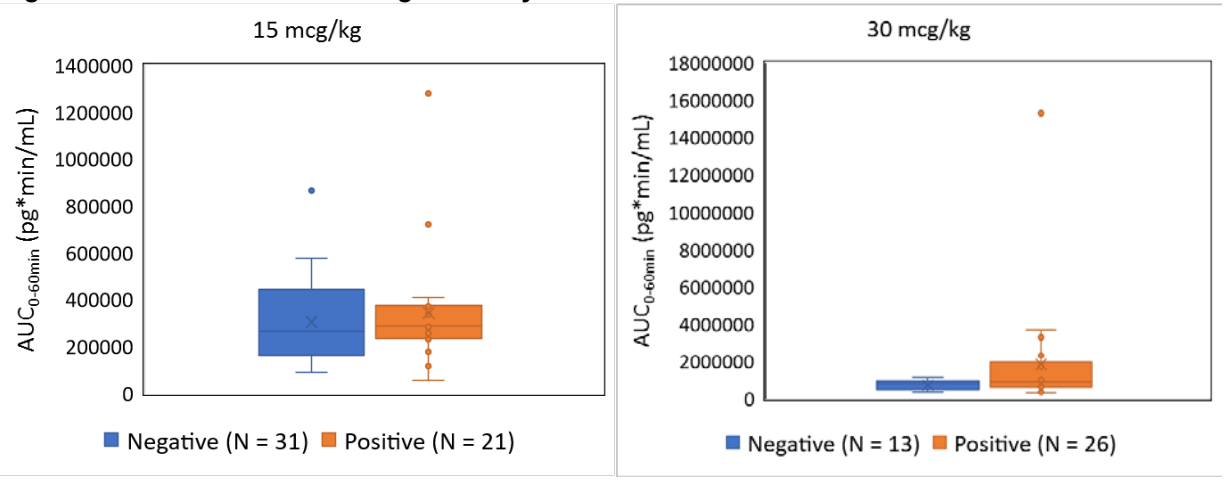
Safety Endpoints Pharmacokinetic Parameter	Model Parameter Estimates (95% Confidence Intervals)	
	Y-Intercept	Slope
Heart rate		
C_{max}	13.9 (12.7, 15.1)	3.94×10^{-5} (1.37×10^{-5}, 6.50×10^{-5})
$AUC_{0-60min}$	13.5 (12.2, 14.7)	2.32×10^{-6} (1.01×10^{-6}, 3.62×10^{-6})
Systolic blood pressure		
C_{max}	-9.49 (-10.7, -8.30)	1.15×10^{-5} (-1.39×10^{-5}, 3.69×10^{-5})
$AUC_{0-60min}$	-9.73 (-11.0, -8.49)	1.03×10^{-6} (-2.71×10^{-7}, 2.33×10^{-6})
Diastolic blood pressure		
C_{max}	-9.84 (-10.9, -8.83)	9.51×10^{-6} (-1.22×10^{-5}, 3.12×10^{-5})
$AUC_{0-60min}$	-9.96 (-11.0, -8.90)	6.20×10^{-7} (-4.92×10^{-7}, 1.73×10^{-6})

Source: Table 9.2.3.2, Table 9.2.3.4, and Table 9.2.3.6 in Study 111-202 Clinical Pharmacology Report

Effect of Immunogenicity on the PK/PD of Vosoritide: Anti-vosoritide antibodies were detected in the serum of 40% (14/35) of subjects in Study 111-202.The potential impact of the presence of serum ADAs on the magnitude of plasma PK of vosoritide was evaluated by comparing PK parameters (C_{max} and AUC_{0-60}) of each subject on matched visits where there was detectable ADA titer. As shown in Figure 48, in subjects receiving 15 µg/kg dose, the presence of ADA had no apparent impact on vosoritide plasma exposure. In subjects receiving 30 µg/kg dose, the presence of ADA was associated with a higher mean AUC_{0-60} of vosoritide (1828 versus 724 ng*min/mL). The higher exposure was partially caused by 1 outlier subject. Subject (b) (6) in Cohort 4 had a marked increase in exposure (AUC_{0-60} = 15321 ng*min/mL) on Visit Day 183. No apparent correlation between exposure (both C_{max} and AUC_{0-60}) and ADA titers was observed. Subjec (b) (6) was associated with titer values that were consistent with the other ADA positive subjects. The potential impact of the presence of ADAs on vosoritide activity was evaluated by comparing the maximum change from predose urine cGMP of each

subject at matched visits. The analysis showed that the presence of serum ADAs had no apparent impact on the changes in urine cGMP.

Figure 48. The Effect of Antidrug Antibody Status on the AUC of Vosoritide



Source: Clinical Pharmacology reviewer's analysis
Note: The line inside the box represents the median, the box represents the limits of the middle half of the data. The cross represents mean of the data. The range of the box, from the first quartile (Q1) to the third quartile (Q3), defines the interquartile range (IQR). The standard span of the data is defined within the range from Q1-1.5*IQR to Q3+1.5*IQR.
Abbreviations: AUC, area under the curve

Neutralizing antibodies (NAbs) were detected in 2 subjects only in Study 111-202 (Subject [redacted] (b) (6) of Cohort 4 at Month 8 and Subject [redacted] (b) (6) of Cohort 4 at Month 24). Although the AUC of vosoritide in Subject [redacted] (b) (6) was high, no obvious impact of NAb positive on efficacy was observed (Table 89).

Table 89. The Effect of Neutralizing Antibody Status on the AUC of Vosoritide

Subject ID	Cohort (Initial Dose)	Dose at NAb Positive	AUC_{0-60} (ng*min/mL)
[redacted] (b) (6)	4 (30 µg/kg)	30 µg/kg	1596
	4 (30 µg/kg)	30 µg/kg	571
Mean AUC_{0-60} of NAb negative subjects receiving 30 µg/kg			892

Source: Clinical Pharmacology reviewer's analysis
Abbreviations: AUC, area under the curve; NAb, neutralizing antibody

Reviewer's comment*: E-R analysis for serum CXM and efficacy revealed that an upper plateau of vosoritide activity was achieved at the exposure observed with 15 µg/kg and 30 µg/kg dose levels. E-R analysis for safety PD endpoints showed no correlation between vosoritide plasma exposure and decrease in SBP or DPB but a correlation between vosoritide plasma exposure and maximum increase in HR.*

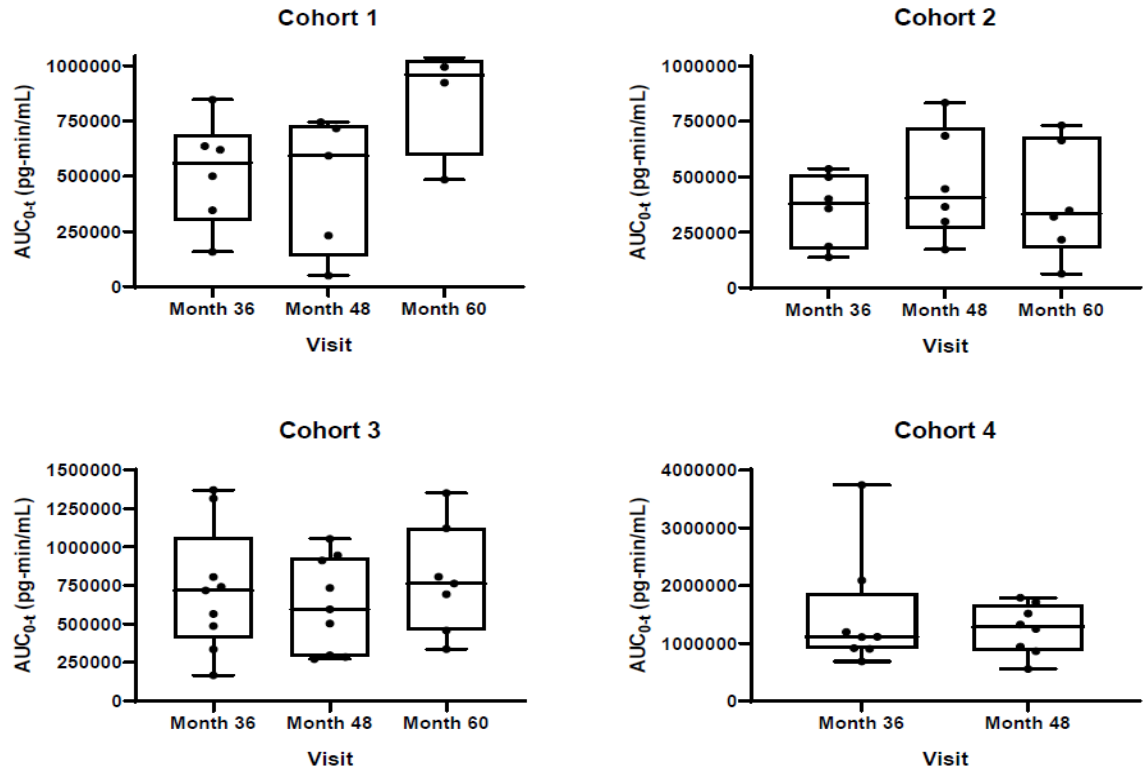
14.2.3. A Phase 2, Open-Label, Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of BMN-111 in Children With Achondroplasia (Study 111-205)

Study Design: Study 111-205 is an ongoing pediatric, multicenter, open-label, phase 2 extension study to evaluate the long-term safety and efficacy of daily BMN-111. Eligible subjects who

have completed 2 years of vosoritide treatment in Study 111-202 were enrolled in the 111-205 extension study to continue receiving the same stable dose of vosoritide received upon completion of Study 111-202 (15 µg/kg for Cohorts 1, 2 and 3, n=22; or 30 µg/kg for Cohort 4, n=8) for 5 years or until subjects reach near-final adult height (NFAH) during the 5-year period. Full PK sampling was performed at Baseline and every 12 months for the duration of treatment. Plasma PK samples were collected predose and at 5 (±2 min), 15 (±2 min), 30 (±5 min), 45 (±5 min), 60 (±5 min), 75 (±5 min), and 90 (±5 min) mins postdose.

PK Results: Study 111-205 is ongoing. For 2 subjects in Cohort 3 and all subjects in Cohort 4, Month 60 data were unavailable at the time of the interim analysis. Mean C_{max} and AUC_{0-t} ranged from 6.89 to 14.2 ng/mL, and 353 to 859 ng*min/mL respectively for 15 µg/kg dose level (Cohorts 1, 2, and 3). For 30 µg/kg dose level (Cohort 4), mean C_{max} and AUC_{0-t} ranged from 20.4 to 24.6 ng/mL and 1240 to 1470 ng*min/mL, respectively. The distributions of vosoritide AUC_{0-t} are shown in Figure 49. Overall, vosoritide exhibited consistent AUC_{0-t} across Visit Month 36, 48 and 60.

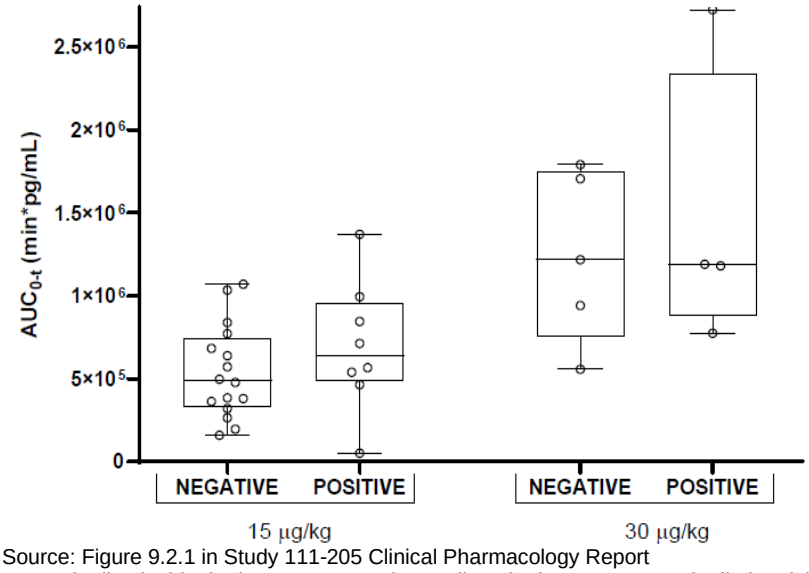
Figure 49. Distributions of Vosoritide AUC_{0-t} in Cohorts 1, 2, 3 and 4 (Study 111-205)



Source: Figure 9.1.3 in Study 111-205 Clinical Pharmacology Report
Note: The box denotes interquartile range and the line inside the box represents the median. Whiskers represent the min and max of the entire dataset at the particular visit in each Cohort. Individual data points are shown as closed circles.

The Effect of Immunogenicity on the PK of Vosoritide: Twelve of the 27 subjects with time-matched PK had quantifiable ADAs. Figure 50 shows the status of positive or negative ADAs with mean AUC_{0-t} of each subject for the entire duration of the study (Months 36, 48, and 60) for both dose levels. The status of ADAs had no impact on the AUC_{0-t} of vosoritide in either dose level. NAbs were not detected in any subject in Study 111-205.

Figure 50. The Effect of Antidrug Antibody Status on the AUC of Vosoritide



Source: Figure 9.2.1 in Study 111-205 Clinical Pharmacology Report
Note: 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). Whiskers are drawn to represent min and max values of the distribution.

14.2.4. A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN-111 in Children with Achondroplasia (Study 111-301)

Study Design: Study 111-301 was a phase 3 randomized, placebo-controlled, double-blind, multicenter study to evaluate the effect of BMN-111 on growth in children with achondroplasia. A total of 121 subjects were enrolled and centrally randomized 1:1 to vosoritide or placebo arms. Vosoritide 15 µg/kg or placebo was administered as a daily subcutaneous injection for 52 weeks. Full PK samples were collected predose and at 5 (±2 min), 15 (±2 min), 30 (±5 min), 45 (±5 min), 60 (±5 min), 90 (±5 min), 120 (±5 min) mins postdose at Day 1, Week 26, and Week 52 visits. Partial PK samples were collected predose and at 15 (±2 min), 30 (±5 min), and 60 (±5 min) mins postdose at Week 13 and Week 39 visits.

PK Results: Among a total of 60 subjects in the PK population, 2 subjects (Subjects (b) (6)) discontinued from treatment on Day 7 and Day 15 respectively. On Day 1, Subject (b) (6) was dosed at 44.4 µg/kg and the associated PK was excluded from summary statistics. Subject (b) (6) had no PK parameters as the actual sampling times were negative for all PK samples. All predose concentrations, with a single exception (Subject (b) (6) at Week 52: 1940 pg/mL), were below the limit of quantitation, indicating no drug accumulation. A trend of decreasing apparent clearance (CL/F) and a trend of increasing $T_{1/2}$ were observed from Day 1 to Week 26 and Week 52 (Table 90). No consistent increasing or decreasing trend in C_{max} or AUC was observed.

Table 90. Plasma PK Parameters of Vosoritide in Subjects Receiving 15 µg/kg Once Daily Dose

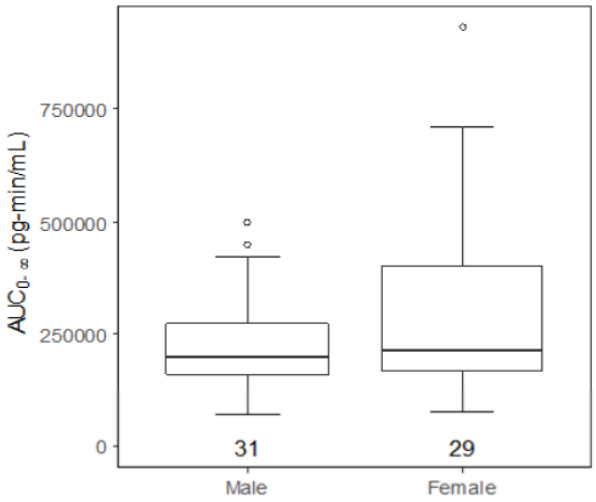
	Visit				
PK Parameter	**Day 1**	**Week 13**	**Week 26**	**Week 39**	**Week 52**
AUC_{0-t} (ng*min/mL)	242±232 (n=58)	161±98.1 (n=56)	256±211 (n=55)	205±129 (n=54)	290±235 (n=56)
AUC_{0-inf} (ng*min/mL)	244±224 (n=55)	N.A.	283±249 (n=53)	N.A.	276±187 (n=48)
C_{max} (ng/mL)	7.18±9.65 (n=58)	4.71±2.32 (n=56)	6.52±7.89 (n=55)	5.72±2.76 (n=54)	5.80±3.68 (n=56)
T1/2 (min)	21.0±4.7 (n=55)	N.A.	26.6±9.1 (n=53)	N.A.	27.9±9.9 (n=48)
CL/F (mL/min/kg)	104±99 (n=55)	N.A.	85.2±53.2 (n=53)	N.A.	79.4±53.0 (n=48)
Vz/F (mL/kg)	2880±2450 (n=55)	N.A.	3020±1980 (n=53)	N.A.	2910±1660 (n=48)

Source: Revised from Table 9.1.1 in Study 111-301 Clinical Pharmacology Report
Abbreviations: CL/F, apparent clearance; PK, pharmacokinetic; Vz/F, apparent volume of distribution during terminal elimination

Reviewer's comment: *Following 15 µg/kg once daily dosing, no drug accumulation was observed in subjects with ACH. The consistent decrease in CL/F of vosoritide was likely due to increased total daily dose over 12 months (pediatric subject's body weight gain over 12 months) and more than proportional PK of vosoritide.*

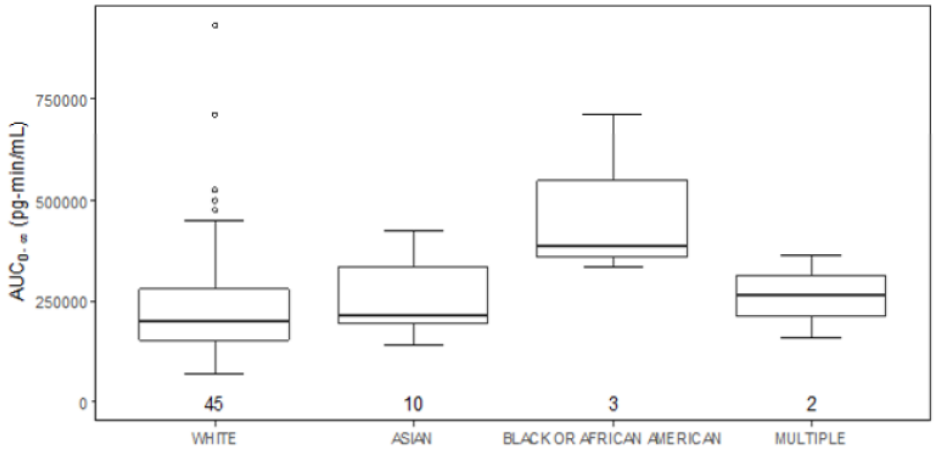
The Effect of Intrinsic Factors on the PK of Vosoritide: The potential impact of sex, race, baseline weight, and baseline age on vosoritide plasma exposure was evaluated by comparing the distribution of individual subject mean PK parameters (C_{max}, AUC_{0-60} and AUC_{0-inf}) across 52 weeks. The sex of a subject had no apparent impact on the AUC of vosoritide (Figure 51). Compared to White, Asian, or multiple race subjects, a higher mean AUC was observed in African American or Black subjects (N=3) (Figure 52). In contrast, African American or Black subjects receiving 15 µg/kg dose in Study 111-101 (N=2) and Study 111-202 (N=2) had slightly lower AUC than White subjects. No meaningful conclusion can be drawn due to the small sample size of African American or Black subjects. Positive correlations between plasma AUC_{0-inf} of vosoritide and subject body weight and age were observed (Figure 53). A total of 10 subjects with creatinine CL between 60 and 90 mL/min (mild renal impairment) were enrolled in Study 111-301 (Table 91). The exposure of vosoritide did not increase in subjects with ACH with mild renal impairment.

Figure 51. The Effect of Sex on the AUC of Vosoritide



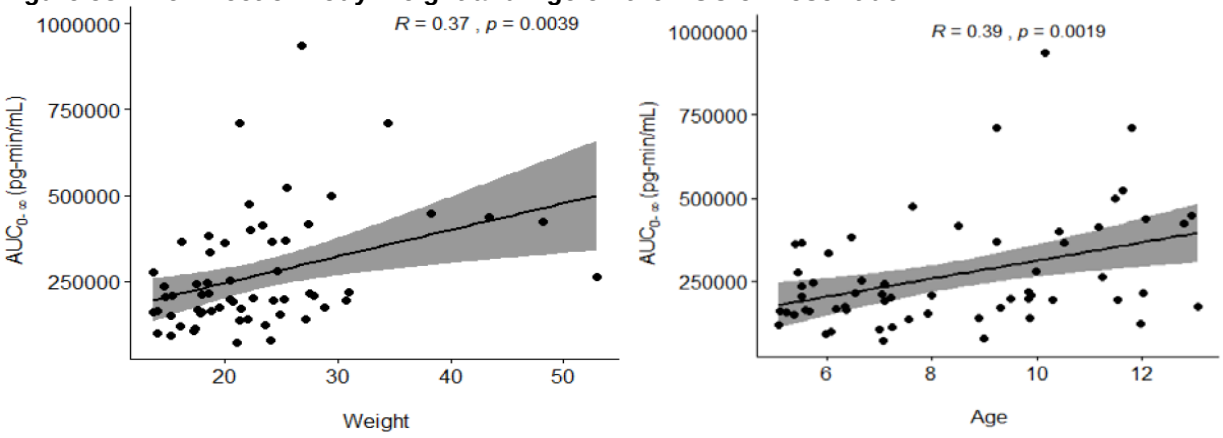
Source: Figure 9.1.1.1 in Study 111-301 Clinical Pharmacology Report

Figure 52. The Effect of Race on the AUC of Vosoritide



Source: Figure 9.1.1.2 in Study 111-301 Clinical Pharmacology Report

Figure 53. The Effect of Body Weight and Age on the AUC of Vosoritide



Source: Figure 9.1.1.3 and Figure 9.1.1.4 in Study 111-301 Clinical Pharmacology Report
Note: Solid line represents the linear fit through the data and the shaded region represents the 95% confidence interval.

Table 91. The AUC of Vosoritide on Day 1 in 10 Subjects in Study 111-301 With Creatinine Clearance of 60-90 mL/min

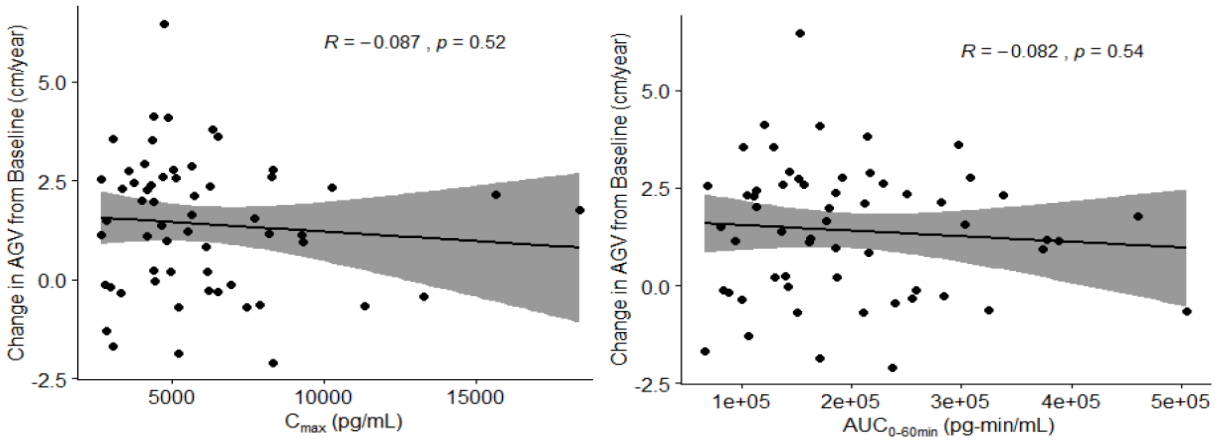
Study ID	Subject ID	Age (Year)	Baseline Body Weight (kg)	Dose (µg/kg)	AUC_{0-t} (Day 1)
301	[redacted] (b) (6)		13.6	15	160365
301			12.5	15	N.A.
301			18.4	15	N.A.
301			21.4	15	123680
301			21.3	15	387878
301			11.6	15	164534
301			12.9	15	58236
301			15.7	15	32695
301			15.6	15	25862
301			19.6	15	206675
Mean AUC of treated subjects with mild renal impairment				15	144990±118442
Mean AUC of all treated subjects on Day 1 in Study 111-301				15	242000±232000

Source: Reviewer's summary

ADAs were detected in the serum of 42% (25/60) of treated subjects by the end of the 52-week study duration. The mean AUC values were comparable between visits where there was detectable ADAs and where there was no detectable ADAs. No NAbs were detected in any subject enrolled in Study 111-301.

Exposure-Response Analyses for Efficacy: No correlation was observed between change in serum BSAP from baseline and vosoritide plasma exposure. Similarly, no correlation was observed between serum CXM and vosoritide plasma exposure. As shown in Figure 54, no obvious correlation was observed between individual vosoritide exposure and change in AGV from baseline (p>0.05).

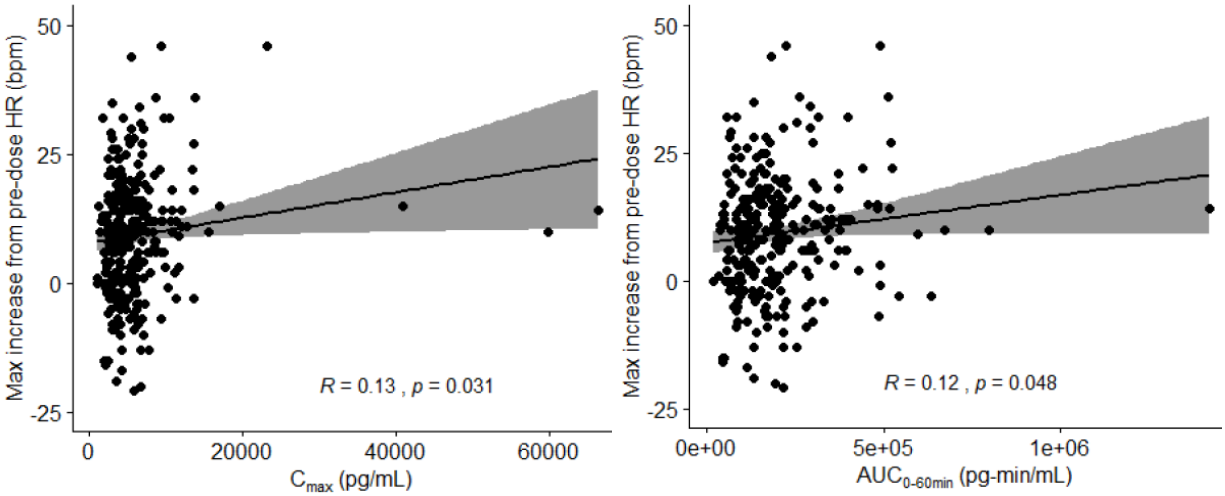
Figure 54. Exposure-Response Analysis for Change in Annualized Growth Velocity



Source: Figure 9.3.2.1 in Study 111-301 Clinical Pharmacology Report
Note: Solid line represents the linear fit through the data and the shaded region represents the 95% confidence interval.
Abbreviations: AGV, annualized growth velocity

Exposure-Response Analyses for Safety: As shown in Figure 55, weak positive correlations between the maximum increase from predose HR and exposure were observed and were statistically significant (p<0.05). However, no correlation was observed between the maximum decrease from predose SBP or DBP and vosoritide exposure.

Figure 55. Exposure-Response Analysis for Maximum Increase in Heart Rate



Source: Figure 9.3.3.1 in Study 111-301 Clinical Pharmacology Report
Note: Solid line represents the linear fit through the data and the shaded region represents the 95% confidence interval.
Abbreviations: HR, heart rate

Reviewer's comment: *In Study 111-301, only 1 dose level (15 µg/kg) was used and the body weight range of pediatric subjects with ACH was relatively narrow (baseline body weight: median 21.3 kg and range 13.6 to 53.0 kg). Therefore, except for several outliers, most individual subjects' AUC and C_{max} values were within a narrow range (i.e., most AUC_{0-60} value are between 50 and 500 ng*min/mL). The E-R analysis based on the efficacy data from Study 111-202 suggested that vosoritide activity was likely to reach a plateau when vosoritide AUC_{0-60} >50 ng*min/mL. This explains the no or poor correlations observed E-R analyses in Study 111-301.*

14.3. Pharmacometrics Review

(b) (4)

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Population PK Simulation for New Weight-Band Dosing

In the 2 phase 3 trials, vosoritide was dosed using body weight-based dosing at 15 µg/kg, (b) (4) [redacted] On October 22nd of 2021, in the applicant's response to Agency's information request, the applicant submitted a new weight-band dosing approach (b) (4) [redacted] (0.24 mg for 10-12 kg subjects, 0.28 mg for 12-16 kg subjects, 0.32 mg for 17-21 kg subjects, 0.4 mg for 22-32 kg subjects, 0.5 mg for 33-43 kg subjects, 0.6 mg for 44-59 kg subjects, 0.7 mg for 60-89 kg subjects, and 0.8 mg for subjects weighing 90 kg or higher). (b) (4) [redacted] Compared with the 15 µg/kg dose used in Study 111-301, the new eight-weight-band dosing would increase the dose in patients with body weight ≤26 kg, while it would reduce the dose in patients with body weight approximately 27 kg and higher (with the exception of 33 kg patients who would receive 15.2 µg/kg). The primary objective of the Applicant's popPK simulation study was to simulate exposure metrics of vosoritide using weight-band dosing with commercial formulation to simplify the dosing table.

Simulation Method: The final PopPK model submitted in original NDA was used for the simulation study. The one-compartment model has first order absorption (including a time-dependent change point in absorption rate coefficient) and first order elimination. The K_a switch time point is at 0.31 h and K_{a1} and K_{a2} values are 2.21 h^{-1} and 0.06 h^{-1}, respectively. (b) (4) [redacted] For the eight-weight-band dosing regimen, a total of 15 subject IDs were included (body weight: 10, 11 12, 16, 17, 21, 22, 32, 33, 43, 44, 59, 60, 89, and 90 kg). The final popPK model was then used to simulate 500 replicates of each subject ID receiving vosoritide at various doses. Summary metrics of the simulated AUC and C_{max} (lower 5th, 50th and upper 95th percentiles) were generated and compared to the same PK parameters for vosoritide observed at the 15 µg/kg daily dose from Study 111-301 and at the 30 µg/kg daily dose from Studies 111-202/205 (Table 100).

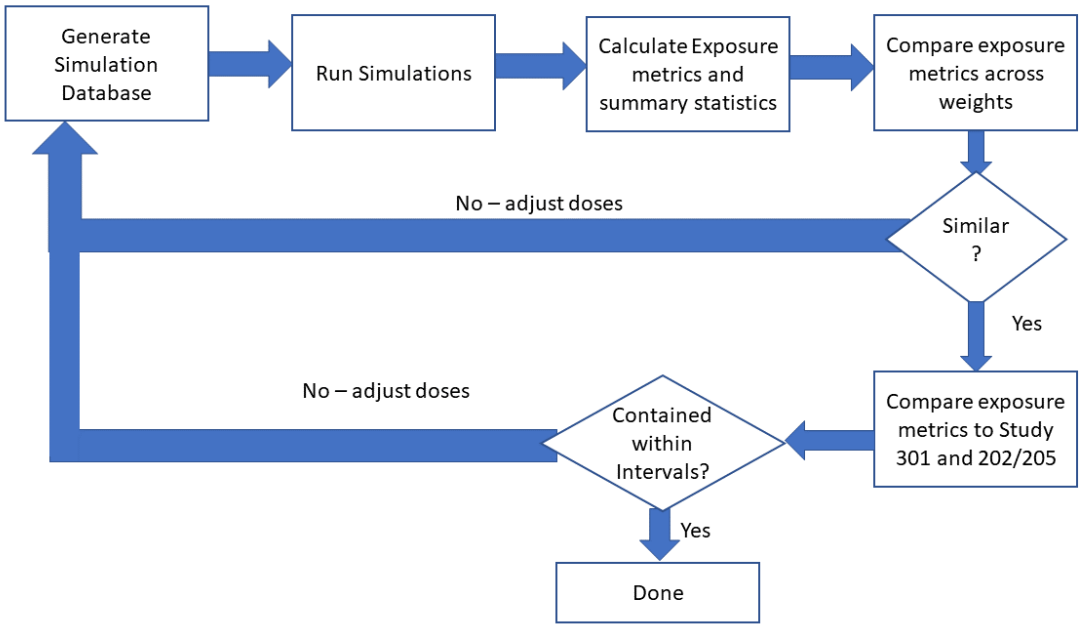
Table 100. Median, 5th and 95th Percentiles for Observed AUC and C_{max} in Studies 111-301 and 111-202/205

Study/Dose Parameter	5th Percentile	Median	95th Percentile
Study 111-301, 15 µg/kg (n=60)			
Observed C_{max} (pg/mL)	2060	4910	11600
Observed $AUC_{0\text{-}inf}$ (ng-min/mL)	70.5	210	653
Study 111-202/205, 15 µg/kg (n=22)			
Observed C_{max} (pg/mL)	2450	6470	14400
Observed $AUC_{0\text{-}inf}$ (ng-min/mL)	182	382	1120
Study 111-202/205, 30 µg/kg (n=9)			
Observed C_{max} (pg/mL)	7920	15800	63600
Observed $AUC_{0\text{-}inf}$ (ng-min/mL)	404	921	3460

Source: Tables 3, 4, and 5 in Applicant's popPK simulation report dated March 31, 2021

Figure 60 presents the schematic of the simulation analysis. The simulations were iterated for various weight strata to obtain the best dosing regimen that would be expected to achieve exposures that fell within exposure ranges observed in earlier clinical studies. The identify final weight-band dosing is shown in Table 101.

Figure 60. Flow Chart of Simulation Process for Weight-Band Dosing Optimization



Source: Figure 1 in Applicant's popPK simulation report dated March 31, 2021

Table 101. Proposed Eight-Weight-Band Dosing for Vosoritide

Body Weight (kg)	SKU 1 Concentration: 0.8 mg/mL (0.50 mL)	SKU 2 Concentration: 0.8 mg/mL (0.70 mL)	SKU 3 Concentration: 2 mg/mL (0.60 mL)
10-11	0.24 mg/0.30 mL (22-24 µg/kg)		
12-16		0.28 mg/0.35 mL (18-23 µg/kg)	
17-21		0.32 mg/0.40 mL (15-19 µg/kg)	
22-32		0.40 mg/0.50 mL (13-18 µg/kg)	
33-43			0.50 mg/0.25 mL (12-15 µg/kg)
44-59			0.60 mg/0.30 mL (10-14 µg/kg)
60-89			0.70 mg/0.35 mL (8-12 µg/kg)
>=90			0.80 mg/0.40 mL (≤9 µg/kg)

Source: Table 2 in Applicant's response letter dated October 22, 2021

Simulation Results: The simulations of median, 5th and 95th percentiles for AUC, and C_{max}, along with the proposed doses, are provided in Table 102. As shown in Figure 61, (b) (4) the simulated median AUC values of vosoritide in different weight bands for the eight-band dosing regimen are more consistent with the median AUC at 15 µg/kg observed in Study 111-301. With the eight-band dosing regimen, the simulated median

AUCs in subjects ≥ 22 kg are slightly higher than the observed median AUC in Study 111-301 (Figure 61B). The lower 5_{th} and upper 95_{th} percentiles of simulated AUC values for the eight-band dosing regimen are either within the range or slightly exceeding the upper 95th percentile of AUC observed in Study 111-301 (Figure 61B).

Similarly, (b) (4) the simulated median C_{max} values of vosoritide in subjects ≤ 59 kg for the proposed eight-band dosing regimen are more consistent with the median C_{max} at 15 µg/kg observed in Study 111-301 (Figure 62). A direct comparison between simulated and observed C_{max} values in subjects >59 kg is inappropriate because no subjects in vosoritide group in Study 111-301 had body weight >53 kg. For (b) (4) 8-band dosing regimens, the lower 5^{th} percentiles of simulated C_{max} are consistently lower than that of observed C_{max} in Study 111-301. The Applicant believes that the popPK model under-estimated C_{max} of vosoritide.

Table 102. Simulated Vosoritide AUC and C_{max} for the Proposed Weight-Band Dosing

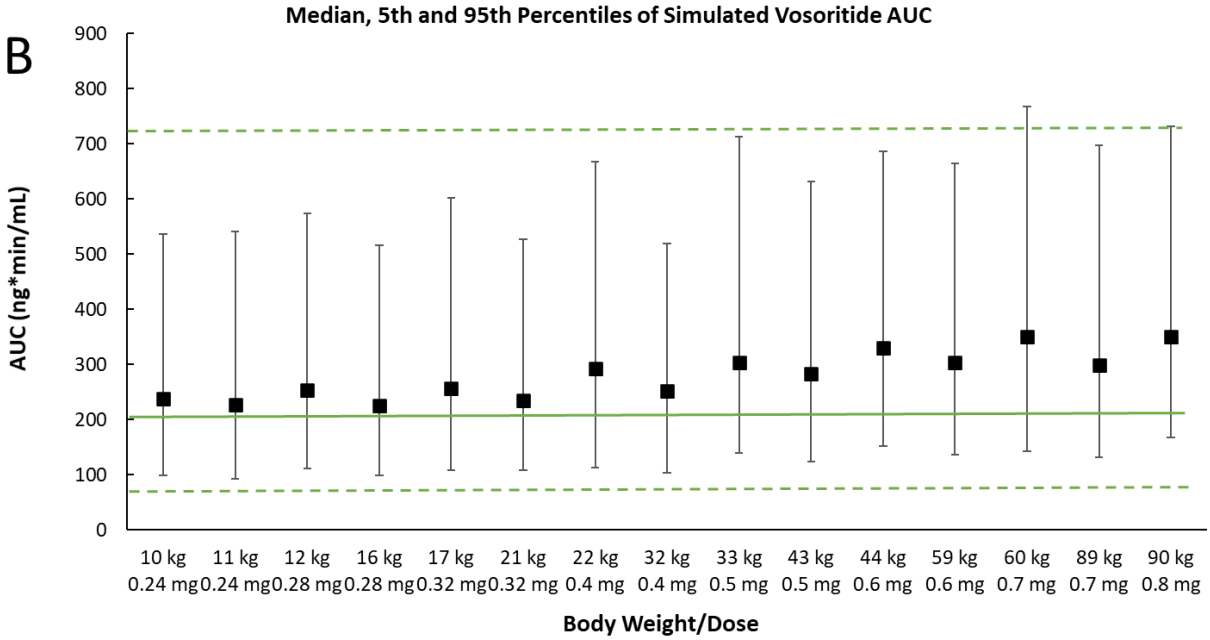
(b) (4)

Body Weight (kg)	Dose (mg)	Reviewer's Simulation for Eight-Band Dosing Regimen: Median (5^{th} and 95^{th} Percentiles)	
		AUC (ng*min/mL)	C_{max} (pg/mL)
10	0.24	238 (99, 536)	5756 (372, 9864)
11	0.24	226 (93, 541)	5384 (326, 9080)
12	0.28	253 (111, 574)	5864 (401, 10265)
16	0.28	225 (98, 516)	4770 (352, 7860)
17	0.3	257 (108, 603)	5075 (452, 8610)
21	0.3	235 (108, 527)	4569 (386, 7284)
22	0.4	293 (113, 668)	5399 (423, 8832)
32	0.4	252 (103, 520)	3880 (339, 6312)
33	0.5	303 (140, 713)	4866 (427, 8434)
43	0.5	284 (123, 632)	3815 (357, 6679)
44	0.6	330 (153, 686)	4607 (470, 7345)
59	0.6	304 (137, 664)	3651 (422, 5967)
60	0.7	350 (142, 768)	3971 (416, 6554)
89	0.7	299 (131, 698)	2808 (394, 4828)
90	0.8	351 (168, 731)	3238 (578, 5368)

Source: Reviewer's simulations using Applicant's popPK model

Figure 61. Simulation of Vosoritide AUC for Proposed (b) (4) Eight-Weight-Band (B) Dosing as Compared to Observed AUC Values at 15 µg/kg from Study 111-301

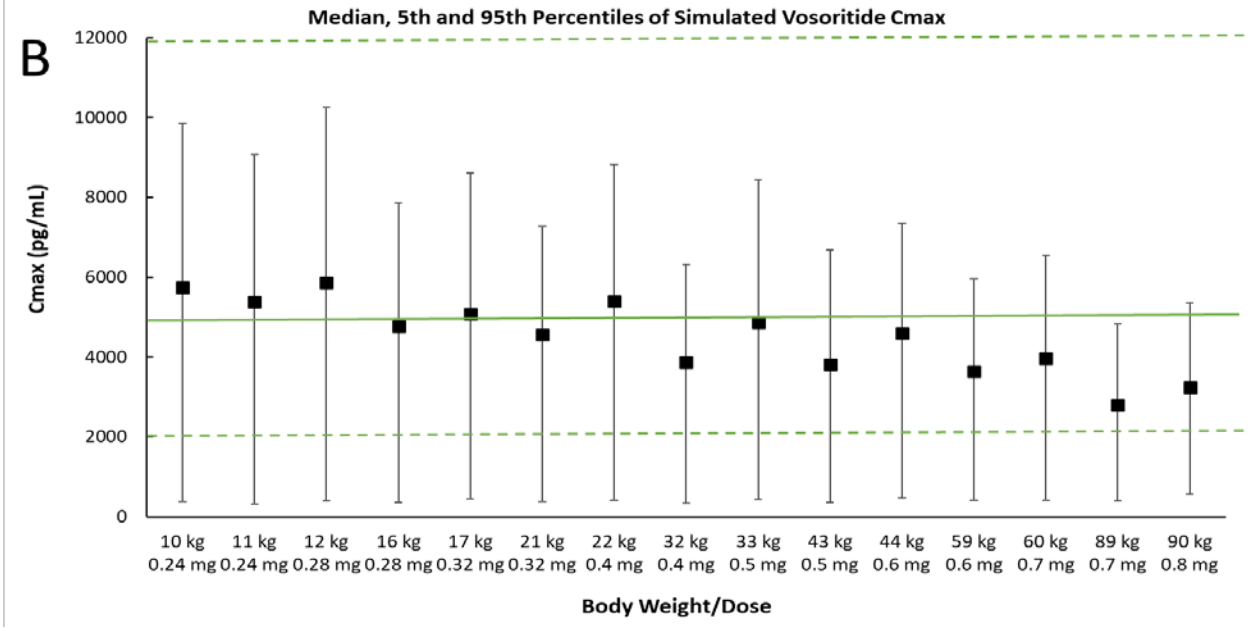
(b) (4)



Source: Plots based on reviewer's simulations using Applicant's popPK model.
Note: Black squares represent the simulated median AUCs for each weight, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of simulated AUCs. The green dashed lines represent the lower 5th and upper 95th percentiles of observed AUCs from study 111-301. The green solid line represents the median of observed AUCs from study 111-301.

Figure 62. Simulation of Vosoritide C_{max} for Proposed (b) (4) Eight-Weight-Band (B) Dosing as Compared to Observed C_{max} Values at 15 µg/kg from 111-301

(b) (4)



Source: Plots based on reviewer's simulations using Applicant's popPK model
Note: Black squares represent the simulated median Cmax for each weight, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of simulated Cmax. The green dashed lines represent the lower 5th and upper 95th percentiles of observed Cmax in study 111-301. The blue solid line represents the median of observed Cmax in study 111-301.

Reviewer's Comments:

- *Compared with the 15 µg/kg QD dosing, the proposed eight-band dosing increases the dose in patients with body weight ≤26 kg, while it reduces the dose in patients with body weight ~27 kg and higher. At the worst-case scenario, in patients weighing 10 kg receiving 0.24 mg QD vosoritide, the simulated AUC and C_{max} values are within the 5th and 95th percentiles of observed values at 15 µg/kg in Study 111-301.*

- *In subjects with body weight ≥ 89 kg, the simulated median AUCs are slightly higher than the median AUC observed at 15 µg/kg in Study 111-301 while the simulated median C_{max} values are approximately 40% lower than the median C_{max} observed at 15 µg/kg. Because vosoritide showed flat dose-response relationships for efficacy and safety in the dose range of 7.5-30 µg/kg, the lower simulated C_{max} is unlikely to have clinically meaningful impact on efficacy. Overall, from clinical pharmacology perspective, the proposed eight-band dosing is acceptable.*

14.4. Bioanalytical Method Validation and Performance

A total of 16 bioanalytical methods were developed to support analysis of PK, PD, and immunogenicity in vosoritide clinical studies. A quantitative enzyme-linked immunosorbent assay (ELISA) method was developed and validated to measure vosoritide concentrations in human plasma samples in phase 1 and 2 studies (Studies 111-101, 111-202, and 111-205). The ELISA method was further developed as an electrochemiluminescence assay (ECLA) to improve sensitivity and range of quantitation to support phase 2 and 3 clinical studies (Studies 111-206, 111-208, 111-301, and 111-302). PK assay bridging studies were conducted to demonstrate equivalence between plasma concentration results from the 2 bioanalytical methods. The validation parameters and performance of the 2 plasma vosoritide PK assays are summarized in Table 103.

Table 103. Summary of Assay Validations and Performance for Vosoritide in Human Plasma Samples

Validation Parameters	PK ELISA Validation	PK ECLA Validation
Range of quantitation	391 to 25,000 pg/mL	0.137 to 100 ng/mL
Intra-assay precision and accuracy	|%RE|: ≤7.1 (QC), ≤10.7 (LOQ) %CV: ≤7.1 (QC), ≤10.0 (LOQ) %TE: ≤12.8 (QC), ≤20.7 (LOQ)	|%RE|: ≤3.8 (QC), ≤2.8 (LOQ) %CV: ≤4.4 (QC), ≤6.3 (LOQ) %TE: ≤8.2 (QC), ≤9.1 (LOQ)
Interassay precision and accuracy	|%RE|: ≤7.1 (QC), ≤10.7 (LOQ) %CV: ≤7.4 (QC), ≤15.2 (LOQ) %TE: ≤12.8 (QC), ≤25.9 (LOQ)	|%RE|: ≤3.8 (QC), ≤2.8 (LOQ) %CV: ≤10.8 (QC), ≤10.1 (LOQ) %TE: ≤14.2 (QC), ≤12.9 (LOQ)
Dilution linearity	Mean |%RE| ≤8.4 at each dilution %CV ≤5.8 across each dilution series No hook effect up to 1 µg/mL vosoritide in plasma	Mean |%RE| ≤5.0 at each dilution %CV ≤: 4.1 across each dilution series No hook effect up to 1 µg/mL vosoritide in plasma
Selectivity	100% of unspiked samples were BLQ	100% of unspiked samples were BLQ
Incurred sample reanalysis	Study 111-101: 45 of 60 (75.0%) ISR samples |%difference| ≤30% Study 111-202/205: 126 of 132 (95.5%) ISR samples |%difference| ≤30%	Study 111-301/302: 232 of 260 (89.2%) ISR samples |%difference| ≤30%

Source: Table 2.7.1.1.1.1.1 in Summary of Biopharmaceutical and Associated Analytical Methods
Abbreviations: BLQ, below the limit of quantitation; CV, coefficient of variation; ECLA, electrochemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; ISR, incurred sample reanalysis; LOQ, limit of quantitation; PK, pharmacokinetics; QC, quality control; RE, relative error; ROQ, range of quantitation; TE, total error

Both ELISA and ECLA PK assays were validated for storage stability. For the ELISA PK assay, vosoritide was stable in human plasma for ≥15 hours at 2 to 8˚C and 18 months at -60 to -80˚C. For the ECLA PK assay, vosoritide was stable in human plasma for ≥12 hours at 2 to 8˚C and 44

months at -60 to -80˚C. The long-term storage stability of both assays covered corresponding sample storage periods.

Immunogenicity assays were validated for semiquantitative measurement of ADA, including assays for total anti-vosoritide antibodies, neutralizing anti-vosoritide antibodies, and anti-vosoritide IgE in serum. Qualitative assays were validated for detection of TAb cross-reactivity with endogenous natriuretic peptides (ANP, B-type natriuretic peptide [BNP], and CNP) as part of the TAb assay method. Exploratory assays to measure potential biomarkers of vosoritide activity in vivo, including cGMP, BSAP, P1NP, cross-linked C-terminal telopeptides of type II collagen (CTXII), CXM, ANP, and N-terminal propeptide of CNP (NT-proCNP) were characterized or validated before use.

Because vosoritide and human endogenous natriuretic peptides (ANP, BNP, and CNP) share some similar C terminal amino acids sequence, vosoritide PK assays and antidrug antibody assays were validated to detect potential cross-reactivity.

- For the ELISA PK assay, no interference was detected from samples containing up to 2.5 µg/mL ANP or BNP or up to 15 ng/mL CNP.
- For the ECLA PK assay, no interference was detected from samples containing up to 5 ng/mL ANP or BNP and up to 0.7 ng/mL CNP.
- For the semiquantitative ECLA assay for ADAs, no interference was detected from samples containing up to 100 µg/mL ANP or BNP, up to 10 µg/mL CNP, or up to 1 µg/mL vosoritide.

Overall, the submitted method validation reports and bioanalytical analysis reports are acceptable.

15. Trial Design: Additional Information and Assessment

15.1. Study 111-301

Design

Stratification by Tanner stage of pubertal development was as follows: Stage I or Stage > I, with no more than 20% > Stage I, due to potential effect of puberty on growth. Original protocol specified stratification by age (<11 or ≥11 years), with 2 subjects randomized in the study according to the strata in the original protocol.

After randomization, the subjects were required to attend the clinic for visits on Days 2, 3, 10, and Weeks 6, 13, 26, 39, and 52. In addition, the subjects were contacted by a study staff member every 4 weeks after the Week 6 visit.

Key Secondary and Exploratory Endpoints

Other secondary endpoints included evaluation of change from baseline to Week 52 of: a) body proportion ratios of the extremities (e.g., upper arm length to lower arm length ratio, upper leg length to knee to heel length ratio, upper leg length to tibial length ratio, and arm span to

standing height ratio); b) Health Related Quality of Life (HRQoL) as measured by the Quality of Life in Short Stature Youth (QoLISSY) and Pediatric Quality of Life Inventory (PedsQL) questionnaires; c) functional independence as measured by the Functional Independence Measure for Children (WeeFIM) clinician-reported outcome; d) bone morphology and pathology by X-ray and dual-X-ray absorptiometry (DEXA) as measured by bone age, bone age Z-score, bone mineral density, BMD Z-score, and BMC. Of note, the content validity of the proposed HRQoL and functional assessment instruments have not been established in ACH population.

Exploratory endpoints included evaluation of presence and severity of sleep-disordered breathing overnight in a subset of subjects by measurement of blood oxygen saturation, pulse rate, and airflow, and evaluation of biomarkers of vosoritide activity (urine cyclic guanosine monophosphate (cGMP) normalized by creatinine concentration).

Eligibility Criteria

Key Inclusion Criteria

(1) Age 5 to <18 years at study entry
(2) ACH, diagnosed by clinical assessments and confirmed by genetic testing
(3) At least 6-month period of pretreatment growth assessment in observational Study 111-901
(4) Willing to use a highly effective method of contraception during the study and for 30 days (females) or 3 months (male subjects) after taking the last dose of the study drug. if sexually active
(5) Females ages 10 and older or who had begun menses must have had a negative pregnancy test at screening and were willing to have additional pregnancy tests during the study

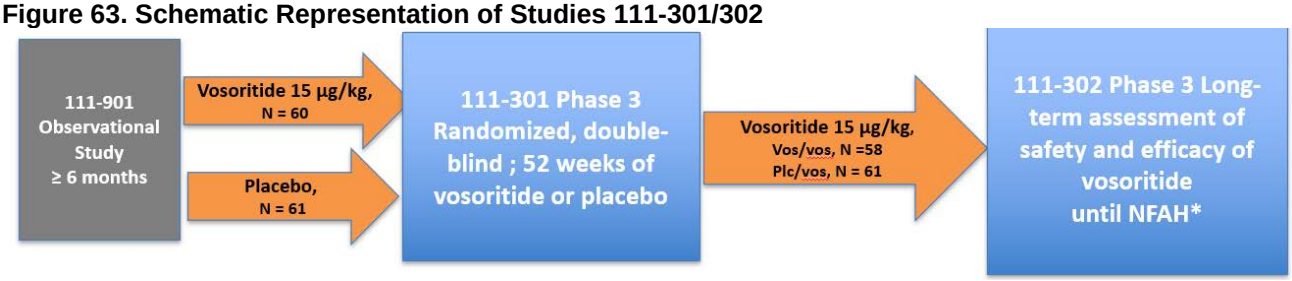
Key Exclusion Criteria

(1) Hypochondroplasia or short stature condition other than ACH (e.g., trisomy 21, pseudoachondroplasia).
(2) 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).
(3) Limb-lengthening surgery within 18 months prior to screening, or planned bone-related surgery during study. Bone-related surgery or fracture of long bones or spine within 6 months prior to screening.
(4) Treatment with growth stimulants (e.g., growth hormone, insulin-like growth factor 1, or anabolic steroids) in the previous 6 months or treatment greater than 6 months at any time. Treatment with corticosteroids for >1 month in the previous 12 months.
(5) Baseline SBP <70 mm Hg or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms i.e., dizziness, fainting) or recurrent symptomatic orthostatic hypotension.
(6) Clinically significant finding or arrhythmia on screening ECG that indicated abnormal cardiac function or conduction or Fridericia's corrected QT interval (QTc-F) >450 msec.

(7) Current chronic therapy with antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, gonadotropin-releasing hormone (GnRH) agonists, any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function
(8) Unstable condition likely to require surgical intervention during the study
(9) Including progressive cervical medullary compression or severe untreated sleep apnea
(10) Evidence of decreased growth velocity (AGV <1.5 cm/year) or of growth plate closure
(11) Hip conditions that might influence clinical hip examination during study (e.g., history of hip surgery or hip dysplasia atypical for achondroplastic subjects, clinically significant hip injury in the 30 days prior to screening, History of slipped capital femoral epiphysis (SCFE) or avascular necrosis of the femoral head)

15.2. Studies 111-302

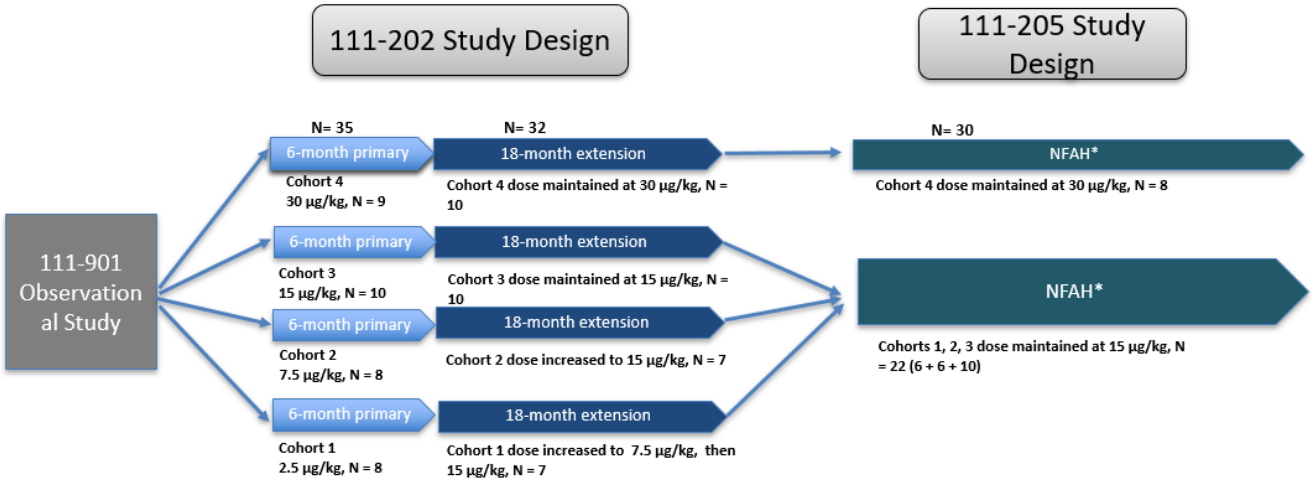
Figure 63. Schematic Representation of Studies 111-301/302



Source: clinical reviewer
*Until subjects have either reached NFAH, or for 5 years if NFAH occurs prior to the end of the 5-year period
Abbreviations: NFAH, near final adult height

15.3. Studies 111-202/205

Figure 64. Schematic Representation of Studies 111-202/205 Design



Source: clinical reviewer
Abbreviations: N, number of subjects; NFAH, near final adult height

Eligibility Criteria

Key Inclusion Criteria

(1) Ages 5 to 14 years at study entry
(2) ACH, diagnosed by clinical assessments and confirmed by genetic testing
(3) At least 6-month period of pretreatment growth assessment in observational Study 111-901
(4) Willing to use a highly effective method of contraception during the study, if sexually active
(5) Females age 10 and older or who had begun menses must have had a negative pregnancy test at screening and were willing to have additional pregnancy tests during the study

Key Exclusion Criteria

(1) Hypochondroplasia or short stature condition other than ACH (e.g., trisomy 21, pseudoachondroplasia).
(2) 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)
(3) Limb-lengthening surgery within 18 months prior to screening, or planned bone-related surgery during study. Bone-related surgery or fracture of long bones or spine within 6 months prior to screening.
(4) Treatment with growth stimulants (e.g., growth hormone, insulin-like growth factor 1, or anabolic steroids) in the previous 6 months or treatment greater than 6 months at any time. Treatment with oral corticosteroids for >1 month in the previous 12 months.
(5) Baseline systolic blood pressure (SBP) <75 mm Hg or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms e.g., dizziness, fainting) or recurrent symptomatic orthostatic hypotension
(6) Clinically significant finding or arrhythmia on screening ECG that indicated abnormal cardiac function or conduction or Fridericia's corrected QT interval (QTc-F) >450 msec.
(7) Current chronic therapy with antihypertensive medications, ACE inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, GnRH agonists, any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function.
(8) Unstable condition likely to require surgical intervention during the study (including progressive cervical medullary compression or severe untreated sleep apnea)
(9) Evidence of decreased growth velocity (AGV <1.5 cm/year) or of growth plate closure
(10) Hip conditions that might influence clinical hip examination during study (e.g., history of hip surgery or hip dysplasia atypical for achondroplastic subjects, clinically significant hip injury in the 30 days prior to screening, history of SCFE or avascular necrosis of the femoral head)

Statistical Analysis Plan

All summary tables include absolute values at baseline and 6-month time points and changes from baseline by 6-month time points, by cohort and overall. Box plots (for AGV) and line plots (mean and SD) for each assessment in the summary tables are provided by cohort and overall.

Changes from baseline every 12 months for interval AGV and every 6 months for the endpoints cumulative AGV, height Z-score, and upper lower body ratio were tested using a paired t test.

15.4. Study 111-206

Study Design

Study 111-206 is an ongoing 52-week, multicenter, phase 2 randomized, double-blind, placebo-controlled clinical study. The main objectives of the study are to evaluate the safety of vosoritide and its impact on growth in infants and younger children recruited from birth to age 60 months (5 years) with genetically confirmed ACH. The target number of subjects to be enrolled in Study 111-206 is 70 at 16 clinical centers worldwide. Subjects are enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects are stratified by age:

- Cohort 1: children ages ≥24 to <60 months (n ≥30 total: 3 sentinel subjects who receive vosoritide, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥24 to <36 months and ≥36 months to <60 months)
- Cohort 2: children ages ≥6 to <24 months (n ≥20 total: 3 sentinel subjects who receive vosoritide, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥6 months to <15 months and ≥15 months to <24 months)
- Cohort 3: children ages 0 to <6 months (n ≥20 total: 3 sentinel subjects receive vosoritide, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥3 months to <6 months after 3 months of observation. At the time of the data cut for this interim report, enrollment in Cohort 3 has not commenced yet.

At least 6 months of baseline growth data for Cohorts 1 and 2, and at least 3 months of baseline growth data for Cohort 3 are collected in Study 111-901. Alternatively, subjects eligible for Cohort 3 (0 months to <3 months old) may enroll directly into Study 111-206 and have a minimum of 3 months of pretreatment observation prior to commencing treatment with investigational product. The planned treatment duration is 52 weeks in Study 111-206, followed by long-term treatment in Study 111-208 until subjects reach near final adult height. Subjects in Cohort 1 who are randomized to vosoritide treatment will receive a dose of 15 µg/kg/day; subjects in Cohort 2 will receive vosoritide 30 µg/kg/day until age 2 then a lower dose of 15 µg/kg/day; and dosing in Cohort 3 will follow the Cohort 2 regimen with respect to age.

The primary efficacy endpoints include length/height Z-score, and secondary endpoints include AGV, body proportion and ratios of extremities, bone morphology/quality, hip function, HRQoL, developmental status, functional independence (age appropriate QoL instruments), sleep apnea, skull and brain morphology (including foramen magnum, ventricular and brain parenchymal dimensions), and incidence of surgical interventions.

16. Efficacy: Additional Information and Assessment

16.1. Additional Efficacy Results

16.1.1. Study 111-301

Table 104. Subject Screening and Randomization, Study 111-301

Screening Disposition	Study 111-301
Subjects screened	124
Not randomized	3
Screening failures	3
Subjects randomized	121

Source: adds.xpt and Clinical Study Report; Software: R

Table 105. ACH-Related Comorbidities Occurring With a Frequency of ≥10% in Any of the Treatment Arms, Full Analysis Set

System Organ Class Preferred Term	VOS 15 µg/kg (N=60) n (%)	Placebo (N=61) n (%)
Subjects with any ACH-related medical history condition	56 (93.3)	58 (95.1)
Surgical and medical procedures	42 (70.0)	37 (60.7)
Ear tube insertion	27 (45.0)	22 (36.1)
Adenoidectomy	20 (33.3)	19 (31.1)
Tonsillectomy	10 (16.7)	14 (23.0)
Spinal decompression	9 (15.0)	8 (13.1)
Adenotonsillectomy	8 (13.3)	7 (11.5)
Infections and infestations[a]	31 (51.7)	36 (59.0)
Otitis media	24 (40.0)	27 (44.3)
Respiratory, thoracic and mediastinal disorders	32 (53.3)	34 (55.7)
Sleep apnea syndrome	27 (45.0)	31 (50.8)
Tonsillar hypertrophy	6 (10.0)	4 (6.6)
Adenoidal hypertrophy	6 (10.0)	1 (1.6)
Musculoskeletal and connective tissue disorders	26 (43.3)	31 (50.8)
Kyphosis	10 (16.7)	11 (18.0)
Knee deformity	11 (18.3)	8 (13.1)
Lordosis	10 (16.7)	5 (8.2)
Arthralgia	8 (13.3)	5 (8.2)
Pain in extremity	3 (5.0)	7 (11.5)
Cervical spinal stenosis	7 (11.7)	2 (3.3)
Congenital, familial and genetic disorders	23 (38.3)	25 (41.0)
Congenital bowing of long bones	18 (30.0)	17 (27.9)
Foramen magnum stenosis	7 (11.7)	7 (11.5)
Ear and labyrinth disorders	20 (33.3)	19 (31.1)
Hypoacusis	12 (20.0)	13 (21.3)
Nervous system disorders	17 (28.3)	19 (31.1)
Speech disorder	7 (11.7)	7 (11.5)
Hypotonia	6 (10.0)	3 (4.9)

Source: adapted from Applicant's CSR 111-301, Table 10.2.3.1.
[a] PTs included are: otitis media, ear infection, otitis media chronic, otitis media acute
Abbreviations: ACH, achondroplasia; VOS, vosoritide

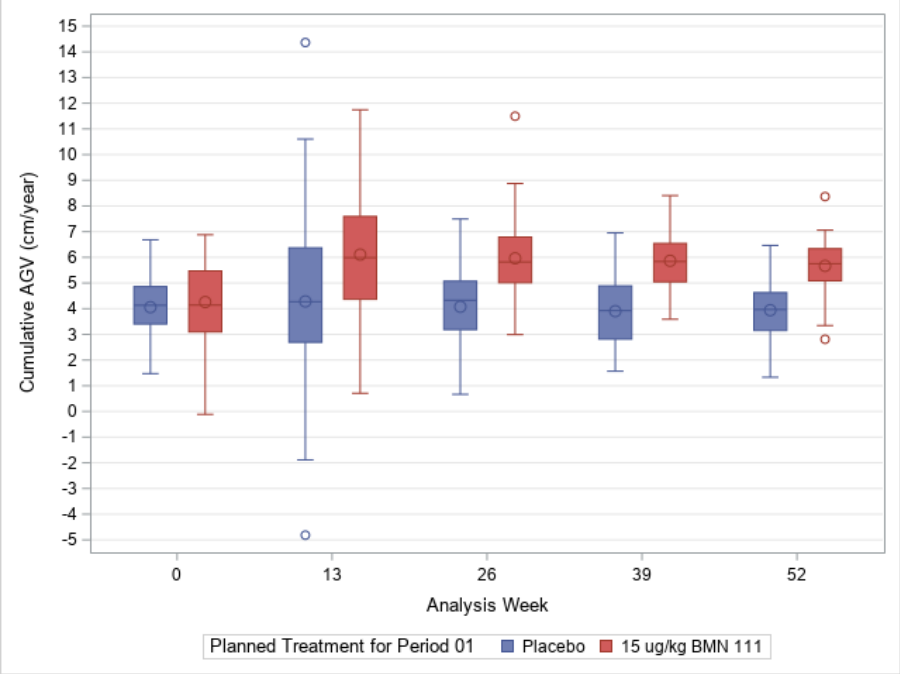
Table 106. Treatment Compliance, Study 111-301

Treatment Compliance	VOS 15 µg/kg (N=60)	Placebo (N=61)
Compliance with protocol-specified treatment regimen, %[a]		
n	60	61
Mean (SD)	99.14(3.22)	98.73 (3.13)
Median	99.49	99.72
Min, max	89.9, 118.8	85.4, 109.8
Compliance with protocol-specified treatment regimen, n (%)[a,b]		
>80%	60(100.0)	61 (100.0)
>90%	59 (98.3)	59 (96.7)
100%	20 (33.3)	20 (32.8)

Source: adapted from Table 10.3.1, CSR 111-301
Max, maximum; Min, minimum; SD, standard deviation.
[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: SD, standard deviation; VOS, vosoritide

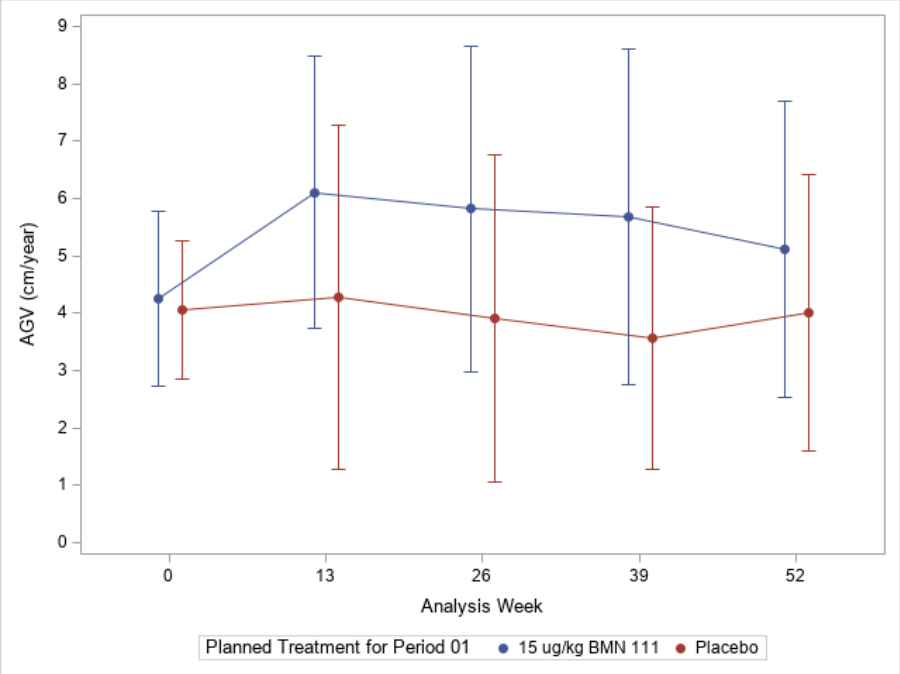
Primary Endpoint – Study 111-301

Figure 65. Box Plot of Cumulative AGV Over Time, Full Analysis Set, Study 111-301



Source: statistical reviewer
Abbreviations: AGV, annualized growth velocity

Figure 66. 3-Month Interval AGV Over Time (Mean ± SD), Full Analysis Set, Study 111-301



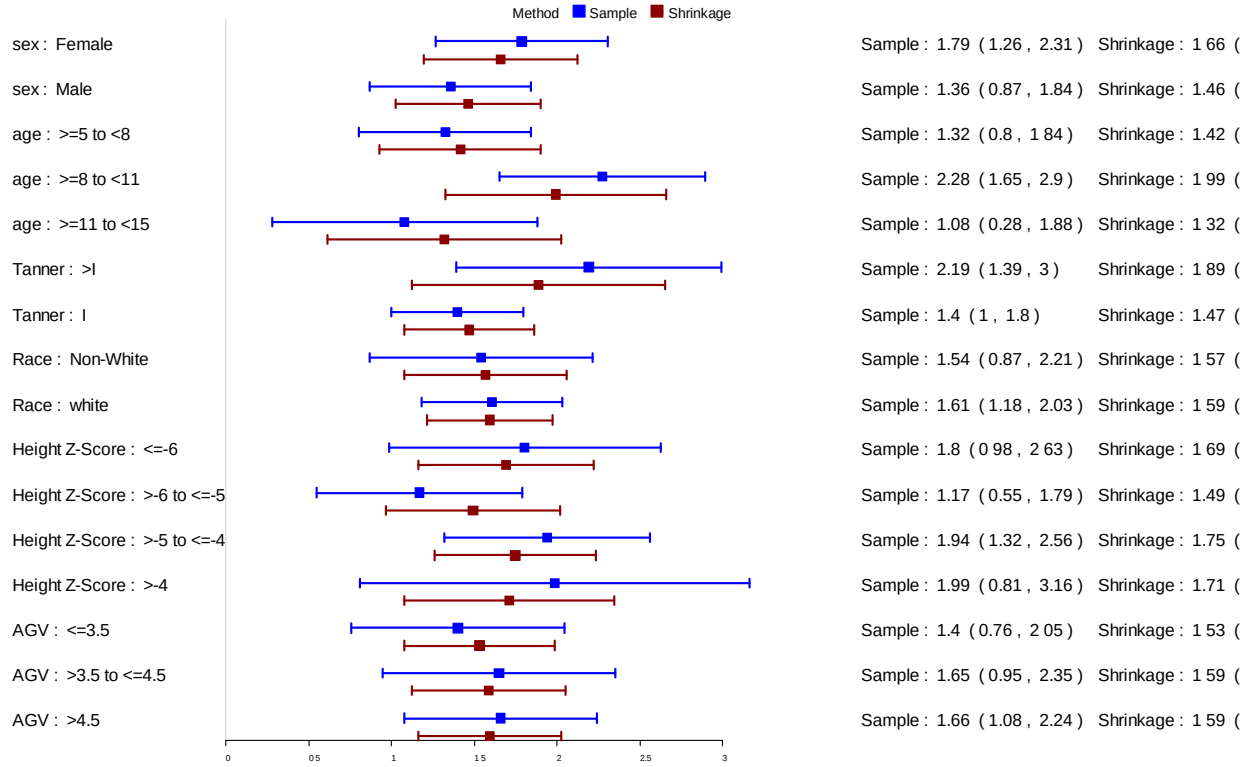
Source: statistical reviewer
Abbreviations: AGV, Annualized growth velocity; SD, standard deviation

Table 107. Mean Change From Baseline in AGV (cm/year) at Week 52 by Subgroupa, Full Analysis Set, Study 111-301

Subgroup Level	N (Vosoritide, Placebo)	Treatment Difference	95% CI	Nominal P-Value
Sex				
Female	29, 28	1.79	1.26, 2.31	<0.0001
Male	31, 33	1.36	0.87, 1.84	<0.0001
Age				
≥5 to <8	31, 24	1.32	0.80, 1.84	<0.0001
≥8 to <11	17, 24	2.28	1.65, 2.90	<0.0001
≥11 to <15	12, 13	1.08	0.28, 1.88	0.0089
Race				
White	45, 41	1.61	1.18, 2.03	<0.0001
Non-white	15, 20	1.54	0.87, 2.21	<0.0001
AGV				
≤3.5	19, 19	1.40	0.76, 2.05	<0.0001
>3.5 to ≤4.5	14, 18	1.65	0.95, 2.35	<0.0001
>4.5	27, 24	1.66	1.08, 2.24	<0.0001
Height Z-score				
≤-6	15, 10	1.80	0.98, 2.63	<0.0001
>-6 to ≤-5	18, 24	1.17	0.55, 1.79	0.0003
>-5 to ≤-4	22, 19	1.94	1.32, 2.56	<0.0001
>-4	5, 8	1.99	0.81, 3.16	0.0012
Tanner				
>I	48, 48	2.19	1.39, 3.00	<0.0001
I	12, 13	1.40	1.00, 1.80	<0.0001

Source: statistical reviewer's analyses
[a] Missing data were imputed in the same way as the primary efficacy analysis. A similar ANCOVA model was fit including additional factors: subgroup and subgroup-by-treatment interaction.
Abbreviations: AGV, annualized growth velocity; CI, confidence interval

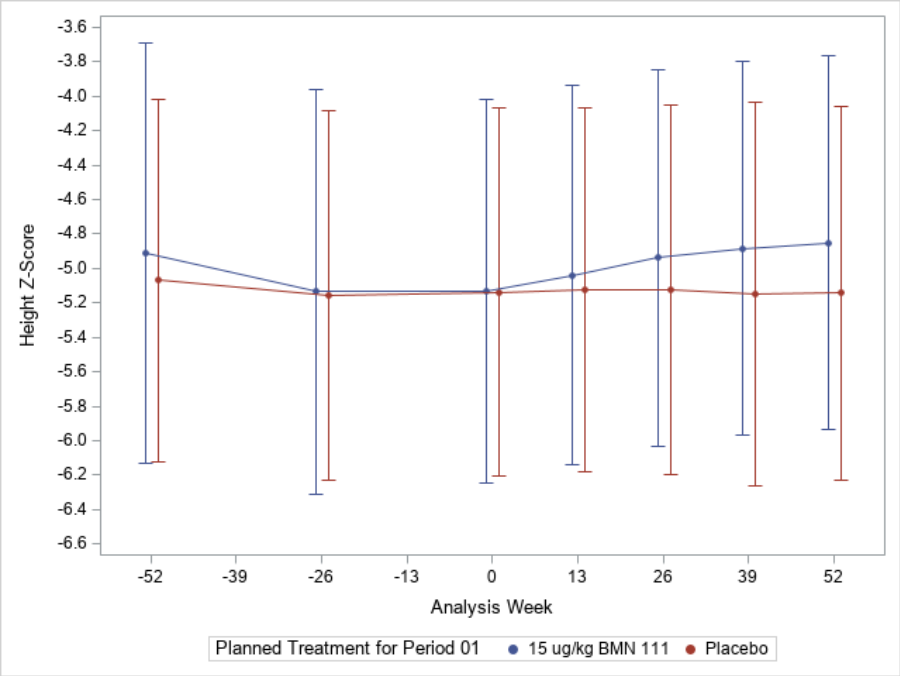
Figure 67. Treatment Difference of Vosoritide Versus Placebo by Subgroup in Change in AGV (cm/year) From Baseline to Week 52, Full Analysis Set, Study 111-301



Source: statistical reviewer's analyses
Sample: estimates from Table 109
Shrinkage: estimates from Bayesian hierarchical model using summary sample estimates. A flat prior with overall mean following a normal distribution was used for mean treatment effect in each subgroup: μi ~ N(μ, τ2), μ ~ N(mean =0, std =4), 1/τ2 ~ Gamma(0.001, 0.001). Patient-level residual standard deviation from the primary efficacy analysis was around 1.
Abbreviations: AGV, annualized growth velocity

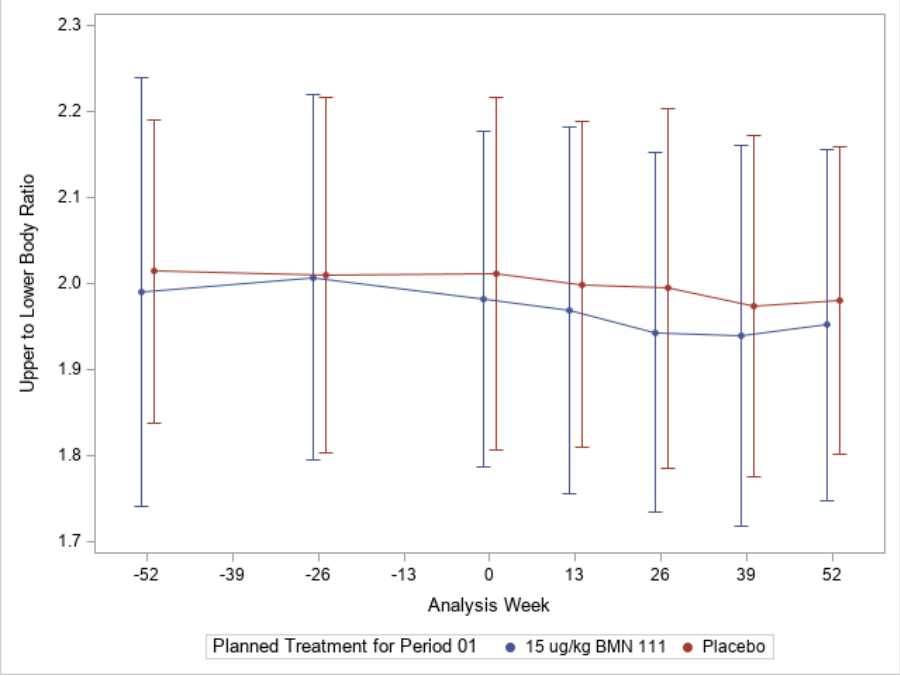
Secondary and Exploratory Endpoints – Study 111-301

Figure 68. Height Z-Score Over Time (Mean ± SD), Full Analysis Set, Study 111-301



Source: statistical reviewer
Abbreviations: SD, standard deviation

Figure 69. Upper to Lower Body Segment Ratio Over Time (Mean ± SD), Full Analysis Set, Study 111-301



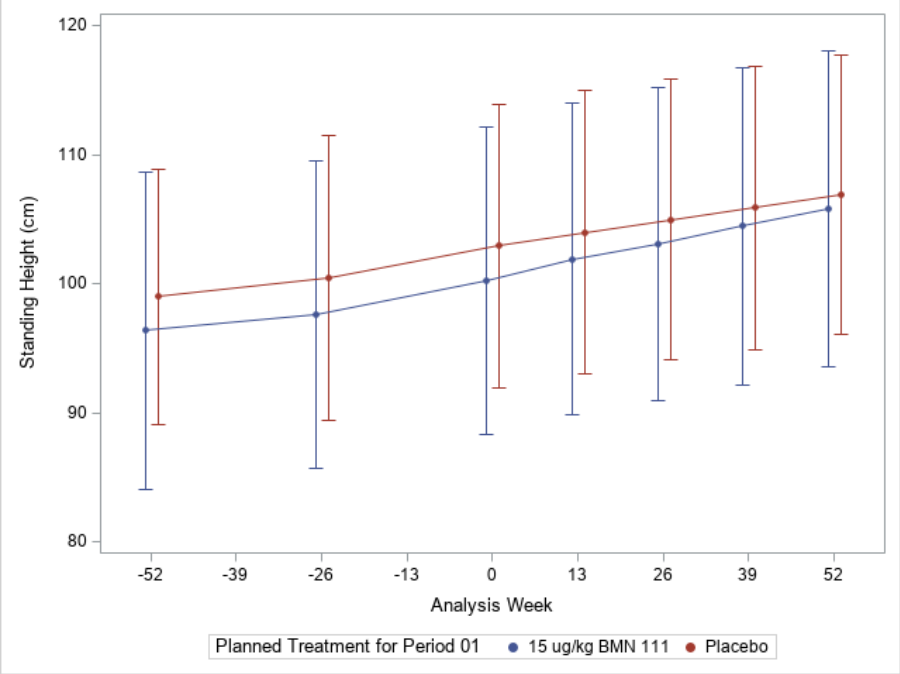
Source: statistical reviewer
Abbreviations: SD, standard deviation

Table 108. Change From Baseline in Standing Height at Week 52a, Full Analysis Set, Study 111-301

Standing Height (cm)	VOS 15 µg/kg (N=60)	Placebo (N=61)
Baseline, mean (SD)	100.20 (11.90)	102.94 (10.98)
Week 52, mean (SD)	105.80 (12.03)	106.87 (10.84)
Change from baseline[b], LS Mean (95% CI)	5.55 (5.30, 5.80)	3.98 (3.72, 4.23)
Difference in change from baseline[b]		
LS Mean (95% CI)	1.57 (1.21, 1.93)	
P-value	<0.0001	

Source: statistical reviewer
[a] Standing height from the 2 subjects with missing data were imputed assuming baseline growth rate for the period with missing data.
[b] ANCOVA model includes treatment, stratum defined by sex and Tanner stage, baseline age, baseline AGV and baseline height Z-score and baseline standing height. LS mean for each group was adjusted according to the distribution of baseline covariates.
Abbreviations: CI, confidence interval; LS mean, least square mean; SD, standard deviation; VOS, vosoritide

Figure 70. Standing Height Over Time (Mean ± SD), Full Analysis Set, Study 111-301



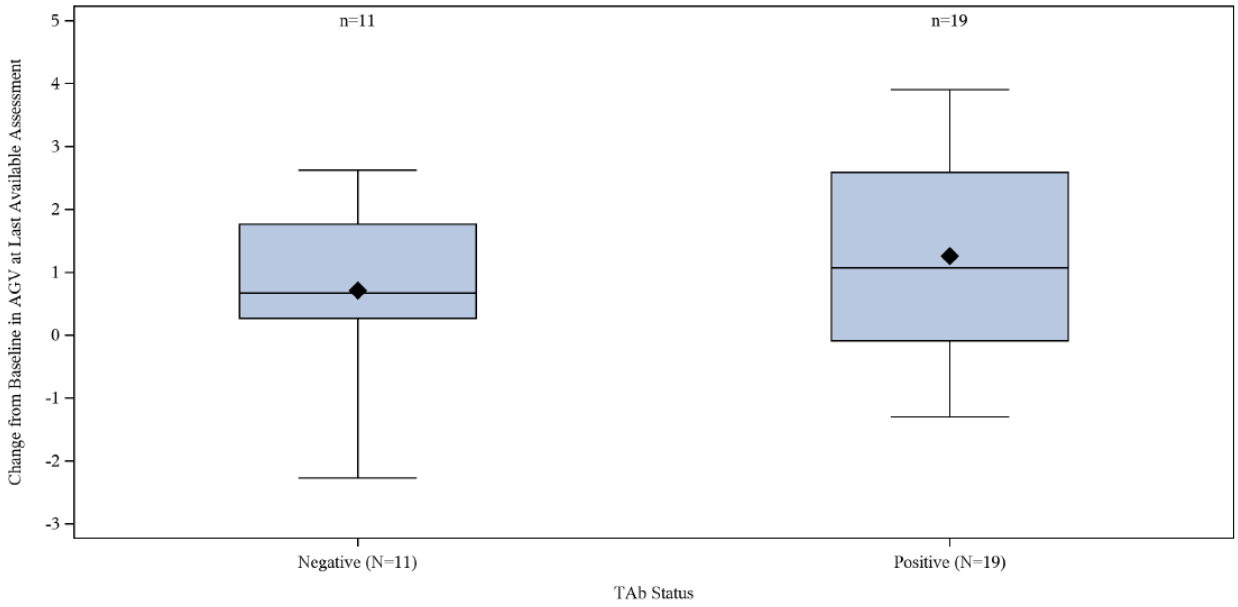
Source: statistical reviewer
Abbreviations: SD, standard deviation

Table 109. Change From Baseline in Body Proportion Ratios at Week 52, Full Analysis Set

Measure Results	Placebo (N = 61)	15 µg/kg Vosoritide (N = 60)
Upper Arm Length to Lower Arm (Forearm) Length Ratio[a]		
n	61	58
LS mean change from baseline (95% CI)	0.03 (0.00, 0.06)	0.02 (−0.01, 0.05)
Difference in LS mean change from baseline (95% CI)[b]	-	−0.01 (−0.04, 0.02)
P-value[c]	-	0.5683
Upper Leg Length (Thigh) to Knee to Heel Length Ratio[d]		
n	61	58
LS mean change from baseline (95% CI)	0.02 (0.00, 0.04)	0.01 (0.00, 0.03)
Difference in LS mean change from baseline (95% CI)[b]	-	−0.01 (−0.02, 0.01)
P-value[c]	-	0.5678
Upper Leg Length (Thigh) to Tibial Leg Length Ratio[e]		
n	61	58
LS mean change from baseline (95% CI)	0.03 (0.01, 0.06)	0.01 (−0.01, 0.04)
Difference in LS mean change from baseline (95% CI)[b]	-	−0.02 (−0.05, 0.01)
P-value[c]	-	0.1949
Arm Span to Standing Height Ratio[f]		
n	61	58
LS mean change from baseline (95% CI)	0.00 (0.00, 0.01)	0.00 (−0.01, 0.00)
Difference in LS mean change from baseline (95% CI)[b]	-	−0.01 (−0.02, 0.00)
P-value[c]	-	0.1226

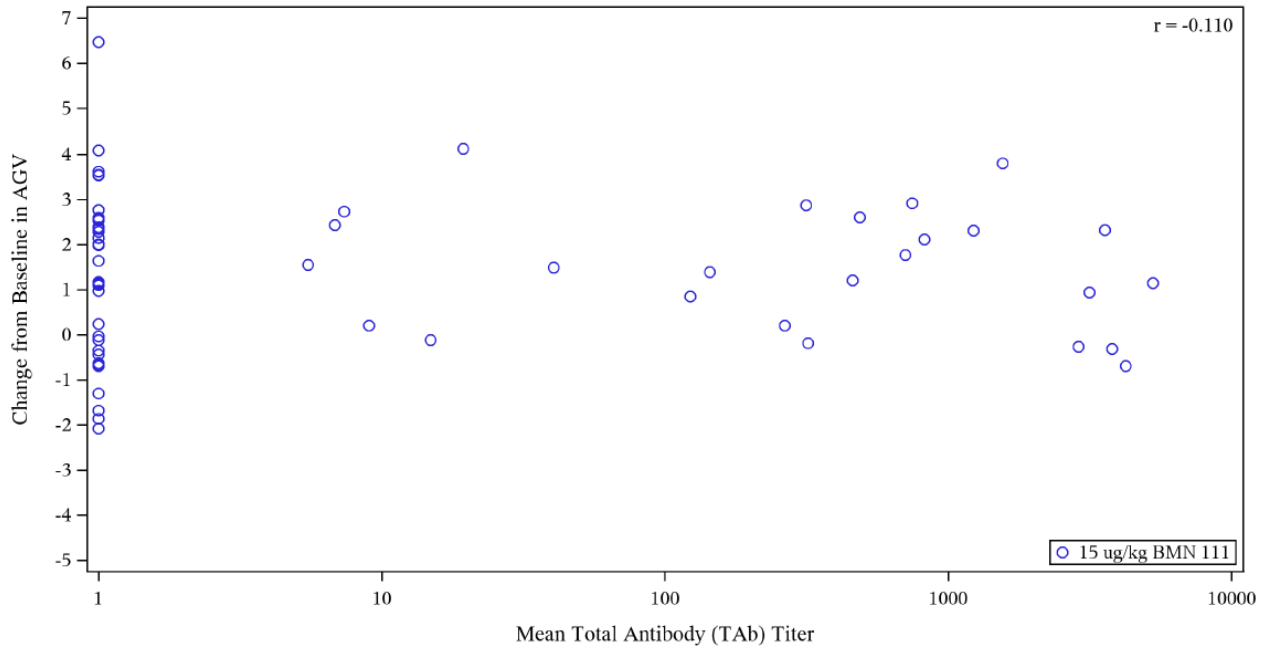
AGV, annualized growth velocity; ANCOVA, analysis of covariance; CI, confidence interval; LS, least-square
Source: Clinical Study Report 111-301, Table 10.4.3.3.1.

Figure 71. Change From Baseline in 12-Month AGV by TAb Status, Immunogenicity Population



Source: Applicant's Figure 11.6.2.1, 111-205 Interim CSR
Abbreviations: AGV, annualized growth velocity; TAb, total anti-vosoritide antibody

Figure 72. Change From Baseline in AGV at Week 52 vs. Mean TAb Titer Analysis, Immunogenicity Population



Source: Applicant Figure 14.3.6.3.2B, CSR 111-301
Abbreviations: AGV, annualized growth velocity; TAb, total anti-vosoritide antibody

16.1.2. Study 111-302

Table 110. 12-Month Interval AGV (cm/year) Over Time, Full Analysis Set, Study 111-301/302

12-Month AGV	Placebo/Vosoritide	Vosoritide/Vosoritide
Baseline		
N	61	60
Mean (SD)	4.06 (1.20)	4.26 (1.53)
1 year		
N	61	58
Mean (SD)	3.94 (1.07)	5.67 (0.98)
Change from baseline to 1 year[a]		
Mean (SD)	-0.12 (1.74)	1.41 (1.71)
95% CI	-0.56, 0.33	0.96, 1.86
2 year		
N	54	52
Mean (SD)	5.65 (1.47)	5.57 (1.11)
Change from baseline to 2 year[a]		
Mean (SD)	1.66 (1.88)	1.29 (1.83)
95% CI	1.15, 2.17	0.78, 1.80
Change from 1 year to 2 year[a]		
Mean (SD)	1.66 (1.61)	-0.14 (1.29)
95% CI	1.22, 2.10	-0.50, 0.22

Source: statistical reviewer
[a] 95% CI for mean change from baseline is from paired t-test between visits.
Abbreviations: AGV, annualized growth velocity; CI, confidence interval; SD, standard deviation

Table 111. Height Z-Score Over Time, Full Analysis Set, Study 111-301/302

Height Z-Score	Placebo/Vosoritide	Vosoritide/Vosoritide
Baseline		
N	61	60
Mean (SD)	-5.14 (1.07)	-5.13 (1.11)
1 year		
N	61	58
Mean (SD)	-5.14 (1.09)	-4.85 (1.09)
Change from baseline to 1 year[a]		
Mean (SD)	-0.005 (0.28)	0.24 (0.31)
95% CI	-0.077, 0.067	0.15, 0.32
2 year		
N	54	52
Mean (SD)	-4.89 (1.13)	-4.54 (1.12)
Change from baseline to 2 year[a]		
Mean (SD)	0.24 (0.46)	0.45 (0.56)
95% CI	0.11, 0.36	0.30, 0.61
Change from 1 Year to 2 Year[a]		
Mean (SD)	0.23 (0.34)	0.21
95% CI	0.14, 0.32	0.11, 0.30

Source: statistical reviewer
[a] 95% CI for mean change from baseline is from paired t-test between visits.
Abbreviations: CI, confidence interval; SD, standard deviation

Table 112. Upper to Lower Body Segment Ratio Over Time, Full Analysis Set, Study 111-301/302

Upper to Lower Body Segment Ratio	Placebo/Vosoritide	Vosoritide/Vosoritide
Baseline		
N	61	60
Mean (SD)	2.01 (0.21)	1.98 (0.20)
1 year		
N	61	58
Mean (SD)	1.98 (0.18)	1.95 (0.20)
Change from baseline at 1 year[a]		
Mean (SD)	-0.03 (0.09)	-0.03 (0.11)
95% CI	-0.05, -0.01	-0.06, -0.0005
2 year		
N	47	45
Mean (SD)	1.95 (0.17)	1.88 (0.21)
Change from baseline at 2 year[a]		
Mean (SD)	-0.06 (0.13)	-0.09 (0.11)
95% CI	-0.10, -0.03	-0.12, -0.06
Change from 1 year at 2 year[a]		
Mean (SD)	-0.03 (0.08)	-0.06 (0.13)
95% CI	-0.06, -0.01	-0.10, -0.02

Source: statistical reviewer
[a] 95% CI for mean change from baseline is from paired t-test between visits.
Abbreviations: CI, confidence interval; SD, standard deviation

16.1.3. Studies 111-202/205

Table 113. Subject Screening and Randomization, Studies 111-202/205

Screening Disposition	Study 202	Study 205
Subjects screened	Not reported	Not applicable for extension trial
Subjects enrolled	35	30

Source: adds.xpt and Clinical Study Report; Software: R

Table 114. Baseline Demographic, Safety Population, Study 111-202

Characteristic	2.5 µg/kg VOS N=8	7.5 µg/kg VOS N=8	15 µg/kg VOS N=10	30 µg/kg VOS N=9	2.5-15 µg/kg VOS N=26
Sex, (n%)					
Female	5 (62.5)	3 (37.5)	6 (60.0)	5 (55.6)	14 (53.8)
Male	3 (37.5)	5 (62.5)	4 (40.0)	4 (44.4)	12 (46.2)
Age, years					
Mean (SD)	7.2 (1.6)	8.2 (2.2)	8 (1.6)	6.9 (1.2)	7.8 (1.8)
Median (min, max)	7 (5, 10)	9.5 (5, 10)	8 (6, 11)	7 (5, 8)	7.5 (5, 11)
Age group, years, (n%)					
≥5 to <8	6 (75.0)	3 (37.5)	4 (40.0)	5 (55.6)	13 (50.0)
≥8 to <10	1 (12.5)	1 (12.5)	4 (40.0)	4 (44.4)	6 (23.1)
≥10 to ≤14	1 (12.5)	4 (50.0)	2 (20.0)	0 (0)	7 (26.9)
Ethnicity, (n%)					
Hispanic or Latino	0 (0)	0 (0)	1 (10.0)	1 (11.1)	1 (3.8)
Not Hispanic or Latino	8 (100)	8 (100)	9 (90.0)	7 (77.8)	25 (96.2)
Not reported	0 (0)	0 (0)	0 (0)	1 (11.1)	0 (0)

Characteristic	2.5 µg/kg VOS N=8	7.5 µg/kg VOS N=8	15 µg/kg VOS N=10	30 µg/kg VOS N=9	2.5-15 µg/kg VOS N=26
Race, (n%)					
Asian	0 (0)	1 (12.5)	3 (30.0)	3 (33.3)	4 (15.4)
Black or African American	1 (12.5)	0 (0)	1 (10.0)	0 (0)	2 (7.7)
Other	0 (0)	1 (12.5)	1 (10.0)	0 (0)	2 (7.7)
White	7 (87.5)	6 (75.0)	5 (50.0)	6 (66.7)	18 (69.2)
Country of participation, (n%)					
Australia	1 (12.5)	3 (37.5)	1 (10.0)	2 (22.2)	5 (19.2)
France	0 (0)	0 (0)	2 (20.0)	0 (0)	2 (7.7)
Great Britain	0 (0)	2 (25.0)	0 (0)	2 (22.2)	2 (7.7)
United States	7 (87.5)	3 (37.5)	7 (70.0)	5 (55.6)	17 (65.4)

Source: adsl.xpt; Software: Python
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; VOS, vosoritide

Table 115. Subject Demographics, Full Analysis Set, Study 111-205

Characteristic	Cohort 1 2.5 µg/kg starting dose N=6	Cohort 2 7.5 µg/kg starting dose N=6	Cohort 3 15 µg/kg starting dose N=10	Cohort 4 30 µg/kg starting dose N=8	Cohorts 1, 2, 3 N=22
Sex, n (%)					
Male	2 (33.3)	4 (66.7)	4 (40.0)	3 (37.5)	10 (45.4)
Female	4 (66.7)	2 (33.3)	6 (60.0)	5 (62.5)	12 (54.5)
Age, years					
Mean (SD)	8.07 (1.43)	8.49 (2.37)	8.54 (1.54)	7.50 (0.95)	8.4 (1.7)
Min, max	6.9, 10.9	6.0, 10.8	6.3, 11.1	5.8, 8.7	6.0, 11.1
Age, n (%)					
≥5 to <8 years	4 (66.7)	3 (50.0)	4 (40.0)	4 (50.0)	11 (50.0)
≥8 to <11 years	2 (33.3)	3 (50.0)	5 (50.0)	4 (50.0)	10 (45.4)
≥11 to <15 years	0	0	1 (10.0)	0	1 (4.5)
Race, n (%)					
Asian	0	1 (16.7)	3 (30.0)	2 (25.0)	4 (18.1)
Other	0	0	1 (10.0)	0	1 (4.5)
White	6 (100.0)	5 (83.3)	4 (40.0)	6 (75.0)	15 (68.1)
Not provided	0	0	2 (20.0)	0	2 (9.0)
Ethnicity, n (%)					
Hispanic or Latino	0	0	1 (10.0)	1 (12.5)	1 (4.5)
Not Hispanic or Latino	6 (100.0)	6 (100.0)	9 (90.0)	7 (87.5)	21 (95.4)
Country, n (%)					
USA	6 (100.0)	2 (33.3)	7 (70.0)	5 (62.5)	15 (68.1)
Not USA	0	4 (66.6)	3 (30.0)	3 (37.5)	7 (31.8)

Source: statistical reviewer
Abbreviations: SD, standard deviation

Table 116. Baseline Characteristics, Full Analysis Set, Study 111-205

Characteristic Variable	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
Tanner stage, n (%)					
I	5 (83.3)	6 (100.0)	10 (100.0)	8 (100.0)	21 (95.5)
Not done	1 (16.7)	0	0	0	1 (4.5)

Characteristic Variable	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
Weight (kg)					
n	6	6	9	8	21
Mean (SD)	18.40 (2.60)	22.23 (4.76)	25.13 (5.74)	19.59 (2.86)	22.38 (5.36)
Median	18.00	21.90	25.10	20.65	20.60
Min, max	15.6, 22.0	17.5, 27.7	18.2, 36.4	15.8, 23.2	15.60, 36.40
BMI (kg/m^2)					
n	6	6	9	8	21
Mean (SD)	20.31 (2.33)	21.55 (1.93)	22.21 (2.69)	20.44 (1.04)	21.48 (2.42)
Median	20.38	21.06	22.51	20.05	21.05
Min, max	16.5, 23.2	19.6, 24.6	19.7, 27.5	19.2, 22.1	16.55, 27.48
AGV (cm/year)					
n	6	6	10	8	22
Mean (SD)	3.18 (1.24)	3.22 (1.06)	4.04 (1.41)	4.19 (1.19)	3.58 (1.29)
Median	3.08	3.08	3.94	4.27	3.60
Min, max	1.8, 5.0	2.1, 5.1	1.6, 6.0	2.9, 6.7	1.59, 5.98
Height Z-score					
n	6	6	10	8	22
Mean (SD)	−6.06 (0.69)	−4.91 (0.77)	−4.61 (1.14)	−5.19 (0.75)	-5.09 (1.09)
Median	−6.21	−4.76	−4.85	−4.96	-4.94
Min, max	−6.7, −4.8	−6.0, −3.9	−6.3, −2.6	−6.4, −4.3	-6.67, -2.61
Standing height (cm)					
n	6	6	10	8	22
Mean (SD)	95.11 (3.22)	101.07 (8.82)	104.61 (8.75)	97.70 (6.93)	101.05 (8.36)
Median	94.83	98.75	103.95	99.15	100.53
Min, max	91.4, 100.2	91.6, 113.2	93.6, 126.1	87.0, 105.2	91.40, 126.05
Sitting height (cm)					
n	6	6	10	8	22
Mean (SD)	64.59 (2.14)	67.78 (4.65)	68.31 (4.27)	64.55 (4.11)	67.15 (4.08)
Median	64.33	66.40	68.35	66.05	66.10
Min, max	62.0, 68.5	63.1, 73.3	60.3, 74.6	59.8, 70.2	60.25, 74.60
Upper to lower body segment ratio					
n	6	6	10	8	22
Mean (SD)	2.12 (0.08)	2.05 (0.17)	1.91 (0.23)	1.96 (0.18)	2.01 (0.20)
Median	2.12	2.02	1.98	1.89	2.05
Min, max	2.0, 2.2	1.8, 2.4	1.4, 2.2	1.8, 2.2	1.45, 2.37

Source: CSR of Study 111-205, statistical reviewer
Abbreviations: AGV, annualized growth velocity; BMI, body mass index; SD, standard deviation

All subjects at baseline reported a medical condition, and majority (96.7%) reported an ACH-related medical history condition. The most common medical conditions were in system organ classes (SOCs) infections and infestations (73.3%) [otitis media (56.7%), otitis media chronic (13.3%)]; musculoskeletal and connective tissue disorders (73.3%) [limb deformity (50%), lordosis (30%), knee deformity, kyphosis and pain in extremities (20% each), arthralgia (16.7%)]; respiratory, thoracic and mediastinal disorders (73.3%) [sleep apnea syndrome (46.7%)]; nervous system disorders (46.7%)[headache and hydrocephalus (10.0% each)]; congenital, familial and genetic disorders (36.7%) [foramen magnum stenosis and macrocephaly (16.7% each), and skull malformation (13.3%)]; and ear and labyrinth disorders (36.7%) [deafness (26.7%)]. While all subjects reported at least 1 concomitant medication during the studies, majority were for short duration use, such as analgesics (e.g., paracetamol, ibuprofen), antibiotics (e.g., amoxicillin), and topical anesthetics (EMLA cream and lidocaine).

Table 117. Treatment Compliance, Studies 111-202/205

Parameter	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Overall (N=30)
Compliance with treatment regimen, %[a]					
n	6	6	10	8	30
Mean (SD)	98.25 (1.78)	98.82 (0.81)	95.21 (6.25)	99.33 (0.54)	97.64 (4.01)
Median	98.75	98.62	97.23	99.49	98.89
Min. Max	95.9, 100	98.1, 99.8	80.0, 100	98.4, 100	80, 100
Compliance with treatment regimen, n (%)[a,b]					
≥80%	6 (100)	6 (100)	10 (100)	8 (100)	30 (100)
≥90%	6 (100)	6 (100)	9 (90.0)	8 (100)	29 (96.7)
100%	0	0	1 (10.0)	1 (12.5)	2 (6.70
Doses missed, mean (SD)	31.8 (33.3)	21.3 (15.9)	100.6 (101.9)	11.1 (8.6)	47.1 (70.7)
Number of subjects who					
Missed >15 consecutive doses	1 (16.7)	0	3 (30.0)[d]	0	4 (13.3)
With gap between studies	0	0	2 (20.0)	1 (12.5)	3 (10.0)
Total number of doses missed	191	128	1006	89	1414
Reason for missed doses					
Parent/caregiver error	75 (39.3)	53	408 (40.6)	16 (18.0)	552 (39.0)
Adverse event	25 (13.1)	16(12.5)	106 (10.5)	11 (12.4)	158 (11.2)
Other[c]	91 (47.6)	58 (45.3)	333 (33.1)	58 (65.2)	540 (38.2)

Source: adapted from Tables 10.3.1 and 14.1.12.1, CSR 111-205

[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.

[c] the subject or subject's parents (administering the treatment) being away

[d] 1 subj (b) (6)) missed a total of 356 doses, 112 consecutive doses in 111-202 due to international travel reasons; in 111-205, the subject missed doses mostly due to 'parent/caregiver error' or 'being away from the house'; 2 subjects (b) (6) had almost 3 months gap between studies (76 doses missed in total, each during the gap period)

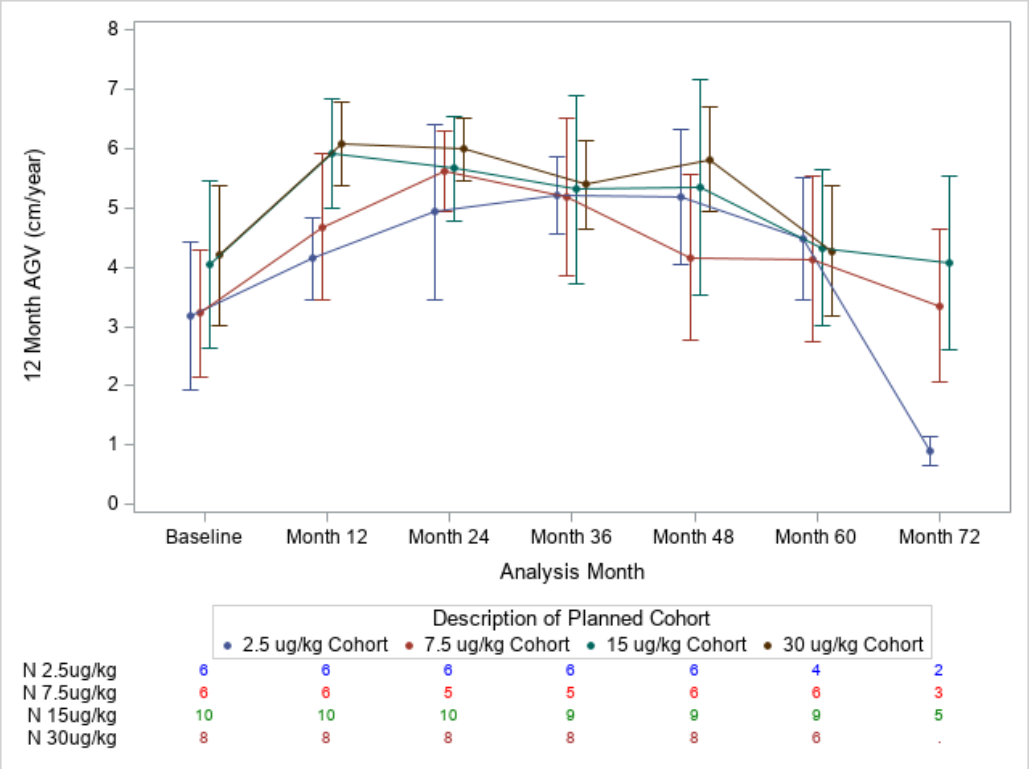
Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.

Table 118. 12-Month Interval AGV (cm/year) Over Time, Full Analysis Set, Study 111-205

Visit	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
Baseline					
n	6	6	10	8	22
Mean (SD)	3.18 (1.24)	3.22 (1.06)	4.04 (1.41)	4.19 (1.19)	3.58 (1.29)
Month 12					
n	6	6	10	8	22
Mean (SD)	4.14 (0.69)	4.67 (1.23)	5.91 (0.92)	6.08 (0.70)	5.09 (1.21)
Change from baseline to Month 12					
Mean (SD)	0.96 (1.18)	1.45 (0.91)	1.87 (1.34)	1.88 (1.66)	1.51 (1.20)
95% CI	-0.28, 2.20	0.50, 2.41	0.92, 2.83	0.49, 3.27	0.98, 2.04
P-value	0.1028	0.0114	0.0017	0.0150	<0.0001
Month 24					
n	6	5	10	8	21
Mean (SD)	4.93 (1.48)	5.62 (0.67)	5.66 (0.88)	5.98 (0.53)	5.44 (1.04)
Change from baseline to Month 24					
Mean (SD)	1.75 (1.81)	2.78 (1.08)	1.62 (1.13)	1.79 (1.03)	1.93 (1.36)
95% CI	-0.15, 3.64	1.44, 4.12	0.81, 2.43	0.93, 2.65	1.31, 2.55
P-value	0.0639	0.0045	0.0014	0.0017	<0.0001
Month 36					
n	6	5	9	8	20
Mean (SD)	5.20 (0.65)	5.18 (1.33)	5.31 (1.58)	5.39 (0.74)	5.24 (1.24)
Change from baseline to Month 36					
Mean (SD)	2.02 (1.16)	2.34 (1.00)	1.36 (1.65)	1.20 (1.50)	1.80 (1.37)
95% CI	0.80, 3.23	1.10, 3.58	0.10, 2.63	-0.05, 2.45	1.16, 2.45
P-value	0.0079	0.0064	0.0378	0.0581	<0.0001
Month 48					
n	6	6	9	8	21
Mean (SD)	5.18 (1.13)	4.16 (1.39)	5.34 (1.81)	5.81 (0.88)	4.96 (1.55)
Change from baseline to Month 48					
Mean (SD)	2.00 (1.32)	0.94 (1.80)	1.40 (1.91)	1.62 (1.35)	1.44 (1.69)
95% CI	0.62, 3.39	-0.95, 2.83	-0.07, 2.86	0.49, 2.75	0.67, 2.21
P-value	0.0138	0.2561	0.0593	0.0117	0.0009
Month 60					
n	4	6	9	0	19
Mean (SD)	4.48 (1.02)	4.14 (1.39)	4.33 (1.32)		4.30 (1.23)
Change from baseline to Month 60					
Mean (SD)	0.86 (0.37)	0.92 (1.43)	0.38 (1.80)		0.65 (1.45)
95% CI	0.27, 1.44	-0.58, 2.42	-1.00, 1.77		-0.05, 1.35
P-value	0.0185	0.1769	0.5395		0.0654
Month 72					
n	2	3	5	0	10
Mean (SD)	0.90 (0.24)	3.35 (1.30)	4.07 (1.46)		3.22 (1.71)
Change from baseline to Month 72					
Mean (SD)	-2.49 (2.48)	0.15 (1.62)	-0.72 (2.26)		-0.81 (2.12)
95% CI					(-2.33, 0.70)
P-value					0.25

Source: statistical reviewer
95% CI and p-value for mean change from baseline are from paired t-test between baseline and each postbaseline visit. Not provided for individual cohorts for Month 72 due to small number of subjects.
Abbreviations: AGV, annualized growth velocity; CI, confidence interval; SD, standard deviation

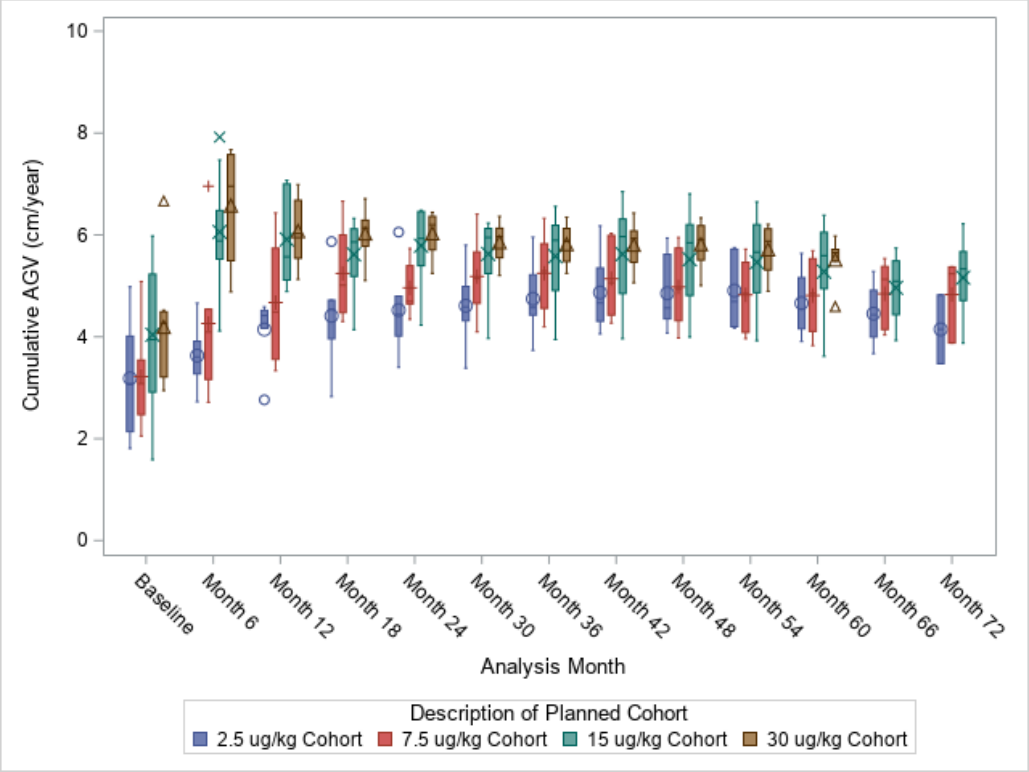
Figure 73. 12-Month Interval AGV Over Time by Cohort (Mean ± SD), Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: AGV, annualized growth velocity; SD, standard deviation

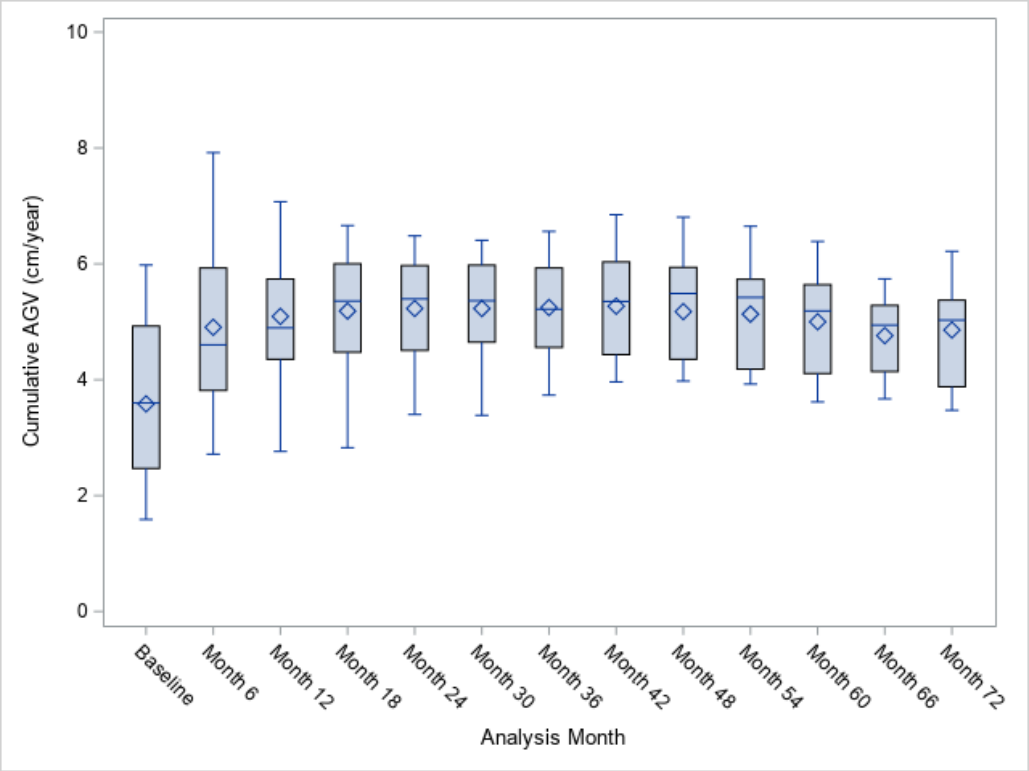
Cumulative AGV over time by each cohort and by pooled cohorts 1, 2, 3 are also presented in Figure 74, Figure 75, and Table 119.

Figure 74. Box Plot of Cumulative AGV Over Time by Cohort, Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: AGV, annualized growth velocity

Figure 75. Box Plot of Cumulative AGV Over Time in Pooled Cohorts 1, 2, and 3, Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: AGV, annualized growth velocity

Table 119. Cumulative AGV (cm/year) Over Time, Full Analysis Set, Study 111-205

Visit	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
Baseline					
N	6	6	10	8	22
Mean (SD)	3.18 (1.24)	3.22 (1.06)	4.04 (1.41)	4.19 (1.19)	3.58 (1.29)
Month 12					
N	6	6	10	8	22
Mean (SD)	4.14 (0.69)	4.67 (1.23)	5.91 (0.92)	6.08 (0.70)	5.09 (1.21)
Change from baseline to Month 12					
Mean (SD)	0.96 (1.18)	1.45 (0.91)	1.87 (1.34)	1.88 (1.66)	1.51 (1.20)
95% CI	−0.28, 2.20	0.50, 2.41	0.92, 2.83	0.49, 3.27	0.98, 2.04
p-value	0.1028	0.0114	0.0017	0.0150	<0.0001
Month 24					
N	6	5	10	8	21
Mean (SD)	4.53 (0.89)	4.96 (0.58)	5.79 (0.69)	6.03 (0.44)	5.23 (0.90)
Change from baseline to Month 24					
Mean (SD)	1.34 (1.34)	2.12 (0.85)	1.75 (1.10)	1.84 (1.33)	1.72 (1.10)
95% CI	−0.06, 2.75	1.06, 3.17	0.96, 2.54	0.73, 2.94	1.22, 2.22
p-value	0.0577	0.0051	0.0007	0.0058	<0.0001

Visit	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
Month 36					
N	6	6	9	8	21
Mean (SD)	4.75 (0.76)	5.25 (0.85)	5.58 (0.88)	5.82 (0.40)	5.25 (0.87)
Change from baseline to Month 36					
Mean (SD)	1.56 (1.24)	2.03 (0.78)	1.64 (1.19)	1.63 (1.33)	1.73 (1.07)
95% CI	0.26, 2.87	1.21, 2.85	0.72, 2.56	0.51, 2.74	1.24, 2.22
p-value	0.0276	0.0014	0.0033	0.0106	<0.0001
Month 48					
n	6	6	9	8	21
Mean (SD)	4.85 (0.76)	4.98 (0.84)	5.52 (1.01)	5.82 (0.46)	5.18 (0.91)
Change from baseline to Month 48					
Mean (SD)	1.67 (1.20)	1.76 (0.96)	1.58 (1.27)	1.62 (1.30)	1.66 (1.11)
95% CI	0.41, 2.93	0.75, 2.77	0.60, 2.55	0.54, 2.71	1.15, 2.16
p-value	0.0190	0.0066	0.0058	0.0096	<0.0001
Month 60					
n	4	6	9	0	19
Mean (SD)	4.66 (0.73)	4.81 (0.82)	5.28 (0.98)	-	5.00 (0.88)
Change from baseline to Month 60					
Mean (SD)	1.03 (0.75)	1.59 (0.93)	1.34 (1.31)	-	1.35 (1.07)
95% CI	−0.16, 2.22	0.61, 2.57	0.33, 2.34	-	0.84, 1.87
p-value	0.0703	0.0087	0.0154	-	<0.0001
Month 72					
n	2	3	5	0	10
Mean (SD)	4.15 (0.95)	4.83 (0.83)	5.16 (0.90)		4.86 (0.88)
Change from baseline to Month 72					
Mean (SD)	0.75 (1.29)	1.63 (1.25)	0.37 (1.23)		0.82 (1.24)
95% CI					-0.06, 1.71
p-value					0.065

Source: adgv, statistical reviewer
95% CI and p-value for mean change from baseline are from paired t-test between baseline and each postbaseline measurements. Not provided for individual cohorts for Month 72 due to small number of subjects.
Abbreviations: AGV, annualized growth velocity; CI, confidence interval; SD, standard deviation

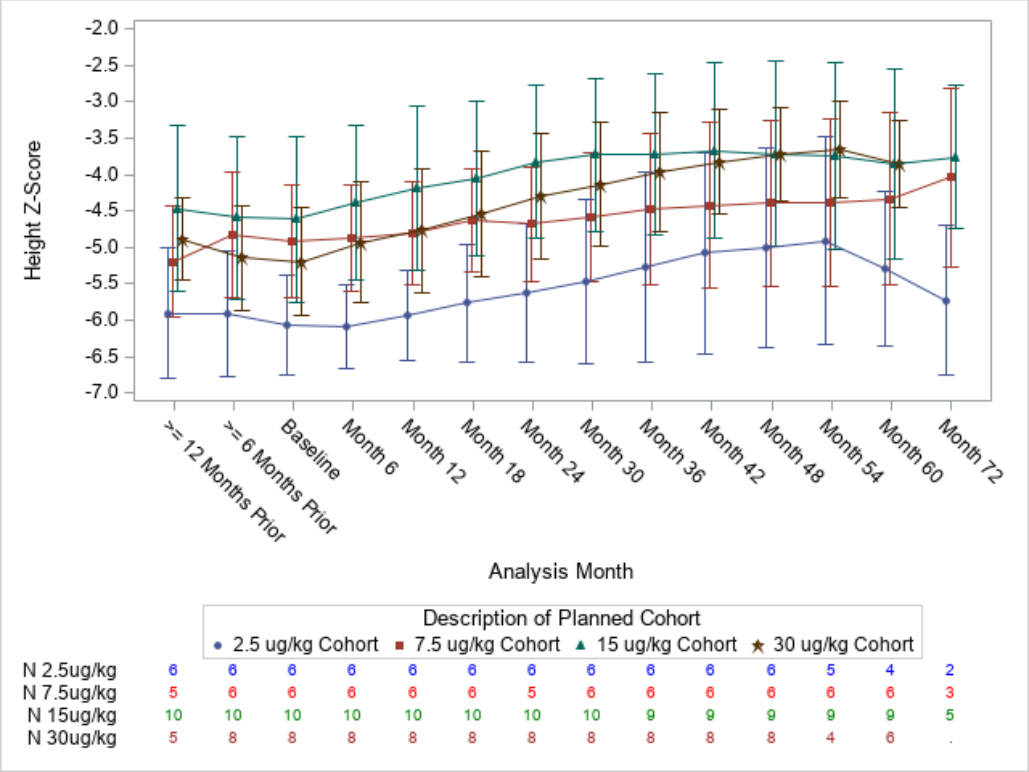
Table 120. Height Z-Score Over Time, Full Analysis Set, Study 111-205

Visit	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
≥12 months prior					
n	6	5	10	5	21
Mean (SD)	−5.90 (0.89)	−5.20 (0.76)	−4.46 (1.14)	−4.88 (0.56)	-5.05 (1.14)
Baseline					
n	6	6	10	8	22
Mean (SD)	−6.06 (0.69)	−4.91 (0.77)	−4.61 (1.14)	−5.19 (0.75)	-5.09 (1.09)
Month 12					
n	6	6	10	8	22
Mean (SD)	−5.93 (0.62)	−4.80 (0.70)	−4.19 (1.12)	−4.77 (0.85)	-4.83 (1.13)
Change from baseline to Month 12					
Mean (SD)	+0.14 (0.17)	+0.11 (0.21)	+0.42 (0.07)	+0.42 (0.21)	+0.26 (0.21)
95% CI	-0.04, 0.32	-0.11, 0.34	0.37, 0.47	0.25, 0.60	0.17, 0.35
p-value	0.1051	0.2480	<0.0001	0.0008	<0.0001

Visit	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
Month 24					
n	6	5	10	8	21
Mean (SD)	-5.62 (0.95)	-4.68 (0.78)	-3.82 (1.06)	-4.30 (0.86)	-4.54 (1.21)
Change from baseline to Month 24					
Mean (SD)	+0.44 (0.47)	+0.30 (0.14)	+0.79 (0.28)	+0.90 (0.30)	+0.57 (0.38)
95% CI	−0.05, 0.93	0.12, 0.47	0.58, 0.99	0.64, 1.15	0.40, 0.74
p-value	0.0691	0.0099	<0.0001	<0.0001	<0.0001
Month 36					
n	6	6	9	8	21
Mean (SD)	−5.27 (1.29)	−4.47 (1.03)	−3.73 (1.11)	−3.96 (0.82)	-4.38 (1.27)
Change from baseline to Month 36					
Mean (SD)	+0.80 (0.94)	+0.44 (0.35)	+0.99 (0.53)	+1.23 (0.38)	+0.77 (0.64)
95% CI	−0.19, 1.78	0.07, 0.81	0.58, 1.39	0.91, 1.54	0.48, 1.07
p-value[a]	0.0917	0.0280	0.0005	<0.0001	<0.0001
Month 48					
n	6	6	9	8	21
Mean (SD)	−5.00 (1.38)	−4.39 (1.14)	−3.72 (1.27)	−3.73 (0.64)	-4.28 (1.32)
Change from baseline to Month 48					
Mean (SD)	+1.06 (0.94)	+0.52 (0.53)	+1.00 (0.69)	+1.46 (0.36)	+0.88 (0.73)
95% CI	0.07, 2.05	−0.03, 1.08	0.47, 1.53	1.16, 1.76	0.55, 1.22
p-value	0.0398	0.0598	0.0024	<0.0001	<0.0001
Month 60					
n	4	6	9	0	19
Mean (SD)	−5.29 (1.07)	−4.33 (1.19)	−3.86 (1.30)	-	-4.31 (1.28)
Change from baseline to Month 60					
Mean (SD)	+0.93 (0.86)	+0.58 (0.57)	+0.85 (0.75)	-	+0.78 (0.70)
95% CI	−0.44, 2.30	−0.02, 1.18	0.27, 1.43	-	0.45, 1.12
p-value	0.1183	0.0553	0.0093	-	0.0001
Month 72					
n	2	3	5	0	10
Mean (SD)	-5.72 (1.02)	-4.04 (1.22)	-3.76 (0.99)		-4.24 (1.23)
Change from baseline to Month 72					
Mean (SD)	0.35 (0.65)	0.67 (0.47)	1.02 (0.68)		0.78 (0.62)
95% CI					0.34, 1.22
p-value					0.003

Source: statistical reviewer
[a] Student's t-test
95% CI and p-value for mean change from baseline are from paired t-test between baseline and each postbaseline visit. Not provided for individual cohorts for Month 72 due to small number of subjects.
Abbreviations: CI, confidence interval; SD, standard deviation

Figure 76. Height Z-Score Over Time by Cohort (Mean ± SD), Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: SD, standard deviation

The mean (SD) upper to lower body segment ratio was 2.01 (0.20) at baseline in pooled cohorts 1, 2, 3, which is slightly higher than reported in literature. The change from baseline to Month 60 in mean (SD) upper to lower body segment ratio was -0.16 (0.17) in pooled cohorts 1, 2,3 (Table 121).

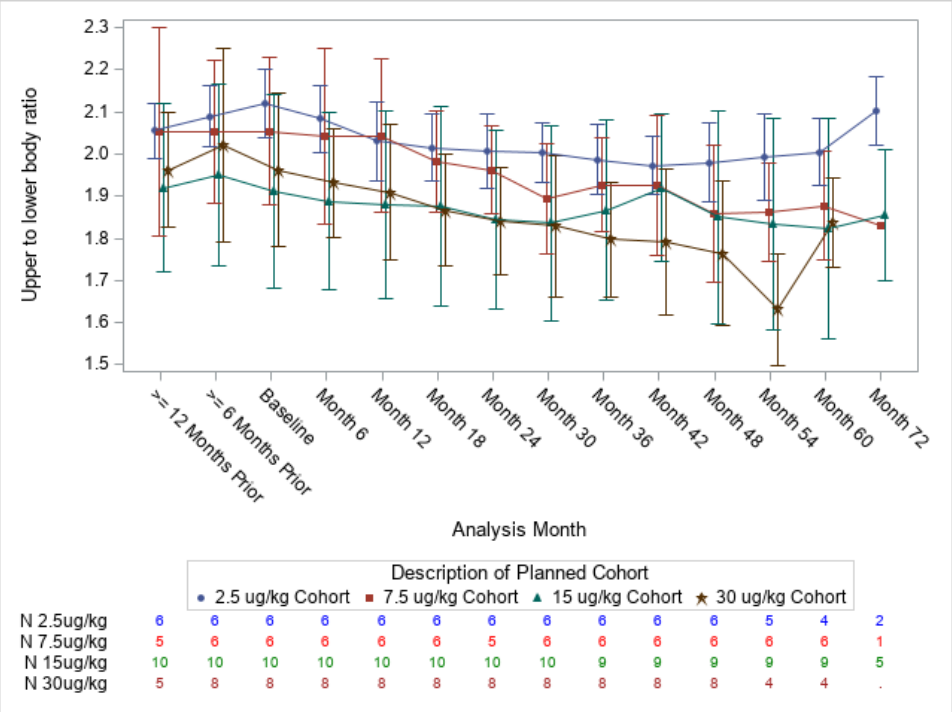
Table 121. Upper to Lower Body Segment Ratio Over Time, Full Analysis Set, Study 111-205

Visit	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
≥12 months prior					
n	6	5	10	5	21
Mean (SD)	2.05 (0.07)	2.05 (0.25)	1.92 (0.20)	1.96 (0.14)	1.99 (0.19)
Baseline					
n	6	6	10	8	22
Mean (SD)	2.12 (0.08)	2.05 (0.17)	1.91 (0.23)	1.96 (0.18)	2.01 (0.20)
Month 12					
n	6	6	10	8	22
Mean (SD)	2.03 (0.09)	2.04 (0.18)	1.88 (0.22)	1.91 (0.16)	1.96 (0.19)
Change from baseline to Month 12					
Mean (SD)	-0.09 (0.07)	-0.01 (0.03)	-0.03 (0.04)	-0.05 (0.08)	-0.04 (0.06)
95% CI	-0.16, -0.02	-0.04, 0.02	-0.06, 0.00	-0.12, 0.01	-0.07, -0.02
P-value	0.0216	0.4585	0.0498	0.1070	0.0021

Visit	Cohort 1 2.5 µg/kg (N=6)	Cohort 2 7.5 µg/kg (N=6)	Cohort 3 15 µg/kg (N=10)	Cohort 4 30 µg/kg (N=8)	Cohorts 1, 2, 3 (N=22)
Month 24					
n	6	5	10	8	21
Mean (SD)	2.01 (0.09)	1.96 (0.10)	1.84 (0.21)	1.84 (0.13)	1.92 (0.17)
Change from baseline to Month 24					
Mean (SD)	-0.11 (0.05)	-0.03 (0.07)	-0.07 (0.05)	-0.12 (0.11)	-0.07 (0.06)
95% CI	-0.17, -0.06	-0.11, 0.06	-0.10, -0.03	-0.21, -0.03	-0.10, -0.04
P-value	0.0036	0.4216	0.0012	0.0142	<0.0001
Month 36					
n	6	6	9	8	21
Mean (SD)	1.99 (0.08)	1.93 (0.11)	1.87 (0.21)	1.80 (0.14)	1.92 (0.16)
Change from baseline to Month 36					
Mean (SD)	-0.13 (0.08)	-0.13 (0.11)	-0.08 (0.06)	-0.16 (0.10)	-0.11 (0.09)
95% CI	-0.22, -0.04	-0.24, -0.01	-0.12, -0.03	-0.25, -0.08	-0.15, -0.07
P-value	0.0120	0.0392	0.0066	0.0023	<0.0001
Month 48					
n	6	6	9	8	21
Mean (SD)	1.98 (0.09)	1.86 (0.16)	1.85 (0.25)	1.76 (0.17)	1.89 (0.20)
Change from baseline to Month 48					
Mean (SD)	-0.14 (0.11)	-0.19 (0.17)	-0.09 (0.10)	-0.20 (0.08)	-0.14 (0.13)
95% CI	-0.26, -0.02	-0.37, -0.02	-0.17, -0.02	-0.27, -0.13	-0.19, -0.08
P-value	0.0287	0.0365	0.0251	0.0003	<0.0001
Month 60					
n	4	6	9	0	19
Mean (SD)	2.00 (0.08)	1.88 (0.13)	1.82 (0.26)		1.88 (0.20)
Change from baseline to Month 60					
Mean (SD)	-0.15 (0.08)	-0.18 (0.14)	-0.12 (0.10)		-0.14 (0.11)
95% CI	-0.28, -0.01	-0.32, -0.03	-0.20, -0.04		-0.20, -0.09
P-value	0.0411	0.0264	0.0078		<0.0001
Month 72					
n	2	1	5	0	8
Mean (SD)	2.10 (0.08)	1.83	1.86 (0.15)		1.91 (0.17)
Change from baseline to Month 72					
Mean (SD)	-0.03 (0.05)	-0.54	-0.13 (0.04)		-0.16 (0.17)
95% CI					-0.30, -0.02
P-value					0.030

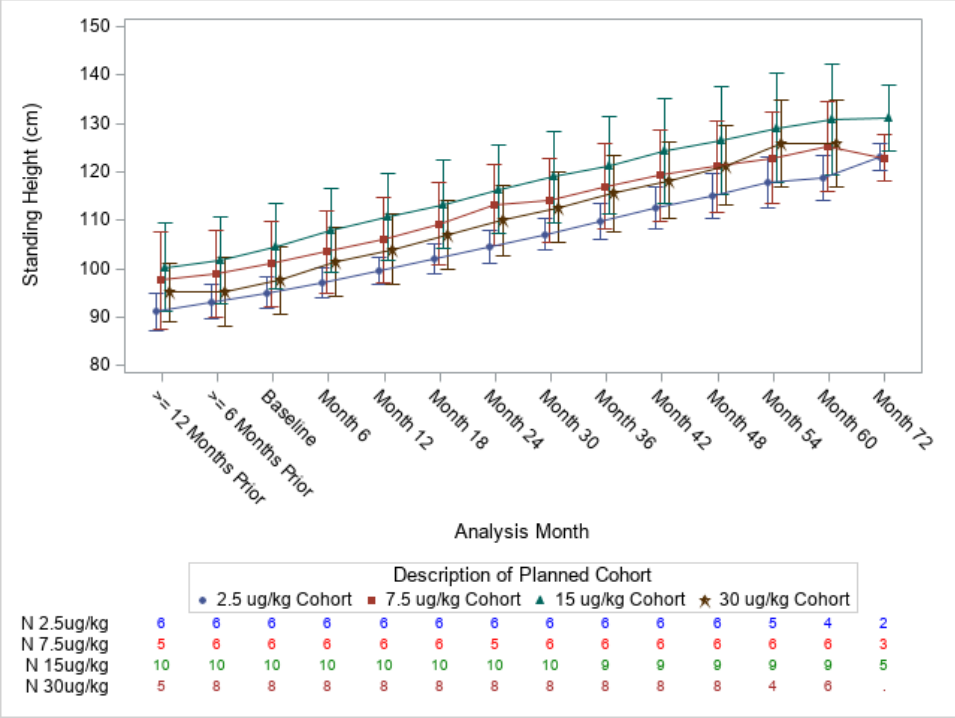
Source: adgm, statistical reviewer
95% CI and p-value for mean change from baseline are from paired t-test between baseline and each postbaseline visit. Not provided for individual cohorts for Month 72 due to small number of subjects.
Abbreviations: CI, confidence interval; SD, standard deviation

Figure 77.Upper to Lower Body Ratio Over Time by Cohort (Mean ± SD), Full Analysis Set, Study 111-205



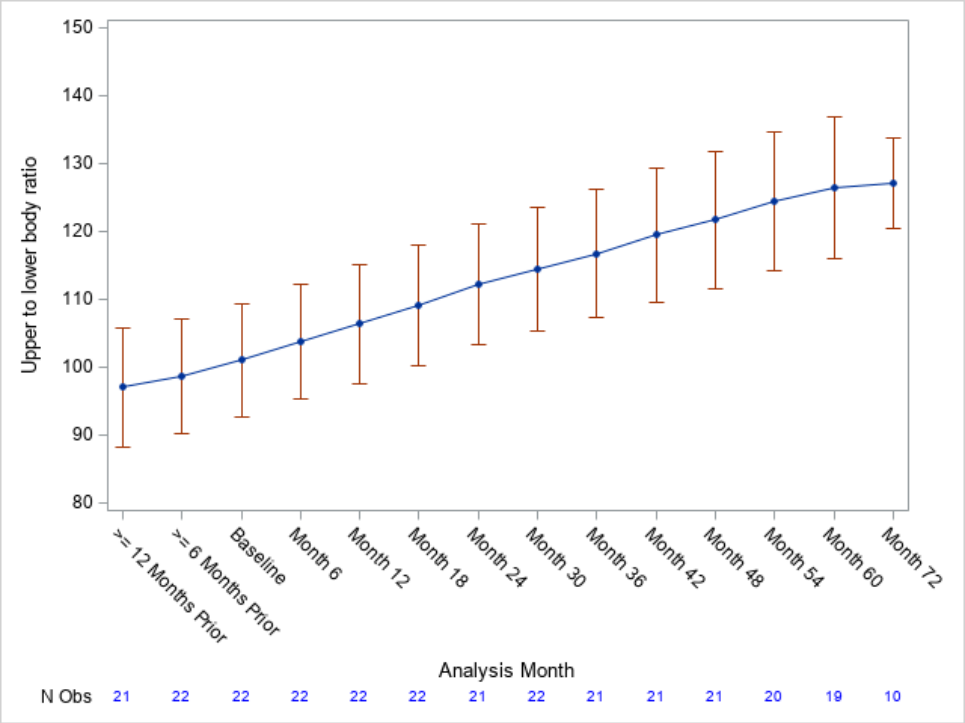
Source: statistical reviewer
Abbreviations: SD, standard deviation

Figure 78. Standing Height Over Time by Cohort (Mean ± SD), Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: SD, standard deviation

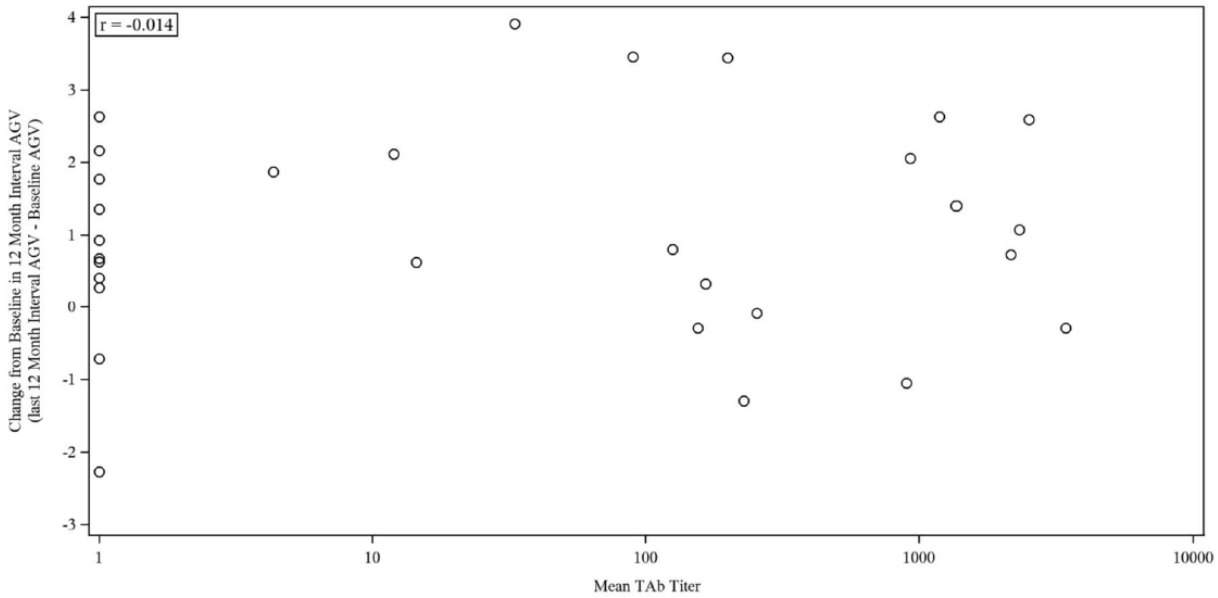
Figure 79. Standing Height Over Time in Pooled Cohorts 1, 2, 3 (Mean ± SD), Full Analysis Set, Study 111-205



Source: statistical reviewer
Abbreviations: SD, standard deviation

In TAb-positive subjects no association was noted between mean TAb titers and change from baseline in 12-month interval AGV (Figure 80). As observed, in subjects who had the highest antibody titers and/or sustained antibodies, the change in AGV measurement was in the same range as those who did not develop antibodies.

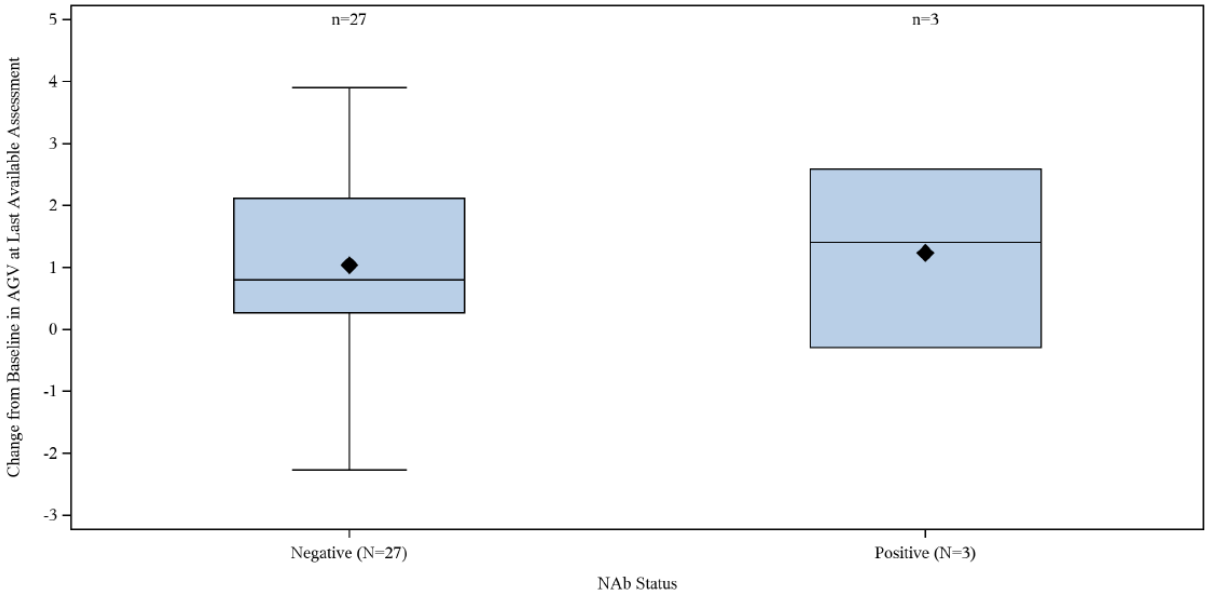
Figure 80. Change From Baseline in 12-Month Interval Annualized Growth Velocity at Last Assessment and TAb Titers, Immunogenicity Population



Source: Applicant's Figure 11.6.2.2, 111-205 Interim CSR
Abbreviations: AGV, annualized growth velocity; TAb, total anti-vosoritide antibody

There was no impact of transient NAb on efficacy in the 3 subjects with detectable NAb titer at a single visit (Figure 81).

Figure 81. Box Plot of Change From Baseline in 12-Month Interval AGV at Last Assessment by NAb Status Analysis, Immunogenicity Population



Source: Applicant's Figure 14.3.6.3.1.4, 111-205 Interim CSR
Abbreviations: AGV, annualized growth velocity; NAb, neutralizing antibody

16.1.4. Comparative Analyses Using AchNH Control

Applicant's 4-Year and 2-Year Analyses (Rebaselined)

The Applicant's 4-year analyses were based on 20 vosoritide-exposed subjects from Study 111-205 Cohorts 1, 2, and 3. They were matched to 439 subjects in the primary, achondroplasia natural history (AchNH) control pool, and to 140 subjects in the supportive control pool at Year 4 in the cross-sectional analysis. Subjects' height measurements were "re-baselined," that is, measured from the time when a subject's vosoritide dose was escalated 15 µg/kg. In the 4-year cross sectional analysis, the baseline-adjusted mean height difference between subjects exposed to vosoritide (Study 111-205 Cohorts 1, 2, 3, n=20, Table 122) and the matched external AchNH control (n=439 at Year 4) was 7.06 cm (95% confidence interval [CI], 5.39 to 8.73). Comparisons with the secondary external control pool (n=140 at Year 4) yielded a height difference of 7.32 cm (95% CI, 5.20 to 9.44).

The 4-year longitudinal analysis yielded a mean difference in change from baseline height between subjects exposed to vosoritide (Cohorts 1, 2, 3, n=20, Table 110, Appendix) and the matched external AchNH control (n=108) of 6.95 cm (95% CI, 5.61 to 8.29). Cross-sectional and longitudinal analyses based on Cohort 4, with a higher (30 µg/kg) dose of vosoritide (n=8), yielded point estimates for mean height difference and height Z-score difference that exceeded those from the cohorts exposed to 15 µg/kg.

To determine if the AGV after 1 year for subjects treated with vosoritide was maintained at Year 2, the Applicant conducted analyses that included 25 subjects from the vosoritide group (22 subjects from Study 111-202/205 and 3 subjects from Studies 111-301/302) and 159 subjects from the external control group (Table 123). Based on a longitudinal analysis of covariance (ANCOVA) model with fixed effects of baseline AGV and baseline height Z-score, treatment, sex, and age matching indicator variables, the change in AGV from baseline at Year 1 (1.54 cm/year) was maintained in Year 2 (1.61 cm/year).

Table 122. Applicant's 4-Year Comparative Analyses for Change in Height, Rebaselined Study 111-205 Versus NH Control

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

Source: summarized from Applicant's natural history integrated analyses report.
[a] At Year 4
[b] The number of matched subjects was not provided
Abbreviations: AchNH, achondroplasia natural history; NH, natural history

Table 123. 2-Year Longitudinal Analysis of Change in AGV and Height, Rebaselined Study 111-205/111-302 vs. AchNH[a]

Vosoritide Exposure Cohort	NH Control	Analysis Time	Mean Height Difference (95% CI)	Mean AGV Difference (95% CI)
Cohorts 1, 2, 3 of Study 111-205 + Study 111-302 N=25	AchNH N=159	Change from baseline at Year 1	1.71 (1.09, 2.34)	1.54 (0.93, 2.15)
		Change from baseline at Year 2	3.43 (2.61, 4.24)	1.61 (1.21, 2.01)

Source: summarized from Applicant's natural history integrated analyses report.
[a] AchNH Control Arm includes all AchNH subjects who are matched by sex and age to Subjects in the Active Treatment Arm at baseline and had at least 1 height assessment at 12±3 and 24±3 months relative to the baseline. Change from baseline at Year 1 and change from baseline at Year 2 were analyzed using the same group of subjects.
Analysis method: ANCOVA model that includes treatment and matching ID as fixed factors
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity

Additional Cross-Sectional Analyses (Not Rebaselined, Exclude Limb Lengthening Surgery)

Table 124. Cross-Sectional Analyses for Change in Height, Study 111-205 Exclude Limb Lengthening Surgery Versus AchNH[a]

Analysis[a]	Vosoritide Exposure Cohort	NH Control	Mean Height Difference (cm) (95% CI)
5-year cross-sectional	Cohort 3: Vosoritide 15 µg/kg N=9	AchNH N=535/346[b]	8.15 (4.83, 11.47)
5-year cross-sectional	Cohorts 1, 2, 3: Vosoritide 15 µg/kg N=19	AchNH N=643/414[b]	7.69 (5.79, 9.59)
4-year cross-sectional	Cohorts 1, 2, 3: Vosoritide 15 µg/kg N=21	AchNH N=639/461[b]	6.06 (4.41, 7.72)

Source: summarized from Applicant's response to FDA's IR dated November 17, 2020, verified by FDA
[a] Analysis method: t-test of difference at Year 5 (or Year 4) and difference at baseline between 2 groups.
[b] Number of NH control subjects matched at baseline and 5 year respectively.
Abbreviations: AchNH, achondroplasia natural history; CI, confidence interval

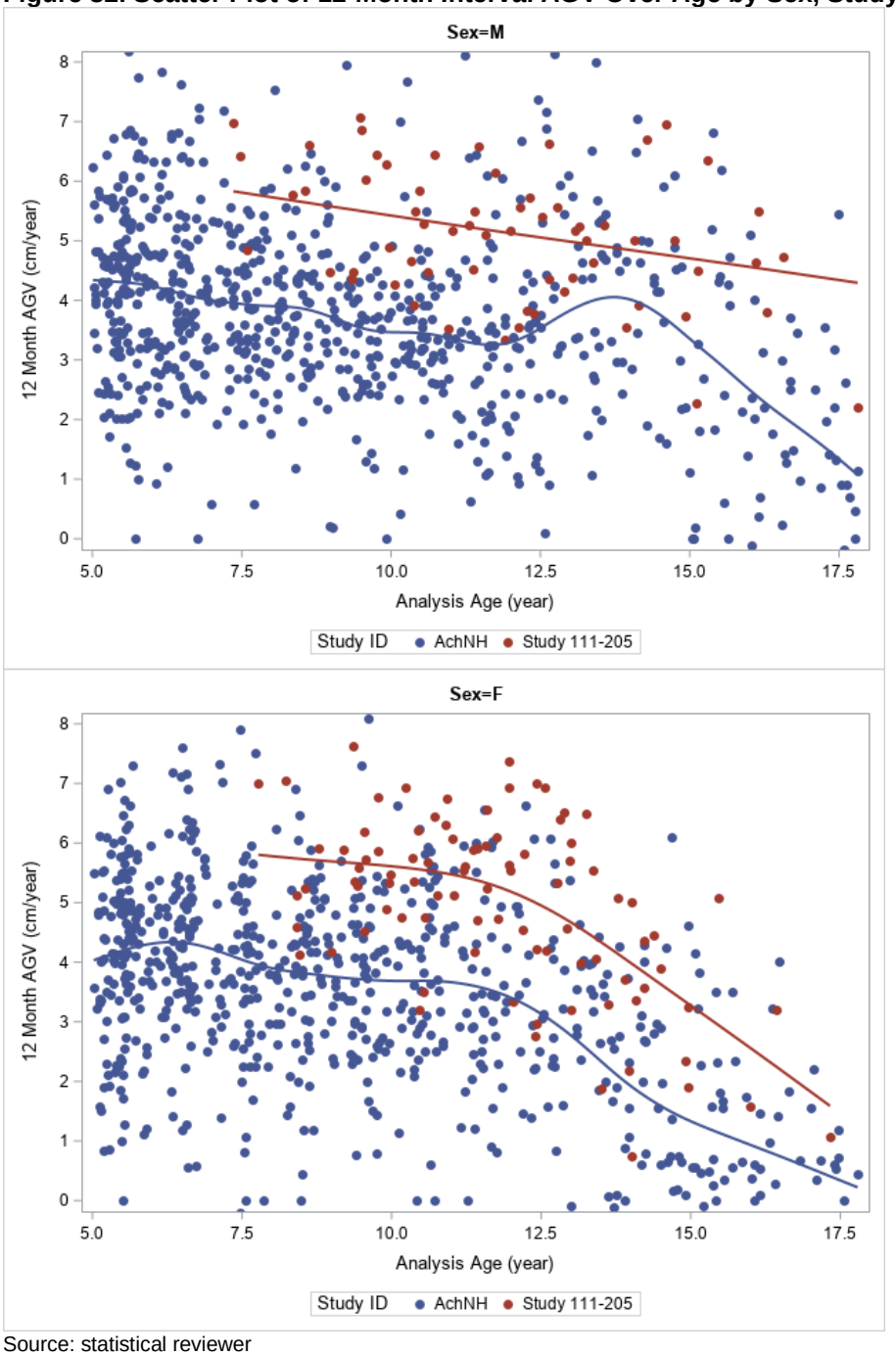
FDA's Exploratory Analysis of 12-Month AGV

We examined 12-month interval AGV in vosoritide-treated subjects in Study 111-205 versus subjects in the AchNH study.

Since subjects in the retrospective NH studies did not have regularly timed visits, the amount of data that can be used to analyze change in 12-month AGV over time was limited. Scatter plots were used for exploratory purpose. For AchNH, all pairs of height assessments that were 12±3 months apart were identified and the AGV for that interval was computed. The midpoint for each interval was identified as the analysis age. In the event a subject had more than one AGV associated with a given age, the AGV interval with maximum overlap with the year was retained. For Study 111-205, height assessments at baseline and Months 12, 24, 36, 48, 60, 72 and 78 were used to compute AGV. Similarly, the midpoint for each interval was identified as the analysis age.

We made a scatter plot for each sex and used the penalized B-splines option in SAS (degree =2) to fit a smooth curve (Figure 82). The splines suggested a small improvement in AGV in subjects in Study 111-205 compared to subjects in AchNH for each sex. However, the variability was high among each group. There was a lot of overlap between the 2 groups.

Figure 82. Scatter Plot of 12-Month Interval AGV Over Age by Sex, Study 111-205a Versus AchNH



Source: statistical reviewer
[a] Postbaseline AGV assessments from pooled cohorts (1 to 4) were included.
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity

Measurement Error in AchNH Data

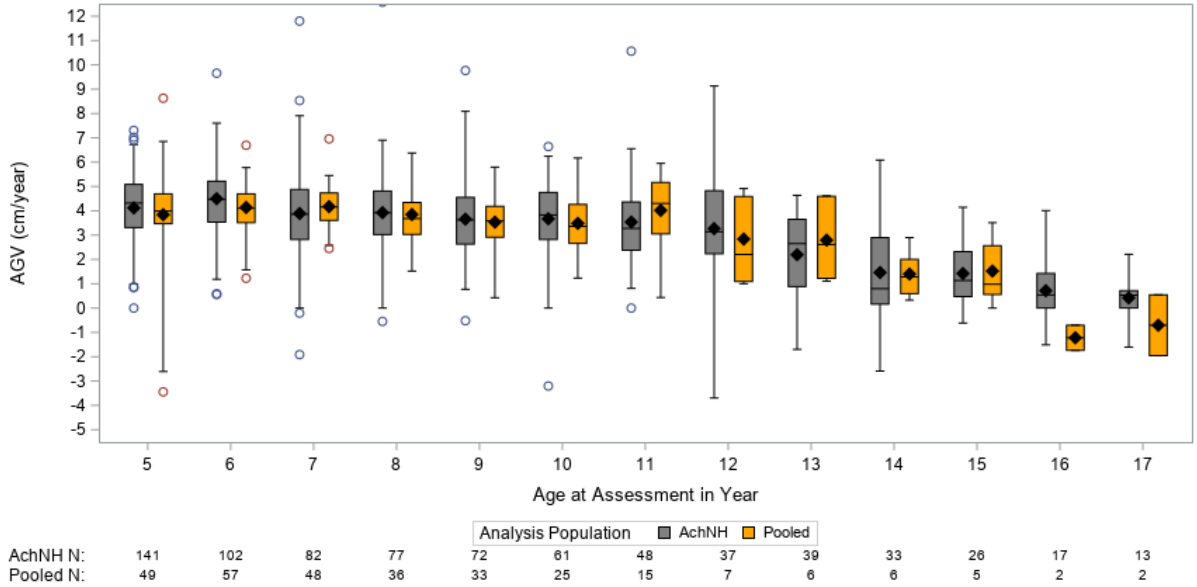
Table 125. Summary of Negative Changes in Height in 2 Consecutive Time Points in AchNH Population

Decreasing Height (cm), n (%)*	All Ages (N * = 13726)	Ages Between 4 and 18 Years (N * = 5394)
0 - 0.5	391 (2.85)	173 (3.21)
>0.5 - 1	309 (2.25)	111 (2.06)
>1 - 2	414 (3.02)	149 (2.76)
>2 - 3	222 (1.62)	62 (1.15)
>3 - 4	126 (0.92)	30 (0.56)
>4 - 5	49 (0.36)	14 (0.26)
>5 - 6	1 (0.01)	0
>6 - 7	1 (0.01)	0
>7 - 8	1 (0.01)	0
>8 - 9	1 (0.01)	0
>9	1 (0.01)	0

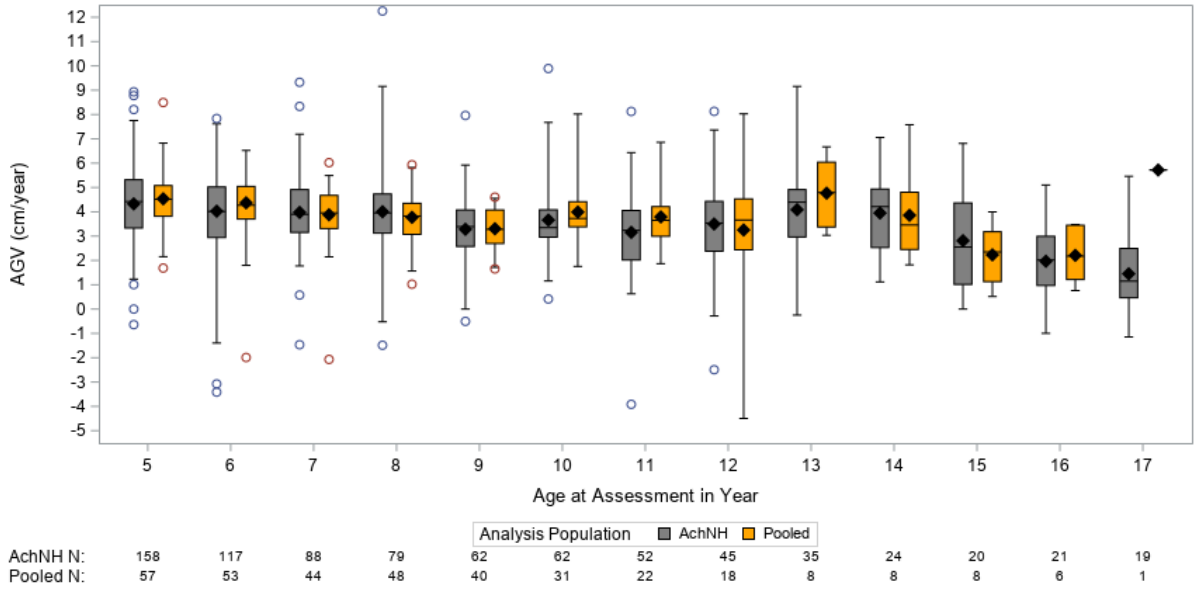
Source: Applicant's response to FDA's IR, dated January 13, 2021
Abbreviations: AchNH, achondroplasia natural history

Figure 83. Box Plot of 12-Month AGV by Sex and Age, AchNH and Supportive Pooled NH Sources

Female:



Male:



Source: statistical reviewer, adapted from Applicant's code
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity

Contemporaneousness of AchNH Data

Table 126. Birth Decades Among Vosoritide Subjects and Various Matched Sets of AchNH Control Subjects

Parameter	Cohort 3, Study 111-202/205	Entire AchNH Database	5-Year Cross-Sectional Analysis, at Baseline	5-Year Cross-Sectional Analysis, at Year 5	5-Year Longitudinal Analysis, Primary	5-Year Longitudinal Analysis, Post hoc
Matching factors		-	Age, sex	Age, sex	Age, sex	Age, sex, height, AGV
Cohort size	N=10	N=1374	N=559	N=360	N=98	N=63
Birth decade (%)						
1970		17.0	9.3	12.2	8.2	9.5
1980		16.8	18.4	22.5	24.5	20.6
1990		22.9	32.4	41.4	41.8	42.9
2000	100.0	25.9	36.1	23.9	25.5	27.0
2010		17.4	3.8			

Source: DEPI reviewer
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity

Table 127. Height in Subjects Born Before Versus After Year 2000 by Sex and Age in AchNH Population

Age (years)	Female				Male			
	Subjects Born Before 2000 (N = 242)		Subjects Born After 2000 (N = 147)		Subjects Born Before 2000 (N = 222)		Subjects Born After 2000 (N = 180)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
5	146	86.93 (4.58)	96	86.88 (4.22)	116	87.60 (4.17)	143	88.16 (4.27)
6	126	91.04 (4.67)	73	91.35 (5.10)	103	92.10 (4.50)	105	93.37 (4.38)
7	115	95.80 (5.04)	53	95.46 (5.54)	88	96.40 (5.12)	77	97.29 (5.11)
8	100	98.89 (5.22)	48	99.71 (5.76)	88	100.43 (4.63)	70	101.82 (4.66)
9	103	103.05 (6.15)	38	103.66 (5.43)	92	104.97 (5.93)	51	105.05 (4.79)
10	91	106.00 (6.21)	30	106.53 (4.97)	84	107.64 (5.42)	45	108.93 (4.77)
11	84	110.53 (6.30)	28	110.37 (5.11)	77	110.99 (5.90)	42	110.77 (5.41)
12	73	113.04 (7.49)	17	111.57 (5.48)	77	113.68 (6.68)	35	114.87 (5.51)
13	74	117.93 (5.94)	19	114.18 (6.21)	57	118.50 (7.04)	24	119.32 (5.50)
14	65	119.15 (5.75)	6	115.65 (5.25)	61	122.21 (6.97)	14	124.95 (6.11)
15	57	120.55 (6.36)	4	115.78 (4.17)	51	124.40 (6.94)	4	124.55 (6.92)
16	45	120.95 (6.15)	4	118.45 (2.66)	47	126.30 (7.52)	2	129.20 (2.69)

Source: Applicant's response to FDA's IR dated March 29, 2029, 2021
Abbreviations: AchNH, achondroplasia natural history; NH, natural history; SD, standard deviation

Sensitivity Analysis for Matching

Table 128. Number of AchNH Subjects Matched to Each Active Subject Under Different Threshold Values for Baseline Height and AGV in 5-Year Longitudinal Analysis

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

Source: Table ir201117.q04.2

Source: Applicant's response to FDA's IR, dated November 17, 2020
The baseline height and baseline AGV in the header of this table refer to threshold differences between treated subjects and NH subjects at baseline. For example, baseline height =10 cm means the difference between a treated subject and matched NH subjects should be no more than 10 cm.
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity; F, female; M, male

Table 129. Goodness of Matching for 5-Year Comparative Analyses for Cohort 3 vs. External Control

Parameter	External Control (Primary)[b] (N=63)
Number of matched AchNH subjects / active control	
N	9
Mean (SD)	7.0 (6.3)
Median (min, max)	5.0 (2.0, 22.0)
25th and 75th percentile	3.0, 8.0
Baseline age difference from active treatment arm (Year)[a]	
N	63
Mean (SD)	-0.01 (0.40)
Median (min, max)	-0.13 (-0.8, 0.7)
25th and 75th percentile	-0.25, 0.33
LS mean difference (95%CI)[c]	-0.09 (-0.33, 0.15)
SMD[d]	-0.07
Baseline AGV difference from active treatment arm (cm/year)[a]	
N	63
Mean (SD)	0.15 (1.11)
Median (min, max)	0.29 (-2.0, 2.0)
25th and 75th percentile	-0.83, 1.16
LS mean difference (95%CI)[c]	0.16 (-0.52, 0.85)
SMD[d]	0.13
Baseline height difference from active treatment arm (cm)[a]	
N	63
Mean (SD)	-1.98 (4.82)
Median (min, max)	-1.80 (-9.9, 9.1)
25th and 75th percentile	-5.65, 1.30
LS mean difference (95%CI)[c]	-2.39 (-5.21, 0.43)
SMD from Bal.Tab.[d]	-0.44

Parameter	External Control (Primary)[b] (N=63)
Baseline height Z-score difference from active treatment arm[a]	
N	63
Mean (SD)	-0.47 (1.06)
Median (min, max)	-0.49 (-2.5, 2.0)
25th and 75th percentile	-1.27, 0.23
LS mean difference (95%CI)[c]	-0.44 (-1.08, 0.20)
SMD[d]	-0.45
Race identical to active treatment arm[a], n (%)	
Yes	35 (55.6)
No	27 (42.9)
Other	1 (1.6)
Duration of follow-up (month)[e]	
N	63
Mean (SD)	59.94 (1.78)
Median (min, max)	59.81 (57.2, 63.0)
25th and 75th percentile	58.44, 61.29

Source: Applicant's response to FDA's IR dated April 6, 2021
[a] Active Treatment Arm includes all subjects in Study 111-202 Cohort 3 (15 µg/kg BMN-111) who continued to Study 111-205 with at least 5 years of total follow-up after excluding Subject (b) (6) who had limb-lengthening prior to entry into the study.
[b] AchNH Control Arm for 5-Year Longitudinal Comparative Analysis includes all subjects from the AchNH Descriptive Analysis Population who are matched by sex, baseline AGV, baseline height, and age to the sex, baseline AGV, baseline height and age at baseline from subjects in the Active Treatment Arm who had at least 1 height assessment between 6 and 12 months prior to the baseline and at least on height assessment at 60±3 months relative to the baseline.
[c] LS mean difference adjusted for matching ID obtained from ANCOVA model with fixed effects of treatment and matching ID.
[d] SMD adjusting for matching ID were computed from bal.tab (cobalt) by using "match strata" option.
[e] The duration of follow-up is provided for the subjects in the control arm only. 'Other" race is unknown.
The Applicant's original goodness of matching tables did not take into consideration variable ratio and assigned equal weights to all control subjects. This table reflects revision according to FDA's advice.
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity; LS mean, least square mean; max, maximum; min, minimum; SD, standard deviation; SMD, standardized mean difference

Table 130. Sensitivity Analyses for Treatment Difference of Study 111-205 Versus AchNH in Terms of Change in Standing Height and Change in Cumulative AGV From Baseline to 5 Year

Analysis Vosorotide Treated Cohort	AchNH Control	Mean Height Difference (cm) (95% CI)	Mean AGV Difference (cm/year) (95% CI)
Applicant's analysis[a]			
Cohort 3, N=9	N=63	7.5 (4.8, 10.1)	1.60 (0.75, 2.44)
Cohorts 1, 2, 3, N=19	N=99	7.1 (5.5, 8.7)	1.71 (1.19, 2.24)
Adjust for baseline height and AGV in ANCOVA[b]			
Cohort 3, N=9	N=63	7.1 (4.3, 9.8)	1.34 (0.83, 1.85)
Cohorts 1, 2, 3, N=19	N=99	7.1 (5.4, 8.8)	1.36 (1.04, 1.68)
Adjust for birth time (≥2000 vs. <2000) in ANCOVA[c]			
Cohort 3, N=9	N=63	7.5 (4.3, 10.6)	1.65 (0.64, 2.65)
Cohorts 1, 2, 3, N=19	N=99	7.1 (5.2, 9.1)	1.83 (1.19, 2.47)
Nearest neighbor matching[d]			
Cohort 3, N=9	N=9	7.4 (4.0, 10.7)	1.60 (0.82, 2.39)
Cohorts 1, 2, 3, N=19	N=19	6.3 (4.3, 8.2)	1.53 (1.10, 1.96)

Source: statistical reviewer
[a] Exact matching on sex and integer age followed by matching on baseline height and AGV using threshold difference of 10 cm for height and 2 cm/year for AGV. An ANCOVA model including treatment and matching ID was used to estimate treatment effect after matching. The analysis for Cohort 3 is the same as the 1st analysis in Table 17.
[b] Same matching method as Applicant's analysis. The ANCOVA model included baseline height and baseline AGV in addition to treatment and matching ID.
[c] Same matching method as Applicant's analysis. The ANCOVA model included birth time categories (≥2000 vs. <2000) in addition to treatment and matching ID.
[d] Based on Mahalanobis distance. Nearest neighbor matching based on propensity score gave similar results (not shown).
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity; CI, confidence interval

Table 131. Sensitivity Analyses Related to Random Selection Among Repeated Measures From a NH Subject Matched to Multiple Active Subjects, Study 111-205 Cohort 3 Versus AchNH

Analysis[a]	Vosoritide Exposure Cohort	NH Control	Mean Height Difference (95% CI)	Mean AGV Difference (95% CI)
Select by closest baseline height	Cohort 3 N=9	AchNH N=63	7.69 (5.11, 10.26)	1.73 (0.89, 2.58)
Select by closest baseline AGV	Cohort 3 N=9	AchNH N=63	7.80 (5.18, 10.43)	1.76 (1.04, 2.49)
All records from a NH subject matched to multiple active subjects were kept	Cohort 3 N=9	AchNH N=93	7.55 (5.16, 9.94)	1.68 (0.88, 2.48)

Source: summarized from Applicant's response to FDA's IR dated March 9, 2021
[a] The analyses in this table were the similar to Applicant's analysis for Cohort 3 in Table 132 except for the changes stated. Repeated measures from a NH subject at different ages may match to multiple active subjects with different ages at baseline. Analyses in Table 132 used random assignment to select among the repeated measures. The analyses in this table either selected based on the closest baseline height or AGV to the matched active subjects or kept all repeated measures, in order to explore the impact of random selection on analysis results.
Analysis method: ANCOVA model that includes treatment and matching ID as fixed factors
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity; CI, confidence interval

Additional Longitudinal Analysis (Not Rebaselined, Matched on Sex, Baseline Height, AGV, Age and Exclude Limb Lengthening)

Table 132. 2-Year Longitudinal Analysis of Change in AGV and Height, Study 111-205/111-302 vs. AchNH[a]

Vosoritide Exposure Cohort	NH Control	Analysis Time	Mean Height Difference (95% CI)	Mean AGV Difference (95% CI)
Cohort 3 of Study 111-205 N=9	AchNH N=70	Change from baseline at Year 1	1.70 (0.81, 2.60)	1.76 (0.66, 2.86)
		Change from baseline at Year 2	3.93 (2.45, 5.41)	2.04 (1.07, 3.02)
Cohorts 1, 2, 3 of Study 111-205+Study 111-302 N=24	AchNH N=124	Change from baseline at Year 1	0.99 (0.30, 1.67)	1.22 (0.39, 2.04)
		Change from baseline at Year 2	3.32 (2.54, 4.10)	1.81 (1.20, 2.42)

Source: summarized from Applicant's response to FDA's IR dated November 17, 2020
[a] AchNH Control Arm includes all AchNH subjects who are matched by sex, baseline AGV, baseline height, and age to Subjects in the Active Treatment Arm at baseline and had at least 1 height assessment at 12±3 and 24±3 months relative to the baseline. Change from baseline at Year 1 and change from baseline at Year 2 were analyzed using the same group of subjects.
Analysis method: ANCOVA model that includes treatment and matching ID as fixed factors
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity; CI, confidence interval

Table 133. 4-Year Longitudinal Analysis of Change in AGV and Height, Study 111-205 vs. AchNH

Analysis[a]	Vosoritide Exposure Cohort	NH Control	Mean Height Difference (95% CI)	Mean AGV Difference (95% CI)
4-year longitudinal[a]	Cohort 3, N=9	AchNH, N=83	6.71 (4.80, 8.63)	1.74 (1.03, 2.46)
	Cohorts 1,2,3, N=21	AchNH, N=125	5.86 (4.47, 7.26)	1.54 (0.96, 2.21)

Source: summarized from Applicant's response to FDA's IR dated November 17, 2020
[a] Analysis method: ANCOVA model that includes treatment and matching ID as fixed factors
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity; CI, confidence interval

There were 3 subjects in Cohort 3 of Study 111-205 with no height assessment at 6 years (1 subject due to coronavirus disease 2019 (COVID-19), 1 subject discontinued study with reasons of other, and 1 subject discontinued study due to reaching near final adult height). In one analysis, their height assessment at 6 years were imputed by last observation carried forward. In another analysis, only subjects with height assessment at 6 years were included.

Table 134. 6-Year Longitudinal Analysis of Change in AGV and Height, Study 111-205 vs. AchNH

Analysis[a]	Vosoritide Exposure Cohort	NH Control	Mean Height Difference (95% CI)	Mean AGV Difference (95% CI)
6-year longitudinal LOCF for 3 subjects with missing data at 6 year	Cohort 3 N=9	AchNH N=59	8.75 (6.32, 11.18)	1.82 (1.10, 2.55)
6-year longitudinal Only include subjects with height assessment at 6 year	Cohort 3 N=6	AchNH N=51	9.19 (6.19, 12.18)	1.52 (0.61, 2.43)

Source: summarized from Applicant's response to FDA's IR dated April 16, 2021
[a] Analysis method: ANCOVA model that includes treatment and matching ID as fixed factors
Abbreviations: AchNH, achondroplasia natural history; AGV, annualized growth velocity; CI, confidence interval; LOCF, last observation carried forward

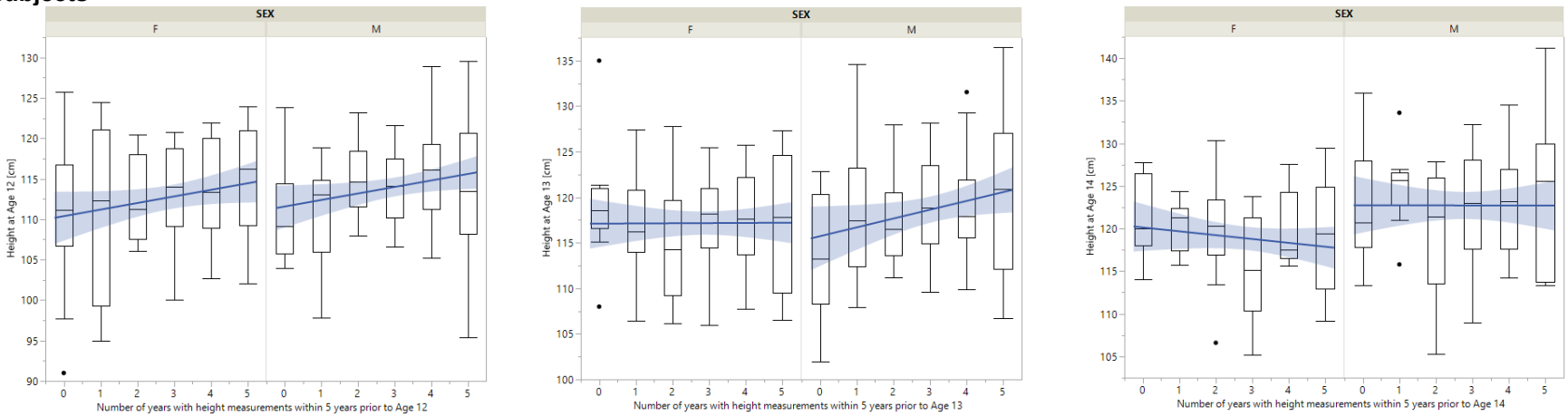
Exploratory Analyses for Selection Bias

Table 135. Comparison of Height at Year 2 Between Subjects With 5-Year Follow-Up Versus Those Without, AchNH Subjects From 5-Year Cross-Sectional Analysis With Height Assessment at Year 2

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

Source: DEPI-I reviewer
Abbreviations: AchNH, achondroplasia natural history

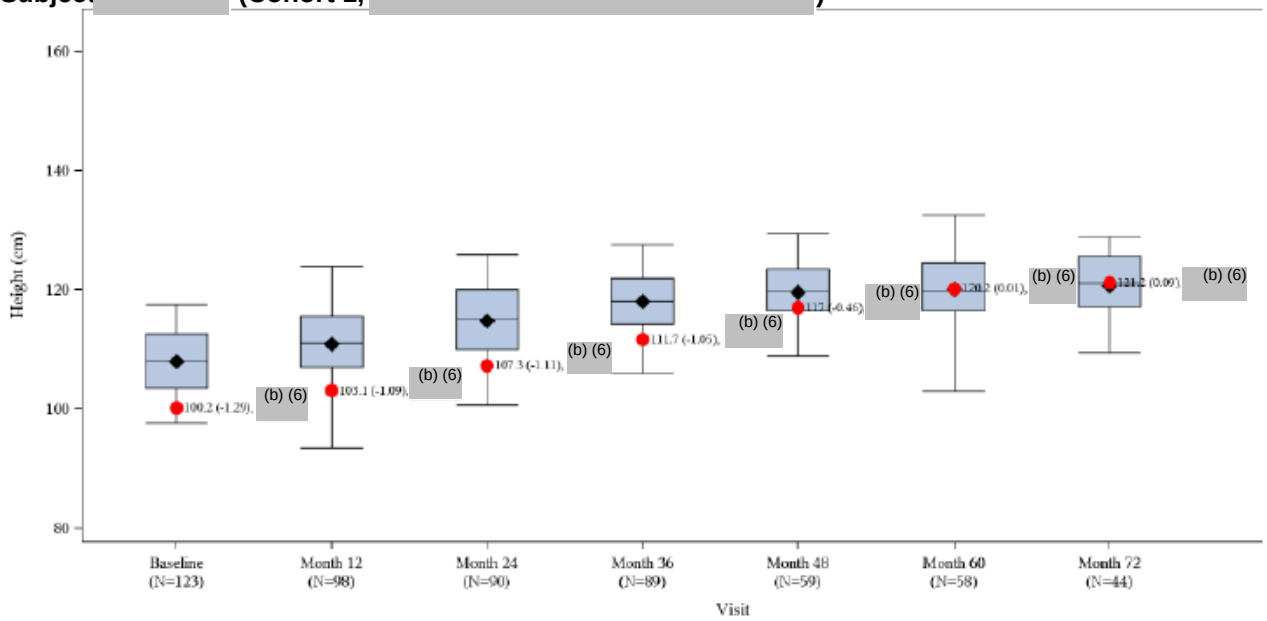
Figure 84. Height at Age 12, 13, 14 Years Versus Number of Years With Height Measurements Within 5 Years Prior to 12 Years Old by Sex, AchNH Subjects



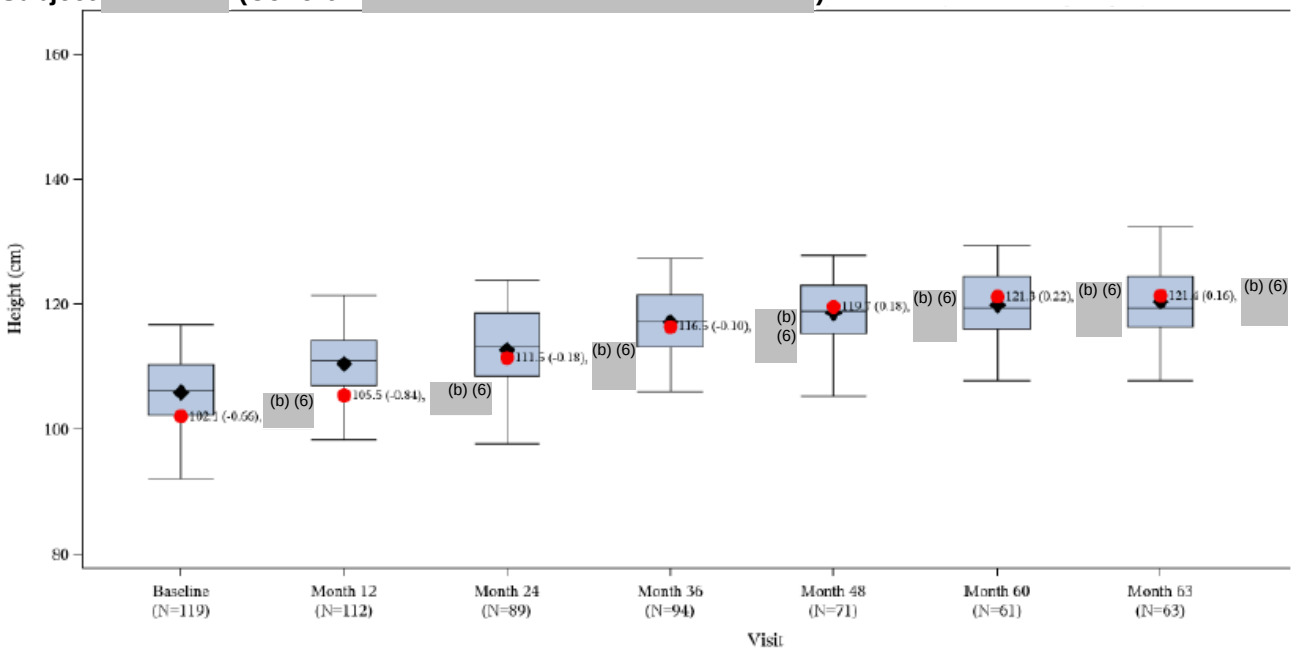
Source: DEPI-I reviewer
Abbreviations: AchNH, achondroplasia natural history

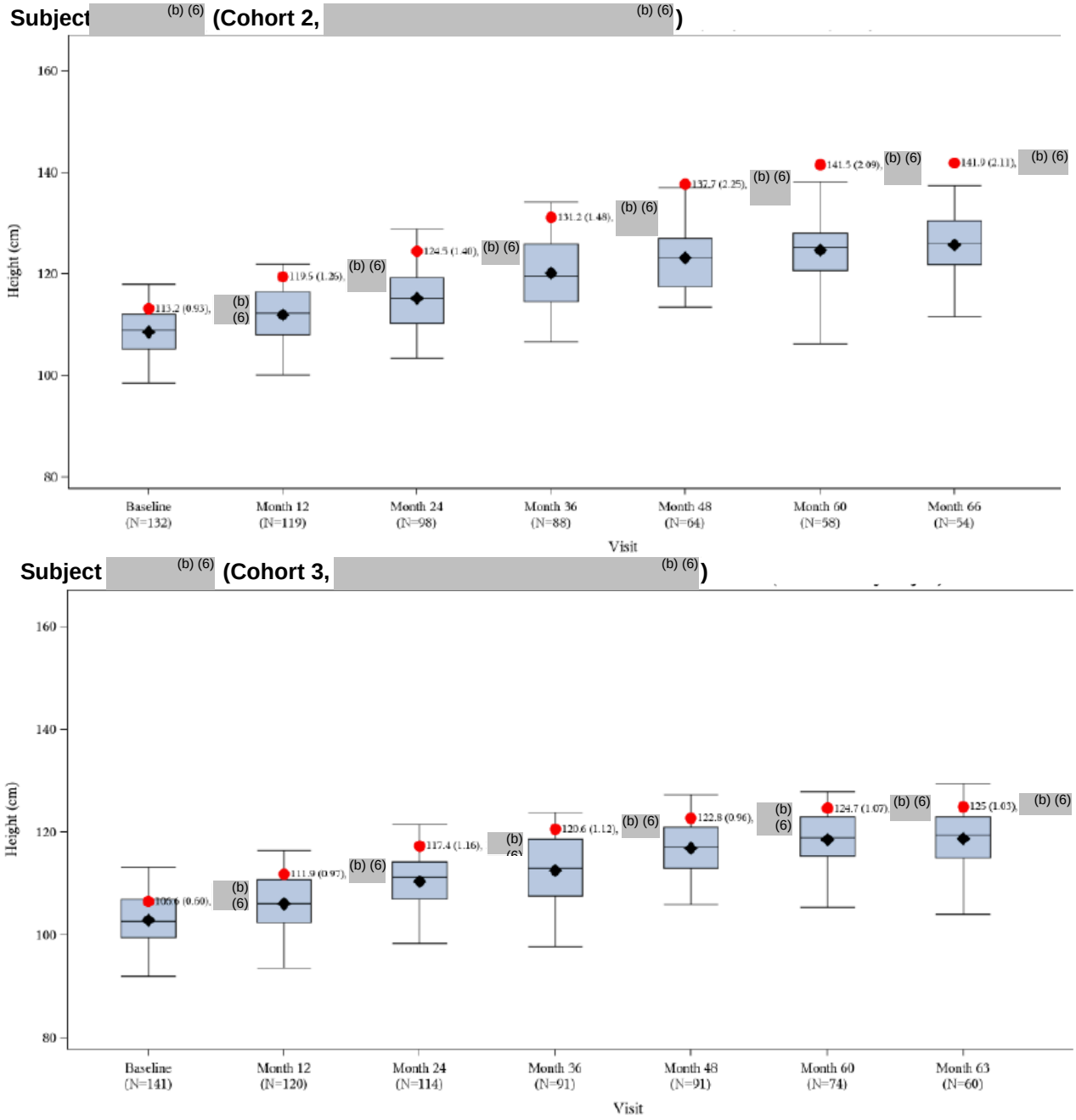
Figure 85. Standing Height Evolution of Subjects Who Reached NFAH, Study 111-205

Subject (b) (6) (Cohort 1, (b) (6))



Subject (b) (6) (Cohort 2 (b) (6))





Source: Applicant's Figures 4.2.1.1 and 4.2.1.2, Efficacy update report, submitted March 31, 2021
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) from AchNH study.
Subjects from AchNH were matched by sex and age +/- 6 months for 111-205 subjects.
Red dots represent height for all subjects in Study 111-205. The numbers beside the red dots are the height of active subject at that visit, the number of standard deviation away from the mean height of the matched AchNH subjects, and age at that visit in order.
Abbreviations: NFAH, near final adult height

Study 111-206

Disposition

At the time of the data cutoff (September 12, 2019) for the interim study report submitted at the time of the NDA, 44 subjects had enrolled in Study 111-206: Cohort 1 with 4 sentinel subjects

and 26 randomized subjects, and Cohort 2 with 4 sentinel subjects and 10 randomized subjects. In Cohort 1, the 4 sentinel subjects completed 52 weeks of treatment [mean (SD) duration of treatment was 366.3 (6.6) days], while all 26 subjects completed the Week 13 visit, and 9 subjects completed the Week 26 visit [mean (SD) duration of treatment was 181.3 (73.7) days]. In Cohort 2, 2 sentinel subjects completed the Week 26 visit. No subjects had discontinued the study drug at the time of data cutoff.

Efficacy Results

(b) (4)

17. Clinical Safety: Additional Information and Assessment

Study 111-301

Table 136. Adverse Events Leading to Discontinuation, Safety Population, Study 111-301

Preferred Term	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Any AE leading to discontinuation	1 (1.7)	0	1.7 (-1.5, 4.9)
Procedural anxiety	1 (1.7)	0	1.7 (-1.5, 4.9)

Source: adae.xpt; Software: Python
[a] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

Table 137. Injection Site Reactions by Preferred Term, Grade 1, Safety Population, Study 111-301

	15 µg/kg VOS, N=60			Placebo, N=61				
Preferred Term	n (%)	Events	Events per Person-Year	n (%)	Events	Events per Person-Year	Risk Difference (95% CI)	Event Rate Difference (95% CI)
Any Injection site reaction	51 (85)	9267	159.8	50 (82)	2041	33.5	3.03 (-10.19, 16.25)	126.3 (122.7, 129.9)
Injection site erythema	44 (73.3)	6177	106.5	42 (68.9)	1412	23.2	4.48 (-11.65, 20.61)	83.3 (80.4, 86.2)
Injection site swelling	37 (61.7)	1862	32.1	22 (36.1)	168	2.8	25.6 (8.38, 42.82)	29.3 (27.8, 30.8)
Injection site urticaria	14 (23.3)	439	7.6	6 (9.8)	56	0.9	13.5 (0.44, 26.55)	6.7 (6, 7.4)
Injection site reaction	12 (20)	322	5.6	1 (1.6)	4	0.1	18.36 (7.75, 28.97)	5.5 (4.9, 6.1)
Injection site bruising	9 (15)	32	0.6	15 (24.6)	27	0.4	-9.59 (-23.68, 4.5)	0.2 (-0.1, 0.5)
Injection site pruritus	8 (13.3)	236	4.1	6 (9.8)	154	2.5	3.5 (-7.9, 14.89)	1.6 (0.9, 2.3)
Injection site pain	5 (8.3)	150	2.6	9 (14.8)	166	2.7	-6.42 (-17.74, 4.9)	-0.1 (-0.7, 0.5)
Injection site hemorrhage	3 (5)	10	0.2	12 (19.7)	30	0.5	-14.67 (-26.07, -3.27)	-0.3 (-0.5, -0.1)
Injection site vesicles	3 (5)	31	0.5	3 (4.9)	15	0.2	0.08 (-7.65, 7.82)	0.3 (0.1, 0.5)
Injection site discoloration	2 (3.3)	4	0.1	4 (6.6)	5	0.1	-3.22 (-10.92, 4.47)	0 (-0.1, 0.1)
Injection site discomfort	1 (1.7)	1	0	0	0	0	1.67 (-1.57, 4.91)	0 (0, 0)
Injection site hematoma	1 (1.7)	1	0	1 (1.6)	3	0	0.03 (-4.52, 4.57)	0 (-0.1, 0.1)
Injection site edema	1 (1.7)	2	0	1 (1.6)	1	0	0.03 (-4.52, 4.57)	0 (-0.1, 0.1)

Source: adae.xpt, adce.xpt; Software: Python
Events per person-year is events divided by total exposure in group (VOS group, 57.99 person-years; placebo group, 60.93 person-years).
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

Table 138. Injection Site Reactions by Preferred Term, Grade 2, Safety Population, Study 111-301

	15 µg/kg VOS, N=60			Placebo, N=61				
Preferred Term	n (%)	Events	Events Per Person-Year	n (%)	Events	Events Per Person-Year	Risk Difference (95% CI)	Event Rate Difference (95% CI)
Any injection site reaction	2 (3.3)	7	0.1	0	0	0	3.33 (-1.21, 7.88)	0.1 (0, 0.2)
Injection site erythema	2 (3.3)	2	0	0	0	0	3.33 (-1.21, 7.88)	0 (0, 0)
Injection site urticaria	2 (3.3)	4	0.1	0	0	0	3.33 (-1.21, 7.88)	0.1 (0, 0.2)
Injection site vesicles	1 (1.7)	1	0	0	0	0	1.67 (-1.57, 4.91)	0 (0, 0)

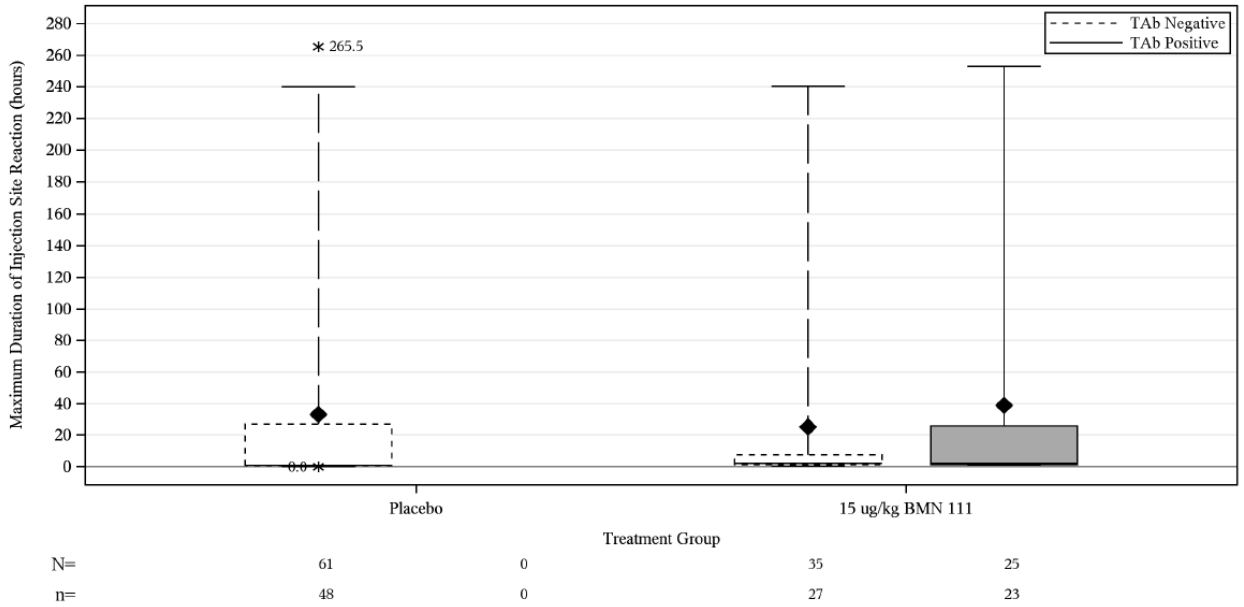
Source: adae.xpt, adce.xpt; Software: Python
Events per person-year is events divided by total exposure in group (VOS group, 57.99 person-years; placebo group, 60.93 person-years).
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

Table 139. Overview of Injection Site Reaction Events, Safety Population, Study 111-301

Event Statistic	15 µg/kg VOS, N=60	Placebo, N=61
Subjects with any event	51	50
Mean events (SD)	136.4 (136)	35.7 (70)
Median events (min, max)	77 (1, 367)	7.5 (1, 355)

Source: adae.xpt; Software: Python
Abbreviations: max, maximum; min, minimum; SD, standard deviation; VOS, vosoritide

Figure 86. Maximum Duration of ISR AEs by TAb Status, Immunogenicity Population



Source: CSR, 111-301
N = number of subjects in TAb positive or TAb negative groups, respectively.
n represents the number of subjects reporting ISRs for TAb negative and positive groups respectively.
Abbreviations: AE, adverse event; ISR, injection site reaction; TAb, total anti-vosoritide antibody

Table 140. Laboratory Abnormalities, Worsened Grade, Safety Population, Study 111-301

Laboratory Test	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Hemoglobin (g/L) increased			
Any grade	13 (21.7)	8 (13.1)	8.6 (-4.9, 22.0)
Grade 3 or 4	0	0	0.0 (0.0, 0.0)
Lymphocytes (10^9/L) increased			
Any grade	11 (18.3)	5 (8.2)	10.1 (-1.8, 22.1)
Grade 3 or 4	0	0	0.0 (0.0, 0.0)
Lymphocytes (10^9/L) decreased			
Any grade	6 (10)	2 (3.3)	6.7 (-2.1, 15.5)
Grade 3 or 4	0	0	0.0 (0.0, 0.0)
Alkaline phosphatase (U/L) increased			
Any grade	10 (16.7)	4 (6.6)	10.1 (-1.2, 21.4)
Grade 3 or 4	0	0	0.0 (0.0, 0.0)
Alanine aminotransferase (U/L) increased			
Any grade	13 (21.7)	11 (18)	3.6 (-10.6, 17.8)
Grade 3 or 4	0	0	0.0 (0.0, 0.0)

Laboratory Test	15 µg/kg VOS N=60 n (%)	Placebo N=61 n (%)	Risk Difference (95% CI)[a]
Aspartate aminotransferase (U/L) increased			
Any grade	6 (10)	4 (6.6)	3.4 (-6.4, 13.3)
Grade 3 or 4	0	0	0.0 (0.0, 0.0)

Source: adlb.xpt; Software: R
Grading Scale: CTCAE v4
[a] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; ULN, upper limit of normal; VOS, vosoritide

Studies 111-202/205

Table 141. Adverse Events Leading to Discontinuation, Safety Population, Studies 111-202/205

Study Arm	USUBJID	Age	Sex	Preferred Term	Verbatim Term	SAE[a]	Study Day of AE Onset	Duration of Adverse Event (Days)	Duration of Exposure (Days)	Relatedness
15 µg/kg-111-202	0111-1030	7	M	Transaminases increased	Transaminase rise	N	1022	256	744	Related
30 µg/kg-111-202	111901-0029-1008	7	M	Wolff-Parkinson-White syndrome	Intermittent Wolf-Parkinson-White syndrome	N	10		10	Related

Source: adae.xpt; Software: Python
[a] Serious adverse events classified by Applicant in adae.xpt.
Abbreviations: AE, adverse event; ID, identification; SAE, serious adverse event

Subject (b) (6) was (b) (6) who completed Study 111-202 (treated with vosoritide for 744 days) and was enrolled in Study 111-205, then discontinued treatment with vosoritide because of elevated transaminases. (b) (6) was off treatment for 76 days between the studies for administrative reasons. One day prior to vosoritide initiation in Study 111-205, the subject had an ALT elevation of 35 U/L (reference range 5 to 25 U/L) and normal AST, mild eosinophilia, and neutropenia. (b) (6) was asymptomatic. After approximately 200 days of treatment with vosoritide in Study 111-205, follow-up LFTs showed ALT 108 U/L and AST 87 U/L. Vosoritide was discontinued 8 days later. Additional testing performed 3 days later after drug disconsolation revealed stable ALT at 103 U/L and decrease in AST to 67 U/L. The subject was also concomitantly treated with antiparasitic medications due to persistent eosinophilia that was presented in this subject prior to initiation of the treatment in Study 111-202. The results of the evaluation for other causes of liver abnormalities (e.g., viral hepatitis, autoimmune and metabolic panels) were negative except slightly increased gamma-globulins. Liver ultrasound showed minimal hepatic steatosis. Liver biopsy showed slight ductular reaction, minimal portal inflammatory infiltration, and nonspecific "star-like" fibrosis but no histological evidence of chronic or acute hepatitis or drug-related injury. Transaminases returned to normal after the drug had been held for 7 months. As the subject was off study treatment for over a year, a decision was made to discontinue study drug permanently. An independent pediatric hepatologist concluded that "the event could be attributable to mild hepatitis with a possible infectious etiology."

The relationship between the study drug and LFTs elevation is unlikely due to negative de-challenge, e.g., evidence of elevated ALT levels prior to vosoritide re-initiation; prolonged period of time (approximately 7 months) of LFTs normalization after drug discontinuation; concomitant eosinophilia and neutropenia, suggesting a possible infectious etiology; and no evidence of drug-induced liver injury on liver biopsy.

Table 142. Duration of Treatment by Cohort and by Dose, Safety Population, Studies 111-202/205)

Treatment Duration	2.5 µg/kg Cohort (N=8)	7.5 µg/kg Cohort (N=8)	15 µg/kg Cohort (N=10)	30 µg/kg Cohort (N=9)	Overall (N=35)
Duration of treatment, months, Overall[a]					
n	8	8	10	9	35
Mean (SD)	53.43 (30.39)	56.83 (31.24)	66.72 (12.36)	55.75 (20.80)	58.60 (23.70)
Median	63.62	74.12	72.46	62.32	64.16
Min. max	4.1. 82.6	5.0, 76.3	33.7, 73.4	0.3, 64.2	0.3, 82.6
Duration of treatment, months, 2.5 µg/kg[a]					
n	8	0	0	0	8
Mean (SD)	9.82 (2.50)				9.82 (2.50)
Median	10.05				10.05
Min. max	4.1. 12.2				4.1, 12.2
Duration of treatment, months, 7.5 µg/kg[a]					
n	7	8	0	0	15
Mean (SD)	2.68 (0.90)	8.46 (1.93)			5.76 (3.33)
Median	2.37	8.23			5.03
Min. max	1.9, 4.6	5.0, 11.9			1.9. 11.9
Duration of treatment, months, 15 µg/kg [a]					
n	6	6	10	0	22
Mean (SD)	55.01 (14.05)	64.49 (4.96)	66.72 (12.36)		62.92(11.99)
Median	59.32	66.05	72.46		67.60
Min. max	33.6. 68.0	54.9. 67.8	33.7, 73.4		33.6, 73.4

Treatment Duration	2.5 µg/kg Cohort (N=8)	7.5 µg/kg Cohort (N=8)	15 µg/kg Cohort (N=10)	30 µg/kg Cohort (N=9)	Overall (N=35)
Duration of treatment, months, 30 µg/kg [a]					
n	0	0	0	9	9
Mean (SD)				55.75 (20.80)	55.75 (20.80)
Median				62.32	62.32
Min. max				0.3, 64.2	0.3, 64.2

Source: Applicant's response to Agency's information request dated June 8, 2021
[a] Duration of treatment was defined as the time between the first dose and data cut-off date (or date of treatment discontinuation, if sooner), in months; data cut-off date for Study 111-205: November 30, 2020.
Abbreviations: Max, maximum; Min, minimum; SD, standard deviation

Table 143. Adverse Events, Safety Population, Studies 202/205[a]

Preferred Term	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)
Any AE	26 (100.0)	9 (100.0)
Injection site reaction	21 (80.8)	9 (100.0)
Injection site erythema	21 (80.8)	9 (100.0)
Pyrexia	16 (61.5)	4 (44.4)
Cough	14 (53.8)	4 (44.4)
Hypotension	14 (53.8)	2 (22.2)
Injection site swelling	14 (53.8)	2 (22.2)
Nasopharyngitis	14 (53.8)	2 (22.2)
Headache	12 (46.2)	3 (33.3)
Upper respiratory tract infection	12 (46.2)	3 (33.3)
Nasal congestion	10 (38.5)	2 (22.2)
Vomiting	9 (34.6)	3 (33.3)
Ear infection	10 (38.5)	2 (22.2)
Oropharyngeal pain	10 (38.5)	1 (11.1)
Arthralgia	8 (30.8)	3 (33.3)
Ear pain	9 (34.6)	2 (22.2)
Pain in extremity	7 (26.9)	4 (44.4)
Viral infection	9 (34.6)	1 (11.1)
Vitamin D deficiency	10 (38.5)	0
Otitis media	7 (26.9)	3 (33.3)
Fall	6 (23.1)	3 (33.3)
Injection site urticaria	5 (19.2)	4 (44.4)
Back pain	8 (30.8)	0
Arthropod bite	7 (26.9)	1 (11.1)
Diarrhea	6 (23.1)	2 (22.2)
Abdominal pain upper	6 (23.1)	1 (11.1)
Rhinorrhea	6 (23.1)	1 (11.1)
Gastroenteritis viral	4 (15.4)	2 (22.2)
Viral upper respiratory tract infection	5 (19.2)	1 (11.1)
Rash	5 (19.2)	1 (11.1)
Sleep apnea syndrome	6 (23.1)	0
Contusion	5 (19.2)	0
Dental caries	5 (19.2)	0
Dizziness	5 (19.2)	0
Neck pain	4 (15.4)	1 (11.1)
Bronchitis	4 (15.4)	1 (11.1)
Nausea	4 (15.4)	1 (11.1)
Gastroenteritis	3 (11.5)	2 (22.2)
Abdominal pain	4 (15.4)	1 (11.1)

Preferred Term	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)
Seasonal allergy	3 (11.5)	2 (22.2)
Influenza	2 (7.7)	3 (33.3)
Injection site pain	2 (7.7)	3 (33.3)
Gastrointestinal viral infection	3 (11.5)	1 (11.1)
Injection site bruising	3 (11.5)	1 (11.1)
Pruritus	3 (11.5)	1 (11.1)
Injection site pruritus	3 (11.5)	1 (11.1)
Otorrhea	3 (11.5)	1 (11.1)
Ear tube insertion	2 (7.7)	2 (22.2)
Thermal burn	3 (11.5)	0
Drug hypersensitivity	3 (11.5)	0
Procedural anxiety	3 (11.5)	0
Conjunctivitis	3 (11.5)	0
Epistaxis	3 (11.5)	0
Fatigue	3 (11.5)	0
Myalgia	2 (7.7)	1 (11.1)
Neutropenia	3 (11.5)	0
Pharyngitis streptococcal	3 (11.5)	0
Rhinitis	3 (11.5)	0
Pharyngitis	2 (7.7)	1 (11.1)
Injection site hemorrhage	2 (7.7)	1 (11.1)
Hypothyroidism	2 (7.7)	0
Oral pain	2 (7.7)	0
Peripheral swelling	2 (7.7)	0
Procedural pain	2 (7.7)	0
Scar	2 (7.7)	0
Urticaria	2 (7.7)	0
Cyst	2 (7.7)	0
Ear swelling	2 (7.7)	0
Hand-foot-and-mouth disease	2 (7.7)	0
Hypoacusis	2 (7.7)	0
Malpositioned teeth	2 (7.7)	0
Medical device pain	2 (7.7)	0
Erythema	2 (7.7)	0
Eye pain	2 (7.7)	0
Ligament sprain	2 (7.7)	0
Lymphadenopathy	2 (7.7)	0
Pneumonia	2 (7.7)	0
Rash generalized	2 (7.7)	0
Sinusitis	2 (7.7)	0
Application site erythema	1 (3.8)	1 (11.1)
Limb injury	1 (3.8)	1 (11.1)
Otitis externa	1 (3.8)	1 (11.1)
Dermatitis	2 (7.7)	0
Dry skin	2 (7.7)	0
Fungal infection	2 (7.7)	0
Presyncope	2 (7.7)	0
Tympanic membrane perforation	2 (7.7)	0
Acne	2 (7.7)	0
Eosinophil count increased	2 (7.7)	0
Tonsillar hypertrophy	2 (7.7)	0
Vitamin D decreased	2 (7.7)	0
Skin abrasion	0	2 (22.2)

Preferred Term	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)
Skin papilloma	0	2 (22.2)

Source: adae.xpt; Software: Python
[a] Note: AEs occurring in ≤1 subject in total in all cohorts were not reported in the table.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

Table 144. Adverse Events by Preferred Term and Year, Safety Population, Studies 111-202/205[a]

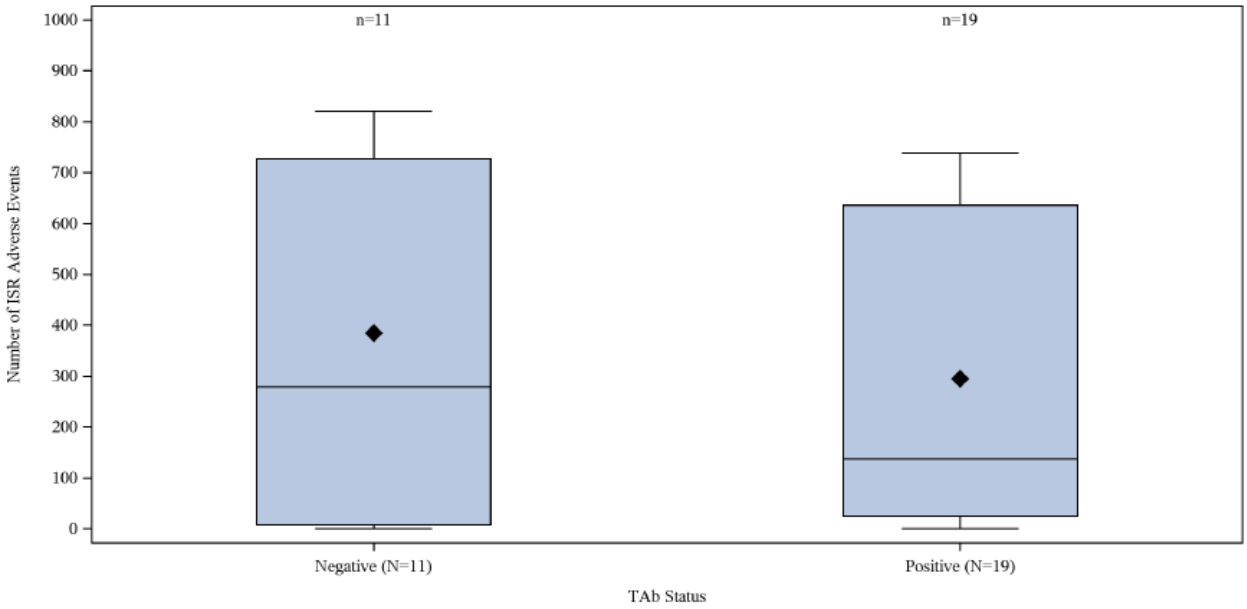
	Year 1		Year 2		Year 3		Year 4		Year 5+	
Preferred Term	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)
Any AE	26 (100)	9 (100)	23 (88.5)	8 (88.9)	21 (80.8)	7 (77.8)	17 (65.4)	7 (77.8)	18 (69.2)	2 (22.2)
Injection site erythema	20 (76.9)	9 (100)	10 (38.5)	5 (55.6)	4 (15.4)	1 (11.1)	0	0	0	0
Injection site reaction	16 (61.5)	9 (100)	16 (61.5)	6 (66.7)	6 (23.1)	3 (33.3)	0	0	1 (3.8)	0
Pyrexia	12 (46.2)	2 (22.2)	1 (3.8)	1 (11.1)	2 (7.7)	1 (11.1)	5 (19.2)	2 (22.2)	5 (19.2)	0
Cough	9 (34.6)	4 (44.4)	3 (11.5)	1 (11.1)	6 (23.1)	0	2 (7.7)	0	1 (3.8)	0
Hypotension	13 (50.0)	2 (22.2)	2 (7.7)	2 (22.2)	1 (3.8)	0	1 (3.8)	0	1 (3.8)	0
Injection site swelling	11 (42.3)	2 (22.2)	8 (30.8)	1 (11.1)	1 (3.8)	0	0	0	0	0
Nasopharyngitis	9 (34.6)	2 (22.2)	4 (15.4)	2 (22.2)	3 (11.5)	0	4 (15.4)	1 (11.1)	3 (11.5)	0
Headache	9 (34.6)	3 (33.3)	5 (19.2)	0	4 (15.4)	0	6 (23.1)	0	3 (11.5)	0
Upper respiratory tract infection	4 (15.4)	2 (22.2)	2 (7.7)	1 (11.1)	4 (15.4)	1 (11.1)	3 (11.5)	1 (11.1)	3 (11.5)	0
Ear infection	7 (26.9)	2 (22.2)	3 (11.5)	1 (11.1)	2 (7.7)	1 (11.1)	4 (15.4)	1 (11.1)	3 (11.5)	0
Nasal congestion	3 (11.5)	1 (11.1)	1 (3.8)	1 (11.1)	6 (23.1)	0	2 (7.7)	0	1 (3.8)	0
Oropharyngeal pain	6 (23.1)	0	3 (11.5)	0	3 (11.5)	1 (11.1)	4 (15.4)	1 (11.1)	3 (11.5)	0
Vitamin D deficiency	1 (3.8)	0	1 (3.8)	0	5 (19.2)	0	1 (3.8)	0	3 (11.5)	0
Ear pain	6 (23.1)	1 (11.1)	3 (11.5)	1 (11.1)	2 (7.7)	2 (22.2)	1 (3.8)	1 (11.1)	1 (3.8)	0
Viral infection	0	0	5 (19.2)	1 (11.1)	1 (3.8)	0	1 (3.8)	1 (11.1)	2 (7.7)	0
Vomiting	5 (19.2)	2 (22.2)	3 (11.5)	2 (22.2)	4 (15.4)	0	0	0	2 (7.7)	0
Arthralgia	1 (3.8)	0	2 (7.7)	1 (11.1)	3 (11.5)	1 (11.1)	0	1 (11.1)	4 (15.4)	1 (11.1)
Back pain	3 (11.5)	0	2 (7.7)	0	0	0	1 (3.8)	0	3 (11.5)	0
Arthropod bite	5 (19.2)	0	1 (3.8)	1 (11.1)	2 (7.7)	0	0	0	0	0
Otitis media	2 (7.7)	2 (22.2)	3 (11.5)	2 (22.2)	3 (11.5)	0	3 (11.5)	1 (11.1)	0	0
Pain in extremity	3 (11.5)	1 (11.1)	0	3 (33.3)	1 (3.8)	1 (11.1)	3 (11.5)	0	1 (3.8)	0
Sleep apnea syndrome	3 (11.5)	0	1 (3.8)	0	3 (11.5)	0	0	0	1 (3.8)	0
Abdominal pain upper	5 (19.2)	1 (11.1)	1 (3.8)	0	0	0	0	0	0	0
Diarrhea	3 (11.5)	2 (22.2)	0	0	0	0	2 (7.7)	0	1 (3.8)	0
Fall	3 (11.5)	1 (11.1)	3 (11.5)	1 (11.1)	0	1 (11.1)	1 (3.8)	0	0	0
Rhinorrhea	3 (11.5)	1 (11.1)	0	0	2 (7.7)	0	1 (3.8)	0	0	0
Contusion	2 (7.7)	0	1 (3.8)	0	0	0	2 (7.7)	0	0	0
Dental caries	3 (11.5)	0	1 (3.8)	0	0	0	0	0	1 (3.8)	0
Dizziness	3 (11.5)	0	1 (3.8)	0	1 (3.8)	0	0	0	1 (3.8)	0
Injection site urticaria	5 (19.2)	3 (33.3)	0	1 (11.1)	0	0	0	0	0	0
Rash	4 (15.4)	1 (11.1)	2 (7.7)	0	0	0	0	0	1 (3.8)	0

	Year 1		Year 2		Year 3		Year 4		Year 5+	
Preferred Term	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**
Viral upper respiratory tract infection	0	1 (11.1)	3 (11.5)	0	2 (7.7)	0	1 (3.8)	0	0	0
Abdominal pain	1 (3.8)	1 (11.1)	1 (3.8)	0	1 (3.8)	0	2 (7.7)	0	2 (7.7)	0
Bronchitis	3 (11.5)	0	0	0	1 (3.8)	0	1 (3.8)	1 (11.1)	0	0
Gastroenteritis viral	4 (15.4)	2 (22.2)	0	0	0	0	0	0	0	0
Nausea	2 (7.7)	1 (11.1)	2 (7.7)	1 (11.1)	0	0	1 (3.8)	0	1 (3.8)	0
Neck pain	1 (3.8)	1 (11.1)	1 (3.8)	0	0	0	1 (3.8)	0	2 (7.7)	0
Conjunctivitis	1 (3.8)	0	1 (3.8)	0	1 (3.8)	0	0	0	0	0
Drug hypersensitivity	2 (7.7)	0	0	0	0	0	1 (3.8)	0	0	0
Epistaxis	2 (7.7)	0	0	0	1 (3.8)	0	0	0	1 (3.8)	0
Fatigue	2 (7.7)	0	1 (3.8)	0	0	0	0	0	0	0
Gastrointestinal viral infection	0	1 (11.1)	0	0	3 (11.5)	0	0	0	0	0
Injection site bruising	3 (11.5)	1 (11.1)	0	1 (11.1)	0	0	0	0	0	0
Injection site pruritus	2 (7.7)	0	1 (3.8)	1 (11.1)	0	0	0	0	0	0
Otorrhea	2 (7.7)	0	0	0	0	1 (11.1)	1 (3.8)	0	0	0
Procedural anxiety	2 (7.7)	0	1 (3.8)	0	0	0	0	0	0	0
Rhinitis	1 (3.8)	0	1 (3.8)	0	2 (7.7)	0	0	0	0	0
Seasonal allergy	1 (3.8)	1 (11.1)	0	0	1 (3.8)	1 (11.1)	1 (3.8)	2 (22.2)	0	0
Ear tube insertion	2 (7.7)	1 (11.1)	0	1 (11.1)	0	0	0	0	0	0
Eosinophil count increased	2 (7.7)	0	1 (3.8)	0	0	0	0	0	0	0
Erythema	2 (7.7)	0	0	0	0	0	0	0	0	0
Eye pain	2 (7.7)	0	0	0	0	0	0	0	0	0
Hypothyroidism	2 (7.7)	0	0	0	0	0	0	0	0	0
Influenza	0	1 (11.1)	0	1 (11.1)	0	2 (22.2)	1 (3.8)	0	1 (3.8)	0
Injection site pain	1 (3.8)	2 (22.2)	1 (3.8)	2 (22.2)	0	0	0	0	0	0
Lymphadenopathy	2 (7.7)	0	0	0	0	0	0	0	0	0
Medical device pain	0	0	0	0	0	0	1 (3.8)	0	2 (7.7)	0
Myalgia	0	1 (11.1)	0	0	0	0	2 (7.7)	0	0	0
Peripheral swelling	0	0	0	0	0	0	0	0	2 (7.7)	0
Pharyngitis	0	0	0	1 (11.1)	2 (7.7)	0	1 (3.8)	1 (11.1)	0	0
Pneumonia	0	0	0	0	0	0	0	0	2 (7.7)	0

	Year 1		Year 2		Year 3		Year 4		Year 5+	
Preferred Term	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**	**2.5-15 µg/kg VOS N=26 n (%)**	**30 µg/kg VOS N=9 n (%)**
Presyncope	0	0	2 (7.7)	0	0	0	0	0	0	0
Procedural pain	2 (7.7)	0	0	0	0	0	0	0	1 (3.8)	0
Rash generalized	2 (7.7)	0	0	0	0	0	0	0	1 (3.8)	0
Sinusitis	1 (3.8)	0	2 (7.7)	0	0	0	0	0	0	0
Tympanic membrane perforation	0	0	0	0	2 (7.7)	0	1 (3.8)	0	0	0

Source: adae.xpt; Software: Python
[a] Note: AEs occurring in ≤1 subject per year regardless of the cohort, were not included in the table.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; VOS, vosoritide

Figure 87. Number of ISR AEs by TAb Status, Immunogenicity Population, Studies 111-202/205



Source: CSR, 111-205
Abbreviations: AE, adverse event; ISR, injection site reaction; TAb, total anti-vosoritide antibody

Table 145. Laboratory Abnormalities, Worsened Grade, Safety Population, Studies 111-202/205

Laboratory Test	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)
Neutrophils (10^9/L) decreased		
Any grade	20 (76.9)	5 (55.6)
Grade 3 or 4	3 (11.5)	0
Leukocytes (10^9/L) decreased		
Any grade	16 (61.5)	6 (66.7)
Grade 3 or 4	0	0
Glucose (mmol/L) increased		
Any grade	13 (50)	4 (44.4)
Grade 3 or 4	0	0
Cholesterol (mmol/L) increased		
Any grade	11 (42.3)	2 (22.2)
Grade 3 or 4	0	0
Alanine aminotransferase (U/L) increased		
Any grade	11 (42.3)	1 (11.1)
Grade 3 or 4	0	0
Hemoglobin (g/L) decreased		
Any grade	5 (19.2)	1 (11.1)
Grade 3 or 4	0	0
Lymphocytes (10^9/L) decreased		
Any grade	3 (11.5)	2 (22.2)
Grade 3 or 4	0	1 (11.1)
Alkaline phosphatase (U/L) increased		
Any grade	12 (46.2)	2 (22.2)
Grade 3 or 4	0	0
Platelets (10^9/L) decreased		
Any grade	10 (38.5)	5 (55.6)
Grade 3 or 4	0	0

Laboratory Test	2.5-15 µg/kg VOS N=26 n (%)	30 µg/kg VOS N=9 n (%)
Aspartate aminotransferase (U/L) increased		
Any grade	4 (15.4)	1 (11.1)
Grade 3 or 4	0	0
Hemoglobin (g/L) increased		
Any grade	10 (38.5)	2 (22.2)
Grade 3 or 4	0	0
Direct bilirubin (µmol/L) increased		
Any grade	3 (11.5)	2 (22.2)
Grade 3 or 4	0	0
Bilirubin (pmol/L) increased		
Any grade	3 (11.5)	1 (11.1)
Grade 3 or 4	0	0
Lymphocytes (10^9/L) increased		
Any grade	1 (3.8)	5 (55.6)
Grade 3 or 4	0	0
Potassium (mmol/L) decreased		
Any grade	3 (11.5)	0
Grade 3 or 4	0	0
Sodium (mmol/L) decreased		
Any grade	8 (30.8)	2 (22.2)
Grade 3 or 4	2 (7.7)	0
Sodium (mmol/L) increased		
Any grade	1 (3.8)	1 (11.1)
Grade 3 or 4	0	0
Potassium (mmol/L) increased		
Any grade	2 (7.7)	0
Grade 3 or 4	0	0
Gamma glutamyl transferase (U/L) increased		
Any grade	1 (3.8)	0
Grade 3 or 4	0	0
Glucose (mmol/L) decreased		
Any grade	1 (3.8)	1 (11.1)
Grade 3 or 4	0	0

Source: adlb.xpt; Software: R
Grading Scale: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; ULN, upper limit of normal; VOS, vosoritide

Table 146. AEs by Preferred Term by Treatment Group Occurring With a Frequency of >5%, Study 111-302

Preferred Term	Placebo/Vosoritide (N=61)		Vosoritide/Vosoritide (N=58)	
	Incidence n (%)	Events (rate, person-years)	Incidence n (%)	Events (rate, person-years)
Nasopharyngitis	8 (13.1%)	13 (0.22)	11 (19.0%)	15 (0.27)
Headache	8 (13.1%)	15 (0.25)	6 (10.3%)	16 (0.29)
Upper respiratory tract infection	7 (11.5%)	8 (0.13)	7 (12.1%)	8 (0.14)
Pyrexia	5 (8.2%)	6 (0.10)	5 (8.6%)	5 (0.09)
Otitis media	2 (3.3%)	2 (0.03)	5 (8.6%)	6 (0.11)
Ear infection	3 (4.9%)	5 (0.08)	4 (6.9%)	4 (0.07)
Influenza	3 (4.9%)	3 (0.05)	4 (6.9%)	4 (0.07)
Cough	4 (6.6%)	4 (0.07)	3 (5.2%)	4 (0.07)
Pain in extremity	2 (3.3%)	2 (0.03)	4 (6.9%)	4 (0.07)
Arthralgia	4 (6.6%)	6 (0.10)	2 (3.4%)	2 (0.04)
Vomiting	4 (6.6%)	5 (0.08)	1 (1.7%)	1 (0.02)
Diarrhoea	1 (1.6%)	1 (0.02)	3 (5.2%)	3 (0.05)
Ear Pain	0	0	3 (5.2%)	5 (0.09)

Source: Applicant's response to information dated April 16, 2021
Abbreviations: AE, adverse event; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality

Study 111-206

Safety Results Summary

According to the Applicant, at the time of the data cutoff (September 12, 2019) for the interim study report submitted at the time of the NDA, all 8 sentinel subjects (100%) and 35 out of the 36 (97.2%) randomized subjects from Cohorts 1 and 2 experienced at least 1 adverse event (AE). There were no deaths or AEs leading to study drug discontinuation, though 1 serious adverse event (SAE) of oxygen saturation decrease (see Section 7.6.3, for details) had occurred in a randomized subject in Cohort 1. The majority of AEs were grade 1, or 2, while the most frequent adverse events reported were injection site reactions (75%).

In conclusion, no new safety signals were identified based on available safety data from the sentinel subjects, as well as blinded safety data. However, there are insufficient clinical data to assess the safety of vosoritide in the age groups 2 to 5 years. The number of sentinel subjects with safety data up to 1 year is small (N=4) and the safety data were assessed in an uncontrolled setting, while the remaining data from the randomized subjects are blinded and of limited duration. Therefore, no meaningful conclusions can been drawn with regards to the safety of vosoritide in the age group 2 to 5 years.

Table 147. MedDRA Adverse Event Terms Recoded by Preferred Term

Verbatim Term	Original Preferred Term	Recoded Preferred Term
acute media otitis	Otitis media acute	Otitis media
acute medium otitis	Otitis media acute	Otitis media
allergic rhinitis	Rhinitis allergic	Rhinitis
blister and redness at injection site	Injection site reaction	Injection site erythema
blister and redness at injection site	Injection site reaction	Injection site vesicles
blister and redness at injection site reaction	Injection site reaction	Injection site erythema
blister and redness at injection site reaction	Injection site reaction	Injection site vesicles
blotch at injection site	Injection site reaction	Injection site discoloration
body temperature increased	Body temperature increased	Pyrexia
both ear infections	Ear infection	Otitis
bruise bone with scrape at right shoulder	Bone contusion	Contusion
bruised coccygeal bone	Bone contusion	Contusion
coughing from environmental allergies	Hypersensitivity	Cough
discharge from right ear	Otorrhea	Otitis
discharging left ear	Otorrhea	Otitis
ear drainage, rt.	Otorrhea	Otitis
ear infection	Ear infection	Otitis
elevated temperature	Body temperature increased	Pyrexia
fluid in ear	Middle ear effusion	Otitis media
injected fluid made a large lump under skin at injection site	Injection site mass	Injection site swelling
injection site appears red like a bug bite	Injection site reaction	Injection site erythema
injection site reaction - large, raised lump	Injection site mass	Injection site swelling
injection site reaction - large raised red lump	Injection site reaction	Injection site erythema
injection site reaction - large raised red lump	Injection site reaction	Injection site swelling
injection site reaction - large red lump	Injection site reaction	Injection site erythema
injection site reaction - large red lump	Injection site reaction	Injection site swelling
injection site reaction - little blood	Injection site reaction	Injection site hemorrhage
injection site reaction - little blood with red area and lump	Injection site reaction	Injection site hemorrhage
injection site reaction - little blood with red area and lump	Injection site reaction	Injection site swelling
injection site reaction - little blood with red area and lump	Injection site reaction	Injection site erythema
injection site reaction - little lump	Injection site mass	Injection site swelling
injection site reaction - little red bump	Injection site reaction	Injection site erythema
injection site reaction - little red bump	Injection site reaction	Injection site swelling
injection site reaction - little red lump	Injection site reaction	Injection site erythema
injection site reaction - little red lump	Injection site reaction	Injection site swelling
injection site reaction - raised pink bump	Injection site reaction	Injection site erythema
injection site reaction - raised pink bump	Injection site reaction	Injection site swelling
injection site reaction - red bump	Injection site reaction	Injection site erythema
injection site reaction - red bump	Injection site reaction	Injection site swelling
injection site reaction - red itchy patch	Injection site reaction	Injection site erythema
injection site reaction - red itchy patch	Injection site reaction	Injection site pruritus
injection site reaction - red raised bump	Injection site reaction	Injection site erythema
injection site reaction - red raised bump	Injection site reaction	Injection site swelling
injection site reaction - red swollen area	Injection site reaction	Injection site erythema
injection site reaction - red swollen area	Injection site reaction	Injection site swelling
injection site reaction - red swollen bump	Injection site reaction	Injection site erythema
injection site reaction - red swollen bump	Injection site reaction	Injection site swelling

Verbatim Term	Original Preferred Term	Recoded Preferred Term
injection site reaction - red swollen two white bumps	Injection site reaction	Injection site erythema
injection site reaction - red swollen two white bumps	Injection site reaction	Injection site swelling
injection site reaction - red with white welt	Injection site reaction	Injection site erythema
injection site reaction - small lump	Injection site mass	Injection site swelling
injection site reaction - small, raised lump	Injection site mass	Injection site swelling
injection site reaction - small red bump	Injection site reaction	Injection site erythema
injection site reaction - small red bump	Injection site reaction	Injection site swelling
injection site reaction - small red lump	Injection site mass	Injection site swelling
injection site reaction - small red patch raised	Injection site reaction	Injection site erythema
injection site reaction - small red patch raised	Injection site reaction	Injection site swelling
injection site reaction – small, raised lump	Injection site mass	Injection site swelling
injection site reaction - two raised lumps	Injection site mass	Injection site swelling
injection site reaction - two red lumps	Injection site reaction	Injection site erythema
injection site reaction - two red lumps	Injection site reaction	Injection site swelling
injection site reaction - two small lumps	Injection site mass	Injection site swelling
injection site reaction - two small, raised areas	Injection site reaction	Injection site erythema
injection site reaction - two small, raised areas	Injection site reaction	Injection site swelling
injection site reaction - two small, raised lumps	Injection site mass	Injection site swelling
injection site reaction - very small red lump	Injection site reaction	Injection site erythema
injection site reaction - very small red lump	Injection site reaction	Injection site swelling
injection site reaction blotch red	Injection site reaction	Injection site erythema
injection site reaction bump 1/4" red	Injection site reaction	Injection site erythema
injection site reaction bump 1/4" red	Injection site reaction	Injection site swelling
injection site reaction pink bump	Injection site reaction	Injection site erythema
injection site reaction pink bump	Injection site reaction	Injection site swelling
injection site reaction raised red mark	Injection site reaction	Injection site erythema
injection site reaction raised red mark	Injection site reaction	Injection site swelling
injection site reaction red blotch	Injection site reaction	Injection site erythema
injection site reaction red blotches	Injection site reaction	Injection site erythema
injection site reaction red bump ~1 inch	Injection site reaction	Injection site erythema
injection site reaction red bump ~1 inch	Injection site reaction	Injection site swelling
injection site reaction red lump	Injection site reaction	Injection site erythema
injection site reaction red lump	Injection site reaction	Injection site swelling
injection site reaction small lump	Injection site mass	Injection site swelling
injection site reaction small, raised lump	Injection site mass	Injection site swelling
injection site reaction splotch red	Injection site reaction	Injection site erythema
injection site reaction- little lump raised	Injection site mass	Injection site swelling
injection site reaction- small red lump	Injection site reaction	Injection site erythema
injection site reaction- small red lump	Injection site reaction	Injection site swelling
injection site reaction- two lumps	Injection site mass	Injection site swelling
injection site reaction. raised lumps	Injection site mass	Injection site swelling
injection site small red bump	Injection site reaction	Injection site erythema
injection site small red bump	Injection site reaction	Injection site swelling
injection site reaction red bump	Injection site reaction	Injection site erythema
injection site reaction red bump	Injection site reaction	Injection site swelling
insect sting on right leg	Arthropod sting	Arthropod bite

Verbatim Term	Original Preferred Term	Recoded Preferred Term
intestinal inflammation	Gastrointestinal inflammation	Gastroenteritis
large red lump around injection site	Injection site reaction	Injection site erythema
large red lump around injection site	Injection site reaction	Injection site mass
large splotchy red patch at injection site	Injection site reaction	Injection site erythema
left ear discharge	Otorrhea	Otitis
left ear drainage	Otorrhea	Otitis
left ear infection	Ear infection	Otitis
left leg itches, red dot about 0,5cm diameter	Injection site reaction	Pruritus
low red rash at injection site	Injection site reaction	Injection site erythema
lower body aches	Pain	Pain in extremity
lump looks like mosquito bite at injection site	Injection site mass	Injection site swelling
migraine	Migraine	Headache
otitis	Ear infection	Otitis
pruritus	Injection site pruritus	Pruritus
purulent discharge from left ear	Otorrhea	Otitis
raised injection site	Injection site reaction	Injection site swelling
raised puncture at injection site	Injection site reaction	Injection site swelling
raised temperature	Body temperature increased	Pyrexia
raised temperature of 37.9	Body temperature increased	Pyrexia
rash	Injection site rash	Rash
red bump at injection site	Injection site reaction	Injection site erythema
red bump at injection site	Injection site reaction	Injection site swelling
red bumps at injection site	Injection site reaction	Injection site erythema
red bumps at injection site	Injection site reaction	Injection site swelling
red lump around injection site	Injection site reaction	Injection site erythema
red lump around injection site	Injection site reaction	Injection site swelling
red lump at injection site	Injection site reaction	Injection site erythema
red lump at injection site	Injection site reaction	Injection site swelling
right ear drainage	Otorrhea	Otitis
right ear infection	Ear infection	Otitis
right ear wax build-up due to infection	Ear infection	Otitis
runny nose	Rhinorrhea	Rhinitis
slight redness and puffy around injection site	Injection site reaction	Injection site erythema
slight redness and puffy around injection site	Injection site reaction	Injection site swelling
slightly red puncture at injection site	Injection site reaction	Injection site erythema
small bump and little bleed at injection site	Injection site reaction	Injection site hemorrhage
small bump and little bleed at injection site	Injection site reaction	Injection site swelling
small lump at injection site	Injection site mass	Injection site swelling
small red bump at injection site	Injection site reaction	Injection site erythema
small red bump at injection site	Injection site reaction	Injection site swelling
temperature raised	Body temperature increased	Pyrexia
white circle at injection site	Injection site reaction	Injection site discoloration

Source: adae.xpt; Software: Python
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Information pertaining to the mechanism of action is summarized in Sections 5 and 13. Refer to those sections for details.

19. Other Drug Development Considerations: Additional Information and Assessment

19.1. Division of Clinical Outcome Assessment (DCOA) Review

The Applicant utilized the following COAs in the pivotal clinical trial (Study 111-301; IND 111299)[2] as exploratory endpoints (i.e., efficacy endpoints that were not multiplicity controlled) to assess the HRQoL in subjects 5 to 18 years with ACH:

- Pediatric Quality of Life Inventory (PedsQL 4.0)
- Quality of Life in Short Stature Youth (QoLISSY®)
- Pediatric Functional Independence Measure (WeeFIM®-II)

The Applicant has not proposed labeling claims for any of the endpoints derived from these instruments.

Pediatric Quality of Life Inventory

The PedsQL is a 23-item instrument designed to assess generic health-related symptoms and impacts in children, adolescents, and young adults. There are self-report and caregiver-reported versions:

- PedsQL 4.0 Child Self-Report: There are 2 versions (ages 8 to 12 years version and ages 13 to 18 years version).
- PedsQL 4.0 - Parent Report: There are 3 versions (ages 5 to 7 years version, ages 8 to 12 years version, and ages 13 to 18 years).

Each version consists of 4 domains: Physical, Emotional, Social, and School functioning.

Each item is assessed on either a 3-point verbal rating scale (0 = Not at all; 2 = Sometimes; 4 = A lot) or 5-point verbal rating scale (0 = Never; 1 = Almost never; 2 = Sometimes; 3 = Often; 4 = Almost always). The recall period is the previous month. In Study 111-301, the PedsQL was administered at screening, Week 26, and Week 52.

The PedsQL generates domain scores (mean score = sum of items scores divided by number of items answered). Items are reverse scored and linearly transformed to a 0 to 100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. If at least 50% of items are completed within a scale, then the mean score is calculated for each domain using the transformed values.

In addition to domain scores, the PedsQL generates 3 summary scores:

- Psychosocial Health Summary Score (Sum of item scores/Number of items answered on Emotional, Social and School scales);

[2] Study 111-301: A phase 3 placebo controlled, randomized, double-blind multicenter clinical trial of BMN-111 of 52 weeks duration in children ages 5-18 years.

- Physical Health Summary Score (Sum of item scores/Number of items answered on Physical scale);
- Total Score (Mean Score, i.e., Sum of all items/Number of items answered on all scales)

Quality of Life in Short Stature Youth

The QoLISSY is a 51-item instrument (3 core domains with 22 items plus 3 mediator domains with 29 items) designed to assess symptoms and impacts in short statured youth. There are self-report and parent versions:

- Self-report: There is a version for subjects (≥8 years) that was used in Study 111-301 the self-report version was administered in participants ≥12 years
- Parent-report: There is a version for subjects (≥8 years) and a parent-report version for subjects 4 to 18 years that was used in Study 111-301.

Each version consists of 3 core domains: Physical, Social, and Emotional. There are 3 mediator domains: Coping, Beliefs, and Treatment. The parent's version contains 2 supplementary domains: Future and Effects on parents. Each item is rated on a 5-point verbal rating scale ranging from 1 ("not at all/never") to 5 ("extremely/always"). The recall period is the previous week. In Study 111-301, the QoLISSY was administered at screening, Week 26, and Week 52.

The QoLISSY generates only a total score, which is calculated by summing up the physical, social, and emotional domains. Raw scores are transformed into 0 to 100 scores with higher values representing higher HRQoL.

Pediatric Functional Independence Measure-II

The WeeFIM®-II is an 18-item performance outcome instrument designed to assess the functional performance in children (6 months to 18 years) and adults (>18 years) with acquired or congenital disabilities by measuring a child's need for assistance and the severity of disability. Three domains are assessed by interviewing or by observing a child's performance of a task: Self-care (eating, grooming, bathing, dressing (upper/lower body), toileting, bladder/bowel management); Mobility (bed/chair/wheelchair, toilet, tub/shower, stairs); and Cognition (comprehension, expression, social interaction, problem solving, memory). Each item is rated on a 7-point verbal rating scale, ranging from 1 ("total assistance") to 7 ("complete independence"). The recall period is not specified. In Study 111-301, the QoLISSY was administered at screening, Week 26, and Week 52.

The WeeFIM®-II generates domain and total scores. The score ranges for each domain and total score are:

- Self-care Score (min score =8, max score =56)
- Mobility Score (min score =5, max score =35)
- Cognition Score (min score =5, max score =35)
- Total score (min =18, max =126)

If individual items (questions) within a domain are missing, the item result is imputed to 1, per guidance in The WeeFIM Clinical Guide v 6.49.

DCOA Conclusion

This review concludes that there is insufficient information to comment on the adequacy of the selected COAs in the absence of clear COA research objectives and endpoint definitions.

Failure to understand the patient experience and decide on the concept(s) of interest most likely to be positively impacted by the treatment increases the chance that a selected COA might not measure important aspects of how the patients feel and/or function in the context of use.

Further, it does not appear that the selected instruments were adequately cognitively tested in the target patient population and population of caregivers. Therefore, the understanding, relevance and comprehensiveness of the measures in the target population is unclear.

Due to the matters described above and the COA results, which did not show a treatment effect, it is difficult to draw conclusions based on the endpoints that were derived from the above instruments (i.e., PedsQL 4.0, QoLISSY®, and WeeFIM®-II). It is also not possible to know whether and to what degree the absence of clear measurement strategy, informed by rigorously collected patient and caregiver input, contributed to the lack of treatment effect on these exploratory COA endpoints.

Recommendations for Future Studies

In planning for future clinical trials in this indication, we recommend that sponsors/applicants specify and define concepts (e.g., signs, symptoms, impacts) that are relevant and important to patients in the target population and that are likely to demonstrate meaningful and interpretable changes in planned clinical trial(s). This should be guided by input from patients who are representative of the target population and other stakeholders (e.g., expert clinicians). Refer to the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients*. Once concepts have been defined, we recommend selecting and prioritizing fit-for-purpose COAs and related endpoints to assess the targeted concepts in the endpoint hierarchy in clinical trials.

Preliminary qualitative work completed by the Applicant suggests physical functioning may be an important aspect of the patient experience. It may be helpful to explore this concept as part of the COA measurement strategy for future studies in this target population.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

20.1. Clinical Inspection Summary

20.1.1. Overall Assessment of Findings and Recommendations

The inspection for this NDA consisted of 4 domestic sites representing 10 clinical study sites in addition to the Applicant.

In general, based on the inspections of the 4 clinical sites and the Applicant, the inspectional findings support validity of data as reported by the Applicant under this NDA.

20.1.2. Background

BioMarin Pharmaceutical Inc. (BioMarin) submitted NDA 214938 for vosoritide (BMN-111; modified recombinant human C-type natriuretic peptide), lyophilized powder for solution for injection, for the treatment of achondroplasia in patients (b) (4) whose epiphyses are not closed. The recommended dose of vosoritide is (b) (4) once daily by subcutaneous injection.

The application was conditionally designated as a Rare Pediatric Disease Product Application on May 26, 2020.

Inspections were requested for the following 3 studies:

(1) **Study 111-202** A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN-111 in Children with Achondroplasia

This was a pediatric, phase 2, open-label dose-escalation study to assess the safety and tolerability of daily BMN-111 (vosoritide) administered to subjects with a clinical diagnosis of ACH. Subjects who were ages 5 to 14 years inclusive with documented ACH confirmed by genetic testing, had at least a 6-month period of pretreatment growth assessment in Study 111-901 (an observational run-in study in pediatric subjects with ACH) immediately before study entry, and met the study eligibility criteria were selected to participate in this study.

In the original protocol, BMN-111 was to be administered SC daily in one of the following dosing regimens:

- Cohort 1: daily morning dose 2.5 μg/kg
- Cohort 2: daily morning dose 7.5 μg/kg
- Cohort 3: daily morning dose 15.0 μg/kg

Amendment 2 added a Cohort 4 arm.

- Cohort 4: daily morning dose 30.0 μg/kg

Amendment 2 also added a Cohort 5 arm with daily doses of 60.0 μg/kg BMN-111. However, Cohort 5 was removed in Amendment 4 because the higher 60.0 μg/kg dose was not expected to demonstrate an improved benefit/risk profile.

Efficacy was assessed by change from baseline in height growth velocity (annualized to cm/year), growth parameters, and in body proportions. These changes were assessed by anthropometric measurements and measurement ratios. Anthropometric measurements included, but were not limited to, standing height, sitting height, weight, head circumference, upper and lower arm and leg, hand and foot.

The study began (b) (6) and completed October 2, 2017. The study was conducted by 9 principal investigators at 9 study centers in 4 countries (United States, Australia, United Kingdom, and France).

There were 43 subjects screened and 35 subjects were enrolled as follows: 8 subjects each for Cohorts 1 and 2, 10 subjects for Cohort 3, and 9 subjects for Cohort 4. One subject discontinued from Cohort 1 and 1 subject discontinued from Cohort 2 during the initial 6-month phase. One subject discontinued from Cohort 1, and 1 subject discontinued from Cohort 2 during the extension period. One subject discontinued from Cohort 4 during the initial 6-month phase, bringing to 30 the total number of subjects who completed the 2-year study.

The study included an optional, open-label extension phase of approximately 18 months that commenced at the end of the initial 6-month period of the study, making a total study duration of 24 months. Subjects who discontinued from treatment or did not continue into the long-term follow-up study had a 1-month safety follow-up visit. In the open-label extension, the protocol allowed for dose escalation of the low dose cohorts based on the prespecified criteria. The target dose of the open-label extension phase was to be the dose from the initial 6-month period that was demonstrated to be well tolerated and led to improvements in efficacy.

(2) **Study 111-205** A Phase 2, Open-Label, Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of BMN-111 in Children with Achondroplasia

This is an ongoing multicenter, open-label, phase 2 extension study to evaluate the long-term safety and efficacy of BMN-111 treatment in children with ACH who had completed Study 111-202. Nine sites worldwide are participating in this study. The data cut-off date is November 20, 2019.

Subjects were sequentially enrolled into 4 cohorts to receive the daily dosing regimens:

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

Eligible subjects who then completed 2 years of BMN-111 treatment in Study 111-202 were enrolled in the extension study (Study 111-205) to continue receiving the same stable dose of BMN-111 received upon completion of Study 111-202 (15 or 30 μg/kg daily). The baseline visit for Study 111-205 was the same day as the final treatment visit and study completion visit (Month 24) for Study 111-202, during which subject consent was obtained. Ongoing AEs from Study 111-202 are collected in the Study 111-205 medical history. In the event of a delay in starting Study 111-205, AEs were also reported in the medical history. This information was included in the overall reporting of AEs.

Subjects are to be followed either until they reached NFAH or for 5 years if NFAH occurred prior to the end of the 5-year period.

Efficacy will be assessed by change from baseline in height growth velocity (annualized to cm/year), growth parameters, and in body proportions. These changes will be assessed by anthropometric measurements and measurement ratios. All efficacy endpoints are assessed on

the full analysis set (FAS) population by the cohort into which they were enrolled into in Study 111- 202 and overall.

First day of enrollment was (b) (6), and the last dose was given October 2, 2017.

A total of 30 of the 35 subjects from Study 111-202 enrolled into Study 111-205: 6 subjects in Cohort 1, 6 subjects in Cohort 2, 10 subjects in Cohort 3 and 8 subjects in Cohort 4. To date, 26 subjects are still receiving BMN-111 treatment; 18 subjects are receiving 15 μg/kg, and 8 subjects are receiving 30 μg/kg. Of the 4 subjects who discontinued treatment, 2 subjects discontinued from Cohort 1 (on Day 1657 and Day 1471 to have limb lengthening surgery), and 2 subjects discontinued from Cohort 3 (on Day 1874 due to investigator's decision based on issues with subject compliance and an AE of transaminases increased on Day 1026). To date, no subject has reached NFAH.

(3) **Study 111-301** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN-111 in Children with Achondroplasia

This was a phase 3 randomized, placebo-controlled, double-blind multicenter study to evaluate the effect of vosoritide on growth in children with ACH. Eligible subjects were between ages 5 to <18 years with documented ACH confirmed by genetic testing and had been in Study 111-901 for at least 6 months.

Subjects were centrally randomized 1:1 to vosoritide 15 μg/kg or placebo daily. In the original protocol, randomization was stratified by sex and age (<11, ≥11 years). The protocol was later amended to introduce stratification by sex and Tanner stage of pubertal development (Stage I or Stage > I). Two subjects were randomized in the study according to the strata in the original protocol.

The primary efficacy endpoint was change from baseline in AGV at Week 52.

A total of 124 subjects were screened, of which 121 subjects were enrolled into the study and 61 subjects were randomized. After 52 weeks of treatment, all 61 subjects in the placebo group completed the study and in the vosoritide group, 58 subjects completed; 2 subjects withdrew from the study.

The study was conducted at 24 study centers in 7 countries. The study began (b) (6) and completed October 30, 2019. All 119 subjects who completed the study enrolled in an open-label long-term extension study (BMN-111-302) for continued follow-up.

20.1.3. Results (by Site)

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ethics committee correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs, and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the Applicant's data line listings.

(1) **Carlos Bacino, M.D.**
Texas Children's Hospital
Baylor College of Medicine

6701 Fannin Street, Suite 1560
Houston, TX 77030-2614

Site: 0005

Study: 111-202

Study: 111-205

Study: 111-301

Dates of inspection: January 12 to 19, 2021

For Study 111-202, there were 7 subjects screened and 4 subjects enrolled into the study; 3 subjects completed the study. There were 7 subject records reviewed.

For Study 111-205, there were 3 subjects screened and 3 subjects enrolled into the study; 3 subjects ongoing in the study. There were 3 subject records reviewed.

For Study 111-301, there were 8 subjects screened and 8 subjects enrolled into the study; 8 subjects completed the study. There were 8 subject records reviewed.

The institutional review board (IRB) of record was initially the Baylor College of Medicine IRB. The Applicant chose (b) (4) for the rollover and extension studies. Both IRBs approved studies annually for continuation.

Dr. Bacino is Vice-President of Clinical Affairs and the Director of Pediatrics Genetics Services at Baylor College of Medicine.

Source records were organized, legible, and available. There was evidence of adequate oversight of study personnel by Dr. Bacino.

For all 3 studies, source records were compared to the Applicant data line listings. There were no discrepancies. All deviations were reported by the Applicant's monitors and addressed properly. There was no under-reporting of adverse events. There were no SAEs reported for any of the studies. The primary efficacy endpoints were verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

(2) **Paul Harmatz, M.D.**
UCSF Benioff Children's Hospital
747 52nd Street
Oakland, CA 94609-1809

Site: 0018

Study: 111-202

Study: 111-205

Study: 111-301

Dates of inspection: October 28 – November 5, 2020

For Study 111-202, there were 7 subjects screened and 4 subjects enrolled into the study; 3 subjects completed the study (1 subject transferred to another site). There were 7 subject records reviewed.

For Study 111-205, there were 3 subjects screened and 3 subjects enrolled into the study; 3 subjects ongoing in the study. There were 3 subject records reviewed.

For Study 111-301, there were 6 subjects screened and 5 subjects enrolled into the study; 5 subjects completed the study (1 subject transferred to another site). There were 6 subject records reviewed.

The IRB of record was UCSF Benioff Children's Hospital Oakland IRB.

Dr. Harmatz has been in his current position for over 15 years. Most subjects were recruited from other clinics or providers who specialized in genetic diseases. There were no promotional materials for the 3 studies.

The source documents were organized in individual binders for each subject. Documents appeared legible and organized. The study coordinator took the information from the source documents and manually entered the source data into the electronic data capture (EDC) system. Source records were compared to the Applicant data line listings. There were minor discrepancies:

- Study 111-301
  - Subject (b) (6) transferred to another site (b) (6), but there was no information in the site's database (EDC) to verify against the source.
  - Subjec (b) (6) source measurements for Day 1 (first day of receiving investigational product), not the screening visit, matched the baseline Applicant line listings.
  - Subject (b) (6) source measurements for Day 1 (first day of receiving investigational product), not the screening visit, matched the baseline Applicant line listings.
- Study 111-205
  - Subject (b) (6) screening measurements (baseline measurements) were used from Study 111-202 instead of the final treatment visit and study completion visit (Month 24) for Study 111-202.
  - Subject (b) (6) reported abdominal pain (b) (6), and mild, intermittent right wrist pain that were not captured as adverse events.
  - Subject (b) (6) screening measurements (baseline measurements) were used from Study 111-202 instead of the final treatment visit and study completion visit (Month 24) for Study 111-202.

All other adverse events were captured. The primary efficacy endpoints were verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

(3) **Julie Hoover-Fong, M.D.**
600 N. Wolfe Street
Blalock 1008
Baltimore, MD 21287-0005

Site: 0151

Study: 111-202

Study: 111-205

Study: 111-301

Dates of inspection: November 3 to 6, 2020

For Study 111-202, there were 5 subjects screened and 5 subjects enrolled into the study; 5 subjects completed the study. There were 5 subject records reviewed.

For Study 111-205, there were 5 subjects screened and 5 subjects enrolled into the study; 2 subjects ongoing (1 subject had COVID-19 travel restriction from Japan, 1 withdrew for lack of expected result, 1 lived in an apartment where several people died from COVID-19 and the research nurse did not want to visit that subject). There were 5 subject records reviewed.

For Study 111-301, there were 8 subjects screened and 8 subjects enrolled into the study; 8 subjects completed the study. There were 8 subject records reviewed.

The IRB of record was John Hopkins Medicine Institutional Review Board. For Study 111- 301, 2 subjects (b) (6) signed an IRB unapproved informed consent form during their screening visits. These subjects were reconsented with an approved consent form during their next visits 2 to 3 months later.

Dr. Hoover-Fong devotes 40% of her time to clinical trial research. Subjects were recruited by word of mouth, general newspaper, and from clinicaltrials.gov. Subjects were visited on-site and through telephone assessments (due to COVID-19 pandemic).

During the trials, there was significant noncompliance discovered by the monitor during interim monitoring visits and by the Applicant during good clinical practice (GCP) auditing visits, such as not signing and dating documents and not putting all source information in the EDC. Corrective and preventive actions (CAPAs) were implemented at the site as soon as the noncompliance was identified, including retraining. Site adherence to the CAPAs was followed and confirmed by the monitor and Applicant.

At the inspection, subject files were organized in individual binders. Hard copy records were considered source documents. Efficacy endpoints for growth measurements were documented on worksheets. Source records appeared attributable, legible, contemporaneous, original, and authentic. Data were transferred to electronic case report forms (eCRF) by study staff.

Source records were compared to the Applicant data line listings. For Study 111-301, Subject (b) (6) had 2 AEs recorded in source records and not in the Applicant data line listings: (1) pain and numbness on the right shin/calf area due to a fall on wet bathroom floor on (b) (6), and (2) fever to 101.9°F (b) (6).

There were no reported SAEs. The primary efficacy endpoints were verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

(4) **William R. Wilcox, M.D., PhD**
Emory University, Department of Human Genetics
Whitehead Biomedical Research Building
615 Michael Street, Suite 301
Atlanta, GA 30322-1047

Site: 0184

Study: 111-301

Dates of inspection: January 19 to 25, 2021

For Study 111-301, there were 11 subjects screened and 9 subjects enrolled into the study; 9 subjects completed the study. There were 9 subject records reviewed.

The IRB of record was Emory University IRB.

Dr. Wilcox has been doing clinical research for over 20 years and is a principal investigator working for the Emory University School of Medicine. Most subjects were recruited from his patient database, and some were referrals from other physicians.

Subject study binders were organized, and the source records appeared to be attributable, legible, contemporaneous, original, and authentic. Source information was recorded onto paper study worksheets and transcribed into the EDC system by study coordinators. It was noted during the inspection that the laboratory results on various visits pertaining to salivary cortisol, serum prolactin, and FSH/LH levels were not in the respective subject's binder during the review of 7 of the 9 subject source records. Prior to the close-out of the inspection, on January 25, 2021, the missing documents were provided to the FDA inspector for review. Dr. Wilcox and staff were unable to determine the reason why these reports were not included in the subjects' binders.

Source records (including the previously missing laboratory reports) were compared to the Applicant data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

(5) **BioMarin Pharmaceutical Inc./Applicant**
770 Lindaro Ave

San Rafael, CA 94901-3991

**BioMarin Pharmaceutical Inc. is headquartered in San Rafael, CA but uses its Novato location as its corporate mailing address (105 Digital Drive, Novato, CA 94949).*

Dates of inspection: October 20 – November 06, 2020

Most of the inspection was conducted remotely with minimal onsite inspection at the BioMarin Pharmaceutical Inc. site due to the COVID-19 pandemic. Documents were electronically copied for review with daily contact via phone, zoom, or WebEx to clarify information and give updates on the progress of the inspection.

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the Applicant/monitor/contract research organization, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

BioMarin Pharmaceutical Inc. (BioMarin) is a manufacturer and distributor of biological and small molecule orphan drug products for the treatment of rare and ultrarare genetic diseases. Pharmacovigilance operations are performed at the San Rafael site and a site in Brisbane, CA (2000 Sierra Point Parkway, 11th & 12 Floors, Brisbane, CA 94005). The firm has several facilities worldwide. Many of the international locations involve commercial operations (i.e., sales). BioMarin Pharmaceutical, Inc. has approximately 3100 employees worldwide and 872 of those employees are located at the San Rafael site.

BioMarin and/or their monitors found significant noncompliance for four clinical sites. The four clinical sites included: 1) Dr. Ginebrenda (Site 1653) for Protocols 111-301 and 111-901; 2) Dr. Julie Hoover-Fong (Site #0151) for Protocols 111-202, 111-205, 111-301, and 111-901; 3) Dr. Luna and Dr. Leiva (Site 1651) for Protocol 111-301; and 4) Dr. Ullot (Site 1618) for Protocol 111-301. BioMarin addressed the significant noncompliance (with CAPAs and additional trainings) as soon as they became aware of the noncompliance. No sites were terminated for noncompliance. Monitoring and oversight by BioMarin appeared to be adequate.

In addition to inspecting Studies 111-202, 111-205 and 111-301, Protocol 111-901 was also inspected. This study is a noninterventional study where anthropometric measurements are being collected from the participants. No study medication was administered to any of the subjects. Protocol 111-901 was initiated on April 20, 2012. As of October 26, 2020, there are 361 subjects enrolled in the study and it is ongoing.

The Office of Scientific Investigations (OSI) received a complaint regarding the standard data tabulation model (SDTM) datasets for the disease registry Study 111-901 and validation failures that had been noted. The data management and validation process for Protocol 111-901 was the same as Protocols 111-202, 111-205, and 111-301, except the data for Protocol 111-901 were not sent to the data monitoring committee since it is an observational clinical study. (b) (4)

BioMarin's SDTM mapping specification documents were included in the NDA submission package for each study. No mapping or programming errors were noted during the inspection. There were also no issues noted with the analysis outputs. Database lock is anticipated to be February 2021.

For Protocol 111-202, the database was unlocked after it was locked. The lock, unlock, and relock processes were conducted in accordance with BioMarin's written procedures. The rationale for unlocking the database included: a) medical history eCRF needed to be coded with Medical Dictionary for Regulatory Activities (MedDRA); and b) the X-ray data from the external vendor, Bioclinica, contained uncalibrated units in pixels.

There were several discussion items:

(1) It was very difficult for the FDA inspector to initially announce the inspection. The contact, Hanna Cho, Director, Regulatory Affairs, at (b) (6) did not have her voicemail set up. The alternate contact number in the application (b) (6) was no longer in service. The customer service number (866-274-0606) that was listed on the BioMarin Pharmaceutical website (www.biomarin.com) was for a distribution center with no other contact numbers for the firm. Finally, an email address for the CEO Mr. Jean-Jacques Bienaimé was found in a past FDA report (JBienaime@bmrn.com) and contact was established.

OSI Reviewer Comment: *During the inspection, BioMarin staff stated that their phones operate through their computer system, and it was out the day that the FDA inspector called. It was stressed that FDA be given accurate phone numbers and that FDA would show up*

unannounced to conduct the next inspection if the firm could not be reached. It was also stressed that an accurate phone number needed to be listed on their website in the event a patient, consumer, or health care professional needed to reach them to report a post marketing adverse drug experience (PADE)

(2) Protocol 111-301 was not registered on ClinicalTrials.gov within 21 days of the first study subject enrollment. Protocol 111-301 was initiated on (b) (6) (i.e., the first study subject's parent(s), Subject (b) (6) signed the consent form). Protocol 111-301 was not submitted to ClinicalTrials.gov until May 23, 2017, which was 6 months after the first study subject signed the ICF on (b) (6)

OSI Reviewer Comment: *During the inspection, it was explained by BioMarin staff that an internal GCP process audit performed by BioMarin GCP auditors was conducted from January 22, 2018 through February 1, 2018. The auditors found that BioMarin was not in compliance with 42 CFR 11.24 for Protocol 111-301. Following the audit, a CAPA plan that included revised SOPs and Work Instructions were implemented by the firm.*

(3) Protocol amendment training documentation was not adequate for Protocols 111-202, 111-205, 111-301, and 111-901. For some sites, there was no documented training, for other sites the documentation had been lost, and for some sites the documentation was inconsistent and contradictory. For example, for Dr. Julie Hoover-Fong's site (Protocol 111-202), there was a note-to-file dated May 4, 2018, that the training document for Amendment 2 was lost, but training had occurred for all study staff. For Dr. Bacino's site (Protocol 111-202), there was no Protocol Amendment training documentation for Amendments 2 and 3. For Dr. Bacino's site and Dr. Hoover-Fong's site (Protocol 111-205), there was no Protocol Amendment training documentation for Amendments 2, 3, or 4.

OSI Reviewer Comment: *BioMarin staff acknowledged the lack of documentation of training and will address this with the contract research organization hired to monitor all future studies.*

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Data from this Applicant appear acceptable.

21. Labeling Summary of Considerations and Key Additional Information

Agreement on the final labeling language has not been reached at the time this review was completed. Refer to the complete labeling in the approval letter. The following sections will be addressed:

- INDICATION AND USAGE:
  - The review team recommends restriction of indication to the improvement in linear growth in pediatric patients with achondroplasia, instead of Applicant's proposed indication of treatment of achondroplasia. The improvement in other signs or symptoms of the disease were not evaluated or demonstrated in the clinical program.
  - This section should include statement that the drug is approved under accelerated approval based on the improvement in annualized growth velocity observed in patients treated with the drug. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial.
  - The review team recommends limitation of the proposed population to pediatric patients ages 5 and older with achondroplasia, (b) (4)

- DOSAGE AND ADMINISTRATION
  - The recommended daily dose is based on the patient's weight, as follows:

    (b) (4)

    The efficacy and safety of these doses is provided from the well-controlled trial in subjects with ACH.

  - The drug should be injected at approximately the same time each day.
  - If the dose is missed, it can be administered within 12 hours of the scheduled time for administration. Beyond 12 hours, the missed dose should be skipped, and the next daily dose administered according to the usual dosing schedule.
  - The review team recommends to not use in patients with eGFR <60 mL/min/1.73 m^2.
  - The patient's body weight and growth should be assessed every 3 to 6 months.
  - Treatment should be stopped upon confirmation of no further growth potential, indicated by closure of epiphyses.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS
  - The review team recommends inclusion of contraindication in patients with achondroplasia who have closed epiphyses.
  - The review team recommends inclusion of risk of low blood pressure to Warnings and Precautions.

- ADVERSE REACTIONS
  - The review team recommends reporting adverse reactions (ARs) in this section based on the results of the FDA analyses using the MedDRA preferred terms (PTs) and FDA MedDRA Queries (FMQs), or Grouped Queries (GQs), which were used to

improve the capture of synonymous adverse event terms and to improve overall safety signal detection.
  - The review team recommends deleting the safety results from other studies from this section (b) (4) No new safety findings were identified in these studies, (b) (4)

- USE IN SPECIFIC POPULATIONS
  - The review team has recommendations for revisions of this section to be consistent with PLLR.
  - Section 8.6 Renal Impairment is added.

  The review team recommends to include the statement that due to lack of data in patients with moderate-severe renal impairment, vosoritide is not recommended for use in patients with eGFR <60 mL/min/1.73 m^2.

- CLINICAL PHARMACOLOGY
  - The statement related to pharmacodynamic endpoints (cGMP and CXM) is removed from section 12.1 to avoid duplicate information in section 12.2.

- NONCLINICAL TOXICOLOGY
  - The review team has recommended revisions to this section.

- CLINICAL STUDIES
  - The review team recommends including the efficacy results from the adequate and well-controlled Study 111-301 only in this section.
  - The review team recommends including the observed changes in secondary endpoints of height standard deviation score (SDS) and disproportionality to make healthcare providers aware of the changes that are expected.
  - (b) (4) .

22. Postmarketing Requirements and Commitments

The review team proposed and discussed with the Applicant the following PMR:

- To Conduct an open-label, external-controlled trial in subjects with ACH ages 5 and older, 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 total exposure to vosoritide for each subject 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 and 111-301/302 and/or treatment-naïve subjects with a genetically confirmed ACH diagnosis.

23. Financial Disclosure

Table 148. Covered Clinical Studies: [111-202/205, 111-301/302, 111-206/208]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 336 (Principal and Sub Investigators)		
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: 0 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): 25		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

24. References

Chemical Hazards Emergency Medical Management (CHEMM), 2010, Pediatric Basic and Advanced Life Support, U.S Department of Health and Human Services, accessed October 19, 2021, https://chemm.hhs.gov/pals.htm.

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Pannier, S, E Mugniery, A Jonquoy, C Benoist-Lasselin, T Odent, JP Jais, A Munnich, and L Legeai-Mallet, 2010, Delayed bone age due to a dual effect of FGFR3 mutation in Achondroplasia, Bone, 47(5):905-915.

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25. Review Team

Table 149. Reviewers of Integrated Assessment

Role	Names
Regulatory Project Manager	Linda Galgay
Nonclinical Reviewer	Daniel Minck
Nonclinical Team Leader	Federica Basso
DPT-CHEN Deputy Director	C. Lee Elmore
Office of Clinical Pharmacology Reviewer	Peng Zou
Office of Clinical Pharmacology Team Leaders	Justin Earp Jaya Vaidyanathan
Clinical Reviewer	Geanina Roman-Popoveniuc
Clinical Team Leader	Marina Zemskova
Statistical Reviewer	Jiwei He
Statistical Team Leader	Feng Li
Cross-Disciplinary Team Leader	Marina Zemskova
Division Director (OCP)	Shirley Seo
Division Director, Deputy (clinical)	Naomi Lowy
Deputy Office Director	Lisa Yanoff

OCP = Office of Clinical Pharmacology
OB = Office of Biostatistics

Table 150. Additional Reviewers of Application

Office or Discipline	Names
OPQ	Muthukumar Ramaswamy
OPDP	Charuni Shah
OSI	Cynthia Kleppinger
OSE/DEPI	Christian Hampp, Youjin Wang
OSE/DMEPA	Jason Flint, Ebony Whaley, Melina Fanari, Sevan Kolejian
OSE/DRISK	Till Olickal, Naomi Boston
OSE/DPV	Amy Chen, Ali Niak, Christian Cao
DMPP	Lonice Carter, Marcia Williams
DPMH	Wenjie Sun, Miriam Dinatale, Ethan Hausman, Shetarra Walket

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
DRISK = Division of Risk Management
DPV = Division of Pharmacovigilance
DMPP = Division of Medical Policy Programs
DPMH = Division of Pediatric and Maternal Health

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Deputy Director	Lisa B. Yanoff, MD	OND/OCHEN	☒ Authored: Sections 1 ☒ Approved: All Sections
Signatory Authority	**Signature:** {See appended electronic signature page}		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Naomi Lowy, MD	OND/OCHEN/ DGE	☒ Authored: Section 2.2 ☒ Approved: All Sections
Deputy Director	**Signature:** Naomi Lowy -S Digitally signed by Naomi Lowy -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Naomi Lowy -S, 0.9.2342.19200300.100.1.1=2000219474 Date: 2021.11.17 12:52:19 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Marina Zemskova, MD	OND/OCHEN/ DGE	☒ Contributed: Sections 2, 3, 6.2, 6.3, 7, 11, 21, 22 ☒ Approved: All Sections
Cross-Disciplinary Team Lead	**Signature:** Marina S. Zemskova -S Digitally signed by Marina S. Zemskova -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011510606, cn=Marina S. Zemskova -S Date: 2021.11.17 12:06:36 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Geanina Roman-Popoveniuc, MD	OND/OCHEN/ DGE	☒ Authored: Sections 3.1, 7, 17, 23 ☒ Contributed: Sections 2.1, 3.2, 6.2, 6.3, 15, 16, 21, 22
Primary Reviewer	**Signature:** Geanina Roman-popoveniuc -S Digitally signed by Geanina Roman popoveniuc S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2000984446 cn=Geanina Roman popoveniuc S Date: 2021 11 17 09 40:57 05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Geanina Roman-Popoveniuc, MD	OND/OCHEN/ DGE	☒ Authored: Sections 3.1, 7, 17, 23 ☒ Contributed: Sections 2.1, 3.2, 6.2, 6.3, 15, 16, 21, 22
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Section Approved/ Regulatory History**
Regulatory Project Mangement	Julie C. Van der Waag, MPH	OND/ORO/ DROCHEN	☒ Contributed: Section 12 ☒ Approved: Section 12
Director, Project Management Staff	**Signature:** Julie C. Van Der Waag -S		Digitally signed by Julie C. Van Der Waag -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300399850, cn=Julie C. Van Der Waag -S Date: 2021.11.17 08:36:22 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Section Authored/ Regulatory History
Regulatory Project Management	Linda V. Galgay, RN, MSN	OND/ORO/ DROCHEN	☒ Authored: Section 12
Regulatory Project Manager	**Signature:** Linda V. Galgay -S		Digitally signed by Linda V. Galgay -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000371858, cn=Linda V. Galgay -S Date: 2021.11.16 14:35:27 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Feng Li, PhD	OTS/OB/DBII	☒ Approved: Sections 6.2, 6.3, 16
Team Leader	**Signature:** Feng Li -S		Digitally signed by Feng Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Feng Li -S, 0.9.2342.19200300.100.1.1=2000332337 Date: 2021.11.16 13:45:08 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Jiwei He, PhD	OTS/OB/DBII	☒ Authored: Sections 6.2, 6.3, 16☒ Contributed: Sections 6.2, 6.3, 16
Primary Reviewer	**Signature:** Jiwei He -S		Digitally signed by Jiwei He -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiwei He -S, 0.9.2342.19200300.100.1.1=2001679955 Date: 2021.11.16 18:10:41 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/ Toxicology	C. Lee Elmore, PhD	CDER/DPTCHEN	☒ Approved: Sections 5, 5.1, 7.1, 8.3, 8.4, 13
Deputy Director	**Signature:** Calvin L. Elmore -S		Digitally signed by Calvin L. Elmore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000356615, cn=Calvin L. Elmore -S Date: 2021.11.17 08:42:41 -05'00'

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/ Toxicology	Federica Basso, PhD	CDER/DPTCHEN	☒ Approved: Sections 5, 5.1, 7.1, 8.3, 8.4, 13
Supervisor	**Signature:** Federica Basso -S Digitally signed by Federica Basso -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Federica Basso -S, 0.9.2342.19200300.100.1.1=0011076316 Date: 2021.11.16 15:32:36 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/ Toxicology	Daniel Minck, PhD	CDER/DPTCHEN	☒ Authored: Sections 7.1, 13 ☒ Contributed: Sections 5, 5.1, 8.3, 8.4
Primary Reviewer	**Signature:** Daniel R. Minck -S Digitally signed by Daniel R. Minck -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000598182, cn=Daniel R. Minck -S Date: 2021.11.17 09:03:19 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Muthukumar Ramaswamy, PhD	DNDPIII/ NDPB5	☒ Authored: Section 9 ☒ Approved: Section 9
Application Technical Lead	**Signature:** Muthukumar Ramaswamy -S Digitally signed by Muthukumar Ramaswamy -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S Date: 2021.11.16 16:31:53 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Shirley K. Seo, PhD	OTS/OCP/ DCEP	☒ Approved: Sections 5, 6.1, 8, and 14
Division Director	**Signature:** Shirley K. Seo -S Digitally signed by Shirley K. Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shirley K. Seo -S, 0.9.2342.19200300.100.1.1=1300365375 Date: 2021.11.17 09:28:03 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jayabharathi Vaidyanathan, PhD	OTS/OCP/ DCEP	☒ Contributed: Sections 5, 6.1, 8, and 14☒ Approved: Sections 5, 6.1, 8, and 14
Team Leader	**Signature:** Jayabharath Vaidyanathan -S Digitally signed by Jayabharath Vaidyanathan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300220018, cn=Jayabharath Vaidyanathan -S Date: 2021.11.17 08:55:08 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/ Pharmacometrics	Justin C. Earp, PhD	OTS/OCP/ DPM	☒ Approved: Sections 5, 6, 1, 8 and 14
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2021.11.17 11:21:00 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/ Pharmacometrics	Peng Zou, PhD	OTS/OCP/DCEP	☒ Authored: Sections 6.1, 8, and 14☒ Contributed Section 5
Primary Reviewer	**Signature:** Peng Zou -S Digitally signed by Peng Zou -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peng Zou -S, 0.9.2342.19200300.100.1.1=2000783342 Date: 2021.11.17 09:13:26 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Epidemiology	Yandong Qiang, MD, PhD, MHS, MPH	OSE/OPE/DEPII	☒ Contributed: Sections 6.2, 6.3 ☒ Approved: Sections 6.2, 6.3
Team Leader	**Signature:** Yandong Qiang -S Digitally signed by Yandong Qiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yandong Qiang -S, 0.9.2342.19200300.100.1.1=2000429213 Date: 2021.11.16 16:48:45 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Human Factors	Jason Flint, MBA, PMP	OSE/OMEPRM/ DMEPAI	☒ Contributed: Section 7.7.4
Associate Director	**Signature:** Jason A. Flint -S Digitally signed by Jason A. Flint -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jason A. Flint -S, 0.9.2342.19200300.100.1.1=2002626679 Date: 2021.11.16 16:03:56 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pediatric and Maternal Health	Miriam C. Dinatale, DO	ORPURM/ DPMH	☒ Approved: Section 8.4
Team Leader	**Signature:** DINATALE.MIRIAM.CARMELA.1026321430 Digitally signed by DINATALE.MIRIAM.CARMELA.1026321430 DN: c=US, o=U.S. Government, ou=DoD, ou=PKI, ou=USPHS, cn=DINATALE.MIRIAM.CARMELA.1026321430 Date: 2021.11.16 15:44:17 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pediatric and Maternal Health	Wenjie Sun, MD	ORPURM/ DPMH	☒ Approved: Section 8.4
Reviewer	**Signature:** Wenjie Sun -S Digitally signed by Wenjie Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wenjie Sun -S, 0.9.2342.19200300.100.1.1=2002747236 Date: 2021.11.16 15:23:46 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

MARINA ZEMSKOVA
11/18/2021 12:57:09 PM

NAOMI N LOWY
11/18/2021 01:01:18 PM

LISA B YANOFF
11/18/2021 01:12:25 PM