14 September 2023
EMA/CHMP/487942/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Voxzogo

International non-proprietary name: vosoritide

Procedure No. EMEA/H/C/005475/II/0006

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%RSD	Percent Relative Standard Deviation
°C	degrees Celsius
µg	microgram
µL	microliter
µM	micromolar
µm	micrometer
µmol	micromole
µS	microSiemens
2D	2 dimensional
4-PL	4-Parameter Logistic
A280	Ultraviolet absorbance at 280 nm
Aa	amino acid
ACH	achondroplasia
ACH HZS	achondroplasia height Z-score
AChE	acetylcholinesterase
AchNH	Achondroplasia Natural History
AD	assay diluent
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AEX	Anion Exchange Chromatography
AGES	Austrian Agency for Health and Food Safety Ltd.
AGV	annualized growth velocity
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANF	Atrial Natriuretic Factor
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
AP	anterior-posterior
API	Active Pharmaceutical Ingredient
APR	Annual Product Review
AQL	Acceptable Quality Level
Asn	Asparagine
AST	aspartate aminotransferase
AT	Austria
ATC	Anatomical Therapeutic Chemical
AU	absorbance units
AUC	area under the plasma concentration-time curve
AUC0-t	area under the plasma concentration-time curve from time 0 to the last
Avg	average
BBB	blood-brain barrier
BCC	back-calculated concentration
BEAD	Biotin Extraction Acid Dissociation
BIL	BioMarin International Ltd
BLOQ or BLQ	below limit of quantitation
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BMN	BioMarin
BMN 111	Vosoritide (active substance)
BMS	building management system
BNP	B-type/brain natriuretic peptide
BP	blood pressure
BP	British Pharmacopoeia
BPC	BioProcess Container
BPI	BioMarin Pharmaceutical Inc
bpm	beats per minute

BQL	below quantifiable limit
BR	Batch Records
BSA	Bovine Serum Albumin
BSAP	bone-specific alkaline phosphatase
BSC	BioSafety Cabinet
BSE	bovine spongiform encephalopathy
BSID-111	Bayley Scale of Infant Development
BSL	BioSafety Laboratory
BUN	blood urea nitrogen
CA	California
CAD	Charged aerosol detector
CAS	Chemical Abstracts Service
CBC	complete blood count
CBCL	Child Behavior Checklist
cc	cubic centimeter
CCA	Clean Compressed Air
CCIT	Container closure integrity testing
CCP	confirmation cut point
CD	Circular Dichroism
CDA	Clean Dry Air
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDF	cumulative distribution function
CDP	clinical development program
CE	capillary electrophoresis
CFR	Code of Federal Regulations
CFU	Colony forming units
CGE	Capillary Gel Electrophoresis
cGMP	cyclic guanosine monophosphate
cGMP	current Good Manufacturing Practice
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CI95	95% confidence interval
CIEX	Cation-exchange Liquid Chromatography
CIP	Clean In Place
CL/F	apparent clearance
cm	centimeter
CM Sepharose	carboxymethyl sepharose
cm/yr	centimeters/year
cm^2	square centimeter
cm^3	cubic centimeter
C_{max}	maximum observed plasma concentration
CMC	Chemistry, Manufacturing, and Controls
cMFG	Clinical Manufacturing
CMO	Contract Manufacturing Organization
CNP	C-type natriuretic peptide
CNS	central nervous system
CO_2	carbon dioxide
CoA	Certificate of Analysis
CoC	Certificate of Conformance
Col II	Collagen Type II
Col-X	Collagen Type X
CPA	Critical performance attribute
CPP	Critical Process Parameter
cPQ	Cleaning Qualification
CQA	Critical Quality Attributes
Cr	creatinine
CRF	case report form
CRO	contract research organization
CSR	clinical study report

CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTX-I	cross linked C-telopeptide of type I collagen
CTX-II	C-terminal telopeptide of type II collagen
CV	cardiovascular
CV	Column Volume
CV, %CV	Coefficient of Variation, Percent Coefficient of Variation
CXM	collagen X
CYPs	cytochrome P450s
Cys	Cysteine
Da	dalton
DBP	diastolic blood pressure
DCP	Data Collection Plan
Df	degrees of freedom
DF	Diafiltration
DLT	dose-limiting toxicity
DMEM	Dulbecco's Modified Eagle Medium
DN	dose normalized
DNA	deoxyribonucleic acid
DO	Dissolved Oxygen
DOE	Design-of-experiment
DRP	Data Review Pending
DXA	dual energy X ray absorptiometry
E. coli	Escherichia coli
EC_{50}	half maximal effective concentration
ECG	Electrocardiogram
ECHO	echocardiography
ECLA	electrochemiluminesence assay
EDTA	ethylenediaminetetraacetic acid
EIA	Enzyme ImmunoAssay
ELISA	enzyme-linked immunosorbent assay
EM	Environmental Monitoring
EMA	European Medicines Agency
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
EOPCs	End of production cells
EU	European Union
EVAM	Ethylene vinyl acetate mono-material
Gen (2a)	(Manufacturing process) generation (2a)
GH	growth hormone
GHD	growth hormone deficiency
GLP	Good Laboratory Practice
Gly	Glycine
GMF	Galli Manufacturing Facility
GMP	Good Manufacturing Practice
GRAS	Generally Recognized as Safe
H&E	Hematoxylin and Eosin
HA	Haemophilia A
HAE	hypersensitivity adverse event
HB-PS	HEPES-buffered physiological saline
HCl	hydrochloride, hydrochloric acid
HCPs	Host cell proteins
HDO	high definition oscillometry
HED	Human Equivalent Dose
HEK	human embryonic kidney
HEPA	High Efficiency Particulate Air
hERG	human *ether-á-go-go* related gene
HLM	human liver microsomes
HLT	High Level Term
HPA	hypothalamic pituitary adrenal
HPLC	high-performance liquid chromatography
HQC	high quality control

HR	heart rate
hr	hour
HRP	horseradish peroxidase
HRQoL	health-related quality of life
HVAC	Heating, Ventilation, and Air Conditioning
HWFI	Hot Water for Injection
IB(s)	Inclusion bodies
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICP	Inductively Coupled Plasma (Spectrometry)
ICP-MS	Inductively coupled plasma optical emission mass spectrometry
ID	Identification
ID	injected dose
IEF	Isoelectric Focusing
IFU	Instructions for use
IgG	immunoglobulin G
IgG1	immunoglobulin G subtype 1
IgM	immunoglobulin M
IHC	immunohistochemistry
IND	Investigational New Drug
INN	International Non-Proprietary Name
IP	investigational product
IP	In-Process
IPC	In-Process Control
IPTG	Isopropyl β-d-1-thiogalactopyranoside
IQ	Installation Qualification
IS	internal standard
ISE	Integrated Summary of Efficacy
ISH	in situ hybridization
ISO	International Organization for Standardization
ISR	incurred sample reanalysis
ISR	injection site reaction
ISS	idiopathic short stature
ISS	Integrated Summary of Safety
ITQoL	Infant Toddler quality of life
IU	International Units
IV	intravenous
JET	jacketed external telemetry
JP	Japanese Pharmacopoeia
JPE	Japanese Pharmaceutical Excipients
K	Potassium
Kb	Kilobases
k_{cat}	enzyme catalytic constant
kDa	kilodalton
kg	kilogram
kGy	kilo Gray
Km	Michaelis-Menten constant
KO	Knockout
L	liter
LAF	Laminar Air Flow
LAL	Limulus Amoebocyte Lysate
LC/MS	Liquid Chromatography/Mass Spectrometry
LC/MS/MS	Liquid Chromatography/Tandem Mass Spectrometry
LCA	Limit of *in vitro* cell age
LCGC	Licensed Certified Genetic Counselor
LD	lactation day
LDH	lactate dehydrogenase
LER	Low Endotoxin Recovery
LH	luteinizing hormone
LLOQ	lower limit of quantification
LOD	Limit of detection

LOESS	locally weighted scatter plot smoothing
LOQ	limit of quantitation
LQC	low quality control
LS	least square
LSLV	last subject last visit
LTS	long-term stability
LV	Latvia
M	male
m	meter
M	Molar
MA	marketing authorisation
MAA	marketing authorisation application
MAD	multiple-ascending dose
MAP	mean arterial pressure
MAPK	mitogen-activated protein kinase
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/mL	milligrams per milliliter
MHLW	Ministry of Health, Labor and Welfare
mil	a unit of length equal to one thousandth of an inch
min	minute(s)
Min	minimum
mL	milliliter
mm	millimeter
mM	millimolar
MMRM	Mixed models repeated measures
mOsm	milliosmole
MP	mid positive
MQC	mid quality control
MRD	minimum required dilution
MRI	magnetic resonance imaging
ms	Milliseconds
mS	milliSiemens
MS/MS	Tandem Mass Spectrometry
MSD	Mesoscale Discovery
MTD	maximum tolerated dose
MW	Molecular Weight
Mw	Weight-averaged molecular weight
N	Normal
N	Newtons
N/A	Not applicable
NA	not applicable
NAb	neutralizing antibody
NaCl	Sodium Chloride
NADPH	Nicotinamide adenine dinucleotide 2’-phosphate
NaOH	Sodium hydroxide
NBF	Neutral Buffered Formalin
NC	not calculated
NC	not collected
NCAs	national competent authorities
NCBI	National Center for Biotechnology Information
NCI	National Cancer Institute
Nd	Not done
ND	Not Detected
NEP	neutral endopeptidase
NF	National Formulary
NFAH	near-final adult height
ng	nanogram
nH	Hill Coefficient
NH	natural history

NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NLT	not less than
nM	nanomolar
nmol	nanomole
NMT	Not More Than
NMU	Neuromedin U
NOAEL	no observed adverse effect level
NOEL	no observable effect level
Non-Est	non-estimable
NOR	Normal Operating Range
NOS	not otherwise specified
NPR	natriuretic peptide receptor
NPR-A	natriuretic peptide receptor type A
NPR-B	natriuretic peptide receptor type B
NPR-C	natriuretic peptide receptor C
NQC	negative quality control
NR	Not Required
NSAID	non-steroidal anti-inflammatory drug
NT	Not tested
N-terminal	Amino terminal
NTx	cross linked N-telopeptide of type I collagen
NZW	New Zealand White
OC	osteocalcin
OD	optical density
OECD	Organization for Economic Co-operation and Development
OQ	Operational Qualification
P1NP	procollagen type 1 N-terminal propeptide
PAC	Pediatric Advisory Committee
PACMP	Post Approval Change Management Protocol
PAR	Proven Acceptable Range
PBS	phosphate buffered saline
PCRA	Process Characterization and Risk Assessment
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
PedsQoL	Pediatric Quality of Life Inventory
PET	positron emission tomography
PFA	paraformaldehyde
PFS	Pre-filled syringes
pg	picogram
Ph Eur	European Pharmacopoeia
pI	Isoelectric point
PIL	Patient Information Leaflet
PINP	N-terminal pro-peptide of type I procollagen
PK	pharmacokinetic(s)
PKG	cGMP-dependent tyrosine kinase / protein kinase G
PKGI	cGMP-dependent tyrosine kinase I
PKGII	cGMP-dependent tyrosine kinase II
plc	Placebo
PND	post-natal day
PP	Process Parameter
ppb	Parts Per Billion
ppm	Parts Per Million
PPG 2000	antifoamic substance
PPQ	Process Performance Qualification
PQ	process qualification
pQCT	peripheral quantitative computed tomography
PR	time from the beginning of the P-wave to the beginning of the next QRS complex
PRAC	Pharmacovigilance Risk Assessment Committee

PR-B	Progesterone
Pro	PRoline
psig	Pounds per Square Inch Gauge
PT	preferred term
PTFE	polytetrafluoroethylene
PV	Process Validation
PVDF	Polyvinylidene Difluoride
PVMP	Process Validation Master Plan
PVR	Process Validation Report
q.s	quantum satis
Q12W	once every 12 weeks
QA	Quality Assurance
QAAA	Quantitative Amino Acid Analysis
QC	quality control
QCL	Quantitative Chromogenic LAL
QoL	quality of life
QoLISSY	Quality of Life in Short Statured Youth
qPCR	Quantitative Real-Time Polymerase Chain Reaction
Q-Q	quantile-quantile
QRM	Quality Risk Management
QRS	deflections in the tracing of the electrocardiogram comprising the Q, R, and S
qRT-PCR	real-time quantitative reverse transcription polymerase chain reaction
qs	quantity sufficient
QT	A measure of the time in the tracing of the electrocardiogram between the start of
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by the Fridericia method
$_R2$	correlation coefficient
$_r2$	coefficient of determination
RABS	Restricted Access Barrier System
RAF-1	fibrosarcoma serine/threonine protein kinase
RAST	RadioAllergoSorbent Test
RBC	red blood cell
RCS	rat chondrosarcoma
RH	Relative Humidity
rhCNP	recombinant human C-type natriuretic peptide
RIA	radioimmunoassay
RIPA	radioimmunoprecipitation assay buffer
RLU	relative light unit
RMP	Risk Management Plan
RNA	ribonucleic acid
ROQ	range of quantitation
RP-HPLC	reverse phase high performance liquid chromatography
RR	respiratory rate
RR	time elapsed between 2 consecutive R waves
RT	room temperature
RTP	Rapid Transfer Ports
RT-PCR	Reverse Transcriptase- Polymerase Chain Reaction
RU	response units
RWE	real world evidence
SAD	single ascending dose
SAE	serious adverse event
SA-HRP	streptavidin-horseradish peroxidase
SAP	statistical analysis plan
SARA	Safe And Rapid Airlock
SAS	Surface Air Sampler
SAX	Strong Anion Exchange
SAX-HPLC	strong anion exchange HPLC
SBP	systolic blood pressure
SC	subcutaneous
SCFE	Slipped Capital Femoral Epiphysis
SCP	screening cut point

SCX	Strong cation exchange
SD	standard deviation
SD	Sprague Dawley
SDA	Sabouraud Dextrose Agar
SDS	standard deviation score
SDS	sodium dodecyl sulfate
SDS CGE	SDS Capillary Gel Electrophoresis
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SE	Sweden
SE	standard error
SEB	systemic error budget
SEC	Size Exclusion Chromatography
SEC-HPLC	Size Exclusion Chromatography High Performance Liquid Chromatography
SEC-MALS	Size Exclusion with Multi-Angle Light Scattering
SE-HPLC-MALS	Size Exclusion High Performance Liquid Chromatography with detection by multi-
SEM	standard error of the mean
SGA	small for gestational age
SGOT	serum glutamic oxalo-acetic transaminase
SGPT	serum glutamic pyruvate transaminase
SI	signal inhibition
SIM	Selected Ion Monitoring
SIP	Steam-In-Place
SK_{CA}/K_A	Potassium Channel
SKU	Stock keeping unit
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedure
SP Sepharose	Sulfopropyl sepharose
SPC	surrogate positive control
SPF	specific pathogen free
sPQ	Steaming Qualification
SSIP	Steam-Sterilization-In-Place
Sst3	Somatostatin
sWFI	sterile water for injection
$t_{1/2}$	half-life
t_{90}	time for activity to decrease to 90% of its initial value at 4°C
TAb	total antibody
TAF	transcription factor 12 fragment
TBD	To be determined
TBS	tris buffered saline
TCP	titer cut point
TD	thanatophoric dysplasia
TE	total error
TEa	total allowable error
TEAE	treatment-emergent adverse event
TEM	Transmission electron microscopy
TFA	Trifluoroacetic acid
TFF	Tangential flow filtration
Ti	Titanium
TIC	Total Ion Current
TK	toxicokinetic(s)
Tm	Melting Temperature
TMAE	Trimethylaminoethyl
TMAE HiCAP	Strong anion exchange chromatography
tmax	time to peak plasma concentration
TMB	tetramethylbenzidine
TPA	tripropylamine
TQC	titer quality control
TQT	thorough QT
Tracp 5b	tartrate resistant acid phosphatase
Tris	tromethamine

Tris-HCl	Tromethamine Hydrochloride
TSA	Tryptic Soy Agar
TSE	Transmissible spongiform encephalopathy
U	Units
U/mg protein	units per milligram of protein
U:L	upper to lower
UF	Ultrafiltration
UF/DF	Ultrafiltration/Diafiltration
ULOQ	upper limit of quantification
UPPP	uvulopalatopharyngoplasty
US or USA	United States
USAN	United States Adopted Name
USP	United States Pharmacopeia
UV	ultraviolet
v/v	Volume to volume
VCD	Viable Cell Density
VMP	Validation Master Plan
vos	vosoritide
VR	Validation report
Vz/F	apparent volume of distribution
w/v	weight/volume
w/w	weight/weight
WBC	white blood cell
WCB	working cell bank
WeeFIM	Functional Independence Measure for Children
WFI	water for injection
WHO	World Health Organization
WRO	written response only
WT	wild type
XAb	antibody cross-reactivity assay
XCP	cross-reactivity cut point
ZVA	Zalu valsts agentura

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioMarin International Limited submitted to the European Medicines Agency on 29 November 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of children less than 2 years of age for Voxzogo, based on final results from the category 1 study BMN 111-206 and interim results from its open-label extension study 111-208.

Trial 111-206 is a phase 2 randomized, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy of BMN 111 in infants and young children with achondroplasia.

- As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated.
- The Annex II and Package Leaflet are updated in accordance. Version 3.0 of the RMP has also been submitted.
- In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Voxzogo, was designated as an orphan medicinal product EU/3/12/1094 on 24/01/2013 in the following condition: treatment of achondroplasia.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0060/2020 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0060/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products since there is no authorised orphan medicinal product for a condition related to the proposed indication in the EU.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 April 2016	EMEA/H/SA/3263/1/2016/PA/PED/III	*Dr Elmer Schabel, Dr Kolbeinn Gudmundsson*
12 October 2017	EMEA/H/SA/3263/1/FU/1/2017/PA/PED/III	*Dr Armin Koch, Dr Jeanette McCaillon*

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

Quality:

- Active substance and finalised product specifications.
- Analytical method for a bioactivity assay.
- CMC data to support a commercial product presentation.
- Active substance and finalised product process performance qualification plans.

Non-clinical:

- Acceptability of the proposed nonclinical development program to support a MAA.

Clinical:

- Acceptability of the proposed Phase 3 study to support a MAA, in particular with regards to primary and secondary endpoints, the proposed dose, the study duration, and plans for safety monitoring.
- Acceptability of the proposed Phase 2 study to support assessment of the risk benefit of the product in the treatment of children ≥ 6 months with ACH.
- Acceptability of the proposed overall development programme.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	29 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	30 March 2023
PRAC Rapporteur Assessment Report	10 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 April 2023

Timetable	Actual dates
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	23 August 2023
PRAC Rapporteur Assessment Report	25 August 2023
PRAC members comments	29 August 2023
Updated PRAC Rapporteur Assessment Report	31 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur Assessment Report	13 September 2023
Opinion	14 September 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Voxzogo is approved for the indication

Treatment of achondroplasia in patients 2 years of age and older and whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

With this Extension of indicaton the applicant applied for the inclusion of ACH patients below the age of 2 years as following:

Voxzogo is indicated for the treatment of achondroplasia in paediatric patients whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

Epidemiology and risk factors, screening tools/prevention

Achondroplasia (ACH) is a rare genetical disorder with an incidence of 1 in 25,000 births. The disease, although being the most common form of short stature with disproportionality, has an overall incidence (according to the COMP decision) in the EU of 0.42 in 10,000 people in the European Union (EU). This was equivalent to a total of around 21,000 people in the area of the 27 EU MSs and Liechtenstein, Norway, and Iceland (based on data from the year 2013).

ACH is the most common form of short-limbed short stature and is characterized by rhizomelic shortening of the extremities, characteristic facies with frontal bossing and midface hypoplasia, increased lumbar lordosis, limitation of elbow extension, and trident hand. The vast majority of individuals with achondroplasia are diagnosed in early infancy or at birth, although prenatal recognition has become more frequent.

The disorder is caused by gain-of-function mutations in fibroblast growth factor receptor 3 (FGFR3), which is a negative regulator of longitudinal bone growth. All instances of achondroplasia arise from mutations that are autosomal dominant. These mutations are fully penetrant and show only modest variability of expression.

Biologic features, Aetiology and pathogenesis

ACH is based on mutations in the FGFR3 gene, and of these virtually almost all mutations in FGFR3 arise in the same nucleotide pair and result in the same glycine to arginine substitution (G380R) in the FGFR3 protein.

Under "normal" conditions the typical FGFR3 is silent. However, various ligands, binding to the FGFR3 results in dimerization of the receptors, transphosphorylation and trans-activation of tyrosine kinases, and propagation of an intracellular signal with an overall negative downstream signal within the growth plate of cartilaginous bones. That is, overall FGFR3 is a negative regulator of chondrocytic bone growth through shortening of the proliferative phase and accelerating terminal differentiation. Consequently, the mentioned mutations are gain-of-function mutations.

Clinical presentation, diagnosis and prognosis

Dysproportionate short stature is the main feature of the disease. Although length at birth may be normal, slow growth is evident shortly thereafter. Moderate to marked short stature is present in all affected individuals. In adult males, average height is about 130 cm with a range from around 120 to 145 cm. Similarly, in females, average height is 125 cm with a range of 115 to 137 cm.

The disease causes or is associated with orthopaedic complications with about 50% of the patients suffering from kyphosis and scoliosis, a potential for osteoarthritis and osteopenia. Development of craniocervical stenosis is also common. Based on the skeletal abnormalities, there is a high occurrence of neurological complications and symptoms with chronic back pain affecting up to 70% of the patients, and spinal stenosis (increasing with age) and its sequelae. Patients regularly suffer from obesity, including abdominal obesity. Based on the craniofacial bone abnormalities, patients also suffer from obstructive sleep apnoea, and middle ear dysfunction. Strabismus and voice abnormalities are also common.

Children with achondroplasia do not suffer from impairment of cognitive function (although there is an increased risk of hydrocephalus and its potential consequences). The children present with motor delays ans display unusual patterns of motor development.

Patients with achondroplasia suffer from impaired health-related quality of life, with decreased physical and mental health scores. Patients with achondroplasia have regularly lower levels of education and work participation.

According to a recently published meta-analytic review of natural history data published between 1970 and 2017 (Fredwal; Clinical Genetics. 2020;97:179–197), the disease includes increased mortality in adult patients (some studies even stating increased mortality in childhood) with an estimated mean disadvantage in life expectancy by 10 years, with the main causes of death being heart disease, neurological complications and accidents.

Management

Nonpharmacological treatments for ACH consist mainly of surgical interventions, including cervicomedullary decompression for foramen magnum stenosis and laminectomy surgery for spinal canal stenosis, and medical devices such as thoracolumbar braces to help ameliorate the kyphosis. Furthermore, invasive limb-lengthening procedures have also been part of treatment.

Growth hormone (GH) has been used in several different studies in subjects with ACH to improve their height. While there is some evidence that growth can be accelerated in the short-term (12-24 months) with GH, the long-term treatment benefit is minimal. GH is not approved in the EU for treating ACH.

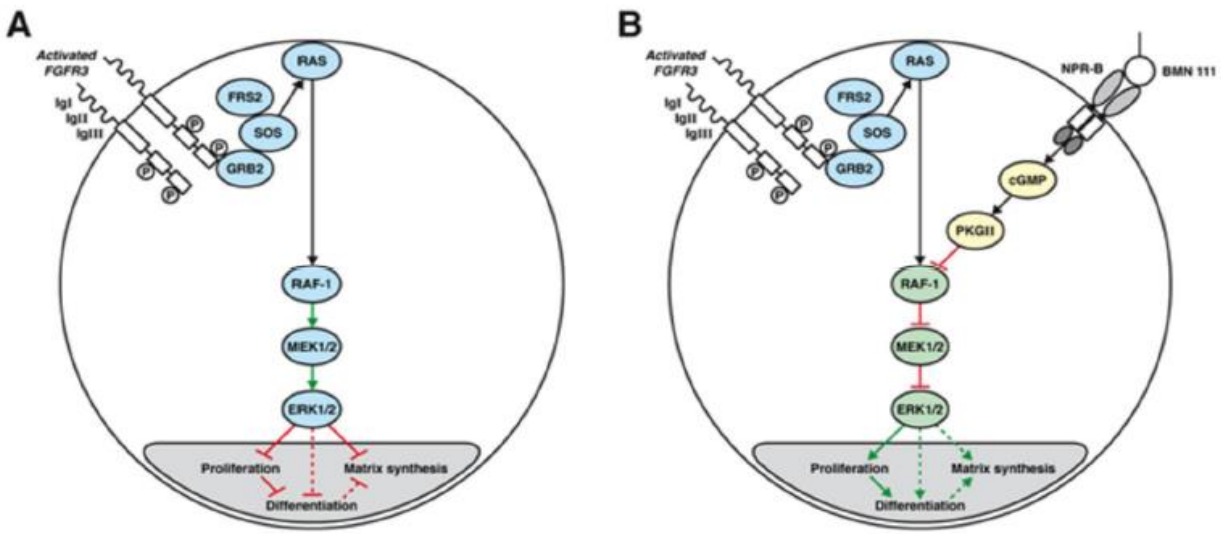
2.1.2. About the product

Vosoritide is a modified recombinant human C-type natriuretic peptide (CNP). The idea to use CNP – which activates natriuretic peptide receptor type B (NPR-B) – was based on the observation of inhibitory effects on the downstream signalling of FGFR-3 activation. CNP is thought to counteract the growth suppressive effects of FGFR-3. This hypothesis has been based on naturally occurring mutations of increased NPR-B signalling, leading to increased growth throughout the growth period, without relevant health effects and has been confirmed in respective animal models.

Vosoritide was designed to be resistant to neutral endopeptidase (NEP) degradation resulting in an extended half-life (t1/2) relative to endogenous CNP which increases exposure to the target growth plate and allows for once daily subcutaneous (SC) administration to produce its desired pharmacologic effect.

The pathophysiology and proposed mechanism of action of the compound is shown in Figure 1.

Figure 1 Fgfr3 and CNP/Vosoritide Signaling Pathways in Chondrocytes



(A) Activated Fgfr3 inhibits chondrocyte proliferation (red arrows) and differentiation and disturbs matrix synthesis. (B) Vosoritide is a 39 amino acid CNP pharmacological analog that inhibits Fgfr3 downstream signaling at the level of Raf 1 in the growth plate and induces chondrocyte proliferation and differentiation (green arrows).

The applicant has based the rationale for the development of vosoritide as a treatment option for children with ACH around promoting endochondral bone formation. Vosoritide therapy aims to restore endochondral bone formation, resulting in sustained improvements in annualized growth velocity (AGV). The severity of the height deficit in ACH associated with medical complications and morbidities

can have a substantial negative impact on day-to-day functioning, HRQoL, and longevity starting from a very early age in the ACH population relative to their average stature peers. Hence the treatment is proposed to bring about health improvements beyond the increased in stature alone.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No specific guideline exists for the clinical investigation of medicinal products in the treatment of ACH. General drug development regulatory guidance documents, including those for rare diseases, regulatory precedents in similar conditions, and advice obtained via regulatory interactions were considered while developing vosoritide for children aged <5 years of age.

Given the feasibility constraints with enrolling population shortly after birth in a rare condition, difficulty in recruiting a large number of paediatric participants shortly after birth, and in line with regulatory guidance, the vosoritide clinical development plan (CDP) includes a single adequate and well-controlled pivotal Phase 3 study (111-301). This aims at demonstrating effectiveness of vosoritide in children aged >5 years, and its long-term extension study 111-302, complemented by evidence from studies 111-206 and 111-208 in children aged <5 years.

Following approval of vosoritide in the EU, the applicant was required to submit the final results of study 111- 206 as a condition to the marketing authorization, to address the remaining uncertainties in the youngest participants aged ≥2 to < 5 years. Considering the intent to submit the 111-206 CSR as part of this Type II variation, the CHMP agreed that the submission of the final 111-206 CSR in this Type II variation would also satisfy the condition of the Marketing Authorization and the Article 46 obligation applicable for a pediatric study 111-206 and 111-208 compared with natural history data from untreated children with ACH. This approach is generally in accordance with the relevant Guideline on Clinical Trials in Small Populations [CHMP/EWP/83561/2005]; Points to Consider on Application with 1. Meta-analyses; 2. One pivotal trial [CPMP/EWP/2330/99].

The use of external controls from NH sources to support regulatory decision-making is not uncommon, especially when studying children with a slowly progressive and heterogeneous rare disease for which no available therapies exist. Flexibility in study design, including the use of NH as an external control, has been well articulated in regulatory guidance and used in the original MAA (ICH guideline E11A on pediatric extrapolation EMA/CHMP/ICH/205218/2022; CHMP Guideline on Clinical Trials in Small Populations [CHMP/EWP/83561/2005]). It outlines factors to ensure optimal utility of retrospective NH and was carefully addressed when selecting the NH data sources.

2.1.4. General comments on compliance with GLP and GCP

The applicant confirmed that all clinical studies included in this application were conducted in accordance with GCP following the relevant guideline recommendation as laid down in European Clinical Trial Directive 2001/20/EC and Good Clinical Practice (GCP) Directive 2005/28/EC, for studies conducted within any European country along with the International Council on Harmonisation, Harmonised Tripartite Guideline: Guideline for GCP E6 (ICH E6) and other relevant guidance.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

Since 26 August 2021 Voxzogo is approved for the treatment of achondroplasia (ACH) in patients aged ≥2 years whose epiphyses are not closed.

While growth in ACH is well-described, and the underlying pathophysiology and potential for targeted pharmacological intervention remains the same across the whole pediatric age range, the approved indication excluded participants who were aged <2 years on the grounds that insufficient data was available at the time of filing. Accordingly, this AR focuses on the results in pediatric participants aged <2 years from completed study 111-206, along with data from the long-term, open-label extension study 111-208 (111-206 Clinical Study Report [CSR] and 111-208 CSR). The applicant is now applying for an extension of the indication to include pediatric participants aged <2 years. Using natural history data, multiple analytical approaches were used to confirm the durability of effect of vosoritide in these studies, including its effect on final adult height.

The approval in pediatric participants aged ≥2 years to <5 years was based on interim data in sentinel participants (i.e., participants enrolled to receive vosoritide) from studies 111-206 and 111-208, and was supported by extrapolation based on pharmacokinetic, efficacy, biomarker and safety data from studies in children with ACH aged ≥5 years. The weightband dosing was approved in the EU for ACH participants weighing ≥10 kg, based on simulations conducted with a population PK model. The data submitted with the present variation application provides further data also for this age group.

To confirm the magnitude, consistency and durability of effect of vosoritide in the completed 111-206 study and its ongoing open-label extension study (111-208), comparative analyses to two mutually independent external natural history controls (referred to as the AchNH external control and the observational/placebo external) are included.

The assessment of safety is based on studies 111-206 and 111-208, and supported by the completed and ongoing studies from the original MAA in participants aged ≥5 years, with a later data cut-off point applied to the ongoing studies (completed: Phase 3, double-blind, placebo-controlled study 111-301 and Phase 2, open-label study 111-202; ongoing: Phase 3, open-label extension study 111-302 and Phase 2 open-label extension study 111-205; Phase 2, open-label study 111-209 in participants aged ≤ 12 months). The total treatment exposure to vosoritide treatment in all of these studies is 715.89 participant-years (an additional 459 participant-years since the initial MA). Treatment exposure in participants aged <2 years is 59.77 participant-years.

Study 111-206 was a Phase 2, double-blind, placebo-controlled study to assess the safety and efficacy of daily subcutaneous injections of vosoritide after 52 weeks of treatment. This study was conducted in the US, Europe, Australia and Japan. Participants were enrolled by a staggered, age-descending recruitment of three age cohorts based on age at study screening: Cohort 1 (age ≥24 to <60 months), Cohort 2 (age ≥6 months to <24 months), and Cohort 3 (age 0 to <6 months).

Randomization was further stratified by age (6 to <15 months, ≥15 to <24 months, ≥24 to <36 months, and ≥36 months to <60 months) for Cohorts 1 and 2. Each cohort included at least 3 sentinel participants receiving vosoritide to evaluate the short-term safety and PK of vosoritide before initiating the rest of the cohort for randomized participants.

The primary efficacy endpoint in this study was the change in height Z-score from baseline to Week 52 (in reference to Centers for Disease Control and Prevention (CDC) normative data on average stature children). Further details on the study design and efficacy variables are described in Section 2.4.2.

Participants who completed study 111-206 continued into study 111-208, a Phase 2, open-label extension to assess the long-term safety and efficacy. Participants who initiated vosoritide treatment in 111-206, and continued into 111-208, had been treated for up to 3 years by the time of the data cut-off point for this dossier.

Participants received a daily dose of 30 µg/kg while they were aged <2 years of age, the daily dose was adjusted to 15 μg/kg during the visit immediately preceding the participants' 2nd year birthday.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies relevant for this Type II Variation**

Study Identifier	**Primary Objective(s)**	**Study Design and Type of Control**	**Dosage Regimen**	**Participants Enrolled**	**Study Population**	**Duration of Follow-Up**	**Date of Study Initiation**
111-206 (pivotal)	To assess the safety and efficacy of daily SC injections of vosoritide in younger children with ACH	Phase 2, randomized, double-blind, placebo-controlled, global, multicenter	Age ≥2 to <5 years: daily dose of vosoritide 15 µg/kg Age ≥6 months to <2 years: daily dose of vosoritide 30 µg/kg Age 0 to <6 months: daily dose of vosoritide 30 µg/kg	75 enrolled	Pediatric participants from birth to <60 months old with ACH	60 to 72 weeks (4 weeks screening 52 weeks of treatment with an additional 4 weeks of safety follow-up; Cohort 3 had a 12-week observational period after screening)	13Jun2018 Status at Time of the Type II Variation: **Completed** Report Data Included in the Type II **Full final CSR**
111-208	To assess the long-term safety, tolerability, and efficacy of daily SC injections of vosoritide in children with ACH	Phase 2 open- label extension of 111-206	Age ≥2 to <5 years: daily dose of vosoritide 15 µg/kg Age ≥6 months to <2 years: daily dose of vosoritide 30 µg/kg	73 enrolled	Pediatric participants with ACH who completed 111-206	Until participant attains NFAH (evidence of growth plate closure and 6 month interval AGV <1.5 cm/year)	13Jun2019 Status at Time of the Type II Variation: **Ongoing** Report Data Included in the Type II Interim full CSR (data cut-off date: 26Jan2022)

Study Identifier	Primary Objective(s)	Study Design and Type of Control	Dosage Regimen	Participants Enrolled	Study Population	Duration of Follow-Up	Date of Study Initiation
111-209	To evaluate the safety of vosoritide in children who are at risk of requiring cervicomedullary decompression surgery	Phase 2 stratified, randomized, controlled, open-label clinical study	0 to ≤12 months: daily dose of vosoritide 30 µg/kg	Approx. 20 planned (16 enrolled)	Pediatric participants aged 0 to ≤ 12 months with documented ACH confirmed by genetic testing	264 weeks	10Oct2020 Status at Time of the Type II Variation: **Ongoing** Report Data Included in the Type II Variation Interim abbreviated CSR (data cut-off date: 25Feb2022)

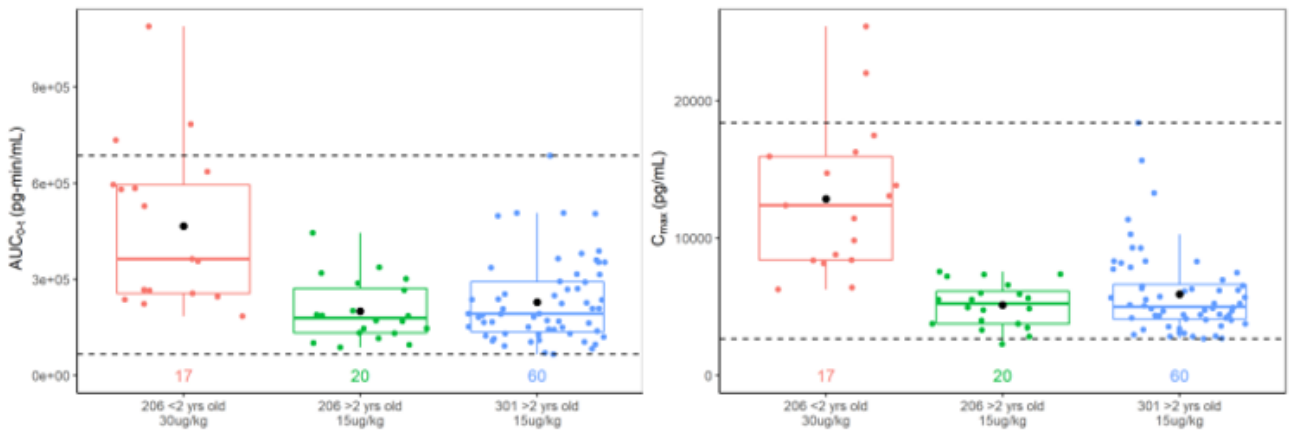
2.3.2. Pharmacokinetics

With respect to information on pharmacokinetics please refer to the AR of the approval procedure (EMEA/H/C/005475/0000). With respect to the scope of this variation an exposure comparison between the approved and the applied for population is important.

Comparison of vosoritide exposure in ACH patients aged 0 to < 5 years and ≥ 5 years

To compare vosoritide exposure in ACH patients aged 0 to < 5 with ACH patients aged ≥5 years, the mean/median and individual Cmax and AUC0-t values are presented in Figure 2 and Table 1 below.

Figure 2 Comparison of vosoritide AUC_{0-t} and C_{max} subjects dosed 30 µg/kg (111-206 aged <2 years) and 15 µg/kg (111-206 2≤5 years and 111-301)



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. Each circle represents individual mean exposure (AUC_{0-t} and C_{max}) across visit. The mean exposure of all the subjects at that visit is shown as a black circle. The numbers at the bottom of each plot indicate the number of subjects with PK data available for each group. Dashed lines represent minimum and maximum limits from 111-301 study.

Table 1 Comparison of vosoritide AUC_{0-t} and C_{max} across 111-206 and 111-301

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

In 111-206, as subjects turned 2 years old their dose was reduced from 30 to 15 µg/kg/day. The randomized subjects mean Cmax and AUC0-t for < 2 years old in 111-206 dosed with 30 µg/kg/day, aged >2 years in 111-206 and 111-301 dosed at 15 µg/kg/day are presented in Figure 2.

Except for one subject in 111-206 Cohort 3, the mean Cmax and AUC0-t reported in all randomized subjects in 111-206 were within the range (max-min) of exposure reported in 111-301.

Except for three AUC0-t values and two Cmax values from subjects < 2 years old in 111-206 dosed with 30 µg/kg/day, the range (min-max) of Cmax and AUC0-t reported in 111-206 were within the range of exposure reported in 111-301.

2.3.3. Pharmacodynamics

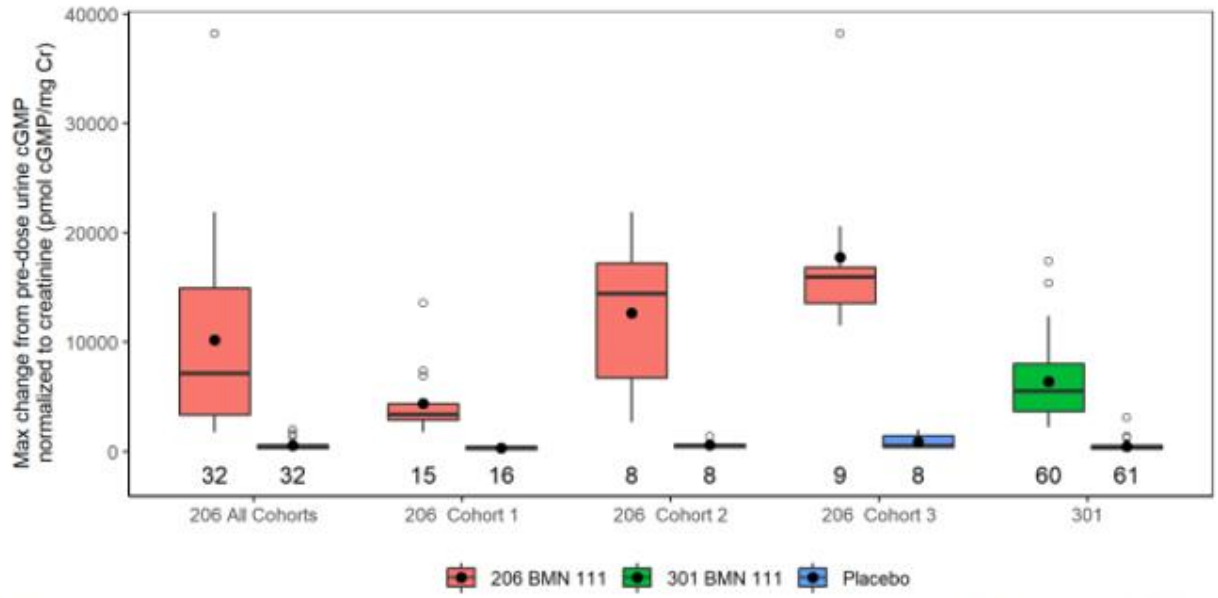
With respect to information on pharmacodynamics please refer to the AR of the approval procedure (EMEA/H/C/005475/0000).

Comparison of biomarker response in ACH patients aged 0 to < 5 years and ≥ 5 years

Urine cyclic guanosine monophosphate normalized to urine creatinine

Changes in serum urine cyclic guanosine monophosphate (cGMP) normalized to urine creatinine levels were analyzed across 111-206 overall and stratified by cohorts in randomized subjects and subjects in 111-301 to assess PD responses following vosoritide treatment. Urine cGMP was measured as an exploratory biomarker of on-target vosoritide activity through the target receptor NPR-B both in the target tissue (growth plate/bone) and in other tissues that express NPR-B (eg, vasculature). Maximum changes in urine cGMP from pre-dose values in 111-206 and 111-301 are presented in Figure 3 and Table 2 below.

Figure 3 Comparison of Urine cGMP across 111-206 and 111-301



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.

Off-note: The mean exposure of the subjects at that visit is shown as a black circle. The numbers at the bottom of each plot indicate the number of subjects with PK data available for that visit.

Table 2 Comparison of Urine cGMP across 111-206 and 111-301

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

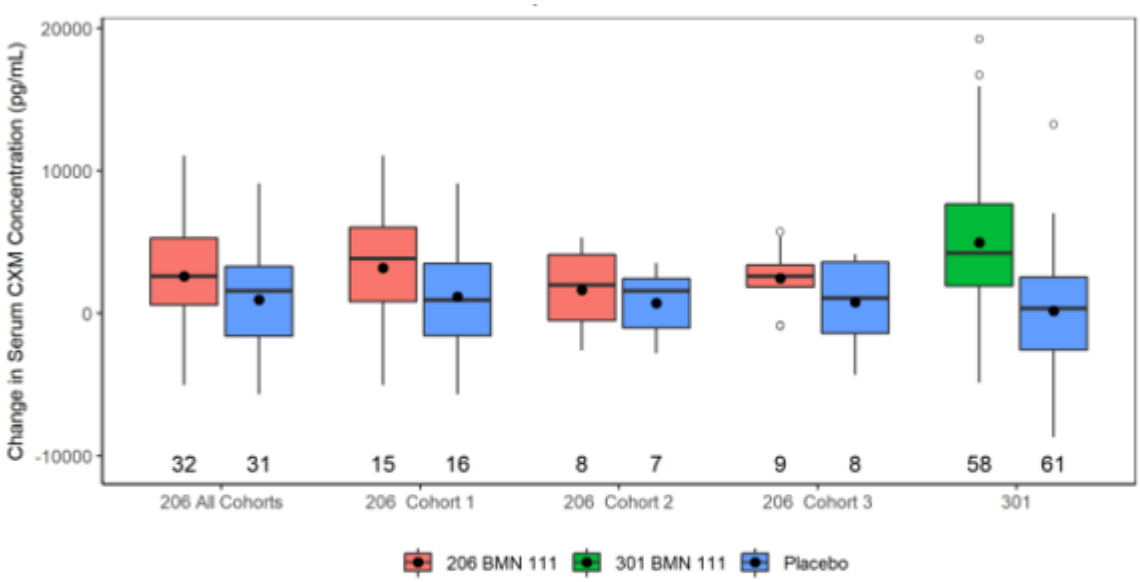
In both studies, cGMP increased on vosoritide compared to pre-dose. The increase was greatest in subjects dosed with 30 µg/kg (those 2 years in 111-206 Cohort 1 and 111-301). In subjects dosed with 15 µg/kg, the maximum change in urine cGMP from pre-dose values were comparable in 111-206 and 111-301.

Comparison of Collagen X Marker in ACH patients aged 0 to < 5 years and ≥ 5 years

Collagen X marker (CXM) is a degradation fragment of type X collagen which is released into the circulation as part of the endochondral ossification process (Coghlan 2017) and measured in serum as an exploratory biomarker of growth plate activity. In average stature children, concentrations of CXM were shown to mimic the trajectory of changes in AGV (Coghlan 2020). In ACH, CXM are much reduced and variable, although show similar pattern as in average stature children (Carroll 2022).

Mean change in serum CXM from baselinein 111-206 stratified by cohorts and 111-301 from Week 6 to Week 52 are presented in Figure 4 and Table 3 below.

Figure 4 Comparison of mean change in serum CXM across 111-206 and 111-301 day 8 onwards



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 mean exposure of the subjects at that visit is shown as a black circle. The numbers at the bottom of each plot indicate the number of subjects with PK data available for that visit.

Table 3 Comparison of mean change in serum CXM across 111-206 and 111-301 day 8 onwards

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

Mean serum CXM levels were higher in subjects treated with vosoritide compared to placebo in all 3 age cohorts. The magnitude of difference between vosoritide treated group and placebo group was highest in the study 111-301 and 111-206 Cohort 1, followed by 111-206 Cohort 2 and Cohort 3.

2.3.4. PK modelling

Population PK analyses were conducted on pooled data from 5 Phase 2 and Phase 3 studies (complete data from 111-301, 111-202 and 111-206 and interim data from 111-205 and 111-302). Population PK results indicated that body weight was the only significant covariate for vosoritide clearance and

volume of distribution which supports dosing by body weight in children. The body weight-normalized apparent clearance of vosoritide decreased with increasing body weight in patients with ACH. Race, sex, age and ADAs were no significant covariates for vosoritide clearance or volume of distribution. Dose solution concentration of 0.2 mg/mL (which was used for 2.5 and 7.5 µg/kg doses in 111-202 and is not available commercially) and treatment duration also appeared to have a positive effect on relative bioavailability. However, the total dose was confounded with weight and time which may also contribute to the effect of time on bioavailability.

2.3.5. Discussion on clinical pharmacology

All randomized subjects in study 111-206 Cohort 1 (age 2-5 years) were dosed with 15 µg/kg daily and subjects in Cohort 2 (age 6-24 months) and Cohort 3 (0-6 months) were dosed with 30 µg/kg daily. A total of 43 subjects in three cohorts were dosed with vosoritide in the study 111-206. In the primary analysis, sentinel subjects were excluded and only the 32 randomized subjects were included.

Cohort 1 sentinel participants received 15 μg/kg/day vosoritide on Day 1. The mean AUC0-t and Cmax values were similar to those achieved with the 15 μg/kg/day dose in patients aged ≥5 years in the study 111-301 and in the Study 111-202 in ACH, indicating that the 15 μg/kg/day dose was appropriate also for patients 2-5 years old.

Cohort 2 sentinel participants received 15 μg/kg/day vosoritide on Day 1. The mean AUC0-t was 65900 pg-min/mL, which was less than the exposure characterized in Study 111-202 at the 15 μg/kg/day dose. Therefore, the dose was increased to 30 μg/kg/day for both sentinels and for the subsequently randomized participants in this cohort as long as they remained < 2 years of age. While the median AUC0-t was clearly increased with the higher dose, most patients remained within the exposure range determined for patients > 5 years of age on the lower dose.

Sentinel exposure in Cohort 3 confirmed the dose of 30 μg/kg/day. Following that, all Cohort 3 participants received 30 μg/kg/day vosoritide.

Male and female participants had similar vosoritide plasma exposure, suggesting that the sex of a participant had no apparent impact on plasma exposure. Positive correlations between plasma exposure and participant weight were observed except for Cmax at 15 μg/kg. In general, participants below age of 2 years receiving 30 μg/kg dose had higher exposure than 15 μg/kg dose groups. AUC0-t increased with increasing age but an effect on Cmax was not observed.

Since the efficacy in the younger children appeared to be smaller than expected the rationale for dose adjustments from 15 µg/kg to 30 µg/kg/day in cohorts 2-3 was further discussed. From the information provided, it appears that the individual mean Cmax and AUC0-t across visits for subjects in Study 111-206 were generally within the higher range (max-min) of exposure reported in study 111-301 in children >5 years of age, with exception of one subject in 111-206 Cohort 3 (aged < 6 months) that exceeded this range. Thus, it seems unlikely that insufficient exposure could be the reason for the initially observed smaller than expected effect size and the recommended posology of 30 µg/kg for patients below 2 years of the age and 15 µg/kg for those 2 to <5 years old remains adequate (see Clinical efficacy section for more details).

An increase in injection site reactions has been observed in the youngest patients. The applicant discussed further the exposure-safety relationship in children below 2 years of the age (see Clinical safety section for more details).

The CHMP discussed further the exposure for patients <2 years due to inconsistency in the reported values for the lowest age and weight group and the results of the popPK modelling. In the committee's

view, the population PK model requires updating to better reflect the dose-exposure in the youngest age group. The applicant committed to providing the updated PopPK model post-approval.

Regarding the biomarkers, mean changes in serum CXM level were higher in subjects treated with vosoritide compared to placebo in both studies 111-206 and 111-301 supporting increased growth plate activity by vosoritide treatment. The magnitude of difference between vosoritide treated group and placebo group was highest in the study 111- 301 and 111-206 Cohort 1, followed by 111-206 Cohort 2 and Cohort 3. In addition, in both studies urine cGMP in subjects dosed with vosoritide increased from pre-dose. The increase was greatest in subjects dosed with 30 µg/kg (those 2 years in 111-206 Cohort 1 and 111-301) as expected. Moreover, in subjects dosed with 15 µg/kg, the maximum change in urine cGMP from pre-dose values were comparable in 111-206 and 111-301. Comparable or greater cGMP response was observed in randomized subjects <5 years from 111-206 compared to subjects in 111-301 at the evaluated doses.

2.3.6. Conclusions on clinical pharmacology

The Applicant has submitted a clinical pharmacology report from study 111-206 including exposure-response analysis of biomarkers/efficacy/safety in Cohorts 1-3 and a comparative Analysis between trial 111-206 and 111-301 PK results.

Based on the PK and cGMP biomarker data collected in 111-206 it can be agreed that the 15 µg/kg vosoritide is appropriate for ACH participants 2 to <5 years old and 30 µg/kg vosoritide is more appropriate for ACH participants < 2 years old.

Further details on the popPK model will be provided post-approval as recommended by the CHMP.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No new presentations of vosoritide are included in this Type II Variation as the currently marketed commercial product was used in clinical studies to support the proposed indication and expanded age range.

The proposed dosage in pediatric participants with ACH aged 0 months to < 5 years is a once daily subcutaneous injection based on the participant's actual body weight and the concentration of reconstituted vosoritide (0.8 mg/mL or 2 mg/mL).

The updated dosage and administration is consistent with approved posology for children weighing ≥ 10 kg. The proposed dosage and administration is supported by observed PK values and by population PK modelling (see discussion on clinical pharmacology and efficacy for more details), which was updated to incorporate final data from 111-206 and to characterize the effect of participant body weight on vosoritide PK.

In 111-206, participants < 2 years old received 30 µg/kg, then switched to 15 µg/kg when they reached 2 years of age (median body weight of 10 kg) to account for the characterized effect of body weight on vosoritide PK.

The following Table 4 shows the updated daily dosing and injection volume table the applicant proposed to include in the Voxzogo PI to reflect these recommendations.

Table 4 Single Dose Volumes by Body Weight

Body weight	**Vosoritide 0.4 mg solvent (water for injections): 0.5 mL concentration: 0.8 mg/mL**	**Vosoritide 0.56 mg solvent (water for injections): 0.7 mL concentration: 0.8 mg/mL**	**Vosoritide 1.2 mg solvent (water for injections): 0.6 mL concentration: 2.0 mg/mL**
	Daily injection volume (mL)		
3 kg	0.12ml		
4 kg	0.15ml		
5 kg	0.20ml		
6-7 kg	0.25ml		
8-11 kg	0.30 mL		
12-16 kg		0.35 mL	
17-21 kg		0.40 mL	
22-32 kg		0.50 mL	
33-43 kg			0.25 mL
44-59 kg			0.30 mL
60-89 kg			0.35 mL
≥90 kg			0.40 mL

2.4.2. Main studies

Title of Study

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

Methods

A total of 70 participants were planned to be enrolled at 16 clinical centers worldwide by a staggered, age-descending recruitment of three age cohorts based on age at study screening; within Cohorts 1 and 2, participants were stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- Cohort 3 – children aged 0 to < 6 months; treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

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 were collected in 111-901 (non-interventional multicenter, multinational study).

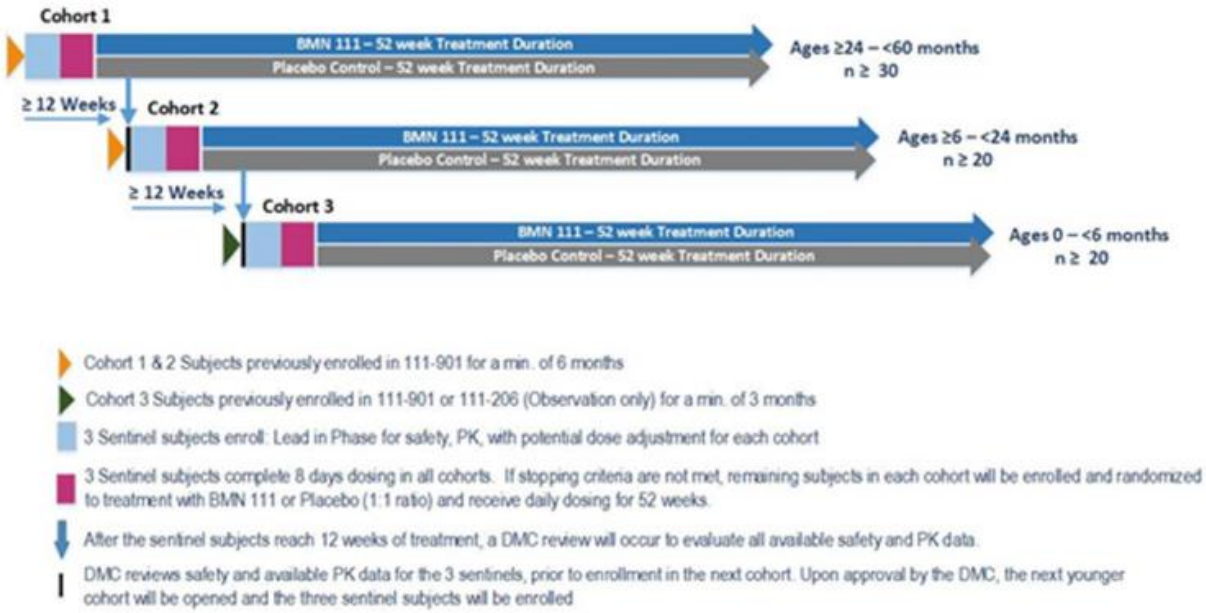
Each cohort included at least three sentinel participants receiving vosoritide to evaluate the short-term safety and PK of vosoritide before opening the rest of the cohort for randomized participants. Participants were randomized on a 1:1 ratio to either vosoritide or placebo. In Japan, participants were randomized separately within each cohort but not within the age stratification because of the small number of participants.

Randomized participants received a daily vosoritide dose determined after the evaluation of the PK data of sentinel participants for each cohort.

An independent data monitoring committee (DMC) was assigned to monitor the safety of this study. DMC data review was performed at regular time periods (approximately every 6 months or ad hoc, if indicated).

Following completion of the study, participants in all treatment groups were eligible to receive vosoritide in the open-label extension study 111-208 to assess the safety and efficacy of vosoritide over a longer-term.

Figure 5 Overview of the Study design of Trial 111-206



Study participants

Participants with a diagnosis of ACH confirmed by genetic testing, aged 0 to <60 months, with at least a 6-month period of pretreatment growth assessment in 111-901 and had one documented measurement of height/body length at a minimum of 6-months prior to Screening (Cohort 1 and Cohort 2) or a minimum of 3-months observation (Cohort 3).

Treatments

Vosoritide supplied as lyophilized, preservative-free, white-to-yellow powder for reconstitution with sterile water for injection (WFI), and administration as a subcutaneous injection.

Participants were dosed according to age 15 µg/kg/day (Cohort 1), 15 µg/kg/day and 30 µg/kg/day (Cohort 2), 30 µg/kg/day (Cohort 3). Participants in Cohort 2 were initially dosed with 15 µg/kg/day and were adjusted to 30 µg/kg/day following the review of safety and PK data then adjusted to 15 µg/kg/day during the visit immediately preceding the 2-year birthday. All sentinel and randomized participants in Cohort 3 received 30 µg/kg/day.

Placebo supplied as lyophilized, preservative-free, white-to-yellow powder for reconstitution with sterile WFI and administered as a subcutaneous injection.

Duration of Treatment: 52 weeks of double-blind treatment with 2 weeks safety follow up; option for inclusion in follow-up trial 111-208.

Objectives

Primary objectives:

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

Secondary objectives:

- Evaluate the effect of vosoritide on change from baseline in annualized growth velocity (AGV) throughout the 52 weeks of the study
- Evaluate the effect of vosoritide on bone morphology/quality by X-ray and dual X ray absorptiometry (DXA)
- Evaluate the pharmacokinetic (PK) of vosoritide in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of vosoritide on Health-related quality of life (HRQoL), developmental status, and /functional independence using age-specific quality of life (QoL) and functional independence questionnaires/QOL status (Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III]), Activity of Daily Living and Functional Independence Measure (Wee-FIM), Infant Toddler Quality of Life Questionnaire (ITQOL), Child Behavior Checklist (CBCL)
- Evaluate immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of vosoritide on bone metabolism and vosoritide pharmacodynamics biomarkers
- Evaluate the effect of vosoritide on growth parameters and body proportions, including change from baseline in upper to lower body segment ratio
- Evaluate the effect of vosoritide on sleep apnea
- Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

Exploratory objectives:

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

Outcomes/endpoints

Primary Efficacy Endpoint:

Change from baseline in height Z-score at Week 52.

Secondary Efficacy Endpoints:

- Change from baseline in height at Week 52
- Change from baseline in AGV at Week 52
- Change from baseline in upper to lower body segment ratio at Week 52
- Change from baseline in other growth measures (upper body length, head circumference, arm span, upper arm length, lower arm length, upper leg length [thigh], knee to heel length, and tibial length) at Week 52
- Change from baseline in other body proportion ratios (arm span to height ratio, upper arm length to lower arm [forearm] length ratio, upper leg length [thigh] to knee to heel length ratio, and upper leg length (thigh) to tibial length ratio) at Week 52
- Change from baseline in BMI and BMI Z-score at Week 52
- Change from baseline in weight Z-score at Week 52
- Change from baseline in ITQoL, WeeFIM, and BSID-III scores at Week 52
- Change from baseline in sleep study indices at Week 52
- Change from baseline in bilateral X-rays of lower extremities, lumbar spine X-rays, bone mineral density (BMD) and bone mineral content (BMC) by DXA, and MRI results at Week 52

Exploratory Efficacy Endpoints:

Change from baseline in physical and phenotypic changes with clinical photography (optional).

Safety: Incidence, severity and relationship to study drug of all treatment-emergent adverse events (TEAEs), including events of interest (EOI). Procedures/intervention/surgery, imaging assessments, clinical laboratory assessments, Child Behavior Checklist (CBCL), vital signs, electrocardiogram (ECG) and clinical hip assessment

Sample size

No formal sample size calculations were performed. Approximately 70 subjects aged 0 to <60 months at study entry were planned for participation in 111-206 and was considered appropriate to evaluate the efficacy and safety of vosoritide in the target population.

At the time of data cut-off of the initial submission, 44 patients were enrolled. After finalisation of the trial a total of 75 participants were enrolled and randomized to study treatment

Randomisation

In study 111-206, sentinel subjects received open-label vosoritide and subsequent subjects were centrally randomized with stratification using an interactive response technology (IRT) in a 1:1 ratio, i.e., injection with placebo:vosoritide.

Subjects were enrolled into three age cohorts based on the age at study screening starting with the eldest population. Cohorts 1 and 2 are stratified by age.

An independent third-party vendor developed the randomization schedule so that applicant and site personnel were blinded to treatment assignments.

Blinding (masking)

In study 111-206, vosoritide and placebo are packaged and labelled in the same way, with the study number and a unique identification number. The vosoritide placebo is designed to be comparable in appearance to vosoritide, is reconstituted in the same way, and contains all the components of the drug product except vosoritide, including commercially sourced sterile WFI. An independent third-party vendor developed the randomization schedule so that applicant and site personnel did not know the treatment assignment. Subjects and the participating site members are blinded to study treatment.

Statistical methods

All efficacy variables in 111-206 were assessed using the Full Analysis Set (FAS), defined as all sentinel and randomized participants with a signed informed consent.

The FAS (randomized) was a subset of the FAS and included randomized participants only and was considered the primary analysis population for the assessment of the efficacy parameters of height Z-score (referenced to average stature), height, AGV and upper to lower body segment ratio. ANCOVA models were used to assess the efficacy endpoints overall and by age group (0 to <6, ≥6 to <24, ≥24 to <60 months); however, for 111-206, all analyses were considered descriptive with no Type I error control since there is no formal hypothesis testing planned.

Beyond linear growth, brain MRI evaluated the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions. Descriptive summary statistics and plots were provided for the data from 111-206 to determine the difference between treatment groups.

For study 111-208, descriptive summary statistics to assess change from baseline (first dose of active treatment) for each growth parameter by age group were provided. The plans for analyzing efficacy in studies 111-206 and 111-208 are provided in the individual statistical analysis plans, and detailed efficacy findings from each study are provided in the individual CSRs.

Height Z-score referenced to untreated ACH population (Hoover-Fong 2021) was summarized for study 111-208 data (not included in the interim CSR). This endpoint has value for assessing growth in the uncontrolled setting because it is expected to remain relatively stable with no directional trends over time.

To further confirm the magnitude of the treatment effect observed in study 111-206, all available efficacy data for participants with at least one year of follow-up from studies 111- 206 and 111-208 were compared to the AchNH and observational/placebo external controls.

Longitudinal ANCOVA models and cross-sectional analyses using t tests adjusted for baseline differences were applied.

Comparative analyses were also performed to determine the durability of treatment effect for each age group (up to 3 years) in 111-206 and 111-208 compared to the AchNH and observational/placebo external controls.

In order to benchmark the growth observed with vosoritide, a comparison of height gain for both treated and untreated ACH participants were compared with height gain for average stature participants of the same age and sex based on the 50th percentile from the CDC growth charts. The ACH treated and untreated height gain (LS mean change from baseline) was presented as a percent relative to the average stature height gain.

Results were compared to the gain in height for the aged ≥ 5 year population using the one year follow up from study 111-301.

Results

Participant flow

A total of 75 participants were enrolled and randomized to study treatment:

Cohort	Sentinel	Voxzogo	Placebo
1	4 participants	15 participants	16 participants
2	4 participants	8 participants	8 participants
3	3 participants	9 participants	8 participants

Recruitment

This study was conducted by 16 principal investigators at 16 study centers in four countries (United States, Australia, United Kingdom and Japan).

Study Duration: 52 weeks of double-blind treatment with 2 weeks safety follow up

Report Period: End of study

First Enrollment: 13 June 2018

Last Patient Last Visit: 26 January 2022

Date of Study Report: 18 July 2022

Conduct of the study

The protocol deviations in the FAS are summarized in Table 5:

Table 5 Protocol Deviations (Overall) [Analysis Population: Full Analysis Set]

Deviation Classification Deviation Category	Sentinel (N=11)	Vosoritide (N=32)	Placebo (N=32)	All Vosoritide (N=43)
Participants with any deviation, n (%)[a]	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
Participants with any major deviation, n (%)[a]	10 (90.9)	26 (81.3)	29 (90.6)	36 (83.7)
Procedure not done	9 (81.8)	25 (78.1)	28 (87.5)	34 (79.1)
Out of window	2 (18.2)	3 (9.4)	4 (12.5)	5 (11.6)
Dosing irregularity	1 (9.1)	1 (3.1)	6 (18.8)	2 (4.7)
Wrong strata group	0	2 (6.3)	0	2 (4.7)
Eligibility criteria	0	1 (3.1)	1 (3.1)	1 (2.3)
Wrong kit	0	0	0	0
Wrong treatment	0	0	0	0
Participants with any minor deviation, n (%)[a]	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
Procedure not done	10 (90.9)	31 (96.9)	32 (100.0)	41 (95.3)
Out of window	10 (90.9)	28 (87.5)	25 (78.1)	38 (88.4)
Dosing irregularity	7 (63.6)	16 (50.0)	19 (59.4)	23 (53.5)

The protocol violations detailed above are not seen as a major quality issue or affect relevantly the interpretation of the final outcome assessment of the trial.

Baseline data

Studies 111-206 and 111-208 included participants with ACH documented by clinical grounds and confirmed by genetic testing, and participants were recruited globally from the US, Europe, Australia and Japan. The characteristics of the participant population were of the target population.

Study 111-206

In 111-206, a total of 75 participants enrolled into the study; 64 were randomized to receive vosoritide treatment or placebo and 11 were sentinel participants.

Cohort 1 [≥24 to <60 months]: 15 randomized to vosoritide, 16 randomized to placebo and 4 sentinels; **Cohort 2** [≥6 to <24 months]: 8 randomized to vosoritide, 8 randomized to placebo and 4 sentinels; **Cohort 3** [0 to <6 months]: 9 randomized to vosoritide, 8 randomized to placebo and 3 sentinels).

Two participants discontinued from study treatment and the study (Cohort 2, placebo; reason for discontinuation: withdrawal by participant; Cohort 3, randomized vosoritide; reason for discontinuation: AE of sudden infant death syndrome, assessed as not related).

Collection of pre-treatment growth measures (baseline growth data) was a requirement of study 111-206. For participants in Cohort 1 and Cohort 2, at least 6 months of baseline growth data were collected in observational study 111-901 prior to treatment in 111-206, and for participants in Cohort 3, at least 3 months of baseline growth data were collected prior to treatment in 111-206. As a result, the earliest age a participant received vosoritide in Cohort 3 was 4.5 months and the lowest weight of a participant was 5 kg.

The mean (SD) age of participants on Day 1 of treatment in the vosoritide and placebo arm was 41.48 (11.07) months and 44.33 (11.54) months, respectively, in Cohort 1; 16.59 (5.11) months and 16.87 (6.21) months, respectively, in Cohort 2; and 5.41 (0.53) months and 5.76 (0.59) months, respectively, in Cohort 3.

As expected, and driven by natural age-related changes in linear growth, baseline growth measures differed between age cohorts, and were aligned with the established growth patterns of children with ACH in these age groups. Cohort 1 (≥24 to <60 months), showed relatively stable and predictable baseline growth. In contrast, Cohort 2 (≥6 to <24 months) and Cohort 3 (0 to <6 months) showed rapid decline in growth velocity with Cohort 3 showing the most significant decline and variability. In Cohort 3, AGV at baseline ranged from 4.8 to 29.7 cm/year in the placebo arm and 16.4 to 30.2 cm/year in the vosoritide arm compared to a baseline range in Cohort 2 of 2.5 to 16.0 cm/year in the placebo arm and 3.9 to 18.5 cm/year in the vosoritide arm. Reflecting rapid accumulation of height deficit during early childhood, the greatest height deficit was observed in Cohort 1, followed by Cohort 2 and Cohort 3.

Table 6 Baseline Characteristics (Overall) Analysis Population: Full Analysis Set

Demographic Characteristic	Cohort 1		Cohort 2		Cohort 3	
	All-Vosoritide (N=19)	Placebo (N=16)	All-Vosoritide (N=12)	Placebo (N=8)	All-Vosoritide (N=12)	Placebo (N=8)
Age at Screening, months						
n	19	16	12	8	12	8
Mean (SD)	40.2 (11.2)	43.1 (11.5)	15.3 (5.1)	15.8 (6.3)	3.8 (0.8)	4.1 (1.0)
Median	39.0	39.5	15.5	17.5	4.0	4.0
25^{th}, 75^{th} Percentile	29.0, 50.0	33.5, 55.0	10.5, 20.0	9.0, 21.0	3.0, 4.5	4.0, 5.0
Min, Max	24, 59	28, 58	8, 22	8, 23	3, 5	2, 5
Age on Day 1, months						
n	19	16	12	8	12	8
Mean (SD)	41.48 (11.07)	44.33 (11.54)	16.59 (5.11)	16.87 (6.21)	5.41 (0.53)	5.76 (0.59)
Median	40.02	40.39	16.54	18.56	5.62	5.91
25^{th}, 75th Percentile	30.19, 51.06	34.55, 56.36	11.63, 21.42	10.46, 22.16	4.86, 5.86	5.72, 5.95
Min, Max	25.4, 59.8	29.2, 59.8	8.7, 23.4	8.9, 23.7	4.5, 5.9	4.4, 6.5
Sex, n (%)						
Male	10 (52.6)	7 (43.8)	9 (75.0)	5 (62.5)	6 (50.0)	1 (12.5)
Female	9 (47.4)	9 (56.3)	3 (25.0)	3 (37.5)	6 (50.0)	7 (87.5)
Race, n (%)						
White	12 (63.2)	13 (81.3)	9 (75.0)	6 (75.0)	8 (66.7)	6 (75.0)
Asian	6 (31.6)	3 (18.8)	2 (16.7)	1 (12.5)	3 (25.0)	2 (25.0)
Japanese	2 (10.5)	3 (18.8)	1 (8.3)	1 (12.5)	2 (16.7)	2 (25.0)
Other	4 (21.1)	0	1 (8.3)	0	1 (8.3)	0
Multiple	1 (5.3)	0	1 (8.3)	0	1 (8.3)	0
Native Hawaiian or Other Pacific Islander	0	0	0	1 (12.5)	0	0
Ethnicity, n (%)						
Not Hispanic or Latino	18 (94.7)	15 (93.8)	12 (100.0)	8 (100.0)	10 (83.3)	6 (75.0)
Hispanic or Latino	1 (5.3)	1 (6.3)	0	0	2 (16.7)	2 (25.0)

Max, maximum; Min, minimum; SD, standard deviation.
a. Percentages were calculated using the total number of participants in the full analysis set of each column as the denominator

Medical History: Overall, >90% of participants across treatment groups had a medical history condition reported at baseline and 63.6 to 78.1% of participants across treatment groups had an ACH-related medical history condition at baseline. The most commonly (>20%) reported medical history conditions by SOC were:

- **Respiratory, Thoracic and Mediastinal Disorders** (67.4% all-vosoritide; 62.5% placebo)
- **Infections and Infestations** (62.8% all-vosoritide; 59.4% placebo)
- **Musculoskeletal and Connective Tissue Disorders** (41.9% all vosoritide; 40.6% placebo)
- **Nervous System Disorders** (41.9% all vosoritide 28.1% placebo)
- **Surgical and Medical Procedures** (41.9% all vosoritide; 37.5% placebo)
- **Congenital, Familial and Genetic Disorders** (39.5% all-vosoritide; 65.6% placebo)
- **Gastrointestinal Disorders** (37.2% all vosoritide; 53.1% placebo)
- **Ear and Labyrinth Disorders** (27.9% all-vosoritide; 28.1% placebo)
- **Skin and Subcutaneous Tissue Disorders** (27.9% all vosoritide; 18.8% placebo)

***Baseline Growth Measures*:** Overall, the mean height deficit at baseline was greatest in the placebo group (-4.28 SDS below average stature) compared to all-vosoritide (-3.88 SDS below average stature), and AGV was greatest in the all-vosoritide group (11.66 cm/year) compared to placebo (9.60 cm/year).

Numbers analysed

Analysis Population rolled, n (%)a		**Randomized**		
	Sentinel (N=11)	**Vosoritide (N=32)**	**Placebo (N=32)**	**All Vosoritide (N=43)**
Participants en	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
Full Analysis Set, n (%)[a]	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
Cohort 1				
≥36 to <60 months	3	7	12	10
≥24 to <36 months	1	8	4	9
Cohort 2				
≥15 to <24 months	2	5	5	7
≥6 to <15 months	2	3	3	5
Cohort 3 (0 to <6 months)	**3**	**9**	**8**	**12**
Full Analysis Set* (randomized)	0	32 (100.0)	32 (100.0)	43 (100.0)
Per-Protocol population, n (%)[a]	6 (54.5)	27 (84.4)	29 (90.6)	33 (76.7)
Excluded	5 (45.5)	5 (15.6)	3 (9.4)	10 (23.3)
Reason for exclusion				
No height/length assessment at Week 52	5 (45.5)	5 (15.6)	3 (9.4)	10 (23.3)
Immunogenicity	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
Safety population, n (%)[a]	11 (100.0)	32 (100.0)	32 (100.0)	43 (100.0)
PK population, n (%)[a]	11 (100.0)	32 (100.0)	0	43 (100.0)

a. Percentages were calculated using the total number of participants in the full analysis set of each column as the denominator.

Full Analysis Set includes all sentinel and randomized participants with a signed informed consent.
Per-Protocol Population is a subset of the FAS population who completed the treatment originally allocated, with a height assessment within the protocol-defined Week 52 visit window, and with treatment compliance of at least 80%.
Safety Population includes all sentinel and randomized participants in the FAS who received at least one dose of vosoritide or placebo in this study.
PK Population includes all sentinel and randomized participants in the safety population who have at least one evaluable PK concentration.
Immunogenicity Population includes all sentinel and randomized participants in the safety population who have at least one evaluable immunogenicity sample.

Outcomes and estimation

Primary Efficacy Endpoint

Change from Baseline (95% CI) for Height Z-Score at Week 52

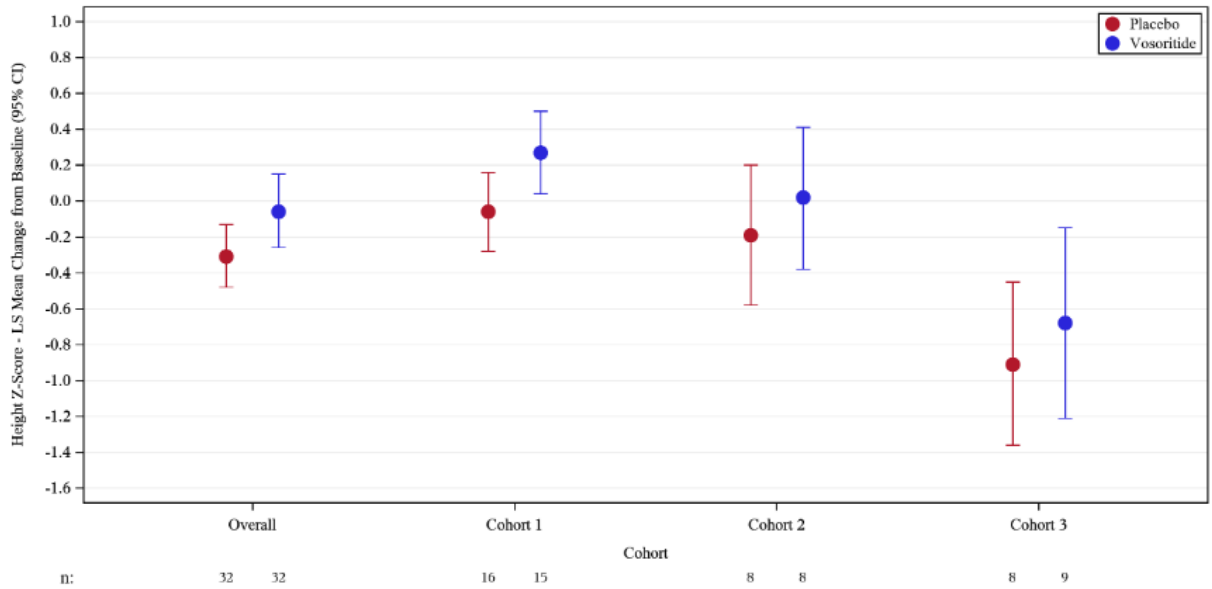
Results for the ANCOVA analysis in the FAS (randomized) showed a numerical improvement at Week 52 of 0.25 SDS (95% CI: -0.02, 0.53) in the vosoritide group compared with placebo in the overall population.

In all cohorts, there was worsening of height Z-score in the placebo group, as indicated by the negative LS mean (LSM) change from baseline at Week 52. This worsening was not observed in the vosoritide group in Cohort 1 and Cohort 2. In Cohort 3, the worsening of height Z-score observed in the vosoritide group was not of the same magnitude as in the placebo group.

The LSM difference between the treatment groups was consistent across the cohorts with point estimates in favour of vosoritide from Cohort 1 to Cohort 3 (Cohort 1: LSM difference of 0.33 [95% CI: 0.00, 0.67] SDS; Cohort 2: LSM difference of 0.21 [95% CI: -0.37, 0.79] SDS and Cohort 3: LSM difference of 0.23 [95% CI: -0.45, 0.91] SDS in the FAS [randomized]).

Similar results were observed in the FAS population (LSM difference of 0.30 [95% CI: 0.07, 0.54]).

Figure 6 LS Mean Change from Baseline (95% CI) for Height Z-Score at Week 52 Analysis Population (Full Analysis Set [Randomized])



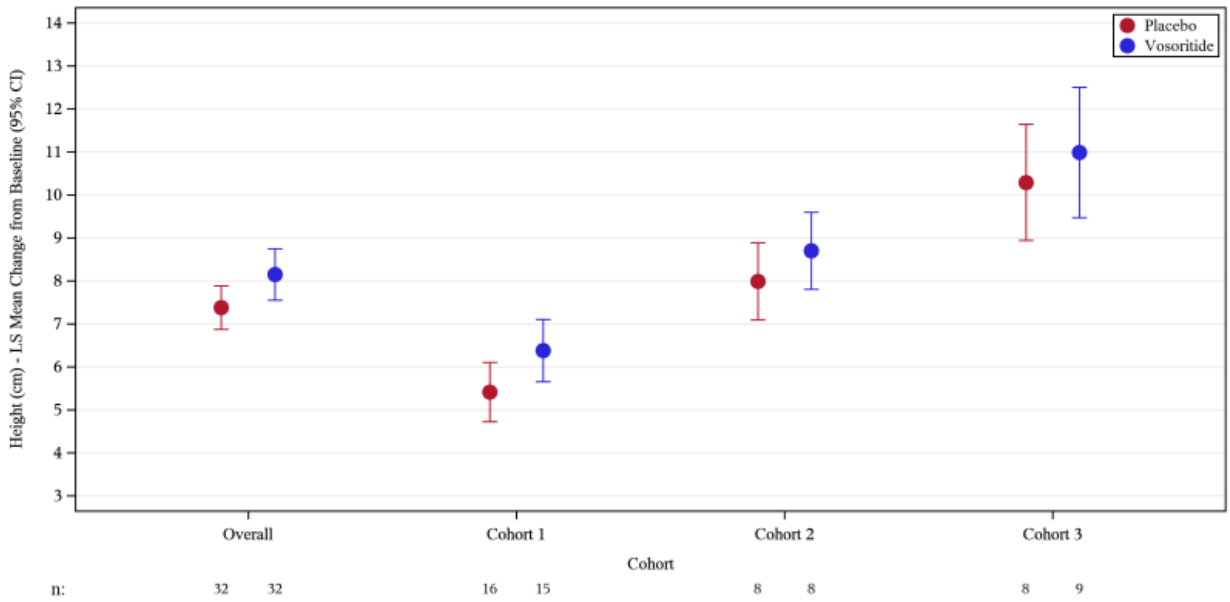
Secondary Efficacy Endpoints

Change in Height at Week 52

Results for the ANCOVA analysis in the FAS (randomized) showed a numerically positive change in standing height (LSM difference of 0.77 cm [95% CI: -0.02, 1.56] in the overall population), which is aligned with the observed change in height Z-score. The overall baseline heights were consistent with the age range of the individual cohorts. In all cohorts, a greater increase in height was observed in the vosoritide group compared with placebo.

The LSM mean difference between the treatment groups was consistent across the cohorts with point estimates in favour of vosoritide from Cohort 1 to Cohort 3 (Cohort 1: LSM difference of 0.96 [95% CI: -0.09, 2.02] cm; Cohort 2: LSM difference of 0.71 [95% CI: -0.62, 2.04] cm and Cohort 3: LSM difference of 0.70 [95% CI: -1.28, 2.68] cm in the FAS [randomized]).

Figure 7 LS Mean Change from Baseline (95% CI) for Height at Week 52 Analysis Population (Full Analysis Set [Randomized])



Similar results were observed in the FAS population (LSM difference of 0.96 [95% CI: 0.26, 1.66]).

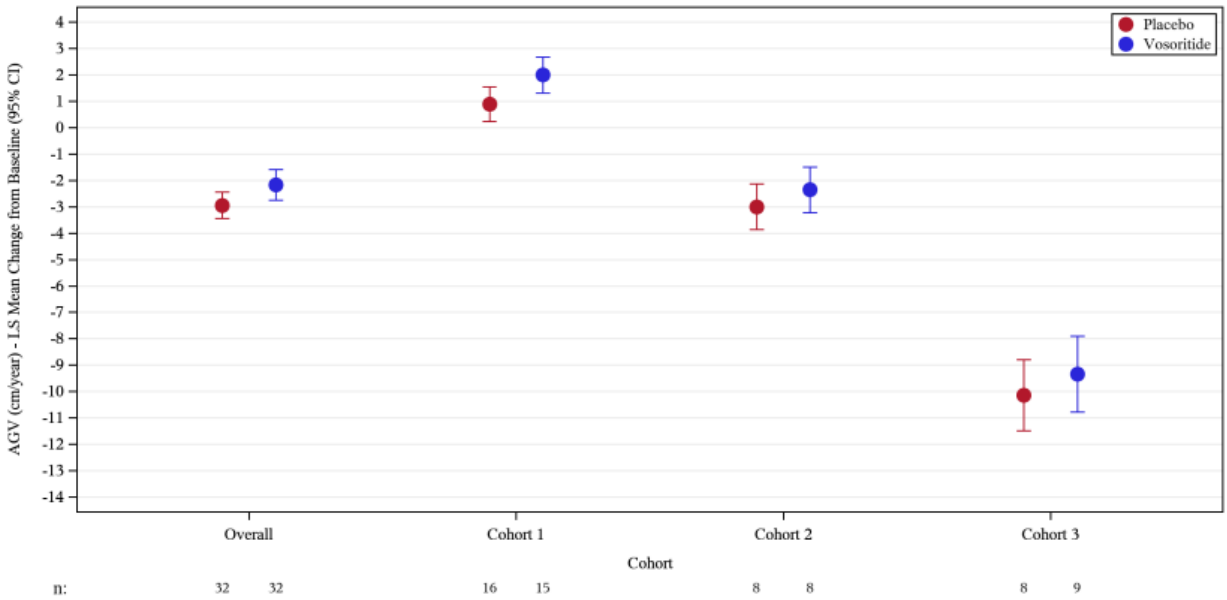
Change in AGV at Week 52

Results for the ANCOVA analysis in the FAS (randomized) showed a numerical improvement in growth velocity at Week 52 in the overall population of approximately 0.8 cm/year in the vosoritide group, compared with placebo. Cohort 1 placebo showed an increase in AGV at Week 52, with a marked increase seen in the vosoritide group. Cohorts 2 and 3 showed a marked decline in AGV with placebo, with the most pronounced decline seen in Cohort 3, consistent with a rapidly declining growth velocity in these younger children.

Cohort 2 and 3 showed less pronounced decline in AGV on vosoritide treatment, indicative of a positive treatment effect.

The LS mean difference between the treatment groups was consistent across the cohorts with point estimates in favour of vosoritide from Cohort 1 to Cohort 3 (Cohort 1: LSM difference of 1.10 cm/year [95% CI: 0.13, 2.07]; Cohort 2: LSM difference of 0.63 cm/year [95% CI: 0.63 [-0.60, 1.87], and Cohort 3: LSM difference of 0.79 cm/year [95% CI: -1.08, 2.67] in the FAS [randomized]).

Figure 8 LS Mean Change from Baseline (95% CI) for Annualized Growth Velocity at Week 52 Analysis Population (Full Analysis Set [Randomized])



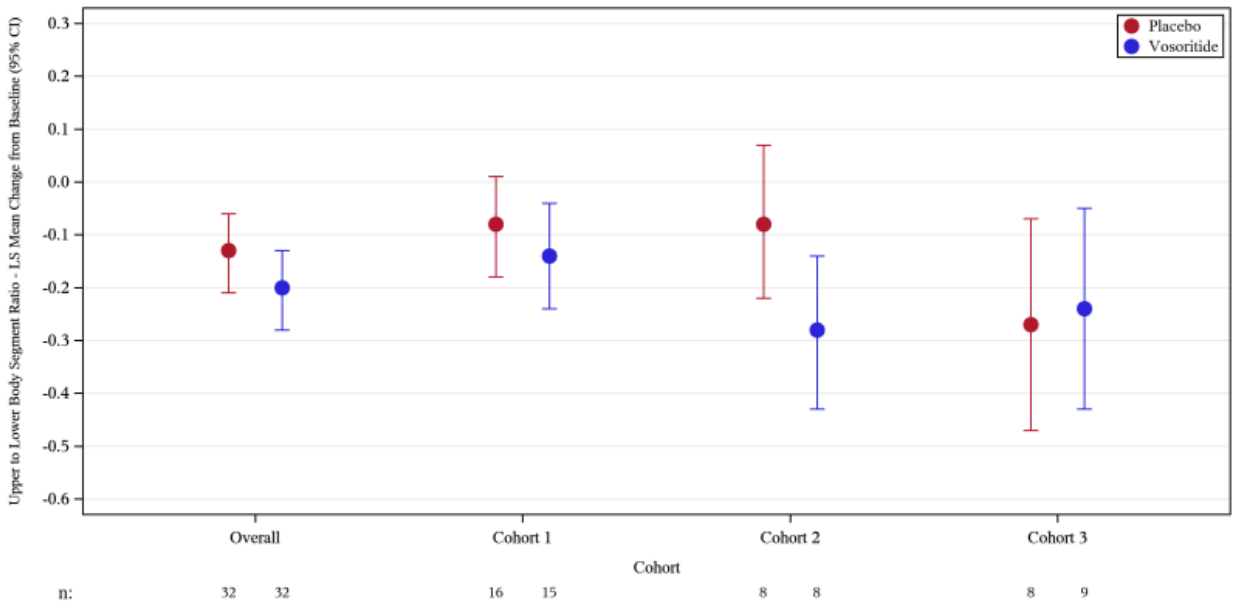
Change in Upper to Lower Body Segment Ratio at Week 52

Results for the ANCOVA analysis in the FAS (randomized) showed a numerically larger decrease in upper to lower body segment ratio in the vosoritide group compared with placebo in the overall population (LSM difference of -0.07 [95% CI: -0.17, 0.04]), driven particularly by changes in Cohort 2 (LSM difference of -0.21 [95% CI: -0.43, 0.00]), with no worsening observed in Cohort 3 (LSM difference of -0.03 [95% CI: -0.27, 0.32]).

The LS mean difference was not consistent across the cohorts and the 95% CIs greatly increased in size from Cohort 1 to Cohort 3.

Similar results were observed in the FAS population (LSM difference of -0.06 [95% CI: -0.15, 0.03]).

Figure 9 LS Mean Change from Baseline (95% CI) for Upper to Lower Body Segment Ratio at Week 52 Analysis Population (Full Analysis Set [Randomized])



Change in HRQoL and functional independence measures at Week 52

After 52 weeks of treatment, no clear difference was observed in change from baseline between the vosoritide and placebo group in HRQoL, functional performance and developmental performance, as measured by ITQoL, WeeFIM-II, and BSID-III. Meaningful changes on HRQoL data are likely to take longer to manifest with a cumulative improvement in height over time.

Ancillary analyses

Sleep apnea

Change from baseline in Sleep Study Indices at Week 52

A sleep study was performed in a limited number of qualified sleep centers. A sleep-testing device was used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea included but were not limited to the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index).

Table 7 Sleep Study Indices by Cohort Analysis Population: Full Analysis Set Change from baseline in Imaging assessments at Week 52

	Cohort 1		Cohort 2		Cohort 3	
Mean (SD)	All Vosoritide	Placebo	All	Placebo	All Vosoritide	Placebo
	(N=19)	(N=16)	(N=12)	(N=8)	(N=12)	(N=8)
n	16	14	9	5	10	7
Apnea Hypopnea Index (Number per Hour)	-1.45 (4.63)	-0.54 (2.70)	-0.72 (1.41)	1.06 (4.80)	-0.94 (2.78)	1.89 (6.31)
Apnea Index (Number per Hour)	-0.83 (1.93)	-1.07 (2.12)	-0.71 (1.61)	0.40 (2.34)	-0.36 (2.54)	-1.09 (1.22)
Central Apnea Index (Number per Hour)	-0.74 (1.86)	-1.26 (2.66)	-0.71 (1.61)	-0.28 (0.89)	0.50 (0.92)	-1.00 (0.97)
Hypopnea Index (Number per Hour)	-0.61 (3.63)	0.52 (1.35)	-0.01 (1.32)	0.66 (2.53)	-0.56 (0.54)	2.97 (5.45)
Desaturation per Hour ≥3% (Number per Hour)	-1.24 (3.98)	-0.41 (1.51)	-0.69 (1.30)	0.98 (3.60)	-0.93 (2.60)	1.71 (6.63)
Obstructive Index (Number per Hour)	-0.09 (0.45)	0.19 (0.73)	-0.01 (0.08)	0.68 (1.52)	-0.86 (2.08)	-0.07 (0.64)

SD: standard deviation.
Change from baseline was based on the participants with available measurements at both time points. Baseline is defined as Day 1 or screening if a Day 1 measurement is not available.

Change in Magnetic Resonance Imaging Parameters at Week 52

On comparison of MRI parameters at Week 52, positive numerical changes were observed with vosoritide treatment compared to placebo, most notably in Cohort 3, including marked positive percentage change from baseline in facial volume, sinus volume and the area of foramen magnum. These parameters are of particular interest in ACH due to mid-facial hypoplasia, obstructive sleep apnea and foramen magnum stenosis, all characteristic features of the condition.

In Cohort 1 and Cohort 2, which recruited older children, changes in these parameters were less pronounced and variable, particularly in foramen magnum, reflecting the natural growth and premature closure of synchondroses in the base of the skull that impact development of foramen magnum in children with ACH.

Table 8 Change in Magnetic Resonance Imaging (MRI) Parameters from Baseline to Week 52 by Cohort Analysis Population: Safety

	Cohort 1		**Cohort 2**		**Cohort 3**	
	All Vosoritide (N=19)	**Placebo (N=16)**	**All-Vosoritide (=12)**	**Placebo (N=8)**	**All-Vosoritide (N=12)**	**Placebo (N=8)**
Baseline, N	16	13	12	8	11	8
Mean (SD)	582.407 (88.151)	573.834 (91.019)	451.478 (61.453)	450.791 (71.198)	340.366 (38.678)	357.529 (51.159)
Week 52, N	14	8	7	7	9	6
Change from BL at W52	34.953 (39.151)	61.454 (23.214)	89.583 (42.331)	68.800 (24.630)	144.378 (24.110)	111.170 (33.088)
% Change at W52	6.32 (7.82)	11.85 (4.96)	20.56 (10.48)	15.08 (5.66)	43.49 (10.33)	33.74 (12.66)
Volume of sinus (cm^3)						
Baseline, N	19	16	12	8	12	8
Mean (SD)	9.481 (4.201)	8.899 (3.905)	4.351 (3.458)	5.376 (4.482)	2.334 (1.621)	2.781 (2.200)
Week 52, N	17	11	8	7	10	6
Change from BL at W52	12.754 (5.511)	11.086 (3.086)	1.110 (3.729)	0.079 (3.428)	1.862 (2.388)	-1.010 (3.395)
% Change at W52	52.01 (82.95)	100.90 (177.15)	44.91 (78.80)	80.91 (160.39)	128.81 (128.18)	48.49 (191.74)
Volume of calvarium (cm^3)						
Baseline, N	19	16	11	8	8	12
Mean (SD)	1743.377 (180.310)	1734.763 (188.348)	1513.967 (169.677)	1384.816 (147.360)	978.373 (83.428)	1005.745 (112.807)
Week 52, N	16	12	8	6	10	6
Change from BL at W52	47.275 (47.638)	48.676 (53.527)	204.236 (106.927)	203.622 (95.583)	485.427 (78.727)	432.735 (142.515)
% Change at W52	2.83 (2.97)	2.82 (2.83)	13.82 (8.16)	15.02 (7.84)	50.41 (8.94)	45.35 (16.65)
Area of foramen magnum (cm^2)						
Baseline, N	19	16	12	8	12	8
Mean (SD)	0.139 (0.021)	0.136 (0.022)	0.140 (0.032)	0.130 (0.031)	0.091 (0.033)	0.094 (0.026)
Week 52, N	17	12	8	7	10	6
Change from BL at W52	-0.012 (0.034)	0.000 (0.022)	-0.001 (0.022)	0.006 (0.018)	0.029 (0.029)	0.018 (0.018)
% Change at W52	-7.26 (21.86)	0.93 (16.07)	0.76 (14.82)	4.00 (11.99)	43.89 (74.44)	24.74 (26.07)
Area of spinal cord at the foramen magnum level (cm^2)						
Baseline, N	19	16	12	8	12	8
Mean (SD)	0.071 (0.009)	0.070 (0.017)	0.075 (0.029)	0.070 (0.012)	0.047 (0.014)	0.048 (0.018)
Week 52, N	17	12	8	7	10	6
Change from BL at W52	-0.001 (0.018)	0.011 (0.014)	-0.005 (0.026)	-0.004 (0.012)	0.009 (0.017)	0.013 (0.020)
% Change at W52	-0.84 (24.52)	19.13 (26.87)	1.66 (27.99)	-6.53 (15.69)	26.40 (43.74)	51.03 (73.33)
Whole brain total volume						
Baseline, N	18	16	11	7	12)	8
Mean (SD)	1309.365 (123.154)	1312.861 (119.078	1109.785 (131.475)	1052.374 (121.499)	756.528 (63.029)	748.348 (79.227)
Week 52, N	16	12	8	6	10	6

	Cohort 1		Cohort 2		Cohort 3	
	All Vosoritide (N=19)	**Placebo (N=16)**	**All-Vosoritide (=12)**	**Placebo (N=8)**	**All-Vosoritide (N=12)**	**Placebo (N=8)**
Change from BL at W52	46.752 (79.899)	53.412 (44.711)	180.820 (79.590)	177.942 (44.896)	376.896 (38.840)	300.223 (66.118)
% Change at W52	3.95 (6.59)	4.27 (3.63))	16.88 (8.87)	16.72 (5.02)	50.16 (7.18)	42.29 (12.39)
Ventricles total volume						
Baseline, N	18	16	12	8	12	8
Mean (SD)	95.289 (65.801)	84.562 (70.350)	50.688 (22.301)	46.658 (25.491)	29.302 (13.979)	23.333 (6.834)
Week 52, N	16	12	8	7	10	6
Change from BL at W52	1.272 (12.314)	3.158 (10.457	15.595 (27.704)	4.614 (11.476)	24.230 (17.253)	23.782 (22.600)
% Change at W52	-0.02 (11.24)	11.12 (32.83)	21.63 (36.97)	10.19 (26.75)	96.44 (48.82)	94.41 (52.03)
Ratio of face volume to calvarium						
Baseline, N	15	14	11	7	11	8
Mean (SD)	0.353 (0.024)	0.314 (0.097)	0.304 (0.033)	0.316 (0.039)	0.347 (0.044)	0.356 (0.035)
Week 52, N	13	8	7	6	9	6
Change from BL at W52	0.007 (0.030)	0.028 (0.015)	0.019 (0.013)	0.000 (0.028)	-0.019 (0.033)	-0.028 (0.031)
% Change at W52	1.82 (8.89)	8.62 (5.04)	6.33 (4.60)	0.61 (9.10)	-5.04 (9.28)	-7.74 (9.08)
Ratio of area of spinal cord to foramen magnum						
Baseline, N	19	16	12	8	12	8
Mean (SD)	0.517 (0.070)	0.509 (0.104)	0.524 (0.129)	0.548 (0.090)	0.537 (0.069)	0.499 (0.092)
Week 52, N	17	12	8	7	10	6
Change from BL at W52	0.039 (0.109)	0.078 (0.096)	-0.031 (0.109)	-0.043 (0.064)	-0.025 (0.139)	0.047 (0.100)
% Change at W52	8.72 (22.60)	18.90 (23.04)	-1.73 (20.48)	-7.25 (11.66)	-3.41 (26.58)	10.25 (23.10)
Ratio of face volume to sinus						
Baseline, N	16	14	12	8	11	8
Mean (SD)	83.346 (54.453)	64.391 (35.636)	565.495 (1067.857)	204.790 (267.7112417)7	719969.649 (136.525)	207.725 (133.753)
Week 52, N	8	14	7	7	6	9
Change from BL at W52	-25.684 (45.236)	-13.700 (22.610)	105.979 (324.013)	-102.499 (256.939)	-65.133 (119.128)	188.615 (433.627)
% Change at W52	-17.19 (32.29)	-15.16 (29.77)	19.02 (76.11)	4.29 (65.28)	-5.95 (81.29)	338.06 (598.22)
Ratio of face volume to calvarium						
Baseline, N	15	14	11	7	11	8
Mean (SD)	0.353 (0.024)	0.314 (0.097)	0.304 (0.033)	0.316 (0.039)	0.347 (0.044)	0.356 (0.035)
Week 52, N	13	8	7	6	9	6
Change from BL at W52	0.007 (0.030)	0.028 (0.015)	0.019 (0.013)	0.000 (0.028)	-0.019 (0.033)	-0.028 (0.031)
% Change at W52	1.82 (8.89)	8.62 (5.04)	6.33 (4.60)	0.61 (9.10)	-5.04 (9.28)	-7.74 (9.08)

Max, maximum; Min, minimum; SD, standard deviation.
a Change from baseline and percent change from baseline was based on the participants with available measurements at both time points. Baseline is defined as Day 1 or screening if a Day 1 assessment is not available.

Exploratory Efficacy Endpoints

Limited data were collected to assess the change from baseline in physical and phenotypic changes with clinical photography at Week 52, and no analyses were performed.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9 Summary of Efficacy for pivotal trial 111-206

<table>
<tr><td colspan="3">Protocol No.: 111-206: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia,Age 0 to < 60 Months</td></tr>
<tr><td>Study identifier</td><td colspan="2">Biomarin Trial 111-206</td></tr>
<tr><td>Design</td><td colspan="2">A total of 70 participants were planned to be enrolled at 16 clinical centers worldwide by a staggered, age-descending recruitment of three age cohorts based on age at study screening; within Cohorts 1 and 2, participants were stratified by age:
• Cohort 1 – children aged ≥ 24 to < 60 months stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
• Cohort 2 – children aged ≥ 6 to < 24 months stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
• Cohort 3 – children aged 0 to < 6 months; treatment begins at ≥ 3 months to < 6 months after 3 months of observation.
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 were collected in 111-901 (non-interventional multicenter, multinational study). Each cohort included at least three sentinel participants receiving vosoritide to evaluate the short-term safety and PK of vosoritide before opening the rest of the cohort for randomized participants.
Participants were randomized on a 1:1 ratio to either vosoritide or placebo. Randomized participants received a daily vosoritide dose determined after the evaluation of the PK data of sentinel participants for each cohort. A total of 75 participants were enrolled and randomized to study treatment.</td></tr>
<tr><td></td><td>Duration of main phase:</td><td>52 weeks of double-blind treatment with 2 weeks</td></tr>
<tr><td></td><td>Duration of Run-in phase:</td><td>6 month Cohort 1+2, 3 months Cohort 3</td></tr>
<tr><td></td><td>Duration of Extension phase:</td><td>Following completion of the study, participants in all treatment groups were eligible to receive vosoritide in the open-label extension study 111-208 to assess the safety and efficacy of vosoritide over a longer-term until closure of growth plates.</td></tr>
<tr><td></td><td>First Enrollment</td><td>13.June 2018</td></tr>
<tr><td></td><td>Last Patient Last Visit</td><td>26.January 2022</td></tr>
<tr><td></td><td>Date of Study Report</td><td>18.July 2022</td></tr>
<tr><td>Hypothesis</td><td colspan="2">No formal hypothesis; Superiority</td></tr>
<tr><td>Treatments groups</td><td>Cohort 1 : children aged ⩾ 24 to < 60 months stratified by age (⩾ 24 to < 36 months and ⩾ 36 months to < 60 months)</td><td>4 sentinel participants, 15 participants randomized to receive vosoritide, and 16 participants randomized to receive placebo</td></tr>
<tr><td></td><td>Cohort 2: children aged ≥ 6 to < 24 months stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)</td><td>4 sentinel participants, 8 participants randomized to receive vosoritide, and 8 participants randomized to receive placebo</td></tr>
</table>

	Cohort 3: children aged 0 to < 6 months; treatment begins at ≥ 3 months to < 6 months after 3 months of observation**.**		3 sentinel participants, 9 participants randomized to receive vosoritide, and 8 participants randomized to receive placebo
Endpoints and definitions	**Primary endpoint**	Height Z score	Change from baseline in height Z-score at Week 52
	Secondary endpoint	Height	Change from baseline in height at Week 52
	Secondary endpoint	AGV change	Change from baseline in AGV at Week 52
	Secondary endpoint	Body segment ratio	Change from baseline in upper to lower body segment ratio at Week 52
	Other secondary endpoints: • Change from baseline in other growth measures (upper body length, head circumference, arm span, upper arm length, lower arm length, upper leg length [thigh], knee to heel length, and tibial length) at Week 52 • Change from baseline in other body proportion ratios (arm span to height ratio, upper arm length to lower arm [forearm] length ratio, upper leg length [thigh] to knee to heel length ratio, and upper leg length (thigh) to tibial length ratio) at Week 52 • Change from baseline in BMI and BMI Z-score at Week 52 • Change from baseline in weight Z-score at Week 52 • Change from baseline in ITQoL, WeeFIM, and BSID-III scores at Week 52 • Change from baseline in sleep study indices at Week 52 • Change from baseline in bilateral X-rays of lower extremities, lumbar spine X-rays, bone mineral density (BMD) and bone mineral content (BMC) by DXA, and MRI results at Week 52		
Database lock	14 February 2022		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	**Intent to treat**				
Descriptive statistics and estimate variability	**Treatment group**	**Cohort 1**	**Cohort 2**	**Cohort 3**	**FAS (random)**
	Number of subject	**Voso: 15 Placeb:16**	**Voso: 8 Place: 8**	**Voso: 9 Place:8**	**Voso: 32 Place: 32**
	Primary endpoint: *negative LS mean (LSM) change in height Z score from baseline at Week 52*	0.33 95% CI: 0.00,0.67 p=0.051	0.21 95% CI: -0.37,0.79 p=0.44	0.23 95% CI: -0.47,0.91 p=0.50	0.25 95% CI: 0.02,0.53 p=0.07
	Secondary endpoint: *LSM difference Change in Height at Week 52* ***(cm)***	0.96 95% CI: -0.09,2.02 (cm) p=0.07	0.71 95% CI: -0.62,2.04 (cm) p=1.02	0.70 95% CI: -1.28, 2.68 (cm) p=0.48	0.77 95% CI: -0.02, 1.56 (cm) p=0.057
	Secondary endpoint: LSM difference Change in AGV at Week 52 (cm/year)	1.10 (cm/year) 95% CI: 0.13,2.07 p=0.02	0.63 (cm/year) 95% CI: -0.60,1.87 p=0.28	0.79 (cm/year) 95% CI: -1.08, 2.67 p=0.40	0.8 (cm/year) p=0.045

	Secondary endpoint: LSM difference Change in Upper to Lower Body Segment Ratio at Week 52	*Results for the ANCOVA analysis in the FAS (randomized) showed a numerically larger decrease in upper to lower body segment ratio in the vosoritide group compared with placebo in the overall population (LSM difference of -0.07 [95% CI: -0.17, 0.04]), driven particularly by changes in Cohort 2 (LSM difference of -0.21 [95% CI: -0.43, 0.00]), with no worsening observed in Cohort 3 (LSM difference of -0.03 [95% CI: -0.27, 0.32]).* *The LS mean difference was not consistent across the cohorts and the 95% CIs greatly increased in size from Cohort 1 to Cohort 3. They were also not statistically significant.*
	Secondary endpoint: Change in HRQoL and functional independence measures at Week 52	**Not reported** "Since interpretation is limited due to small sample sizes, heterogeneity introduced by developmental stage and age preclude the ability to draw meaningful inferences within a 52-week timeframe."
	Secondary endpoint: Change from baseline in Sleep Study Indices at Week 52	Overall, a reduction in all the polysomnography parameters was observed at Week 52 in the vosoritide group, with the exception of Apnea Index in Cohort 3, while changes were mixed in the placebo group No worsening in the polysomnography parameters were observed with vosoritide at Week 52 compared to placebo. Whilst directional positive change in all but one polysomnography parameters were seen with vosoritide in all cohorts, it is unclear whether these changes represent a clinically meaningful effect of treatment on sleep apnea.
	Secondary endpoint: Change from baseline in Imaging assessments at Week 52:	On comparison of MRI parameters at Week 52, positive numerical changes were observed with vosoritide treatment compared to placebo, most notably in Cohort 3, including marked positive percentage change from baseline in facial volume, sinus volume and the area of foramen magnum. These parameters are of particular interest in ACH due to mid-facial hypoplasia, obstructive sleep apnea and foramen magnum stenosis, all characteristic features of the condition. In Cohort 1 and Cohort 2, which recruited older children, changes in these parameters were less pronounced and variable, particularly in foramen magnum, reflecting the natural growth and premature closure of synchondroses in the base of the skull that impact development of foramen magnum in children with ACH.

Analysis performed across trials (pooled analyses and meta-analysis)

Participants Aged ≥24 to <60 Months

The efficacy data from 111-206 in children aged ≥24 to <60 months support the currently approved indication for treatment of ACH in children > 2 years old. The positive effects of vosoritide were consistently demonstrated using comparative analyses of NH data and multiple analytical approaches (Figure 10 and Figure 11). For children ≥24 to <60 months of age, the results confirm a consistent treatment effect of vosoritide on growth and maintenance of that effect through 3 years of follow-up, with a gain in height Z-score of > 1 SDS and >5.5 cm in height with no evidence of tachyphylaxis.

In addition, the summary of height -Z score referenced to untreated ACH using longer-term data from study 111-208 confirms the benefits of vosoritide treatment.

Vosoritide participants achieved 94% height gain of average stature children and untreated children with ACH showed 65% of height gain compared to the height gain of average stature children of the same age and sex over 3 years.

Figure 10 Forest Plot of Differences in Mean Change from Baseline in Height Z-Score at Year 1, 2 and 3 Age Group ⩾24 to <60 Months

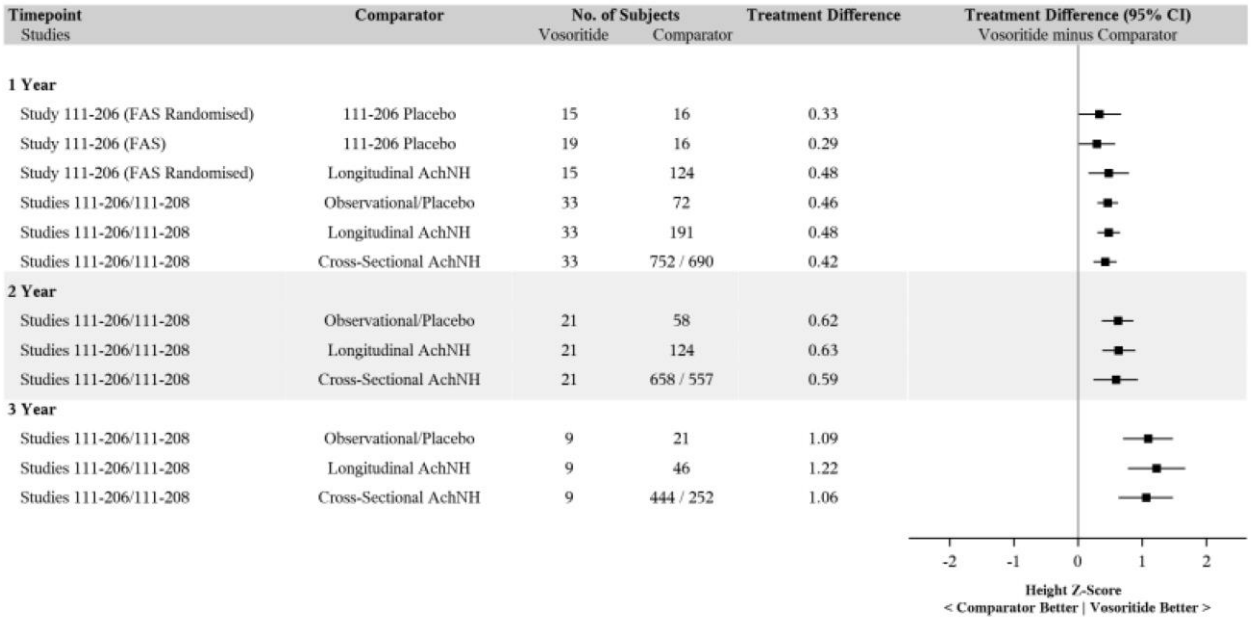
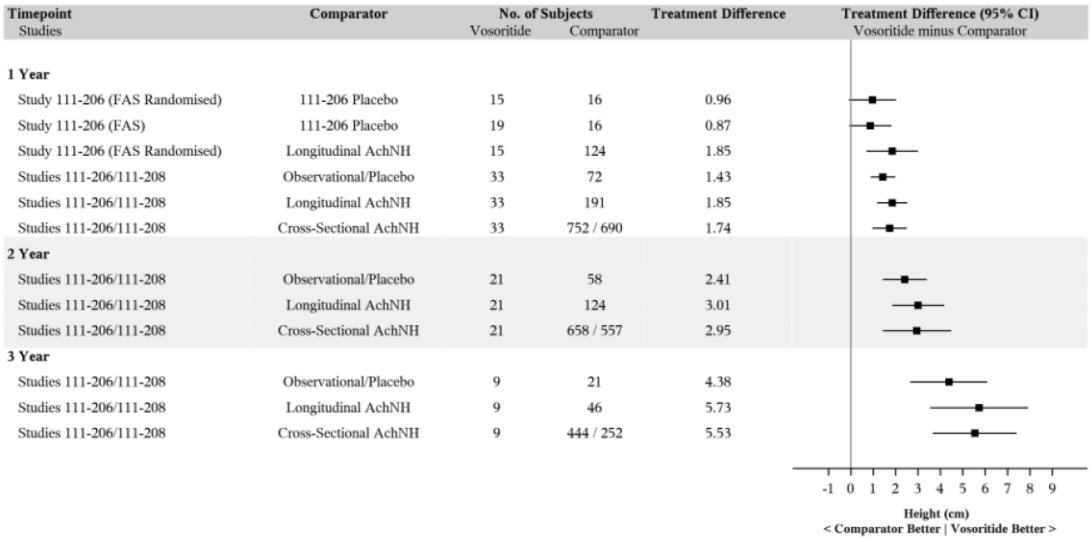


Figure 11 Forest Plot of Differences in Mean Change from Baseline in Height at Year 1, 2 and 3 Age Group ⩾24 to <60 Months



Participants Aged ≥6 to <24 Months

Overall, efficacy results confirm a consistent treatment effect of vosoritide on growth in children with ACH ≥6 to <24 months irrespective of the control used, and maintenance of that effect through 2 years of follow-up.

The effects of vosoritide were consistently demonstrated using comparative analyses of NH data with multiple analytical approaches (Figure 12 and Figure 13) as well as in a summary of height -Z score referenced to untreated ACH using longer term data from study 111-208.

Vosoritide participants achieved 83% height gain of average stature children and untreated children with ACH showed 67% of height gain compared to average stature children after 2 years.

Figure 12 Forest Plot of Differences in Mean Change from Baseline in Height Z-Score at Year 1, 2 and 3 Age Group ⩾6 to <24 Months

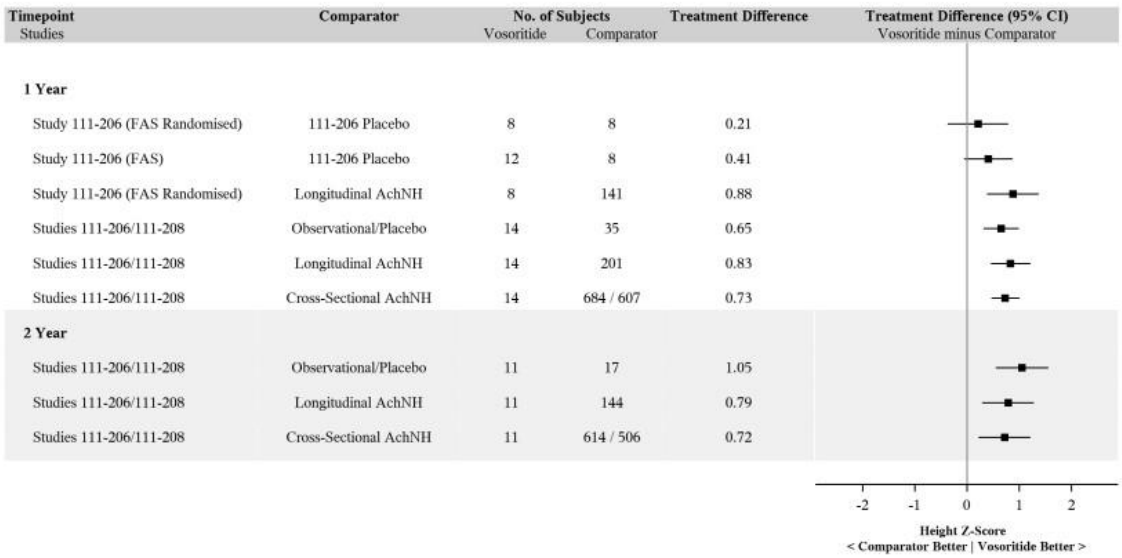
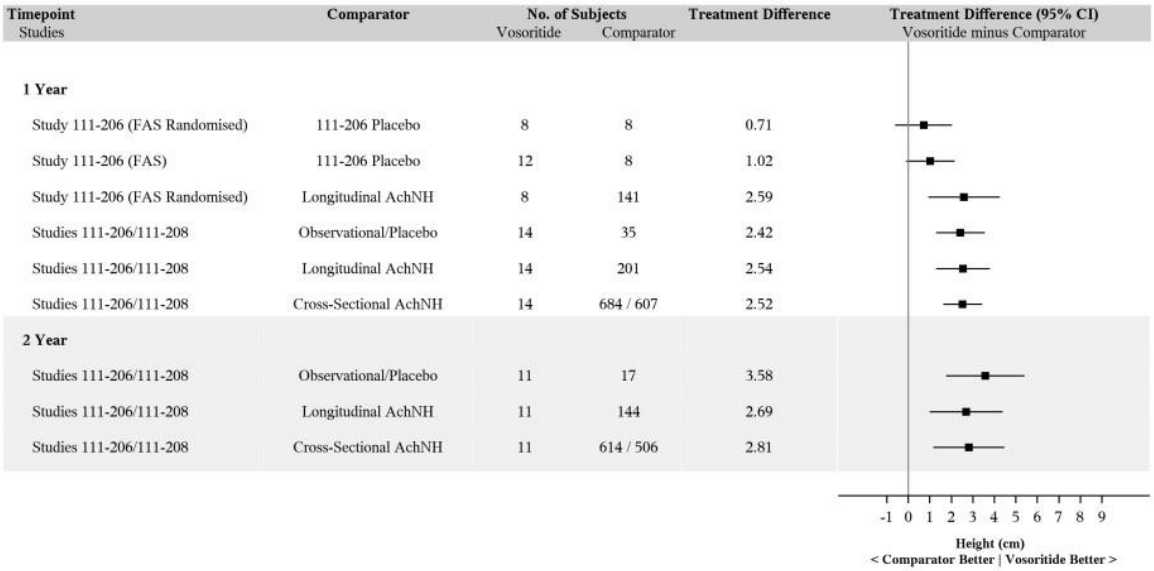


Figure 13 Forest Plot of Differences in Mean Change from Baseline in Height at Year 1 and 2 Age Group ⩾6 to <24 Months



Participants Aged 0 to <6 Months

After 1.5 years of treatment (n=6), the positive effect of vosoritide on height Z-score and incremental gain in height was observed in three comparative analyses using different NH controls.

Vosoritide participants achieved a 77% height gain compared to average stature children and AchNH participants achieved a 70% height gain compared to average stature children at 1.5 years.

Figure 14 Forest Plot of Differences in Mean Change from Baseline in Height Z-Score at Year 1 and 1.5 Age Group 0 to <6 Months

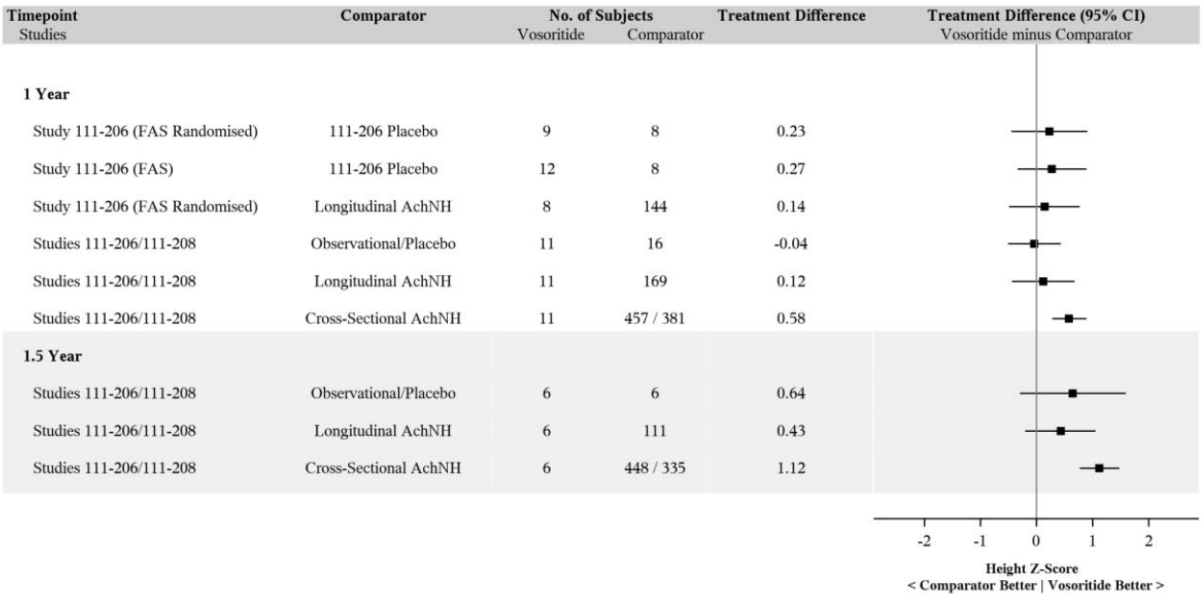
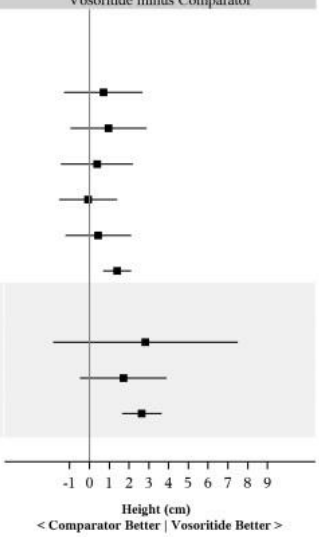


Figure 15 Forest Plot of Differences in Mean Change from Baseline in Height at Year 1 and 1.5 Age Group 0 to <6 Months

Timepoint Studies	Comparator	No. of Subjects Vosoritide	 Comparator	Treatment Difference	Treatment Difference (95% CI) Vosoritide minus Comparator
1 Year					
Study 111-206 (FAS Randomised)	111-206 Placebo	9	8	0.70	
Study 111-206 (FAS)	111-206 Placebo	12	8	0.96	
Study 111-206 (FAS Randomised)	Longitudinal AchNH	8	144	0.38	
Studies 111-206/111-208	Observational/Placebo	11	16	-0.07	
Studies 111-206/111-208	Longitudinal AchNH	11	169	0.44	
Studies 111-206/111-208	Cross-Sectional AchNH	11	457 / 381	1.39	
1.5 Year					
Studies 111-206/111-208	Observational/Placebo	6	6	2.83	
Studies 111-206/111-208	Longitudinal AchNH	6	111	1.71	
Studies 111-206/111-208	Cross-Sectional AchNH	6	448 / 335	2.65	



Consistent with observations in other age groups, improvement in height Z-score in reference to untreated ACH population was seen in the youngest treated participants.

Overall, a favourable effect on growth was observed with vosoritide in the youngest age group, particularly as the participants' age increased. The large variability in the background growth velocity at this age range will have had impact on the result.

Clinical studies in special populations

Not availalble.

Supportive study

Study 111-208

Critical Design Features

Study 111-208 is an ongoing Phase 2 open-label long-term extension study to evaluate the safety and efficacy of vosoritide in children with ACH.

The primary objectives of the study are to evaluate the long-term safety, tolerability of vosoritide and to evaluate change in height Z-score in children with ACH treated with vosoritide. Participants will continue to be evaluated in this study until they reach near final adult height (defined as evidence of growth plate closure and < 1.5 cm/year AGV).

Participants in Study 111-208 were to receive the daily dose of vosoritide determined to be appropriate for their age in 111-206. Participants received a daily dose of 30 µg/kg while they were < 2 years of age. The daily dose was adjusted to 15 µg/kg during the visit immediately preceding the 2-year birthday.

Interim Key Efficacy Results

As of the 26 January 2022 data cut-off, 73/75 participants who had completed treatment in 111-206 had enrolled in 111-208 and received vosoritide. Of the 73 participants treated, 31 had previously received placebo in Study 111-206 and 42 had previously received vosoritide.

Analyses included all 73 participants grouped according to their age at first dose of active treatment. A total of 11 participants were aged 0 to < 6 months, 22 were aged ≥ 6 to < 24 months, 34 were ≥ 24 to < 60 months old and 6 were ≥ 60 months old when they received their first dose of vosoritide in either study 111-206 or 111-208. At the time of the data-cut off, all participants remained in the study and were continuing treatment.

Data is presented from the first dose of vosoritide, either from the start of Study 111-206 for those participants who received vosoritide in the parent study (N=42) or from the start of 111-208 for participants who received placebo in Study 111-206 (N=31).

Baseline was defined as the last assessment before the first dose of vosoritide treatment.

Summaries are presented for change from baseline over time. Interpretation of long-term changes in height Z-score (as well as AGV) in this population of vosoritide treated participants in the absence of a control group will have taken into account the natural trajectory of growth in children with ACH, with rapid accumulation of growth deficit compared to average stature children up to the age of 5, and general decrease in height Z-score and AGV over time in the untreated children with ACH of this age group.

Demographics and Baseline Characteristics

In trial 208, participants' ages ranged from 4.5 months to 72 months. Overall, there were similar percentages of male and female participants. Baseline growth patterns differed substantially between the age groups. The mean (SD) Height-Z score, AGV and upper to lower body segment ratio decreased with increase in age. Mean (SD) height ranged from 56.83 cm (2.03) in participants aged 0 to < 6 months old to 91.86 cm (4.65) in participants ≥ 60 months old.

Efficacy Results

Change in Height-Z Score

There was a total of 21 participants in the ≥ 24 to < 60 months group who had assessments up to Week 104 (Week 104 completers). For these participants the mean (SD) height Z-score (compared to healthy children) improved from -4.43 (0.82) at baseline to -4.09 (0.92) at Week 104. The corresponding mean (SD) change from baseline at Week 104 was 0.33 (0.82). When untreated AchNS patients were used as reference, the mean (SD) height Z-score improved from 0.39 (0.62) at baseline to 0.64 (0.55) at Week 104.

The change from baseline in height Z-score over time in Week 104 completers was consistent with that seen in the overall treated population (111-208 Interim CSR), by age group, and shows improvement in height Z-score over time in children aged ≥ 24 to < 60 months, shallow decline in children aged ≥ 6 to < 24 months group and a more profound decline in the 0 to < 6 months group.

Table 10 Height Z-Score Referenced to Average Stature Over Time -Week 104 Completers / Height Z-Score Referenced to Untreated ACH Over Time – Week 104 Completers

Height Z-Score	**Age on Day 1 of Vosoritide (Months)**			
	0 to <6 N=3	**≥6 to <24 N=11**	**≥24 to <60 N=21**	**≥60 N=1**
Baseline				
n	3	11	21	1
Mean (SD)	-3.54 (0.87)	-3.76 (0.81)	-4.43 (0.82)	-2.80 (NA)
Mean (SD) **Untreated ACH NHS**	-0.29 (0.44)	0.45 (0.80)	0.39 (0.62)	2.48 (NA)
Week 52				
n	3	11	21	1
Mean (SD)	-4.10 (0.58)	-3.47 (0.73)	-4.19 (0.73)	-2.68 (NA)
Mean (SD) change from baseline to Week 52	-0.55 (0.43)	0.29 (0.46)	0.24 (0.53)	0.12 (NA)
Mean (SD) change from baseline to Week 52 **Untreated ACH NHS**	0.26 (0.38)	0.73 (0.34)	0.42 (0.34)	0.16 (NA)
Week 78				
n	3	11	19	1
Mean (SD)	-3.78 (0.46)	-3.95 (0.99)	-4.19 (0.83)	-2.23 (NA)
Mean (SD) change from baseline to Week 78	-0.23 (0.49)	-0.19 (0.56)	0.17 (0.70)	0.57 (NA)
Mean (SD) change from baseline to Week78 **Untreated ACH NHS**	0.75 (0.40)	0.55(0.47)	0.44 (0.45)	0.63 (NA)
Week 104				
n	3	11	21	1
Mean (SD)	-4.51 (0.65)	-3.96 (0.97)	-4.09 (0.92)	-1.81 (NA)
Mean (SD) change from baseline to Week 104	-0.97 (0.91)	-0.19 (0.60)	0.33 (0.82)	1.00 (NA)
Mean (SD) change from baseline to Week 104 **Untreated ACH NHS**	0.26 (0.77)	0.68 (0.62)	0.64 (0.55)	1.10 (NA)

NA: not applicable; SD: standard deviation

Given the natural increase in height deficit over time in children with ACH, the interpretation of the observed changes is limited by the absence of a concomitant control group; however, to provide further clinical context, height Z-scores referenced to untreated children with ACH were derived for 111-206 and 111-208 study data using the published CLARITY study (Hoover-Fong 2021, source for AchNH dataset reference ranges). It would be expected that for untreated children with ACH the mean height Z-score stays relatively stable with no directional trends over time.

Change in Height

The increase in height over time in Week 104 completers was most pronounced in the 0 to < 6-month-old group, followed by ≥ 6 to < 24 months old, followed by ≥ 24 to <60 months old (Table below). In one participant who started treatment with vosoritide at the age of > 60 months, an increase in height of over 16.6 cm was observed after two years of treatment.

Table 11 Height Over Time – Week 104 Completers

Height (cm)	**Age at Day 1 of Vosoritide (Months)**			
	0 to <6 N=3	**≥6 to <24 N=11**	**≥24 to<60 N=21**	**≥60 N=1**
Baseline				
n	3	11	21	1
Mean (SD)	55.04 (0.51)	68.93 (4.76)	80.14 (4.68)	100.90 (NA)
Week 52				
n	3	11	21	1
Mean (SD)	67.31 (0.29)	77.92	86.53	107.23 (NA)
Mean change from baseline to Week 52	12.27 (0.80)	8.98 (2.01)	6.39 (1.63)	6.33 (NA)
Week 78				
n	3	11	19	1
Mean (SD)	7	79	89	1
Mean change from baseline to Week 78	1	10	8.	1
Week 104				
n	3	11	21	1
Mean (SD)	7	82	92	1
Mean change from baseline to Week	1	13	12	1

Change in Annualized Growth Velocity

Both 12-month and 6-month interval AGV were derived for this study; however, in this young population, data changes over 6-month intervals are the most informative due to the rapid decrease in growth velocity, therefore, changes over 6-month intervals are discussed.

At baseline, mean (SD) AGV decreased with increase in age as would be expected in this population. Six-month interval AGV for those participants who completed 104 weeks of treatment (completers) are presented in Table 12. In participants aged ≥ 24 months, following the natural pattern of deceleration of growth velocity in this age group, positive changes from baseline in mean AGV were observed at all but one timepoint (Month 18). In participants aged ≤ 24 months, decreases in AGV were seen at all timepoints post baseline. This decrease was more pronounced in participants aged 0 to < 6 months than in participants aged ≥ 6 to < 24 months. Of note, AGV decreased dramatically after 12 months but rebounded by 24 months (Table 12).

Table 12 6-Month Interval Annualized Growth Velocity (AGV) Over Time (All Treated) – Week 104 Completers

6-Month Annualized Growth Velocity (cm/year)	Age at Day 1 of Vosoritide (Months)			
	0 to <6 N=3	≥6 to <24 N=11	≥24 to<60 N=21	≥60 N=1
Baseline				
n	3	11	21	1
Mean (SD)	24.78 (5.39)	11.56 (4.82)	5.22 (1.84)	6.12 (NA)
Months 6				
n	1	10	19	0
Mean (SD)	14.43 (NA)	9.07 (2.99)	6.30 (2.69)	-
Mean (SD) change from baseline to Month 6	-5.03 (NA)	-1.80 (5.13)	1.08 (3.49)	-
Months 12				
n	1	10	19	0
Mean (SD)	9.67 (NA)	8.56 (2.43)	6.37 (1.80)	-
Mean (SD) change from baseline to Month 12	-9.79 (NA)	-2.30 (2.67)	1.15 (2.10)	-
Months 18				
n	3	11	19	1
Mean (SD)	10.49 (1.11)	3.96 (2.56)	4.98 (2.15)	10.37 (NA)
Mean (SD) change from baseline to Month 18	-14.29 (5.52)	-7.60 (5.97)	-0.24 (2.40)	4.25 (NA)
Months 24				
n	3	11	19	1
Mean (SD)	2.09 (3.19)	5.77 (2.76)	6.23 (2.07)	9.92 (NA)
Mean (SD) change from baseline to Month 24	-22.69 (8.56)	-5.79 (5.10)	1.01 (3.13)	3.80 (NA)

AGV: annualized growth velocity; FAS: full analysis set; SD: standard deviation

Change in Upper to Lower Body Ratio

Mean (SD) upper to lower body segment ratio at baseline was highest in participants aged 0 to < 6 months old and decreased with increase in age (Details in Table 13).

In all age groups, there was a decline in the upper to lower body segment ratio over time which is consistent with the natural pattern of growth in this age group of participants with ACH. Due to the natural improvement (decline) in upper to lower body segment ratio, and in absence of the untreated control group, it is not clear whether treatment with vosoritide was associated with clinically meaningful incremental improvement in proportionality.

Table 13 Upper to Lower Body Segment Ratio Over Time – Week 104 Completers

Upper to Lower Body Segment Ratio	Age at Start of Vosoritide (Months)			
	0 to <6 N=3	≥6 to <24 N=11	≥24 to<60	≥60 N=1
Baseline				
n	3	11	21	0
Mean (SD)	3.12 (0.37)	2.58 (0.23)	2.35 (0.18)	-
Week 52				
n	3	11	21	0
Mean (SD)	2.64 (0.23)	2.40 (0.20)	2.23 (0.21)	-
Mean change from baseline to Week 52	-0.48 (0.15)	-0.18 (0.22)	-0.12 (0.19)	-
Week 78				
n	3	11	19	0
Mean (SD)	2.42 (0.08)	2.46 (0.29)	2.17 (0.18)	-
Mean change from baseline to Week 78	-0.69 (0.43)	-0.11 (0.27)	-0.19 (0.14)	-
Week 104				
n	3	11	21	0
Mean (SD)	2.18 (0.44)	2.27 (0.16)	2.15 (0.19)	-
Mean change from baseline to Week 104	-0.94 (0.69)	-0.31 (0.15)	-0.20 (0.15)	-

FAS: full analysis set; SD: standard deviation

2.4.3. Discussion on clinical efficacy

Achondroplasia and rationale behind the clinical development of vosoritide

Vosoritide targets directly the pathodynamics of the underlying genetic abnormality in ACH and therefore the treatment of ACH with vosoritide has a strong mechanistic rationale.

Vosoritide has shown a statistically significant, robust and clinically relevant growth-promoting effect in children with ACH in the age range 5 to 18 years that appears to be maintained long-term without acceleration of bone maturation as seen in the data submitted for the initial MA and now.

At the time of approval, clinical data in ACH children aged 2 to < 5 years was very limited. The observed effects from the 130-weeks growth data in 4 sentinel subjects from study 111-206/208 in ACH children in the age range between 2 to < 5 years were assessed as promising and efficacy in this patient subgroup was further supported by the similar PD (CXM) responses and the shared disease mechanism across age groups in addition to the identification of an acceptable dosage based on PK modelling. It was also noted that starting treatment as soon as possible may be important to achieve optimal effects on final height and potentially other complications of ACH.

Provision of the final results from study 111-206 was imposed as a condition to the marketing authorization to address the remaining uncertainties in patients 2 to < 5 years.

For patients < 2 years of age, CHMP decided that data were insufficient and approved vosoritide only for *the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed.*

With this variation procedure, the applicant has fullfilled the MA condition and applies also for the extension of the indication including the younger children (< 2 years of age).

The initially proposed indication of vosoritide is for the treatment of ACH in participants whose epiphyses are not closed.

Design and conduct of clinical studies

The clinical evidence for the efficacy of vosoritide in participants with ACH aged <5 years is derived from the results from Phase 2 study 111-206 and its open-label extension study 111-208 and the comparison to NH data.

The clinical development program including the study design of trial 111-206 was discussed and agreed by CHMP during a previous SAWP advice. More details can be found in the documents of vosoritide's initial approval procedure.

Pivotal Study 111-206 has been concluded in the meanwhile. It is a 52-week multicentre, phase 2 randomized, double-blind, placebo-controlled clinical trial. The main objectives of the study were to evaluate the safety of vosoritide and its impact on growth in infants and younger children recruited from birth to 60 months (5 years) of age with genetically confirmed ACH. Subjects were enrolled into three age cohorts [Cohort 1: ≥ 24 to < 60 months (n ≥ 30) / Cohort 2: ≥ 6 to < 24 months (n ≥ 20) / Cohort 3: 0 to < 6 months (n: ≥ 20)] starting with the oldest population. Of note, the youngest child was 4.4 month at the time of inclusion in the trial, consequently the indication has been modified to include the lower age limit of 4 months.

At the time of initial approval, data from study 111-206 was only available for 11 sentinel patients between 2 and 5 years of age, who were subsequently transferred to the extension trial 208.

Studies 111-206 (and 111-208) included participants with ACH confirmed by genetic testing and recruited participants globally from the US, Europe, Australia and Japan. The characteristics of the patient population are representative of the target population.

A total of 75 participants enrolled into the study; 64 were randomized to receive vosoritide treatment or placebo [FAS (random): primary analysis population] and 11 were sentinel participants. Two participants discontinued from study treatment (one patient in Cohort 2 on placebo withdrew from study; one patient in Cohort 3 on vosoritide experienced an AE of sudden infant death syndrome, assessed as not related).

The primary efficacy endpoint in study 111-206 was the change in height Z-score from baseline to Week 52 (in reference to Centers for Disease Control and Prevention (CDC) normative data on average stature of healthy children). Selection of this endpoint as the primary measure of efficacy is justified due to the rapidly declining growth velocity between 0 to 3 years of age, making an endpoint of annualized growth velocity (AGV) unsuitable due its high variability. Key Secondary efficacy endpoints were Height, Annualised growth velocity (AGV) and Upper to lower body segment ratio. In addition, CXM levels as an important biomarker indicating effects on growth plates as well as Brain MRI, which evaluates the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions were included. All these endpoints are clinically meaningful and acceptable. They are established in clinical trials investigating growth effects.

Trial conduct and particular protocol deviations do not raise any specific concern regarding the validity of the results.

Statistical analysis is descriptive with no hypothesis testing; sample size is established in an arbitrary manner; it is a randomized, placebo controlled and blinded trial.

Supportive evidence regarding long treatment and efficacy during 104 weeks duration is available from an interim report of the ongoing extension trial 111-208. In this trial, ACH subjects who finalised treatment in trial 111-206 will receive vosoritide until they reach final or near final height. Thus, more long-term efficacy data can be expected in the next years. With the present application, 2-year (104 week) treatment results have been submitted.

Efficacy data and additional analyses

As mentioned earlier treatment of ACH with vosoritide has a strong mechanistic rationale, since vosoritide targets directly the pathodynamics of the underlying genetic abnormality in ACH subjects. However, while vosoritide had previously shown a statistically significant, robust and clinically relevant growth-promoting effect in children with ACH in the age range 5 to 18 years in the pivotal trial 111-301, a smaller effect size was observed in the pivotal trial 111-206 in the younger population aged between 0 and 60 months. In fact, an even more pronounced treatment effect may have been expected in the younger vosoritide treated population. The small number and the variable growth of patients in this age cohort may have contributed to the seemingly smaller effect size. Therefore, the CHMP requested an in-depth analysis of study results to better understand the observed outome (please see below).

Approved Population ≥24 to <60 months: 15 randomized to vosoritide, 16 randomized to placebo (and 4 sentinels):

The final data from study 111-206 confirm efficacy of vosoritide in the already approved age range ≥24 to <60 months with a placebo-adjusted LS mean (LSM) change in height Z-score from baseline at Week 52 of 0.33 [95% CI: 0.00,0.67 p=0.051]. It is noted that the results were only statistically significant for the secondary endpoint AVG. Considering that no formal sample size calculations were performed, the trial and the groups were probably underpowered and analyses were descriptive only, this issue should not be overemphasised. Taking into account the orphan disease nature of ACH, a comparison of vosoritide-treated patients in 111-206 and 111-206/208 versus the AchNH and observational/placebo external controls is also considered meaningful.

At year 1, the magnitude of treatment effect compared to the two external control groups was numerically consistently larger than in the 111-206 placebo-controlled analyses.

At year 2, longitudinal analyses of vosoritide treatment in 111-206/208 versus the AchNH and observational/placebo external controls show consistency and confirm a durable treatment effect of vosoritide on height Z-score and height.

At year 3, the baseline-adjusted mean (95% CI) difference in height Z-score was 1.06 (0.63, 1.48) SDS, in favour of vosoritide, compared to the AchNH external control arm, and the baseline-adjusted mean (95% CI) difference in height was 5.53 (3.65, 7.41) cm, in favour of vosoritide.

The data suggest an increasing height benefit with vosoritide treatment over time.

Insofar, the final results from pivotal trial 111-206 supported by those available from extension trial 111-208 confirm efficacy of vosoritide in patients ≥2 years of age.

Population aged between 0 and 24 months (*Cohort 2 [≥6 to <24 months]*: 8 randomized to vosoritide, 8 randomized to placebo and 4 sentinels and *Cohort 3 [0 to <6 months]*: 9 randomized to vosoritide, 8 randomized to placebo and 3 sentinels)

The MAH intitally applied for an extension of indication allowing treatment with vosoritide from birth. However, because of lack of data in patients below the age of 4 months, and uncertainties about the PK model and regarding the appropriate dose, a lower age cut-off of 4 months in the indication was agreed.

Initially, no pooled analyses of efficacy as well as safety outcome exclusively in this population were provided. Presented analyses were conducted for the total population of trial 111-206 and partially for the two younger Cohorts. Treatment benefit appeared smallest in the youngest patients below age 6 months.

Compared to the placebo arm, LSM change in height Z score from baseline (PEP) at Week 52 was the lowest in Cohort 2 out of the three cohorts, 0.21 [95% CI:-0.37,0.79; p=0.44] and corresponds to a LSM difference in Change in Height at Week 52 of 0.71 cm (95% CI: -0.62,2.04 (cm); p=1.02). In consequence, also the LSM difference in Change in AGV at Week 52 was the lowest, showing a 0.63 cm/year [95% CI: -0.60,1.87; p=0.28].

Similarly, results for the youngest children between >0 and < 6 month (Cohort 3) of age showed a relatively small numerically positive trend. LSM change in height Z score from baseline (PEP) at Week 52 is reported 0.23 (95% CI:-0.47,0.91; p=0.44] and corresponds to a LSM difference in Change in Height at Week 52 of 0.70 cm (95% CI: -1.28,2.68 cm; p=1.48). In consequence, also the LSM difference in Change in AGV at Week 52 was low, showing a 0.79 cm/year [95% CI: -1.08,2.67; p=0.40].

Hence, based on the limited data from the pivotal trial 111-206 during an observational period of 52 weeks, the treatment benefit in the applied for population aged 0 to 24 months appeared smaller than for the population aged > 2 years (mainly in the pivotal trial 111-301). However, several factors may have affected the trial outcome (small number, larger effects in subjects in the placebo group compared with AchNH and age-specific differences in intrinsic growth characteristics).

In the initial EoI dossier, the applicant has also provided data from the longitudinal analyses of vosoritide in studies 111-206 and 111-206/208. This was based on a comparison of vosoritide treatment outcome versus a larger untreated population of 101 AchNH and observational/placebo external controls. This explorative approach resulted in a significantly better outcome as illustrated by a 1-year height Z-score of 0.88 SDS (vosoritide versus AchNH external control) and 0.65 SDS (vosoritide versus observational/placebo external control), compared with 0.21 SDS (8 vosoritide versus 8 placebo in 111-206 Cohort 2). Similarly, the differences regarding change in height was more pronounced: 2.59 cm (vosoritide versus AchNH external control) and 2.42 cm (vosoritide versus observational/placebo external control), compared with 0.71 cm (8 vosoritide versus 8 placebo in 111-206).

Cross-sectional analyses of vosoritide in 111-206/208 versus the AchNH external control at 1-year for height Z-score and height were consistent with the longitudinal analyses.

After two years of treatment, the treatment effect was maintained as indicated by a gain in height of 2.30 cm and 3.58 cm at 2-years compared to AchNH external control and observational/ placebo external control, respectively. It is noted that the additive effect regarding height and Z-score outcome in the second year of treatment in the population of ≥ 6 to < 24 months in analyses from trial 206/208 was smaller than during the first year. More data will be generated post-marketing to better estimate the cumulative treatment effect. In the ongoing long-term studies, patients will be followed up to (near) final height.

The same approach using the two external controls instead of the 9 placebo subjects alone results in a treatment effect at 1-year in participants aged 0 to < 6 months (Cohort 3) varied from -0.04 to 0.27 SDS for height-Z score and -0.07 to 0.96 cm for height, with overlapping confidence intervals. Cross-sectional analyses of vosoritide in 111-206/208 versus the AchNH external control at 1-year for height Z-score and height differed from the longitudinal analyses with much smaller confidence intervals. At baseline, the mean (95% CI) difference between groups in height Z-score and height were -0.50 (-1.04, 0.05) SDS and -1.03 (-2.18, 0.12) cm, respectively. At 1-year follow up, the baseline-adjusted mean difference in height Z-score was 0.58 (0.28, 0.89) SDS, in favour of vosoritide, compared with the AchNH external control arm, and the baseline-adjusted mean difference for height was 1.39 (0.68, 2.10) cm, in favour of vosoritide, compared to the AchNH external control arm.

Again, the size of the treatment effect on height gain over 1.5 years represents restoration of a substantial proportion of the estimated height deficit observed between treated children with ACH and average stature children of the same sex and age range. Vosoritide participants achieved a 77% height gain compared to average stature children and AchNH participants achieved a 70% height gain compared to average stature children at 1.5 years.

Considering the differences between the different age clusters which would have affected the outcomes in these subpopulations additional analyses were requested.

In response the applicant provided aggregated data and analyses on the target population below 2 years of age (Cohorts 2 and 3) and discussed potential reasons for the growth difference to placebo in the youngest patients. The results showed that compared to placebo, the size of the treatment effect with vosoritide in the pooled group (< 2 years old) at Week 52 in height Z-score was consistent with Cohort 1 and Study 111-301. Although, the size of the improvement in height Z-score was similar, due to differences in height distribution between older and younger children (the spread in height distribution increases with age such that a change of 1 SDS in a 2-year-old male represents 3.49 cm whilst in an 8-year-old male represents 5.83 cm, CDC 2000), this did not translate into the same height gain (measured in centimeters) across age groups. It is for this reason that, although the impact on height deficit is comparable across the age groups, absolute height gain (cm) in Study 111-301 was greater than in Study 111-206 (pooled Cohort 2 and 3 and Cohort 1).

More mature data with a cut-off of 19 December 2022 (compared to 26 January 2022 in the EoI initial dossier) confirmed that after a longer treatment follow-up an accumulation of treatment benefit was shown with each year of treatment versus NH controls for the combined age groups ≥ 3 to < 24 months: Years 1 to 3, with a gain of between 0.26 to 0.74 SDS at year 1, 0.48 to 0.74 SDS at year 2 and 0.79 to 0.98 at year 3, in favour of vosoritide in height Z-score. These updated analyses also confirm a cumulative height gain between year 1 and year 3, with a gain of between 0.65 to 2.07 cm at year 1, 1.57 to 2.29 cm at year 2 and 3.45 to 3.87 cm at year 3, in favour of vosoritide.

With respect to the data in Cohort 3 in the ≥3 to < 6 months age group from the later cut-off (19 December 2022), it is acknowledged that, although confidence intervals overlapped, the point estimates differed in size; change in height Z-score at year 1 ranged from -0.04 to 0.58 SDS. Whilst there is evidence of a treatment effect in year 1, due to the variability in growth, the size of the effect is not clear. Overall, the difficulty in determining the effect in this age group remains, probably due to the underlying rapid decrease in growth velocity.

In this context it appears however reassuring that for year 2, the point estimates for the two cross sectional analyses using both external controls (same methodology; data not shown) were also consistent; 0.66 and 0.87 SDS in favour of vosoritide with lower bound of the 95% CI above zero. Also for height, point estimates ranged from -0.07 to 1.39 cm at year 1. For year 2, point estimates for the two cross-sectional analyses using different external controls (data not shown) and same methodology were consistent; 1.62 and 1.96 cm in favour of vosoritide with lower bound of the 95% CI above zero. However, for both parameters the point estimate was 0.12 SDS for change in height-Z-score and 0.25 cm for height. The percent height gain at year 2, compared to average stature children was based on the LS mean change in the longitudinal analysis, consequently the height gain in vosoritide-treated participants aged 3 to < 6 months over average stature compared to untreated ACH children was minimal (70% versus 69%). The reasons remain unknown. It is not clear why the AChNH longitudinal analyses are discordant with the two cross sectional analyses particularly when using the same control. The Applicant therefore conducted an additional analysis using a different statistical approach and different control arms. Considering the additional analyses presented (results not shown) the majority of the results indicated consistent efficacy, while some inconsistent findings may be explained by the differences in growth velocity during the first and second years of life analysed in small cohorts.

Finally, the studied parameters included upper to lower body segment ratio, leg ratio, arm ratio, arm span ratio, arm span, head circumference and body ratio were not consistently reported; however the applicant informed that no apparent trends were observed over time in participants aged ≥ 6 to < 24 months. Since particularly the upper to lower body segment ratio may indicate an important efficacy of vosoritide, the applicant was requested to report when mature outcome regarding this secondary endpoint may be available during the long term follow up. The applicant clarified that the difference between the general population and children with ACH is that the U/L- ratio itself differs, with the mean value at birth being 1.7 for the general population which decreases to about 1.1 by 5 to 6 years of age and reaches a final value of 1 by 10 years of age. In contrast, for children with ACH, the mean value at birth is about 2.6 at birth, reaching about 2 at 5 to 6 years of age and plateauing around 1.8 at 10 years. Thus, assessment of this parameter can only be expected reliably at the age of about 10 years. This information will be obtained from an ongoing safety/efficacy study 111-209 (cat. 3 commitment in the RMP)

Positive numerical changes with vosoritide treatment compared to placebo, including positive percentage change from baseline in facial volume, sinus volume and the area of foramen magnum were reported. In responding on the RSI, the applicant provided a sufficient discussion regarding the potential impact of the MRI findings in the context of current knowledge and the relevance of the magnitude of changes observed.

According to the data, a reduction in all the polysomnography parameters was observed at Week 52 in the vosoritide group, with the exception of Apnea Index in Cohort 3, while changes were mixed in the placebo group. Considering the case of death that occurred in Cohort 3 it seems most important that no worsening in the polysomnography parameters were observed with vosoritide at Week 52 compared to placebo. Whilst directional positive changes in all but one polysomnography parameters were seen with vosoritide in all cohorts, it was unclear whether these changes represented a clinically meaningful effect of treatment on sleep apnea. With the response on the RSI, the applicant provided a discussion better illustrating the clinical relevance of the findings and the limitations of the current data which was accepted.

Moreover, given the the seemingly smaller treatment effects in Cohort 2+3 of study 111-206, the CHMP requested the applicant to provide again a justification for the proposed posology, particularly for the 30 µg kg BW dose in patients weighing less than 10 kg and to demonstrate that the outcome in Cohort 2+3 was not the consequence of a underdosing in this subpopulation. Based on the PK and cGMP biomarker data collected in 111-206 the CHMP agreed that the 15 µg/kg vosoritide is appropriate for ACH participants 2 to <5 years old and 30 µg/kg vosoritide is more appropriate for ACH participants < 2 years old. As mentioned in the PK section, the applicant will provide updated popPK model to further support the applied posology as a post-approval commitment.

Interpretation of the results on HRQoL, functional independence, and developmental performance, as measured by ITQoL, WeeFIM-II, and BSID-III, is limited due to small sample sizes, and heterogeneity introduced by developmental stage and age, which precludes meaningful inferences within a 52-week timeframe. These outcomes will be assessed in the ongoing extension study 111-208.

Assessment of paediatric data on clinical efficacy

Vosoritide is intended exclusively for the use in the paediatric population.

2.4.4. Conclusions on the clinical efficacy

In conclusion, treatment benefit of vosoritide has been confirmed in patients aged 2-5 years. It has been reasonably shown in the newly applied for patient population below the age of 2 years. However, due to the absence of data in patients below 4 months of age, and remaining uncertainties abouts the popPK model and the appropriated dose in these small infants, the indication has been restricted to treatment of patients with ACH of at least 4 months of age. As mentioned in the PK section the applicant will provide updated popPK model to further support the proposed posology as a post-approval commitment recommended by the CHMP.

2.5. Clinical safety

Introduction

During the initial approval procedure, vosoritide's general safety profile was characterised for subjects ≥ 5 years old (at time of vosoritide initiation) from studies 111-202, 111-205 and the pivotal trials 111-301 and 111-302.

The clinical safety evaluation for vosoritide included in this Type II variation is based on data from the placebo-controlled study 111-206 population in children with ACH aged < 5 years, with analyses of pooled data from ongoing and completed studies, focusing on < 5 year-old children (compared to ≥ 5 years) and particularly on the subgroup of children who started treatment aged < 2 years (compared to ≥ 2 years) now applied for.

Studies contributing to analyses of < 5 years old at time of vosoritide initiation

- **111-206:** A Phase 2, randomized, sequential cohort, double-blind, placebo- controlled study to assess the efficacy and safety of vosoritide (15 µg/kg and 30 µg/kg) in participants with ACH aged 0 up to < 5 years.
- **111-208:** An ongoing, Phase 2, long-term open-label extension of Study 111-206.
- **111-209:** An ongoing Phase 2, randomized, controlled, open-label study to assess the safety of vosoritide (dose) in participants with ACH aged 0 to ≤ 12 months at risk of requiring cervicomedullary decompression surgery followed by an open label extension phase.

The evaluation of safety includes data from the completed double-blind, placebo-controlled Phase 2 study 111-206 over 52 weeks (vosoritide 15 μg/kg or 30 μg/kg or placebo) presented by Cohort (Cohort 1 (age ≥24 to <60 months), Cohort 2 (age ≥6 months to <24 months), and Cohort 3 (0 to <6 months)), and discussed in reference to previously reported placebo controlled study 111-301.

Studies contributing to analyses of ≥ 5 years old at time of vosoritide initiation

- **111-202:** A Phase 2, open-label, sequential cohort, dose-escalation study in participants with ACH aged 5 to 14 years.
- **111-205:** An ongoing, Phase 2, open-label long-term extension of Study 111-202.
- **111-301:** A Phase 3, double-blind, placebo-controlled study in participants with ACH aged 5 to < 18 years.
- **111-302:** An ongoing, Phase 3, open-label, long-term extension study of Study 111-301.

Safety assessments from these studies included the examination of treatment-emergent adverse events (AEs), adverse events of special interest (EOI), clinical laboratory results, vital signs and

physical examination findings, electrocardiogram (ECG), radiographic imaging assessments and polysomnography.

Based on the physiologic effects of CNP injection site reactions (ISRs), blood pressure (BP) decreases, heart rate (HR) changes, hypersensitivity, fractures, slipped capital femoral epiphysis, and osteonecrosis/avascular necrosis were defined as Adverse event of special intest.

Due to the biological effects of CNP on vascular tone, the potential for vosoritide to act as a peripheral vasodilator, BP and pulse rate were monitored frequently during the initial study visits; in studies 111-206 and 111-208, up to 8 hours post-dose on days 1 and 2 of treatment, up to 4 hours post-dose on days 3 and 8 (111-206 only), and for 1 hour on subsequent visits. While Investigators utilized clinical judgment to report any changes in vital signs as AEs, specific guidance was provided to the Investigators on reporting of any documented drop in BP associated with symptoms in "documented symptomatic hypotension CRF".

In addition, safety data with up to 8 years of daily treatment with vosoritide, presented as pooled safety data across seven studies allowed comparison of safety in younger participants to older participants (< 2 years ≥2 years and < 5 years ≥ 5 years).

Three pooled groups were defined:

- **All Vosoritide Treated group**: This consists of all participants with ACH who received any dose of vosoritide, regardless of age or the dose administered.
- **Vosoritide initiated aged < 5 years group**: consists of all participants with ACH who took their first dose of vosoritide at an age < 5 years.
- **Vosoritide initiated aged ≥ 5 years group**: consists of all participants with ACH who took their first dose of vosoritide at an age ≥ 5 years.

The following subgroups were considered of interest to evaluate safety: baseline age (in particular <2 years, >= 2 years, as well as other age cut-offs), sex, race and region.

Data cut-off of the clinical trials mentioned above are listed in the Table 14:

Table 14 Completion or Data Cut-Off Date for Vosoritide Clinical Studies

Study	Date of Data Cut-Off a/Last Participant Last Visitb	Person Years of Exposure	Study Status
111-202	LPLV: 02 October 2017	62.90	Completed
111-205	Data Cut-off: 25 February 2022	104.07	Ongoing
111-206	LPLV: 26 January 2022	42.73	Completed
111-208	Data Cut-off: 26 January 2022	104.07	Ongoing
111-209	Data Cut-off: 25 February 2022	44.10	Ongoing
111-301	LPLV: 30 October 2019	58.03	Completed
111-302	Data Cut-off: 25 February 2022	313.68	Ongoing
Overall	-	715.89	-

a. For ongoing studies.
b. For completed studies.
c. c Derived up to the date of the data cut-off for ongoing participants and, for extension studies, does not include exposure in the parent study.
LPLV: last participant last visit
In all data sections, results from the completed placebo-controlled studies 111-206 and 111-301 (where applicable) will precede results from the pooled analysis of the safety data. All data from Study 111-301 were reported in the previous submission (EMEA/H/C/005475/0000).

Patient exposure

Double-Blind Placebo Controlled Study 111-206

In the pivotal Study 111-206, a total of 64 participants were randomized to receive vosoritide (N = 32) or placebo (N = 32), and 11 sentinel participants were enrolled to receive vosoritide.

Thus, the "All vosoritide group (N = 43)" consists of the randomized and sentinel participants who received vosoritide.

Pooled Safety Population

In the pooled safety population, as of the data cut-off, a total of 239 participants in the Phase 2 and 3 studies have been exposed to any dose of vosoritide. Participants in the All Vosoritide Treated group had been exposed to vosoritide for a duration ranging from 0 months (participant had received only one dose of vosoritide at the time of the cut-off) to 97.4 months, with a median duration of 32.69 months, corresponding to 715.89 person-years of exposure. Note that for the AE exposure adjusted summaries the derivation for participant years considers up to last dose received and is 698.58 participant-years.

Due to the higher number treated and the longer duration, exposure was greater in participants aged ≥ 5 years (N = 162; 575.30 person-years) than in participants aged < 5 years (N = 77; 140.59 person-years). Consistent with this, the mean (SD) duration of treatment was greater in participants aged ≥ 5 years (42.61 (19.77) months (range 0.2 to 97.4 months) than in participants aged < 5 years (21.91 (12.13) months range 0.0 to 43.5 months).

In consequence, also exposure in participants aged ≥ 2 years (N = 196; 656.13 person-years) was greater than in participants aged < 2 years (N = 43; 59.77 person-years).

The duration of treatment during the study was comparable between the all-vosoritide and placebo group (mean [SD]: 363.0 [25.3] days and 365.5 [10.2] days, respectively), and few doses were missed (mean [SD]: 4.8 (8.1) in all-vosoritide group and 7.5 (10.9) in placebo group). The duration of treatment during the study was similar between the all-vosoritide and placebo groups across all three cohorts.

Table 15 Extent of Exposure to Vosoritide by Clinical Study, Dose and Duration – Pooled Safety Population

	Age at Day 1 of Vosoritide				**All Vosoritide Treated N=239**	
	< 5 years		**≥ 5 years**			
	Persons n (%)	**Person-years**	**Persons n (%)**	**Person-years**	**Persons n (%)**	**Person-years**
Total Exposure [a,b]	**77 (100.0)**	**140.59**	**162 (100.0)**	**575.30**	**239 (100.0)**	**715.89**
Exposure by study						
111-202 (complete)	0	0	35 (21.6)	62.90	35 (14.6)	62.90
111-205 (ongoing)	0	0	30 (18.5)	129.52	30 (12.6)	129.52
111-301 (complete)	0	0	60 (37.0)	58.03	60 (25.1)	58.03
111-302 (ongoing)	0	0	119 (73.5)	313.68	119 (49.8)	313.68
111-206 (complete)	43 (55.8)	42.73	0	0	43 (18.0)	42.73
111-208 (ongoing)	67 (87.0)	93.40	6 (3.7)	10.66	73 (30.5)	104.07
111-209 (ongoing)	9 (11.7)	4.41	0	0	9 (3.8)	4.41
Exposure by dose						
2.5 µg/kg	0	0	8 (4.9)	6.54	8 (3.3)	6.54
7.5 µg/kg	0	0	15 (9.3)	7.21	15 (6.3)	7.21
15 µg/kg	59 (76.6)	113.45	156 (96.3)	516.73	215 (90.0)	630.18
30 µg/kg	40 (51.9)	27.13	9 (5.6)	44.81	49 (20.5)	71.95
By duration of exposure (at least)						
< 6 months	11 (14.3)	2.06	5 (3.1)	0.85	16 (6.7)	2.91
≥ 6 months	66 (85.7)	138.53	157 (96.9)	574.45	223 (93.3)	712.98
≥ 1 year	59 (76.6)	133.01	156 (96.3)	573.77	215 (90.0)	706.78
≥ 2 years	36 (46.8)	98.35	148 (91.4)	560.63	184 (77.0)	658.98

	Age at Day 1 of Vosoritide				All Vosoritide Treated N=239	
	< 5 years		≥ 5 years			
	Persons n (%)	Person-years	Persons n (%)	Person-years	Persons n (%)	Person-years
≥ 3 years	9 (11.7)	29.87	89 (54.9)	408.74	98 (41.0)	438.61
≥ 4 years	0	0	39 (24.1)	230.23	39 (16.3)	230.23
≥ 5 years	0	0	28 (17.3)	184.17	28 (11.7)	184.17

Adverse events

Double Blind Placebo Controlled Study 111-206

Table 16 Study 111-206: Overview of Adverse Events - Safety Population

AE Category	Placebo N=32		All Vosoritide N=43	
	Incidence n (%)a	Event Rate m (rate)b	Incidence n (%)a	Event Rate m (rate)b
Any AE	**32 (100.0)**	**2357 (73.6)**	**43 (100.0)**	**8737 (204.5)**
AEs leading to dose interruption	15 (46.9)	40 (1.2)	14 (32.6)	38 (0.9)
AEs leading to study drug discontinuation	0	0	0	0
AEs leading to study discontinuation	0	0	1 (2.3)	1 (0.0)
AEs leading to study drug or study discontinuation	0	0	1 (2.3)	1 (0.0)
Any SAE				
SAEs leading to dose interruption	5 (15.6)	5 (0.2)	1 (2.3)	1 (0.0)
SAEs leading to study drug or study discontinuation	0	0	1 (2.3)	1 (0.0)
Any treatment-related AEc	17 (53.1)	1930 (60.3)	37 (86.0)	8232 (192.7)
Treatment-related SAEs	0	0	0	0
Any AE of CTCAE Grade ≥3	3 (9.4)	5 (0.2)	2 (4.7)	3 (0.1)
Participants who died	0	0	**1 (2.3)**	**1 (0.0)**
Any EOI a				
Injection site reactions d	3 (9.4)	70 (2.2)	13 (30.2)	133 (3.1)
Injection site reactions e	17 (53.1)	1939 (60.5)	37 (86.0)	8281 (193.8)
Hypotension	2 (6.3)	2 (0.1)	2 (4.7)	2 (0.0)
Heart rate change	0	0	0	0
Hypersensitivity (SMQ Narrow Terms)	11 (34.4)	11 (0.3)	17 (39.5)	44 (1.0)
Avascular necrosis or osteonecrosis	0	0	0	0
Slipped capital femoral epiphysis	0	0	0	0
Fractures	1 (3.1)	2 (0.1)	1 (2.3)	1 (0.0)
Sponsor defined Algorithmic Anaphylaxis	0	0	0	0

AE, adverse event; CTCAE, common terminology criteria for adverse events; EOI, event of interest; ISR, injection site reaction; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer

Institute; SAE, serious adverse event.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version 24.1 and graded for severity using NCI CTCAE version 4.03.
a Percentages were calculated using the total number of participants in the safety population (N for each pooled group) as the denominator. Participants with more than one AE of the same category were counted only once for that category.
b Exposure-adjusted event rates were calculated by dividing the total number of events (n) by the total treatment exposure up to the last dose reported in each column. Multiple occurrences of an AE in the same category for a participant were counted for each occurrence for that category.
c Relationship to study drug was assessed by the investigator.
d Only ISRs that are CTCAE Grade ≥ 2, or any ISR (excluding bruising) lasting > 24 hours for ISRs with non missing, or partially reported start and end dates.
e All ISRs, regardless of CTCAE grade or duration. EOIs were identified using pre-defined criteria.

In Study 111-206, an about three-fold higher total of 8737 AEs (42.73 person-years of exposure, exposure adjusted rate of 204.5 AEs/person-year) were reported in the all-vosoritide group compared with and 2357 AEs (32.02 person-years of exposure, exposure adjusted rate of 73.6 AEs/person-year) were reported in the placebo group. Also, the treatment-related AE frequency was significantly higher in 37/43 (86.0%) participants in the All Vosoritide group compared with 17/32 (53.1%) participants in the placebo group. The difference is better illustrated by exposure adjusted rate of 192.7 AEs/person-year in vosoritide) compared with 60.3 AEs/person-year) for treatment-related AEs.

The most commonly (> 20%) reported AEs by SOC in the All Vosoritide and placebo groups were:

- General disorders and administration site conditions (V: 88.4% and P: 75.0%),
- Infections and infestations (V: 86.0% and P: 93.8%),
- Gastrointestinal disorders (V: 58.1% and P: 81.3%),
- Respiratory, thoracic and mediastinal disorders (V: 58.1% and P: 59.4%),
- Skin and subcutaneous tissue disorders (V: 37.2% and P: 37.5%),
- Injury, poisoning and procedural complications (V: 32.6% and P: 34.4%),
- Ear and labyrinth disorders (V: 25.6% and P: 37.5%),
- Musculoskeletal and connective tissue disorders (V: 18.6% and P: 21.9%), and
- Nervous system disorders (V: 9.3% and P: 25.0%).

The comparison shows that only adverse events in the SOC "General disorders and administration site conditions", triggered mainly by injection site reactions (ISRs), are more frequent in the vosoritide than in the placebo arm.

Focusing on more rare events, the incidence of AEs mapping to Immune disorders and Vascular disorders (driven by hypotension) were numerically higher in the vosoritide group versus the placebo group. However, these AEs were already identified as drug-related and adverse events of special interest during the approval procedure.

Incidence of AEs mapping to other SOC were lower or comparable in the all-vosoritide group compared to placebo cohorts. Moreover, it is noted, that AEs listed in the SOC "Immune disorders" were all assessed as unrelated to vosoritide and attributed to food, seasonal or animal allergy, or reaction to immunization.

Table 17 Study 111-206: Incidence of Treatment Emergent Adverse Events Reported in ⩾ 10% of Participants in any Group by System Organ Class - Analysis Population: Safety

	Incidence, n (%)							
	Cohort 1		Cohort 2		Cohort 3		Overall	
System Organ Class	All Vosoritide (N=19)	Placebo (N=16)	All Vosoritide (N=12)	Placebo (N=8)	All Vosoritide (N=12)	All Placebo Vosoritide	All Vosoritide (N=43)	Placebo (N=32)
General disorders and administration site conditions	16 (84.2)	10 (62.5)	10 (83.3)	6 (75.0)	12 (100.0)	8 (100.0)	38 (88.4)	24 (75.0)
Infections and infestations	17 (89.5)	15 (93.8)	11 (91.7)	8 (100.0)	9 (75.0)	7 (87.5)	37 (86.0)	30 (93.8)
Gastrointestinal disorders	11 (57.9)	12 (75.0)	6 (50.0)	7 (87.5)	8 (66.7)	7 (87.5)	25 (58.1)	26 (81.3)
Respiratory, thoracic and mediastinal disorders	13 (68.4)	8 (50.0)	5 (41.7)	5 (62.5)	7 (58.3)	6 (75.0)	25 (58.1)	19 (59.4)
Skin and subcutaneous tissue	6 (31.6)	6 (37.5)	4 (33.3)	2 (25.0)	6 (50.0)	4 (50.0)	16 (37.2)	12 (37.5)
Injury, poisoning and procedural complications	10 (52.6)	7 (43.8)	3 (25.0)	2 (25.0)	1 (8.3)	2 (25.0)	14 (32.6)	11 (34.4)
Ear and labyrinth disorders	4 (21.1)	7 (43.8)	3 (25.0)	4 (50.0)	4 (33.3)	1 (12.5)	11 (25.6)	12 (37.5)
Musculoskeletal and connective tissue	5 (26.3)	3 (18.8)	1 (8.3)	1 (12.5)	2 (16.7)	3 (37.5)	8 (18.6)	7 (21.9)
Immune system disorders	3 (15.8)	0	0	1 (12.5)	2 (16.7)	1 (12.5)	5 (11.6)	2 (6.3)
Investigations	2 (10.5)	2 (12.5)	1 (8.3)	1 (12.5)	1 (8.3)	0	4 (9.3)	3 (9.4)
Nervous system disorders	2 (10.5)	5 (31.3)	1 (8.3)	0	1 (8.3)	3 (37.5)	4 (9.3)	8 (25.0)
Psychiatric disorders	0	0	1 (8.3)	1 (12.5)	1 (8.3)	0	2 (4.7)	1 (3.1)
Vascular disorders	0	0	1 (8.3)	1 (12.5)	1 (8.3)	0	2 (4.7)	1 (3.1)
Blood and lymphatic system disorders	1 (5.3)	0	0	0	0	1 (12.5)	1 (2.3)	1 (3.1)
Metabolism and nutrition disorders	0	2 (12.5)	0	0	1 (8.3)	1 (12.5)	1 (2.3)	3 (9.4)
Endocrine disorders	0	0	0	0	0	1 (12.5)	0	1 (3.1)

AE: adverse event; CTCAE: common terminology criteria for adverse events; m: event rate; MedDRA: Medical Dictionary for Regulatory Activities; n: number of
participants; NCI: National Cancer Institute; PT: preferred term; SOC: system organ class.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA
version 24.1 and graded for severity using NCI CTCAE version 4.03.
a Percentages were calculated using the total number of participants in the safety analysis set of each column as the denominator. Participants with more than one AE
of the same SOC were counted for each occurrence for that SOC.

b Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure up to the last dose reported in each column.
Multiple occurrences of an AE with the same SOC for a participant were counted for each occurrence for that SOC.

Across cohorts, the following SOCs had AE higher incidence rates in the vosoritide group compared to placebo by cohort:

Cohort 1:

- General disorders and administration site conditions (All Cohorts), driven by ISRs.
- Respiratory thoracic and mediastinal disorders,
- Injury, poisoning and procedural complications,
- Musculoskeletal and connective tissue disorders, and
- Immune system disorders

Cohort 2:

- Infections and Infestations and skin and subcutaneous disorders

Cohort 3:

- Ear and labyrinth disorders

Whilst there are small numerical differences, the rates were comparable with the placebo group with no identifiable trends or patterns in events across Cohorts (e.g. respiratory infections and other infections), with the majority of the events being attributed to conditions common in a pediatric study population as judged by the investigators.

Table 18 Study 111-206: Incidence and Exposure-adjusted Event Rates of Treatment Emergent Adverse Events by Preferred Term (⩾ 10% in Either Group –Safety Population)

System Organ Class	Placebo (N=32		All Vosoritide	
	Incidence n (%)[a]	Event Rate m (rate)[b]	Incidence n	Event Rate m
Total treatment exposure (person-	**-**	**32.02**	**-**	**42.73**
Any AE	**32 (100.0)**	**2357**	**43**	**8737**
Injection site reaction	13 (40.6)	154 (4.8)	34 (79.1)	**3057**
Injection site erythema	13 (40.6)	1738 (54.3)	33 (76.7)	**5100(119.4)**
Pyrexia	19 (59.4)	37 (1.2)	16 (37.2)	37 (0.9)
Upper respiratory tract infection	11 (34.4)	30 (0.9)	16 (37.2)	35 (0.8)
Nasopharyngitis	9 (28.1)	15 (0.5)	12 (27.9)	21 (0.5)
Teething	10 (31.3)	19 (0.6)	12 (27.9)	**32 (0.7)**
Vomiting	17 (53.1)	47 (1.5)	11 (25.6)	22 (0.5)
Diarrhoea	7 (21.9)	15 (0.5)	8 (18.6)	14 (0.3)
Ear infection	6 (18.8)	13 (0.4)	8 (18.6)	13 (0.3)
Injection site swelling	2 (6.3)	3 (0.1)	8 (18.6)	**36 (0.8)**
Rhinorrhoea	6 (18.8)	11 (0.3)	8 (18.6)	13 (0.3)
Viral infection	4 (12.5)	8 (0.2)	8 (18.6)	**28 (0.7**)

System Organ Class	Placebo (N=32		All Vosoritide	
	Incidence n (%)[a]	Event Rate m (rate)[b]	Incidence n	Event Rate m
Total treatment exposure (person-	**-**	**32.02**	**-**	**42.73**
Fall	3 (9.4)	5 (0.2)	7 (16.3)	9 (0.2)
Rash	4 (12.5)	4 (0.1)	7 (16.3)	**10 (0.2)**
Arthropod bite	2 (6.3)	2 (0.1)	6 (14.0)	6 (0.1)
Conjunctivitis	6 (18.8)	8 (0.2)	6 (14.0)	7 (0.2)
Injection site urticaria	1 (3.1)	1 (0.0)	6 (14.0)	**22 (0.5)**
Nasal congestion	6 (18.8)	8 (0.2)	6 (14.0)	10 (0.2)
Otitis media	6 (18.8)	14 (0.4)	6 (14.0)	9 (0.2)
Constipation	2 (6.3)	4 (0.1)	5 (11.6)	7 (0.2)
Injection site bruising	6 (18.8)	39 (1.2)	5 (11.6)	26 (0.6)
Injection site induration	0	0	5 (11.6)	14 (0.3)
Cough	7 (21.9)	9 (0.3)	4 (9.3)	5 (0.1)
Ear pain	4 (12.5)	6 (0.2)	4 (9.3)	5 (0.1)
Gastroenteritis	5 (15.6)	5 (0.2)	3 (7.0)	9 (0.2)
Headache	4 (12.5)	8 (0.2)	0	0

AE: adverse event; CTCAE: common terminology criteria for adverse events; m: event rate; MedDRA: Medical Dictionary for Regulatory Activities; n: number of participants; NCI: National Cancer Institute; PT: preferred term; SOC: system organ class.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version 24.1 and graded for severity using NCI CTCAE version 4.03.
a Percentages were calculated using the total number of participants in the safety analysis set of each column as the denominator. Participants with more than one AE of the same PT were counted for each occurrence for that PT.
b Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure up to the last dose reported in each column. Multiple occurrences of an AE with the same PT for a participant were counted for each occurrence for that PT.

In Study 111-206, the five most commonly reported AEs by PT in the All Vosoritide and placebo groups were injection site reaction (79.1% and 40.6%), injection site erythema (76.7% and 40.6%), pyrexia (37.2% and 59.4%), upper respiratory tract infection (37.2% and 34.4%) and nasopharyngitis (27.9% and 28.1%). All events reported in ≥ 10% of participants in either treatment group are presented in Table 18. In general, the incidence of AEs by PT was numerically lower in the All Vosoritide group compared with the placebo group, except for ISRs, injection site erythema, and upper respiratory tract infection.

Across all cohorts, the most commonly reported AEs by PT were injection site erythema and ISR. While there were some numerical differences in the number of events across cohorts, given the small number of events observed, they were not considered clinically meaningful and the nature of events observed were consistent with the known safety issues commonly encountered in the pediatric population and particularly encountered in younger children with ACH as judged by the investigators.

Table 19 Study 111-206 - Adverse Events Occurring at a Difference in Incidence of ⩾ 5% Higher in the Vosoritide Group Compared with the Placebo Group

	Placebo		Vosoritide	
	Incidence n (%)	**Events m (rate)**	**Incidence n (%)**	**Events m (rate)**
Injection site reaction	13 (40.6)	154 (4.8)	34 (79.1)	3057 (71.5)
Injection site erythema	13 (40.6)	1738 (54.3)	33 (76.7)	5100 (119.4)
Injection site swelling	2	3 (0.1)	8 (18.6)	36 (0.8)
Injection site urticaria	1	1 (0.0)	6 (14.0)	22 (0.5)
Injection site induration	0	0	5 (11.6)	14 (0.3)
Viral Infection	4 (12.5)	8 (0.2)	8 (18.6)	28 (0.7)
Fall	3	5 (0.2)	7 (16.3)	9 (0.2)
Arthropod bite	2	2 (0.1)	6 (14.0)	7 (0.2)
Constipation	2	4 (0.1)	5 (11.6)	7 (0.2)
Dermatitis Diaper	1	1 (0.0)	4 (9.3)	5 (0.1)
Lower respiratory tract	1	3 (0.1)	4 (9.3)	4 (0.1)
Rhinitis	0	0	4 (9.3)	8 (0.2)
Sleep apnea syndrome	0	0	3 (7.0)	3 (0.1)
Viral upper respiratory tract infection	0	0	3 (7.0)	3 (0.1)
Epistaxis	0	0	3 (7.0)	3 (0.1)

In the pivotal trial 111-206, AEs of Grade ≥ 3 were reported in 4.7% participants in the All Vosoritide group and in 9.4% participants in the placebo group. All Grade ≥ 3 AEs in both the vosoritide and placebo groups were reported in Cohort 3 only. None were considered related to study treatment and were reflective of common conditions particularly observed in younger children with ACH.

With the exception of one Grade 5 (death) AE, all events of Grade ≥ 3 were of Grade 3 (severe). None were Grade 4 (life-threatening). Overall, 6/7 Grade 3 AEs were reported as serious: respiratory syncytial virus bronchiolitis, vomiting, parainfluenza virus infection, respiratory distress, skull fracture, and otitis media, and one Grade 3 AE of kyphosis was non-serious.

Grade 3 events were reported in 10.4%, 12.3% and 11.7% of participants in the < 5 years, ≥ 5 years and All Vosoritide Treated groups, respectively, with little difference in the corresponding exposure adjusted event rates (0.07, 0.04 and 0.05 AEs/person-year, respectively). Of the 34 Grade 3 events reported in 28 (11.7%) participants, only one event was assessed as related to treatment. This was an event of knee deformity in a participant in the ≥ 5 years age group.

Pooled Safety data

Table 20 provides an overview and summary of relevant safety outcome during treatment in the population aged below 60 months at the time of initiation of treatment.

Table 20 Summary of safety outcomes in the population < 60 months at the time of initiation of treatment

Participants with:	**Year 1 N = 239**		**Year 2 N = 214**		**Year 3 N = 180**		**Year 4 N = 96**		**Year 5 N = 39**		**Year 6 N=27**	
	Incidence n (%)a	**Event rate m (rate) b**	**Incidence n (%)a**	**Event rate m(rate)b**	**Incidence n (%)a**	**Event rate m (rate) b**	**Incidence n (%)a**	**Event rate m (rate)b**	**Incidence n (%)a**	**Incidence n (%)a**	**Event rate m (rate)b**	**Incidence n (%)a**
Yearly treatmen	**-**	**223.11**	**-**	**199.37**	**-**	**140.97**	**-**	**65.87**	**-**	**29.30**	**-**	**23.21**
Any AE	**223 (93.3)**	**2012 9.02)**	**178 (83.2)**	**1026 (5.15)**	**128 (71.1)**	**534 3.79)**	**58 (60.4)**	**261 3.96)**	**27 (69.2)**	**130 (4.44)**	**24 (88.9)**	**78 (3.36)**
AEs leading	0	0	0	0	0	0	0	0	0	0	0	0
AEs leading to dose	60 25.1)	140 0.63)	27 12.6)	56 0.28)	21 11.7)	41 0.29)	10 10.4)	18 0.27)	5 12.8)	12 0.41)	5 18.5)	7 0.30)
AEs leading to study	2 (0.8)	2 0.01)	0	0	1 (0.6)	1 0.01)	0	0	0	0	0	0
AEs leading to study	1 (0.4)	1 0.00)	0	0	0	0	0	0	0	0	0	0
AEs leading to study	3 (1.3)	3 0.01)	0	0	1 (0.6)	1 0.01)	0	0	0	0	0	0
SAEs	**(7.5)**	**23 0.10**	**11 5.1)**	**11 0.06)**	**3 1.7)**	**3 0.02**	**1 1.0)**	**1 0.02**	**2 5.1)**	**2 0.07)**	**1 3.7)**	**1 0.04)**
SAEs leading to dose reduction	0	0	0	0	0	0	0	0	0	0	0	0
SAEs leading to dose	12 5.0)	16 0.07)	6 (2.8)	6 0.03)	1 (0.6)	1 0.01)	0	0	1 (2.6)	1 0.03)	0	0
SAEs leading to study drug discontinuation	0	0	0	0	0	0	0	0	0	0	0	0
SAEs leading to study discontinuat	1 (0.4)	1 0.00)	0	0	0	0	0	0	0	0	0	0
SAEs leading to study drug or study discontinuation	1 (0.4)	1 0.00)	0	0	0	0	0	0	0	0	0	0
Any treatment-related AE[C]	**67 (28.0)**	**274 (1.23)**	**21 (9.8)**	**26 (0.13)**	**7 (3.9)**	**10 (0.07)**	**4 (4.2)**	**4 (0.06)**	**1 (2.6)**	**2 (0.07)**	**1 (3.7)**	**1 (0.04)**
Treatment-	0	0	0	0	0	0	1 (1.0)	1	0	0	0	0
Any AE of	18	23	5 (2.3)	5	4 (2.2)	4	1 (1.0)	1	2 (5.1)	2	1 (3.7)	1
Participants who died	**1 0.4)**	**1 0.00**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Any Adverse event of special Interest												
Injection site reactions	2 (0.8)	5 (0.02)	0	0	0	0	0	0	0	0	0	0

Injection site reactions (excluding bruising) lasting > 24 hours	35 14.6)	189 (0.85)	9 (4.2)	18 (0.09)	2 (1.1)	5 (0.04)	0	0	1 (2.6)	2 (0.07)	1 (3.7)	1 (0.04)
Injection site reactions CTCAE grade ≥ 2 or (excluding bruising) lasting > 24 hours	37 15.5)	194 (0.87)	9 (4.2)	18 (0.09)	2 (1.1)	5 (0.04)	0	0	1 (2.6)	2 (0.07)	1 (3.7)	1 (0.04)
Hypotension	30 12.6)	46 (0.2	6 (2.8)	11 (0.06)	4 (2.2)	4 (0.03	1 (1.0)	2 (0.03	1 (2.6)	1 (0.03)	0	0
Heart rate change	0	0	1 (0.5)	11 (0.06)	0	0	0	0	0	0	1 (3.7)	1 (0.04)
Hypersensitivity (SMQ	44 18.4)	63 (0.2	19 (8.9)	28 (0.14)	6 (3.3)	7 (0.05	5 (5.2)	7 (0.11	1 (2.6)	1 (0.03)	2 (7.4)	3 (0.13)
Avascular necrosis or	0	0	0	0	0	0	0	0	0	0	0	0
Slipped capital	0	0	0	0	0	0	0	0	0	0	0	0
Fractures	3 (1.3)	4 (0.0	1 (0.5)	1 (0.01)	3 (1.7)	3 (0.02	0	0	0	0	0	0
Adverse Events in ≥ 10% of Participants in the All Vosoritide Treated Group												
Nasopharyngitis	61 25.5)	98 (0.44)	34 (15.9)	58 (0.29)	21 (11.7)	24 (0.17	11 (11.5)	15 (0.23	2 (5.1)	4 (0.14)	3 (11.1)	3 (0.13)
Pyrexia	61 25.5)	111 (0.50)	30 (14.0)	63 (0.32)	22 (12.2)	27 (0.19	11 (11.5)	13 (0.20	6 (15.4)	6 (0.20)	2 (7.4)	2 (0.09)
Vomiting	52 21.8)	118 (0.53)	23 (10.7)	49 (0.25)	12 (6.7)	18 (0.13	2 (2.1)	3 (0.05	4 (10.3)	4 (0.14)	-	-
Upper respiratory	48 20.1)	85 (0.38)	30 (14.0)	34 (0.17)	14 (7.8)	17 (0.12	5 (5.2)	7 (0.11	3 (7.7)	3 (0.10)	1 (3.7)	1 (0.04)
Headache	36 15.1)	60 (0.27)	26 (12.1)	64 (0.32)	18 (10.0)	49 (0.35	12 (12.5)	42 (0.64	4 (10.3)	15 (0.51)	4 (10.3)	15 (0.51)
Ear infection	35 14.6)	59 (0.26)	22 (10.3)	36 (0.18)	10 (5.6)	13 (0.09	8 (8.3)	13 (0.20	1 (2.6)	1 (0.03)	2 (7.4)	2 (0.09)
Cough	34 14.2)	42 (0.19)	24 (11.2)	41 (0.21)	8 (4.4)	10 (0.07	3 (3.1)	3 (0.05	2 (5.1)	2 (0.07)	1 (3.7)	1 (0.04)
Viral infection	27 11.3)	63 (0.28)	26 (12.1)	48 (0.24)	9 (5.0)	15 (0.11	3 (3.1)	4 (0.06	1 (2.6)	1 (0.03)	1 (3.7)	1 (0.04)
Injection site reaction	26 10.9)	94 (0.42)	5 (2.3)	10 (0.05)	1 (0.6)	1 (0.01	-	-	1 (2.6)	2 (0.07)	-	-
Diarrhoea	25 10.5)	43 (0.19)	8 (3.7)	10 (0.05)	3 (1.7)	3 (0.02	2 (2.1)	2 (0.03	2 (5.1)	2 (0.07)	-	-
Back pain	9 (3.8)	10 (0.04)	8 (3.7)	8 (0.04)	7 (3.9)	7 (0.05	5 (5.2)	6 (0.09	3 (7.7)	3 (0.10)	4 (14.8)	4 (0.17)
Arthralgia	1 (3.7)	1 (0.04)	16 (7.5)	23 (0.12)	13 (7.2)	20 (0.14	4 (4.2)	6 (0.09	7 (17.9)	7 (0.24)	1 (3.7)	1 (0.04)
Oropharyngeal pain	19 7.9)	29 (0.13)	18 (8.4)	28 (0.14)	6 (3.3)	9 (0.06	6 (6.3)	7 (0.11	4 (10.3)	4 (0.14)	1 (3.7)	1 (0.04)

AE, adverse event; EOI, event of interest; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; NCI,
National Cancer Institute; SAE, serious adverse event; SMQ, standard MedDRA query.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version
24.1 and graded for severity using NCI CTCAE version 4.0.
Only treatment emergent AEs that started during the year are included only for that yearly assessment.
For Study 111-206, some Cohort 1 participants randomized to placebo were aged ≥ 5 years when receiving their first dose of vosoritide in Study 111-208. All Vosoritide
Treated group includes all participants who took any dose of vosoritide.

a Percentages were calculated using the total number of participants in the safety population (N for each pooled group for each year) being followed up for safety at the
start of the year under assessment as the denominator. Participants with more than one AE of the same PT were counted only once for that PT.
b Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure up to the last dose reported in each pooled
group. Multiple occurrences of an AE in the same category were counted for each occurrence for that category.
c Relationship to study drug was assessed by the investigator.

For the pooled safety analysis, at the time of data cut-off, a total of 239, 214, 180 and 96 participants were included in the safety assessment for Years 1, 2, 3 and 4, respectively. Thereafter fewer participants were considered in Years 5 (39 participants), 6 (27 participants), 7 (19 participants), 8 (9 participants) and 9 (1 participant). Due to the variable follow-up of participants in a given year, the exposure-adjusted events rates are considered more clinically relevant. The exposure adjusted event rates for the overall AEs and treatment-related AEs were highest in the first year (Year 1) of treatment (9.02 and 1.23 AEs/person-year, respectively) and showed a downward trend with each subsequent year of treatment with vosoritide (5.15, 3.79, 3.96, 4.44 and 3.36 AEs/person-year, and 0.13, 0.07, 0.06, 0.07 and 0.04 treatment-related AEs/person-year in Years 2, 3, 4, 5 and 6, respectively).

Treatment-Related Adverse Events

Double Blind Placebo Controlled Study 111-206

Table 21 shows the results regarding incidence and exposure-adjusted Event Rates of Drug-Related Treatment Emergent Adverse Events.

Table 21: Study 111-206: Incidence and Exposure-adjusted Event Rates of Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Analysis Population: Safety

System Organ Class	Placebo (N=32		All Vosoritide (N=43	
	Incidence n (%)[a]	Event Rate m (rate)[b]	Incidence n (%)[a]	Event Rate m (rate)[b]
Total treatment exposure (person-	**-**	**32.02**	**-**	**42.73**
Any treatment-related AE	17 (53.1)	1930	37 (86.0)	8232
General disorders and administration site conditions	**16 (50.0)**	**1928**	**37 (86.0)**	**8229**
Injection site reaction	13 (40.6)	153 (4.8)	34 (79.1)	3037 (71.1)
Injection site erythema	13 (40.6)	1730	33 (76.7)	5071
Injection site swelling	2 (6.3)	3 (0.1)	8 (18.6)	36 (0.8)
Injection site urticaria	1 (3.1)	1 (0.0)	6 (14.0)	22 (0.5)
Injection site bruising	5 (15.6)	37 (1.2)	5 (11.6)	26 (0.6)
Injection site induration	0	0	5 (11.6)	14 (0.3)
Injection site haemorrhage	2 (6.3)	2 (0.1)	4 (9.3)	4 (0.1)
Injection site mass	2 (6.3)	2 (0.1)	4 (9.3)	17 (0.4)
Injection site rash	0	0	1 (2.3)	2 (0.0)
Gastrointestinal disorders	**0**	**0**	**1 (2.3)**	**1 (0.0)**
Diarrhoea	0	0	1 (2.3)	1 (0.0)
Investigations	**1 (3.1)**	**1 (0.0)**	**1 (2.3)**	**1 (0.0)**
Blood pressure decreased	1 (3.1)	1 (0.0)	1 (2.3)	1 (0.0)
Vascular disorders	**0**	**0**	**1 (2.3)**	**1 (0.0)**
Hypotension	0	0	1 (2.3)	1 (0.0)
Infections and infestations	**1 (3.1)**	**1 (0.0)**	**0**	**0**
COVID-19	1 (3.1)	1 (0.0)	0	0

AE: adverse event; CTCAE: common terminology criteria for adverse events; m: event rate; MedDRA: Medical Dictionary for Regulatory Activities; n: number of participants; NCI: National Cancer Institute; PT: preferred term; SOC: system organ class.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version 24.1 and graded for severity using NCI CTCAE version 4.03.

[a] Percentages were calculated using the total number of participants in the safety analysis set of each column as the denominator. Participants with more than one AE of the same SOC/PT were counted for each occurrence for that SOC/PT.

[b] Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure up to the last dose reported in each column. Multiple occurrences of an AE with the same SOC/PT for a participant were counted for each occurrence for that SOC/PT.

In Study 111-206, the incidence of AEs assessed as related to study treatment was higher in the All Vosoritide group (86.0%, 8232 events, 192.7 AEs/person-year) compared with the placebo group (53.1%, 1930 events, 60.3 events/person-year).

This difference was mainly driven by the incidence of ISRs. In both the All Vosoritide and placebo groups, treatment-related events were most commonly (> 10%) reported in the General disorders and administration site conditions SOC (86.0% and 50.0%, respectively). By PT, the most commonly (> 10%) reported study drug-related AEs in the All Vosoritide and placebo groups were injection site reaction (79.1% and 40.6%), injection site erythema (76.7% and 40.6%), injection site swelling (18.6% and 6.3%), injection site urticaria (14.0% and 3.1%), injection site bruising (11.6% and 15.6%), and injection site induration (11.6% and 0%). All ISRs related to study treatment were Grade 1 in severity, non-serious, and transient.

Other AEs reported at a higher incidence All Vosoritide vs Placebo included diarrhea and hypotension (2.3% versus 0 %). Hypotension is already categorized as an ADR, and the overall incidence and event rate of diarrhea was lower in Vosoritide group compared to placebo (21.9% versus 18.6%; 0.5 versus 0.3 events/year).

Across cohorts, the number of events assessed as related to vosoritide was higher in Cohort 1 compared to Cohorts 2 and 3 (which were similar), and the incidence of events was higher in Cohort 3 compared to Cohorts 1 and 2.

There was no discernible difference in the pattern of events assessed as related to vosoritide across cohorts. Other than ISR's, fewer AEs were attributed to vosoritide in Study 111-206 compared to Study 111-301.

Pooled safety population

The incidence and exposure-adjusted event rates of investigator assessed treatment related AEs by SOC and PT are summarized in Table 22.

Table 22 Treatment-Related (Investigator-Assessed) Adverse Events by Reported in > 1 Participant in the All Vosoritide Treated Group – Pooled Safety Population

	Age at Day 1 of Vosoritide				**All Vosoritide Treated N=239**	
	< 5 years N=77		**≥ 5 years N=162**			
	Incidence, n (%)[a]	**Event rate (rate)**	**Incidence, n (%)[a]**	**Event rate m (rate)[b]**	**Incidence, n (%)[a]**	**Event rate m (rate)[b]**
Total treatment exposure, person-years	**-**	136.20	**-**	**562.38**	**-**	**698.58**
Any treatment related AE	**15 (19.5)**	**144 (1.06)**	**64 (39.5)**	**180 (0.32)**	**79 (33.1)**	**324 (0.46)**
General disorders and administration site conditions	**13 (16.9)**	**139 (1.02)**	**32 (19.8)**	**72 (0.13)**	**45 (18.8)**	**211 (0.30)**

Injection site reaction	8 (10.4)	44 (0.32)	20 (12.3)	50 (0.09)	28 (11.7)	94 (0.13)
Injection site erythema	7 (9.1)	92 (0.68)	11 (6.8)	14 (0.02)	18 (7.5)	106 (0.15)
Fatigue	0	0	2 (1.2)	2 (0.00)	2 (0.8)	2 (0.00)
Injection site induration	2 (2.6)	2 (0.01)	0	0	2 (0.8)	2 (0.00)
Injection site swelling	0	0	2 (1.2)	2 (0.00)	2 (0.8)	2 (0.00)
Injection site urticaria	**1 (1.3)**	1 (0.01)	1 (0.6)	2 (0.00)	2 (0.8)	3 (0.00)
Vascular disorders	**1 (1.3)**	1 (0.01)	**23 (14.2)**	**37 (0.07)**	**24 (10.0)**	**38 (0.05)**
Hypotension	1 (1.3)	1 (0.01)	22 (13.6)	34 (0.06)	23 (9.6)	35 (0.05)
Pallor	0	0	2 (1.2)	3 (0.01)	2 (0	3 (0.00)
Investigations	**1 (1.3)**	1 (0.01)	**12 (7.4)**	**14 (0.02)**	**13 (5.4)**	**15 (0.02)**
Blood pressure decreased	1 (1.3)	1 (0.01)	10 (6.2)	12 (0.02)	11 (4.6)	13 (0.02)
Nervous system disorders	**0**	0	**12 (7.4)**	**18 (0.03)**	**12 (5.0)**	**18 (0.03)**
Dizziness	0	0	7 (4.3)	8 (0.01)	7 (2.9)	8 (0.01)
Headache	0	0	3 (1.9)	5 (0.01)	3 (1.3)	5 (0.01)
Presyncope	0	0	3 (1.9)	3 (0.01)	3 (1.3)	3 (0.00)
Gastrointestinal disorders	**1 (1.3)**	**1 (0.01)**	**7 (4.3)**	**9 (0.02)**	**8 (3.3)**	**10 (0.01)**
Vomiting	0	0	5 (3.1)	5 (0.01)	5 (2.1)	5 (0.01)
Nausea	0	0	2 (1.2)	2 (0.00)	2 (0.8)	2 (0.00)
Musculoskeletal and connective tissue disorders	**0**	**0**	**7 (4.3)**	**13 (0.02)**	**7 (2.9)**	**13 (0.02)**
Kyphosis	0	0	2 (1.2)	3 (0.01)	2 (0.8)	3 (0.00)
Back pain	0	0	1 (0.6)	2 (0.00)	1 (0.4)	2 (0.00)
Pain in extremity	0	0	1 (0.6)	2 (0.00)	1 (0.4)	2 (0.00)
Infections and infestations	**1 (1.3)**	**1 (0.01)**	**1 (0.6)**	**2 (0.00)**	**2 (0.8)**	**3 (0.00)**
Ear infection	1 (1.3)	1 (0.01)	1 (0.6)	2 (0.00)	2 (0.8)	3 (0.00)
Vomiting	0	0	5 (3.1)	5 (0.01)	5 (2.1)	5 (0.01)
Nausea	0	0	2 (1.2)	2 (0.00)	2 (0.8)	2 (0.00)
Musculoskeletal and connective tissue disorders	**0**	**0**	**7 (4.3)**	**13 (0.02)**	**7 (2.9)**	**13 (0.02)**

Kyphosis	0	0	2 (1.2)	3 (0.01)	2 (0.8)	3 (0.00)

AE, adverse event; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activitie s; NCI, National Cancer
Institute; PT, preferred term; SOC, system organ class.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA
version 24.1 and graded for severity using NCI CTCAE version 4.0.
Only ISRs that are CTCAE Grade ≥ 2, or any ISR (excluding bruising) lasting > 24 hours for ISRs with non-missing, or partially reported start and end dates are included.
For Study 111-206, some Cohort 1 participants randomized to placebo were aged ≥ 5 years when receiving their first dose of vosoritide in Study 111-208. All
Vosoritide Treated group includes all participants who took any dose of vosoritide.
a Percentages were calculated using the total number of participants in the safety population (N for each pooled group) as the denominator. Participants with more than one AE of the same SOC/PT/CTCAE grade were counted only once for that SOC/PT/CTCAE grade.
b Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure up to the last dose reported in each pooled group. Multiple occurrences of an AE with the same category were counted for each occurrence for that category.

In the All Vosoritide Treated group, 324 treatment related AEs were reported in 79 (33.1%) participants with an event rate of 0.46 AEs/person-year. Treatment related events were reported at a lower frequency in participants aged < 5 years old [15 (19.5%)] than in participants ≥ 5 years old [64 (39.5%)].

However, when corrected for exposure, events were reported at a higher rate in participants aged < 5 years old (1.06 AEs/person-year) than in participants aged ≥ 5 years old (0.32 AEs/person-year). This was due to the higher reporting of events in the general disorders and administration site conditions SOC in the younger participants, all but one (PT: fatigue) were injection site reactions. The higher reporting rate in the < 5 years old age group was largely driven by the higher reporting of injection site erythema in this group (0.68 AEs/person-year) compared with the ≥ 5 years old group (0.02 AEs/person-year).

In the All Vosoritide Treated group, the only PT reported in ≥ 10% of participants was injection site reaction [28 (11.7%), 0.3 AEs/patient year]. The only other PT reported in ≥ 10% of participants in any group was hypotension. This event was reported in 1 (1.3%), 22 (13.6%) and 23 (9.6%), participants in the < 5 years old, ≥ 5 years old and All Vosoritide Treated groups, respectively with exposure adjusted rates of 0.01, 0.06 and 0.05 AEs/patient year.

Of note: Two treatment related events resulted in discontinuation of study drug. These were a Grade 2 event of transaminases increased and a Grade 1 event of Wolff-Parkinson-White syndrome. Both events were reported in the original MA and no new data related to these cases are available.

Based on review of the 'All Vosoritide treated' population, amongst events assessed as related to vosoritide, the majority of events were already considered to be ADR's including events of ISRs, hypotension, BP decrease, dizziness, syncope, vomiting and nausea. Pallor was considered to be a manifestation of hypotension.

Adverse events of special interest

Similar to previous trials, injection site reactions (ISRs), blood pressure decreases, hypersensitivity (SMQ narrow terms), fractures, and heart rate changes were defined as adverse events of special interest since they may be caused by the vosoritide's mode of action.

In particular, there were no events of slipped capital femoral epiphysis or avascular necrosis or osteonecrosis reported with vosoritide during any of the clinical studies. These complications were considered as a potential complication derived from non-clinical findings in animals, discussed as a potential signal also already during the approval procedure.

Injection Site Reactions: In Study 111-206, there was a numerical higher frequency of ISR events in the all-vosoritide participants compared to placebo (37 (86.0%), 193.8 AEs/person-year versus 17 (53.1%), 60.5 AEs/person-years, respectively). The most commonly (>10% participants) reported ISRs in the all-vosoritide and placebo groups included injection site reaction (79.1% and 40.6%), injection site erythema (76.7% and 40.6%), injection site swelling (18.6% and 6.3%), injection site urticaria (14.0% and 3.1%), and injection site bruising (11.6% and 18.8%), and injection site induration (11.6% and 0%).

The number of ISR events decreased with age with the highest event rate observed in Cohort 3 (cohort 1: 166.1 versus 21.1 AEs/person-years, cohort 2: 199.9 versus 81.8 AEs/person years, cohort 3: 232.8 versus 118.1 AEs/person-years in the vosoritide versus placebo group, respectively). The nature of ISR events were similar across the three cohorts. ISRs were transient, non-serious, and the majority were mild, and resolved without medical intervention. No participants discontinued from treatment due to ISR-related events.

In the All Treated population ISR events (excluding bruising) lasting > 24 hours were reported in 42 (17.6%) participants with an exposure-adjusted rate of 0.30 AEs/person-years. When adjusted for exposure, ISR events were more frequently reported in participants < 5 years old (1.04 AEs/person-year) than in participants ≥ 5 years old (0.12 AEs/person-year). This was largely driven by the higher rate of injection site erythema in participants < 5 years old (0.68 AEs/person-year) than in participants ≥ 5 years old (0.02 AEs/person-year). Similarly, ISR events were more frequently reported in participants < 2 years old (0.53 AEs/person-year) than in participants ≥ 2 years old (0.53 AEs/person-year). Notably, the pattern and severity of ISRs did not change or worsen over time with prolonged exposure to vosoritide.

Hypersensitivity AEs: In study 111-206, there was a numerical higher incidence of hypersensitivity events in the all-vosoritide participants compared to placebo (17 (39.5%) versus 11 (34.4% respectively) driven by a higher number of injection site urticaria events in the vosoritide arm. The most common AEs by PT under the hypersensitivity SMQ in the All Vosoritide and placebo groups were rash [7 (16.3%) versus 4 (12.5%)], injection site urticaria [6 (14.0%) versus 1 (3.1%)], and eczema [2 (4.7%) versus 3 (9.4%)].

All hypersensitivity events were non-serious and did not lead to study treatment discontinuation. The majority were Grade 1 with no events of Grade ≥ 3 or events meeting NIAID/FAAN criteria for anaphylaxis. The frequency and type of hypersensitivity events were similar across cohorts.

In the All Treated population, 116 hypersensitivity events were reported in 65 (27.2%) participants with and exposure-adjusted event rate of 0.17 AEs/person-years.

Blood pressure decreased: One (2.3%) all-vosoritide participant and 2 (6.3%) placebo participant reported 1 event each of blood pressure decreased. One (2.3%) all-vosoritide participant experienced 1 event of symptomatic hypotension; all events were mild (Grade 1), transient and resolved without medical intervention.

Incidences of decreases in SBP were generally consistent across cohorts. Cohort 3 participants, who received 30 ug/kg, experienced a higher incidence of DBP changes as well as weak correlation between the maximum increase from pre-dose HR and study drug exposure. This was not considered clinically meaningful given that no adverse events were reported concurrent with these changes.

Fractures and Bone disorders: In study 111-206, one participant in the all-vosoritide group experienced 1 event of fracture (Cohort 1, non-serious, Grade 2, metaphyseal corner fracture) and 1 participant in the placebo group experienced 1 events of fracture and 1 event of fracture related pain

(Cohort 3, one serious Grade 3 skull fracture and one non-serious Grade 1 fracture pain associated with the SAE of skull fracture). Both fracture events were assessed as not related to drug.

In the pooled population, there were 8 participants (3.3%) who had 9 fracture events on vosoritide with an exposure adjusted event rate of 0.01 AEs/person year. Events were reported in 2 (2.6) participants aged < 5 years old (2 events, 0.01 AEs/person year) and 6 (3.7%) participants aged ≥ 5 years old (7 events, 0.01 AEs/person year). In each case, the type of fracture was as expected for age in the general pediatric population.

Since data cut, 3 serious events of femur fracture were reported (all in age > 5 years) such that as of August 25, 2022, 10 treated participants (4.1%) in the vosoritide program experienced 11 adverse events of fracture, with the most common type a femur fracture in 4 participants (1.7%, annual event rate 0.005). All events of fracture were reported in the context of a traumatic event and assessed as unrelated to vosoritide treatment by the investigators, except for the most recent event of femur fracture that was reported as possibly related to vosoritide treatment.

Of the 10 participants who experienced a fracture, 7 were male and 3 were female ranging in age from 4 months to 14 years. Fracture events were distributed evenly across several years, with no pattern related to timing or type of fracture.

Based on a full review of fractures in the vosoritide clinical program performed by the applicant, there are no apparent indications that vosoritide treatment contributed to the fractures:

- A lack of preclinical evidence: a juvenile monkey study (BMN111-11-035; 26 weeks duration) did not show significant differences in BMC/BMD by DEXA (but some trends in increased BMC) and no fractures. Bone mechanical testing results illustrated that BMN 111 had no effect on femoral shaft strength as determined by three-point bend test and vertebral body (LV3) strength as determined by vertebral compression test.

- All fractures in the vosoritide treated cohorts, including femur fractures, occurred following a traumatic event. Importantly no atypical, spontaneous or pathological fractures have been reported to date. None occurred across the growth plate.

- Overall, the rate of fracture in the vosoritide program, was comparable to the rate reported in the general pediatric population by the Global Burden of Disease study (GBD) and untreated ACH population as included in the Clinical Practice Research Datalink (CPRD Aurum). While the point estimate for femur fracture in the vosoritide program is numerically higher than the CPRD reference range, the 95% CIs are overlapping.

- None of the participants were reported to have worsening bone density or imaging studies which would predispose them to increased risk of fracture. In fact, DEXA scan data from studies 111-301, 111-302 and 111-206 show no significant difference in vosoritide treated participants versus placebo suggesting no change in bone mineralization and particularly no evidence of worsening of bone mineral density while on treatment.

- There was no increase rate of fracture across different bones (which would likely be the case if fracture was due to vosoritide). There was also no preference for fracture to occur at growth plate (site of vosoritide action), with all fractures occurring following a trauma and no reports of spontaneous fractures. All fractures have healed normally while on treatment with no reports of complications.

- Given the femur fractures were not along the long axis and not transverse, bone quality was not considered to be an issue and instead a biomechanical etiology in conjunction with trauma for the femur fracture was hypothesized.

Estimated annualized incidences of fracture in vosoritide treatment versus placebo were 0.013 versus 0.011, and Relative Risk for vosoritide exposed participants was 1.18 compared to control.

- There were no events of slipped capital femoral epiphysis and avascular necrosis or osteonecrosis in the study.
- There was no evidence of disproportionate skeletal growth, accelerated bone age, or abnormal bone morphology.

Musculoskeletal Adverse Events: In Study 111-206, the incidence (and event rate) of events mapping to Musculoskeletal SOC was higher in the placebo group [21.9 % (0.4 events/ year)] compared to the vosoritide group [18.6 % (0.2 events/ year)].

In Study 111-301, the incidence (and event rate) of events mapping to this SOC was 21.3% (0.3 events/year) in the placebo group compared to 26.7% (0.4 events/ year) in the vosoritide group.

No trends or patterns observed in AEs mapping to musculoskeletal SOC across both placebo-controlled studies.

In the All treated population, a total of 327 events were reported in 101 (42.3%) participants at an adjusted event rate of 0.47 AEs/person-year in the Musculoskeletal SOC.

In examining events within the Musculoskeletal and connective tissue disorders SOC, 3 particular clusters of adverse events were apparent; **pain related AEs, spine disorders, and AEs related to skeletal deformity**.

Pain related AEs were the most frequently reported PTs , stemming from deformities associated with ACH. The most common PTs related to pain were pain in extremity (19.2%, 0.11 event per person-year), arthralgia (17.2%, 0.11 event per person-year), and back (12.6%, 0.06 event per person-year). The majority of pain events were grade 1. There were no events of > Grade 3. The pain events were consistent with the pain commonly reported due to the skeletal aberrations of ACH (Pauli 2019). In medical history at enrollment, pain in extremity was reported in 6.7% participants, arthralgia in 8.4% participants, and back pain in 1.7% participants.

Lordosis was reported in 6 (2.5%) participants and was the most commonly reported spinal abnormality to date with an event rate of 0.01 event per person-year. This event has been reported at frequencies as high as 80% in people with ACH (Kopits 1998). All events were non serious, and did not lead to discontinuation of treatment.

Kyphosis was reported in 5 participants (2.1%), with an event rate of 0.01 event per person year.

All but one of the events were grade 1 or 2. Only one event of kyphosis Grade 3 was noted during the study period. All events were non serious and none of the events lead to discontinuation of study drug. Additionally, one participant (0.4%) over 5 years of age, experienced one non serious, grade 1 event of scoliosis which was assessed as unrelated to vosoritide. One participant (0.4%) over 5 years of age experienced an event of kyphoscoliosism which was reported as serious and related to vosoritide. Kyphosis was assessed as non-serious and related to vosoritide in 2 participants and unrelated in others.

The most commonly reported PT under skeletal deformity was knee deformity, encompassing genu varum and genu valgum event terms. Eight participants (3.3%) experienced a total of 10 events of PT knee deformity (event rate 0.014/year), one of which predated drug administration, so that there were actually 7 participants with 9 events whilst receiving vosoritide. There was no apparent temporality in the onset of the events in relation to duration of treatment, and no action was taken with study drug in response to the events.

No new risks in the musculoskeletal SOC emerged in participants with over 8 years of exposure to vosoritide.

CNS-Disorders: There were no trends related to AEs in the neurological or psychiatric disorders SOC; there was no evidence of any off-target CNS effects, and there were no abnormal hip examinations reported for any participant during the study. Similarly, there was no evidence of changes in behavior, in particular anxiety or depression, during the study.

Heart Rate Changes: No AEs related to heart rate change were reported in study 111-206. In the All-Treated population, there were 4 events of heart rate change in 3 (1.3%) participants with an exposure adjusted event rate of 0.01 AEs/person year. These included three events of tachycardia in 3 (1.2%) participants and one event of sinus tachycardia in 1 (0.4%) participant. No heart rate events were reported that could be attributed to changes in QTc All events were recorded in participants aged ≥ 5 years old. All events were of CTCAE Grade 1 or Grade 2, were not assessed as SAEs and did not lead to discontinuation from study drug.

Sleep Apnea

In study 111-206, a sleep study was performed to assess episodes of sleep apnea. Overall, a reduction in all polysomnography parameters was observed at Week 52 in the vosoritide group, with the exception of Apnea Index in Cohort 3, while changes were mixed in the placebo group. No worsening in the polysomnography parameters were observed with vosoritide at Week 52 compared to placebo. Whilst directional positive change in all but one polysomnography parameters were seen with vosoritide in all cohorts, it is unclear whether these changes represent a clinically meaningful effect of treatment on sleep apnea.

Three out of 43 (7%) participants in the all-vosoritide group reported AEs of obstructive sleep apnea, and one participant in the placebo group (1/32, 3.1%) had an AE of sleep study abnormal. All 3 AEs of obstructive sleep apnea reported in the all-vosoritide group (2 in Cohort 2, and 1 in Cohort 3) were assessed as non-serious, mild to moderate, and unrelated to study drug.

Polysomnography parameters in all 3 participants remained unchanged or improved between baseline and Week 52. Two of these AEs were reported following completion of the protocol mandated 52-week sleep study.

In the All Treated population, 23 events of sleep apnoea syndrome were reported in 18 (7.5%) participants with an exposure-adjusted rate of 0.03 AEs/person-year. Events of sleep apnoea syndrome were reported at similar frequencies in participants aged < 5 years old [(5 (6.5%), 0.04 AEs/person-year] and those ≥ 5 years old [13 (8.0%), 0.03 AEs/person-year].

Serious adverse event/deaths/other significant events

Serious adverse events

Double Blind Placebo Controlled Studies

In Study 111-206, 4 SAEs were reported in 3 (7.0%) participants in the all-vosoritide group (oxygen saturation decreased, respiratory syncytial virus bronchiolitis, sudden infant death syndrome (fatal), pneumonia), and 8 SAEs were reported in 6 (18.8%) participants in the placebo group (petit mal epilepsy, autism spectrum disorder, gastroenteritis, vomiting, parainfluenzae virus infection, respiratory distress, skull fracture, otitis media). All SAEs were assessed as not related to study treatment.

Across both vosoritide and placebo cohorts, most SAEs were reported in Cohort 3: 2 (16.7%) participants in the all-vosoritide group versus 3 (37.5%) participants in the placebo group. No participants on vosoritide and 2 (25.0%) participants on placebo in Cohort 2 experienced an SAE and 1 participant each in the all-vosoritide (5.3%) and placebo group (6.3%) in Cohort 1 experienced an SAE.

Differences regarding the types of SAEs reported in Study 111-206 from those reported in Study 111-301 may be explained by the distinct pediatric issues encountered in these age groups. In the Study 111-301 vosoritide group, four SAEs were reported in 3 (5.0%) participants. These included influenza, radius fracture, sleep apnoea syndrome and adenoidal hypertrophy, which were each reported in 1 (1.7%) participant. In the placebo group, five SAEs were reported in 4 (6.6%) participants. These included appendicitis, dyspnoea, adenoidal hypertrophy, spinal cord compression and intracranial pressure increased, each of which were reported in 1 (1.6%) participant (EMEA/H/C/005475/0000, Study 111-301).

Deaths

One participant (Cohort 3, vosoritide) with pre-existing respiratory morbidity had a fatal respiratory arrest, reported as sudden infant death syndrome; the death was assessed as not related to study treatment by the applicant.

Laboratory findings

Table 23 Laboratory Abnormalities Reported as Adverse Events – Safety Population

Laboratory Abnormality	Age at Day 1 of Vosoritide				All Vosoritide Treated N=239	
	< 5 years N=77		≥ 5 years N=162			
	Incidence n (%)[a]	Event rate m (rate)[b]	Incidence n (%)[a]	Event rate m (rate)[b]	Incidence n (%)[a]	Event rate m (rate) [b]
Total treatment	**-**	**136.2**	**-**	**562.38**	**-**	**698.58**
Vitamin D decreased	3 (3.9)	3	22 (13.6)	22 (0.04)	25 (10.5)	25 (0.04)
Vitamin D deficiency	1 (1.3)	1	16 (9.9)	19 (0.03)	17 (7.1)	20 (0.03)
Neutropenia	0	0	4 (2.5)	4 (0.01)	4 (1.7)	4 (0.01)
Eosinophil count increased	0	0	2 (1.2)	3 (0.01)	2 (0.8)	3 (0.00)
Eosinophil percentage	0	0	2 (1.2)	2 (0.00)	2 (0.8)	2 (0.00)
Hypothyroidism	0	0	2 (1.2)	2 (0.00)	2 (0.8)	2 (0.00)
Alanine aminotransferase	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Blood immunoglobulin E	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Blood prolactin abnormal	1 (1.3)	1	0	0	1 (0.4)	1 (0.00)
Blood triglycerides	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Eosinophilia	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Hyperbilirubinaemia	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Hypercholesterolaemia	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Hyperglycaemia	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Hyperphosphatasaemia	1 (1.3)	1	0	0	1 (0.4)	1 (0.00)
Lymphocyte count increased	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Pollakiuria	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Polyuria	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Transaminases increased	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)
Vitamin D abnormal	0	0	1 (0.6)	1 (0.00)	1 (0.4)	1 (0.00)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were includ ed. AEs were coded using MedDRA v24.1.
Only treatment emergent AEs that started during the year are included for each yearly assessment.

Only ISRs that are CTCAE grade ≥ 2, or any ISR (excluding bruising) lasting > 24 hours for ISRs with non-missing, or partially reported start and end dates are included
For Study 111-206, some Cohort 1 participants randomized to placebo were aged ≥ 5 years when receiving their first dose of vosoritide in Study 111-208. All Vosoritide Treated group includes all participants who took any dose of vosoritide.
a Percentages were calculated using the total number of participants in the safety population (N for each pooled group) as the denominator. Participants with more than one AE of the same
SOC were counted only once for that SOC.
b Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure up to the last dose reported in each pooled group. Multiple occurrences of an AE with the same category were counted for each occurrence for that category.

Hematology

Double Blind Placebo Controlled Study 111-206

In Study 111-206, 5 participants who received vosoritide had 7 laboratory anomalies reported as AEs, of which all 5 participants had low neutrophil count and one of the five participants had 2 AEs of neutrophil count decreased and one AE of alkaline phosphatase elevations. In comparison, 4 participants in placebo group had 4 laboratory anomalies reported as AEs including one event low platelet, one event of low neutrophil and 2 events is increased alkaline phosphatase. In Study 111-206, the majority of shifts in hematology parameters were from normal to Grade 1 with no significant difference between placebo and vosoritide groups.

For neutrophil count decreased, normal to Grade 3 shifts were observed in 2 (4.7%) participants in the all-vosoritide group and a Grade 2 to Grade 3 shift was noted in 1 (2.3%) participant in the all-vosoritide group. A normal to Grade 4 shift was observed in 1 (3.1%) participant in the placebo group.

Most hematology shifts were transient, resolved without medical intervention before the next scheduled assessment, were not associated with any AEs, and were deemed not clinically relevant. There was no trend noted within or across the three cohorts for any of the hematological parameters.

Clinical Chemistry

Mean values of chemistry parameters over time were reported summarized for albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatinine, direct bilirubin, glucose, lactate dehydrogenase, phosphate, potassium, sodium, bilirubin, cholesterol, protein, thyrotropin, bicarbonate and vitamin D.

Double Blind Placebo Controlled Study 111-206

In Study 111-206, the majority of shifts were from normal to Grade 1, were single occurrences and/or transient in nature, resolved without medical intervention, were not associated with any AEs, and were therefore considered not clinically relevant.

One participant each in the all-vosoritide and placebo groups had a normal (at baseline) to Grade 3 increase in alkaline phosphatase. Since increases in alkaline phosphatase can be expected as a CNP effect on bone growth and thus not a safety issue. Regarding the observed low levels of bicarbonate noted across all participants' post-baseline, the applicant informed that this was probably due to unstable samples due to instability of bicarbonate in the uncapped tubes, which caused a decrease in the sample. Interpretation that the low levels seen were therefore not clinically relevant seems correct.

There were no other clinically relevant changes in any chemistry parameters at any time in the three cohorts.

There was no trend noted within or across the three cohorts for any of the chemistry parameters.

During the clinical studies with vosoritide, participant shifts in the < 5 year-old group (N = 77) included:

- Shifts from normal at baseline to Grade 1: alkaline phosphatase increased [9 (11.7%)], alanine amino transferase [10 (13.0%)], aspartate aminotransferase increased [6 (7.8%)], creatinine increased [4 (5.2%)], hypoglycemia [12 (15.6%)], hyperglycemia [39 (50.6%)], hyponatremia [(7 (9.1%)], blood bilirubin increased [1 (1.3%)]
- Shifts from normal at baseline to Grade 2: alkaline phosphatase increased [1 (1.3%)], alanine aminotransferase [1 (1.3%)], hyperglycemia [3 (3.9%)], hypernatremia [2 (2.6%)], hypoalbuminemia [1 (0.6%)]
- Shifts from Grade 1 at baseline to Grade 3: alkaline phosphatase increased [1 (1.3%)], creatinine increased [1 (1.3%)] In the < 5 years old group, shifts to Grade 3 were reported in two participants. In both cases, this involved elevation of alkaline phosphatase and included 1 (1.3%) participant who was normal at baseline and 1 (1.3%) participant who was Grade 1 baseline.

Bone metabolism, blood and/or urine biomarkers included but were not limited to, assessment of changes in bone and collagen metabolism (serum bone-specific alkaline phosphatase, serum collagen type X, and urine C terminal telopeptide of collagen type II [CTX-II]) and vosoritide bioactivity (plasma and urine cGMP). These parameters are seen as exploratory biomarker and included in the efficacy endpoints.

Safety in special populations

Safety analyses in special populations were performed regarding gender, ages, and race/ethnicity groups (intrinsic factors) and geographical regions (extrinsic factors) in that affected the safety of treatment with vosoritide. Overall, no clinically relevant differences were revealed in the profile of AEs by any of these parameters considering the small numbers of subjects and safety events.

With the exception of hypotension which occurred more frequently in participants aged ≥ 2 years, exposure adjusted rates of EOIs were numerically higher in participants aged < 2 years than in participants aged ≥ 2 years. Exposure adjusted rates of fractures were similar between age groups.

As already mentioned above, in the participants aged < 2 years, the exposure-adjusted rate of 11.02 AEs/person-year was higher than in the ≥ 2 years old group (5.46 AEs/person-year). The same is true with respect the exposure adjusted-rates of SAEs and AEs of CTCAE Grade ≥ 3 which were also higher in the < 2 year age group (0.18 and 0.16 AEs/person-year, respectively) than in the ≥ 2 years age group (0.05 and 0.04 AEs/person-year, respectively).
The incidence of SAEs and Grade ≥ 3 AEs were lower in the vosoritide groups compared with the placebo groups in Cohort 2 and 3 participants enrolled in Study 111-206. In particular, in Cohort 2 and Cohort 3, the incidence of SAEs was lower in the vosoritide group than in the placebo group (Cohort 2: 0% versus 25%; Cohort 3: 16.7% versus 37.5%). While no participants in Cohort 2 (> 6 months to 2 years) experienced Grade ≥ 3 AEs, the incidence of Grade ≥ 3 AEs in Cohort 3 was lower in the vosoritide group than in the placebo group (16.7% vs 37.5 %).

Safety related to drug-drug interactions and other interactions

Results from the transporter inhibition study suggested that vosoritide did not inhibit the transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp or BSEP. Based on the

results from the microsome stability study, CYP inhibition and induction studies and transporter study, CYP or transporter mediated drug-drug interactions for vosoritide are unlikely.

Discontinuation due to adverse events

In Study 111-206, one participant discontinued from study: Participant 0003-1095 [5.32 months old, Cohort 3, randomized vosoritide]; related to fatal event of respiratory arrest (reported as sudden infant death syndrome, not related, and occurred in a participant with previous co-morbidities. In the pooled safety population (All Treated population), a total of 3 (1.9%) participants discontinued the study due to an AE. However, the three participants who experienced events leading to discontinuation of study drug (PTs: procedural anxiety, transaminases increased and Wolff-Parkinson-White syndrome) were reported in the original MA (in participants aged ≥5 years and discussed during the initial MAA procedure.

With vosoritide treatment for up to 9 years, a total of 4 (1.7%) participants in the All Vosoritide Treated group discontinued the study drug or withdrew from study due to an AE.

Except for the above death, no new AES leading to withdrawal have been reported since the original MA (EMEA/H/C/005475). While all the 3 study drug discontinuations due to AEs reported during the studies occurred only in males (none in females), given the very small numbers a meaningful comparison seems not possible.

Temporary cessation of study drug by the Investigator was permitted in response to AEs during the studies until improvement in the status of the participant or resolution of the event, as per the Investigator's clinical judgement. In Study 111-206, adverse events led to study drug interruption in 32.6% of the All Vosoritide group and 46.9% of the placebo group. No events leading to study drug interruption were assessed as related to treatment with vosoritide.

Also, in the pooled safety population the pattern was similar in the < 5-year-old and ≥ 5-year-old age groups. These events were all consistent with acute paediatric illnesses. There were no AEs leading to dose reduction.

Immunogenicity

Scheduled samples were tested in one or more of the following assessments:

- Anti-vosoritide TAb
- Anti-vosoritide antibody cross-reactivity with endogenous CNP, ANP, and BNP (TAb)
- Anti-vosoritide NAb

Testing for the presence of cross-reactive antibodies that bind to endogenous CNP, ANP, or BNP and for the presence of vosoritide NAbs was only performed on baseline samples and anti-vosoritide TAb-positive samples. Baseline NAb sample and cross-reactive TAb sample testing was done at any time prior to the end of study.

Double Blind Placebo Controlled Study 111-206

In Study 111-206, 19% (8/43) of all vosoritide-treated participants tested positive for TAb and all placebo-treated participants tested negative for TAb. All of the TAb-positive participants tested negative for NAb at all time points. Drug-specific IgE was planned to be tested in the event of a significant hypersensitivity adverse event. However, since no significant hypersensitivity adverse events occurred during the study, no drug-specific IgE testing was performed. Overall, the

immunogenicity results obtained in participants aged < 5 years were consistent with the immunogenicity profile of vosoritide observed in participants aged > 5 years and support the safety profile of vosoritide.

In the pooled Safety pooled population no Grade 3 or higher severity HAEs or anaphylaxis were reported in the study. Therefore, no drug-specific IgE testing in response to a safety signal was required per protocol. All reported HAEs excluding ISRs were Grade 1 or Grade 2. A comparison of serum Tab negative and positive participants showed no association between TAb positivity and incidence or severity of HAEs as reported by CTCAE Grade in any of the treatment cohorts.

In the participants who were TAb positive, no association was detected between mean or proximal TAb titer and incidence or severity of HAEs. A comparison of TAb negative and positive participants showed no association between TAb positivity and incidence of injection site reactions (ISRs) in any of the treatment cohorts. Lastly, no association was found between TAb cross-reactivity with endogenous ANP/BNP/CNP and AEs associated with cardiovascular, renal function, or electrolyte imbalance assessing Cardiac Disorder, Fluid and Electrolyte Balance AEs.

Post marketing experience

Global marketed patient exposure to vosoritide (Voxzogo 0.4 mg/0.56 mg/1.2 mg powder and solvent for solution for injection) is estimated to be 220 patients during the reporting period of the first Periodic Benefit Risk Evaluation Report (PBRER) with a data cut-off of 25 February 2022. Cumulative marketed patient exposure is estimated to be 220 patients.

The safety profile of vosoritide appears consistent with the experience in clinical trials. The majority of the events in the post market setting were non-serious injection site reactions. The next most commonly reported adverse events were those related to drop in blood pressure. Both events were already known to be drug-related and are listed in the PI.

2.5.1. Discussion on clinical safety

The combined study exposure was 716 person-years for the assessment of long-term safety signals with vosoritide. With respect to the applied for extension of indication to patients below age of 2 years, mainly the safety outcome of Study 111-206 and the preliminary outcome of the extension trial 111-208 was considered important. Database from trial 111-206 is still restricted to 64 participants in three Cohorts representing a total of 140.59 person-years with vosoritide.

A total of 37/43 (86.0%) participants in the All Vosoritide group versus 17/32 (53.1%) participants in the placebo group reported TEAEs. Considering the differences in treatment duration in the pooled safety population, exposure-adjusted rates of 192.7 AEs/person-year for vosoritide versus 60.3 AEs/person-year for placebo for treatment-related AEs reflect best the increase of adverse events. This rate for treatment related adverse event was three-fold higher in the population below the age of 5 years compared to patients > 5 years of age. However, the increase was mainly caused by a higher frequency of injection site reactions as reflected in the Product information and further below.

For children ≥24 to <60 months of age, initial approval of vosoritide was based on interim data in sentinel participants only and supported by extrapolation based on pharmacokinetic, efficacy, biomarker and safety data from studies 111-206 and 111-208. At that time, the safety assessment concluded that vosoritide had an acceptable safety profile and treatment was generally well tolerated, a notion which is further supported by the updated safety data submitted with this appliation.

In general, the information on safety outcomes was sufficiently reported to identify key findings. However, the initially provided data did not allow a separate evaluation of safety outcome in the newly applied for population of children younger than 24 months. A pooled safety analysis for the applied for population of children aged < 24 months was requested together with a comparison with Cohort 1 of trial 111-206 and the pivotal trial 111-301.

The comparison provided in the MAH's response showed that vosoritide was overall well tolerated in participants <2 years of age, with no treatment limiting adverse effects. The safety profile in children < 2 years appeared to be generally consistent with that seen in participants >2 years of age with the exception of a higher rate of injection site reactions (ISRs). These included: injection site reaction, erythema, swelling, urticaria, bruising and induration at the injection site. Almost all events were of grade 1 severity and all fully reversible.

CHMP considered whether the increase in ISRs in the youngest patients may be dose-related. The analyses of ISRs in study 111-206 by vosoritide dose (15 and 30 µg/kg) showed that the incidence in Cohort 3 participants, all of whom received 30 µg/kg and in Cohort 2 participants receiving 30 µg/kg, was comparable with Cohort 1 participants, all of whom received 15 µg/kg; but Cohort 2 participants receiving 15 µg/kg had a lower incidence of ISRs. Therefore, an association of ISRs with vosoritide dosage is not obvious but cannot be excluded. Since similar trends towards increasing ISRs with lower age were also noted in the corresponding placebo groups, other causes such as increased susceptibility or reduced area for rotation of injection sites may have contributed to the increased ISRs in the youngest compared to older children. [Of note, Cohort 3 participants who received placebo had the highest incidence of ISRs]. Injection site reactions are described in detail in SmPC section 4.8. Furthermore, they will be evaluated in the ongoing safety study 111-603.

Cohort 3 participants (< 6 months of age), who received 30 ug/kg, appeared to experience a higher incidence of reduced diastolic blood pressure (DBP). However, no dose effect was observed regarding the incidence or event rates for hypotension. Since the incidence of hypotension events in 111-206 was generally low, no firm conclusions can be drawn from these data. Hypotension is an ADR in the SmPC section 4.8 and information on management of decrease in blood pressure and associated symptoms is described in SmPC section 4.4.

The higher incidence of pyrexia, upper respiratory tract infection, cough, teething and diarrhoea was reported in Study 111-206 in both treatment arms compared to Study 111-301, however is not unexpected given these are all known issues commonly encountered in younger children. This is demonstrated also by similar event rates between vosoritide and placebo cohorts in Study 111-206.

Most importantly, no new safety concerns were identified with use of vosoritide in the younger population or in older children who have received vosoritide for over 8 years. The incidence of AEs mapping to all other SOCs was comparable to older participants or similar to placebo group with no trends suggestive of new safety issues emerging in participants <2 years of age.

Across cohorts, the number of events assessed as related to vosoritide was higher in Cohort 1 compared to Cohorts 2 and 3 (which were similar), and the incidence of events was higher in Cohort 3 compared to Cohorts 1 and 2. Whether this reflects more age specific differences or the fact, that reporting of adverse events at least partially depends on acquisition of speech or other issues remains open.

AEs of Grade ≥ 3 were reported at a lower rate in the All Vosoritide than in the placebo group (4.7% vs 9.4%). 4 SAEs were reported in 3 (7.0%) participants in the all-vosoritide group (oxygen saturation decreased, respiratory syncytial virus bronchiolitis, sudden infant death syndrome (fatal), pneumonia). 8 SAEs were reported in 6 (18.8%) participants in the placebo group (petit mal epilepsy, autism spectrum disorder, gastroenteritis, vomiting, parainfluenzae virus infection, respiratory distress, skull

fracture, otitis media). With the exception of one Grade 5 (death caused by Sudden infant death-Syndrome – see below) all AEs Grade ≥ 3 were of Grade 3 (severe). None was Grade 4 (life-threatening). None of these events was considered to be related to the study treatment. Most of them reflect common conditions particularly observed in younger children with ACH.

One case of death due to SIDS occurred in trial 111-206 and another case in the observational non-interventional study 111-901. Considering the total information provided, the SIDS case in study 111-206 may be reasonably classified as not related to vosoritide. Moreover, it is acknowledged that the incidence of SIDS of 0.4% in the clinical development program in over 243 participants exposed to vosoritide is substantially lower than the rate reported in both the literature for children with achondroplasia and as observed in the observational study BMN 111-901.

The incidence of sleep apnoea reported in the vosoritide program is below that reported in the literature. In general, the sleep apnoea data from trial 111-206 suggest an improvement in all polysomnography parameters at Week 52 in the vosoritide group, while changes were mixed in the placebo group. Central apnoea and restrictive breathing problems are commonly observed in young infants with ACH and children; adults with ACH are known to have an exceedingly high frequency of obstructive sleep apnea. The percentage of people with achondroplasia having sleep apnea ranges (in all age groups) from 10 to 87% in the literature (Tenconi 2017). In the youngest population, these events may contribute significantly to the 50-fold increase in SIDS rates reported in the literature compared with the average healthy population.

The CHMP noted that the MAH will continue to monitor for SIDS through ongoing clinical trials and routine pharmacovigilance activities and report to CHMP/PRAC.

Data available indicate no increased risk of fracture with vosoritide in the population below the age of 5 years and particularly not in the applied for population below the age of 24 months. The two reported events were both assessed as not related to study drug (Voso: 1 and Plc: 1). Similarly, data from the pooled population confirmed the absence of increased fracture risk due to vosoritide treatment. Furthermore, the type of fracture was as expected for age in the general paediatric population and was due to traumatic events. Importantly no atypical, spontaneous, pathological or across the growth plate fractures occurred. However, a recent event of femur fracture was reported as possibly related to vosoritide treatment. The applicant clarified that the Grade 3 SAE of left femur fracture (PT: femur fracture) was associated with an adequate trauma (twisting injury) in a 10-year-old participant in study 111-302. While there was no clear causal relationship, the investigator reported "relationship was assessed as possibly related to vosoritide" based on pre-clinical data (in mouse models) and the rarity of event. Since a conservative assessment was undertaken until sponsor completed a full signal evaluation of all fractures including femur fractures, this event is classified correctly. The outcome of the event was reported as Recovered/Resolved. In the end, the applicant assessed the event as "unlikely" to be related to vosoritide, which can be endorsed.

There have been no new fractures of any type reported in either the clinical development program, in the post marketing setting since the signal evaluation. At the most recent data lock point for PBRER #3 (25 Feb 2023), incidence rate of fracture has decreased. This may allow to consider the applicant's statement that "fractures including femoral fractures are not considered to be adverse drug reactions at this time" is endorsed. Nevertheless, fractures continue to remain Events of Special Interest, and along with skeletal events will be monitored in ongoing clinical studies and in the post-marketing setting as outlined in the risk management plan.

It is reassuring that no events of slipped capital femoral epiphysis, avascular necrosis or osteonecrosis, or fracture changes occurred even after longer exposure as now shown by the updated longer exposure dataset (compared with initial MAA data cut-off).

Considering that ossification in the scull (intramembranous ossification) differs from that in growth plates (endochondral ossification), the applicant was requested to clarify potential effects of vosoritide. The responses reported no adverse event of accelerated or abnormal ossification of the flat bones of the cranial vault in participants on treatment. Particularly, there have been no adverse event reports of unexpectedly delayed, accelerated, or abnormal closure of fontanelles or cranial sutures which may have been expected in case of a deleterious vosoritide effect on intramembranous bone growth.

The MAH concluded that, based on a comprehensive review of preclinical studies and data from clinical trials (adverse events, MRI data including volume of calvarium, and head circumference), there is no evidence that vosoritide affects the process of intramembranous bone ossification. Moreover, there are no data suggesting that vosoritide adversely affects skull development and the currently available data may even indicate a small favourable effect of vosoritide on bone neuro-cranial anatomy. However, the current database regarding this outcome is too limited to confirm any claim or to rule out a potential risk. Some uncertainties remain since the effect of FGFR3 gain of function mutations on intramembranous bone growth including the skull, and the potential effect of signal inhibition by vosoritide, have been less clearly defined. All musculoskeletal events are further monitored as outlined in the risk management plan.

There were no trends related to AEs in the neurological or psychiatric disorders SOC and no evidence of any off-target CNS effects.

Assessment of laboratory findings did not reveal any clinically meaningful changes in hematology and clinical chemistry parameters with vosoritide in any of the age cohorts. Shifts in alkaline phosphatase with up to grade 3 increase can be expected as a consequence of CNP effect on bone growth and is thus not considered a safety issue.

No new or additional aspects need to be discussed regarding safety related drug-drug interactions and other interactions. This item was already sufficiently evaluated and discussed during the initial approval. No specific aspects for the population below the age of 5 years needs to be discussed.

Except for the above death, no new AEs leading to study discontinuation or withdrawal have been reported since the original MA (EMEA/H/C/005475). In Study 111-206, adverse events led to study drug interruption in 32.6% of the All Vosoritide group and 46.9% of the placebo group. Pattern of interruptions were similar in the < 5 year old and ≥ 5 year old age groups and caused by acute paediatric illnesses. No AEs leading to dose reduction were reported.

Immunogenicity results obtained in participants aged < 5 years were consistent with the immunogenicity profile of vosoritide observed in participants aged > 5 years and reported in the original NDA. Anti-drug antibody (ADA) development did not affect efficacy or safety of vosoritide.

The safety profile of vosoritide observed post-authorisation appears consistent with the experience in clinical trials. The majority of the events in the postmarketing setting were non-serious injection site reactions followed by adverse events related to a drop in blood pressure. Some additional postmarketing data from Japan from 11 children with ACH aged ≤6 months who have received vosoritide revealed no new safety signals for drug-related adverse events.

All safety findings are adequately reflected in the PI (SmPC section 4.4 and 4.8) and monitored through the RMP.

2.5.2. Conclusions on clinical safety

During the initial approval procedure, vosoritide was found to have an acceptable safety profile and to be generally well tolerated, based on the safety data in children aged > 5 years and the 11 sentinel patients aged 24 to 60 months available at that time.

The applicant has now provided the complete study results from trial 111-206 including patients aged 4 to 60 months and applied for the treatment of that population until growth plate closure.

In general, no signals regarding new safety risks were identified.

The observed increase in the exposure-adjusted event rate in the younger age cohort children appears to be attributable to drug-related Grade 1 transient ISRs and other, more age-specific, not treatment-related AEs.

The case of death due to SIDS in one child below the age of 6 months receiving vosoritide has ben sufficiently described and may be reasonably classified as not related.

Long-term safety risk, particularly risk for bone and joint malformation potentially leading to osteonecrosis and cartilage dysfunction after longer treatment duration remains still an uncertainty. However, the available data do not suggest disproportionate skeletal growth or abnormal bone morphology. Considering that ossification in the scull (intramembranous ossification) differs from that in growth plates (endochondral ossification), the applicant clarified potential effects of vosoritide. It appears that the currently available data indicate a trend to normalisation of the skull physiology in ACH population by vosoritide without any worsening of existing pathology. All musculoskeletal events are further monitored as outlined in the risk management plan. No evidence suggestive of any off-target effects including renal or CNS system was detected.

In conclusion, the safety profile of vosoritide is considered acceptable, also in patients below age of 2 years.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted submit an updated RMP version 3.4 (data lock point on 25 February 2022, date of final sign off on 14 September 2023) with this application. The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 3.4 is acceptable.

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	• None
Important Potential Risks	• Medication errors related to the change of the type of the syringe
Missing Information	• Long-term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential • Use in pregnancy • Use in patients 4 months to 5 years old

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 – Required additional pharmacovigilance activities				
111-205 Ongoing	To assess long-term safety and efficacy	• Long term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential	Safety Report (Anticipated):	Q3 2023 and subsequently at 2-yearly intervals
			Final CSR (Anticipated)	February 2028
111-208 Ongoing	To assess long-term safety and efficacy	• Long term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential • Use in patients 4 months to 5 years old	Safety Report (Anticipated):	Q3 2023 and subsequently at 2-yearly intervals
			Final CSR (Anticipated)	June 2037
111-302 Ongoing	To assess long-term safety and efficacy	• Long term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential	Safety Report (Anticipated):	Q3 2023 and subsequently at 2-yearly intervals
			Final CSR (Anticipated)	July 2030
111-209 Ongoing	To assess safety and efficacy	• Long term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential • Use in patients 4 months to 5 years old	Interim Safety Report (Anticipated): Final CSR (Anticipated)	Q1 2025 Q1 2028
111-603 Vosoritide PASS Ongoing	To assess long-term impact on safety and skeletal effects in a real-world setting	• Long term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential • Use in patients 4 months to 5 years old	Registration to EU PAS register	EU PAS Register Number: EUPAS47514
			Safety Report (Anticipated) Final CSR (Anticipated):	December 2023 and subsequently at 2-yearly intervals 2036

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Activities
Medication Error related to the change of the type of the syringe **(Important Potential Risk)**	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC and PL Introduction of a new dosing table in Section 4.2 of the SmPC plus the addition of a new Instruction for Use (IFU) document, illustrating the new devices provided in the pack. Other routine risk minimisation measures beyond the Product Information: Prescription only medicine: Voxzogo should be initiated and directed by a physician appropriately qualified in the management of growth disorders or skeletal dysplasias.
Long-term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential (**Missing information**)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Prescription only medicine: Voxzogo should be initiated and directed by a physician appropriately qualified in the management of growth disorders or skeletal dysplasias.
Use in pregnancy **(Missing information)**	Routine risk communication: SmPC Sections: 4.6, 5.3 PL Section: 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Sections: 4.6, 5.3 Section 4.6 states that there are no or limited amount of data from the use of vosoritide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of vosoritide during pregnancy. Section 5.3 provides preclinical data on reproductive and developmental toxicity. PL Section 2 states the following: The use of this medicine is not recommended during pregnancy and breast-feeding. If you or your child are being treated with this medicine and are pregnant or breast-feeding, think you or your child may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Other routine risk minimisation measures beyond the Product Information: Prescription only medicine: Voxzogo should be initiated and directed by a physician appropriately qualified in the management of growth disorders or skeletal dysplasias.

Safety Concern	Routine Risk Minimisation Activities
Use in patients 4 months to 5 years old **(Missing information)**	Routine risk communication: SmPC Sections: 4.8, 5.1, 5.2 PL Sections: None SmPC Section 4.8 presents safety of vosoritide in clinical studies involving children aged < 5 years, overall and by age cohorts ≥24 to <60 months and ≥6 to <24 months. Section 5.1 presents the details on subjects enrolled in a randomized, double-blind, placebo-controlled 52-week study (111-206) in age cohorts ≥24 to <60 months and ≥6 to <24 months. At 52 weeks, consistent effect in favour of Voxzogo was observed in all age cohorts compared to placebo. SmPC 5.2: updated to reflect the PK exposures of patients under 5 years of age. Other routine risk minimisation measures beyond the Product Information: Prescription only medicine: Voxzogo should be initiated and directed by a physician appropriately qualified in the management of growth disorders or skeletal dysplasias.

2.7. Changes to the Product Information

As a consequence of the extension of indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Additionally, Annex II has been updated to remove the fulfilled obligation to conduct post-authorisation measures. Minor editorial changes have been introduced throughout the PI.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: These changes are sufficiently minor that they should not impact the validity of the readability result from October 2020.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Voxzogo (vosoritide) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

- It is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Achondroplasia (ACH) is a rare genetical orphan disease disorder with an incidence of 1 in 25,000 births. ACH is the most common form of short-limbed short stature and is characterized by rhizomelic shortening of the extremities, characteristic facies with frontal bossing and midface hypoplasia and increased lumbar lordosis. The vast majority of individuals with achondroplasia are diagnosed in early infancy or at birth, although prenatal recognition has become more frequent.

Dysmorphic short stature is the obvious main feature of the disease. Although length at birth may be normal, slow growth is evident shortly thereafter. Moderate to marked short stature is present in all affected individuals. In adult males, average height is about 130 cm with a range from around 120 to 145 cm. Similarly, in females average height is 125 cm with a range of 115 to 137 cm.

The disease causes or is associated with obvious orthopaedic complications with about 50% of the patients suffering from kyphosis and scoliosis, a potential for osteoarthritis and osteopenia. Development of craniocervical stenosis is also common. Based on the skeletal abnormalities, there is a high occurrence of neurological complications and symptoms with chronic back pain affecting up to 70% of the patients, hydrocephalus and spinal stenosis (increasing with age) and its sequelae. Patients regularly suffer from obesity, including abdominal obesity. Based on the craniofacial bone abnormalities, patients also suffer from obstructive sleep apnoea, and middle ear dysfunction. Strabismus and voice abnormalities are also common.

The disease is associated with an increased mortality in adult patients (some studies report increased mortality in childhood) with an estimated mean disadvantage in life expectancy by 10 years, with the main causes of death being heart disease, neurological complications, and accidents.

The disorder is caused by gain-of-function mutations in fibroblast growth factor receptor 3 (FGFR3), which is a negative regulator of longitudinal bone growth. All instances of achondroplasia arise from mutations that are autosomal dominant. These mutations are fully penetrant and show only modest variability of expression.

3.1.2. Available therapies and unmet medical need

In the EU, vosoritide is indicated for the treatment of ACH in participants 2 years of age and older whose epiphyses are not closed; however, there remains an unmet need in participants with ACH < 2 years of age given the absence of an approved pharmacological therapy in this age group.

Given the finite window for growth in a child and considering the rapid accumulation of height deficit in patient with ACH during the first years of life, early treatment start would be desirable to maximise treatment benefit.

3.1.3. Main clinical studies

The applicant has provided a comprehensive clinical data package with results from 7 prospective clinical studies in genetically confirmed ACH subjects: [111-101-FIM, healthy volunteers only], 111-202(+111-205) dose-finding, 111-301 (+111-302) pivotal phase 3 RCT (≥5-≤18 years) and **111-206**

(+**111-208**) phase 2 RCT (0-≤5 years) pivotal for this application. In order to optimise disease characterisation of the untreated population at baseline and for further comparisons of the short and long-term outcome, the applicant has performed one observational study (111-901) and generated RWE from different NH sources.

All patients in the clinical programme were initially included in the baseline observational growth study for at least 6 months before they could be recruited for one of three studies (and there corresponding extension trials):

Dose-finding:

Study *111-202* was an open-label, dose-escalation phase 2 study which included 34 ACH subjects at the age range of 5-14 years of age, who received vosoritide daily in doses of 2.5µg, 7.5µg, 15µg and 30µg s.c. in 4 sequential cohorts of at least 8 subjects. Duration was 6 months, with an optional treatment extension of 18 months. Type I error was adequately controlled by hierarchical testing. After reaching the end of 24 months treatment in trial 111-202, the 30 subjects could be rolled over to the long-term *extension study 111-205*. In this, subjects are followed until reaching near final adult height (NFAH) or a minimum of 5 years. Subjects in the low dose cohorts were transferred after completion of 202 into the 15 µg/kg dose cohort to increase the information about the selected posology.

Pivotal trial(s) for subjects from 5 to <18 years of age:

Study *111-301* is a completed multicentre, randomized, double-blind, placebo-controlled Phase 3 trial which evaluated the efficacy and safety of 52 weeks of treatment with vosoritide (15 µg/kg daily) compared with placebo in children aged 5 to <18 years with a clinical diagnosis of ACH confirmed by genetic testing. Randomization (1:1) was stratified by sex and Tanner stage (Tanner stage 1, or Tanner stage >1), with no more than 20% of Tanner stage >1 to be enrolled. A total of 121 subjects were enrolled into the study; 61 subjects were randomized to receive placebo and 60 subjects to receive daily vosoritide 15 µg/kg. After 52 weeks of treatment, all 61 subjects in the placebo group completed the study and in the vosoritide group, 58 subjects completed and 2 subjects withdrew from the study. All subjects were transferred to the ongoing *extension trial 111-302*, in which patients are treated with vosoritide until they either attains NFAH or a minimum of 5 years. NFAH was defined as evidence of growth plate closure and 6-month interval AGV < 1.5 cm/year AGV or for 5 years, if NFAH occurs prior to the end of the 5-year period.

Pivotal trial(s) for subjects from 0 to 60 months of age relevant for this Variation procedure:

Study 111-206 is a completed 52-week multicentre, 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 60 months (5 years) of age with genetically confirmed ACH. Subjects are enrolled into three age cohorts based on age [Cohort 1: ≥ 24 to < 60 months (n = 35) / Cohort 2: ≥ 6 to < 24 months (n = 20) / Cohort 3: 0 to < 6 months (n: 20)] starting with the eldest population. Subjects in the *extension trial 111-208* received vosoritide until they reached final or near final height. As of the 26 January 2022 data cut-off point, 73/75 participants who had completed treatment in 111-206 had enrolled in extension *Study 111-208* and receive vosoritide. Of the 73 participants treated, 31 had previously received placebo in 111-206 and 42 had previously received vosoritide. Analyses included all 73 participants grouped according to their age at first dose of active treatment. A total of 11 participants were aged 0 to <6 months, 22 were aged ≥6 to <24 months, 34 were ≥24 to <60 months old and 6 were ≥60 months old when they received their first dose of vosoritide in either *study 111-206* or *111-208*. At the time of the data-cut off, all participants remained in the study and were continuing treatment. A total of 9 participants who started vosoritide treatment in *111-206* and continued into the *extension study 111-208* up to the data cut-off point had been treated for at least 3 years.

3.2. Favourable effects

The initial approval of children ≥24 to <60 months of age was based on interim data in 4 sentinel participants and supported by extrapolation based on pharmacokinetic, efficacy, biomarker and preliminary safety data from studies 111-206 and 111-208 and needed confirmation from the now available data. The efficacy data provided from pivotal trial 111-206/208 for children aged ≥24 to <60 months in this Type II Variation, confirm and support the currently approved indication, as illustrated by a gain in height Z-score of >1 SDS, corresponding to >5.5 cm in height after 3 years of follow up and no evidence of tachyphylaxis.

For the proposed extension of indication to ACH patients age < 2 years, results from study 111-206 and longer-term data from the extension study 111-208 are relevant.

Study 111-206: The LSM differences between the treatment groups for height-Z-score at week 52 showed point estimates consistently in favour of vosoritide (Cohort 1: LSM difference of 0.33 [95% CI: 0.00, 0.67] SDS, Cohort 2: LSM difference of 0.21 [95% CI: -0.37, 0.79] SDS and Cohort 3: LSM difference of 0.23 [95% CI: -0.45, 0.91] SDS in the FAS [randomized]). Corresponding LSM mean differences in height were observed in favour of vosoritide (Cohort 1: 0.96 [95% CI: -0.09, 2.02] cm, Cohort 2: LSM difference of 0.71 [95% CI: -0.62, 2.04] cm and Cohort 3: LSM difference of 0.70 [95% CI: -1.28, 2.68] cm in the FAS [randomized]).

Study 111-208: Multiple analytical approaches including longitudinal and cross-sectional analyses were used to compare participants receiving vosoritide in 111-206/208 with AchNH external control and the observational/placebo external control. Since placebo comparison is limited to one year in trial 111-206 only, this was the only possibility to assess efficacy in the long-term.

- In participants ≥3 to <6 months, the totality of the data, including individual growth data, provided evidence of a positive impact of vosoritide in this age group in comparison to untreated age- and sex-matched participants with ACH (after 2 years, the improvement in height Z-score compared to untreated ACH children was up to 0.87 SDS). New analyses provided with the response confirm this treatment benefit at 2 years.
- The favourable effects on growth were not associated with accelerated bone maturation, increased rates of fractures or impaired bone health. No events of slipped capital femoral epiphysis, avascular necrosis or osteonecrosis, or fracture changes occurred even after longer exposure as now available compared with initial MAA data cut-off. Skeletal effects of voxzogo are monitored in the ongoing studies.

3.3. Uncertainties and limitations about favourable effects

The continuous increase in treatment gain as shown by the more mature data provided justifies the interpretation that efficacy is maintained over 3 years of follow-up. The sharp decline and high variability of growth in patients < 2 years of age, esp. in infants, together with the small sample size is considered a reasonable explanation for the seemingly smaller effect size in these patients. However, the gain in height-SDS during the first year of treatment appeared similar across age groups.

In addition, extrapolation of efficacy from older children is considered possible based on the same pathophysiology of the disease. There is no indication to suggest that the pharmacology of vosoritide is different in the younger population. Comparable to higher drug exposure and levels of cGMP (systemic marker of biological activity) were observed between participants < 2 years and ≥ 2 years.

Body disproportionality in ACH is caused by reduced growth of legs and arms and worsens over time. Consequently, starting treatment from infancy may have the potential to provide greater benefits with

respect to growth and proportionality and thus avoiding some of the complications associated with disproportionate short stature in children with ACH. However, current data do not allow a conclusion that vosoritide can relevantly diminish disproportionality. This information is being collected in the ongoing study 111-209 (cat. 3 commitment in the RMP). It is acknowledged that assessment of such potential benefit will require several years.

Impact of vosoritide treatment on HRQoL and functional parameters, as well as comorbidities in ACH associated with the impaired endochondral ossification is not proven at present. These outcomes are being recorded in the ongoing extension study 111-208.

The postulated positive effect of vosoritide on a number of clinical manifestations of ACH where impaired endochondral ossification plays a key pathogenic role appears not sufficiently proven at present. The impact of the positive numerical change observed on MRI in volume of the face and sinus in the youngest age group, which could be indicative of positive changes to the overall bone structure of the face/skull, remains uncertain. This aspect is being assessed in the ongoing studies (111-208, -209, -603)

In younger children with ACH, severe clinical complications such as central and/or obstructive sleep apnoea may occur as a result of the foramen magnum stenosis. Due to a deficit in endochondral ossification, an anterior extension of the squamous occipital bone develops, which in combination with premature fusion of the posterior synchondroses results in abnormal growth of the foramen magnum. Beneficial effects of vosoritide in terms of reducing or even preventing stenosis of the foramen magnum have not been demonstrated at present. This information is being collected in the ongoing study 111-209 (cat. 3 commitment in the RMP).

It remains uncertain at present whether a clinically meaningful reduction of apnoea and neurocranial complications as well as SIDS in ACH babies can be achieved with early start of vosoritide treatment, although small overall improvements in polysomnographic parameters compared to placebo were observed. Further data is being collected in ongoing studies.

The CHMP discussed further the exposure of vosoritide in patients <2 years due to inconsistency in the reported values for the lowest age and weight group. In the committee's view, the popPK model requires further update to better capture the exposure in the youngest patients. The applicant committed to provide the requested update post-approval.

3.4. Unfavourable effects

The combined study reflects an exposure of 716 person-years for the assessment of long-term safety of vosoritide, mainly in subjects aged > 5 years; the exposure in the population below the age of 5 years amounts to 140.59 person-years.

The safety profile and the types of adverse events observed in pivotal trial 111-206 appears similar to that in subjects > 5 years. However, the frequencies in terms of exposure–adjusted event rates were found to be significantly higher in the population below 2 years compared with those > 2 years. In the age group applied for (patients < 2 years of age), the exposure-adjusted AE rate was 192.7 AEs/person-year for vosoritide versus 60.3 AEs/person-year for placebo for treatment-related AEs in the pooled safety population, which means a three-fold higher frequency of AEs/person-years. Also, the frequency of events assessed as related to vosoritide was higher in younger patients.

In the age group applied for (patients < years of age), the exposure-adjusted AE rate was 192.7 AEs/person-year for vosoritide versus 60.3 AEs/person-year for placebo for treatment-related AEs in the pooled safety population, which means a three-fold higher frequency of AEs/person-years. Also the frequency of events assessed as related to vosoritide was higher in younger patients.

The increase in the overall exposure adjusted adverse event rate appears to be mostly caused by higher rates of injection site reactions in the younger patients. Most treatment-related AEs were grade 1 and some grade 2 injection site reactions (ISRs). The ISRs were transient, generally self-limiting with no participants experiencing any long-term sequelae at injection site. None of the treatment related AEs were serious. AEs of Grade ≥ 3 were reported at a lower rate in the All Vosoritide than in the placebo group (V: 4.7% vs P:9.4%).

SAEs were also lower in the All Vosoritide group than in placebo group: 3 (7.0%) participants in the all-vosoritide group (oxygen saturation decreased, respiratory syncytial virus bronchiolitis, sudden infant death syndrome (fatal), pneumonia) versus 8 SAEs were reported in 6 (18.8%) participants in the placebo group (petit mal epilepsy, autism spectrum disorder, gastroenteritis, vomiting, parainfluenzae virus infection, respiratory distress, skull fracture, otitis media).

One case of "Sudden Infant Death-Syndrome" (SIDS) was observed and assessed as not drug-related. Central/obstructive apnoea and restrictive breathing problems as well as neurocranial pathology are commonly observed in young infants with ACH and the respective patient was already treated with supplemental oxygen with CPAP due to obstructive sleep apnea. ACH is known to have an exceedingly high frequency of obstructive sleep apnoea contributing significantly to a 50-fold increase in SIDS rates reported in the literature compared with the average healthy population. This is additionally illustrated by a second case of SIDS which occurred in the NH non-interventional trial 111-901 in an untreated child.

With respect to the mode of action and the non-clinical data, injection site reactions (ISRs), blood pressure (BP) decreases, hypersensitivity, fractures, and heart rate changes were identified as adverse events of special interest.

Injection site reactions were considered related in the vosoritide as well as in the placebo group. Grade 1 and Grade 2 ISR events were the most frequent finding. A trend for a decrease in frequency with increasing age (cohort 1: 166.1 versus 21.1 AEs/person-years, cohort 2: 199.9 versus 81.8 AEs/person years, cohort 3: 232.8 versus 118.1 AEs/person-years in the vosoritide versus placebo group, respectively) was observed.

There was a numerically higher incidence of hypersensitivity events in the all-vosoritide participants compared to placebo (17 (39.5%) versus 11 (34.4% respectively)) driven by a higher number of injection site urticaria events in the vosoritide arm. All hypersensitivity events were non-serious and did not lead to study treatment discontinuation. The majority were Grade 1 with no events of Grade ≥ 3 or events meeting NIAID/FAAN criteria for anaphylaxis.

Arterial hypotension was rarely symptomatic, however, Cohort 3 participants, who received 30 ug/kg, experienced a higher incidence.

In the pooled population, there were 8 participants (3.3%) who had 9 fracture events on vosoritide with an exposure-adjusted event rate of 0.01 AEs/person-year. Events were reported in 2 (2.6) participants aged < 5 years old (2 events, 0.01 AEs/person year) and 6 (3.7%) participants aged ≥ 5 years old (7 events, 0.01 AEs/person year). All events of fracture were reported in the context of a traumatic event and were consistent with reports of fractures generally common in children, with the event rate similar to the general pediatric population and ACH population.

3.5. Uncertainties and limitations about unfavourable effects

Cohort 2 and 3 participants, who received more frequently the 30 ug/kg dose, experienced a higher incidence of treatment related adverse events like ISRs /Hypersensitivity Reactions and Hypotension. The reasons remain partially unknown. Although, a dose-relationship was not obvious, a potential dose

dependence for ISRs cannot be excluded; however, other reasons (e.g., age specific increased susceptibility of the skin) may contribute. This notion is supported by the observation that ISRs were also increased in young placebo-treated patients.

The immunogenicity results currently available do not suggest an effect of anti-drug antibodies on efficacy or safety of vosoritide but the data are still limited and do not allow definite conclusions.

Information available in this small orphan disease population is not sufficient to address adequately the long-term safety including potential adverse skeletal effects as impaired function of extremities and joints and immunogenic potential particularly in the applied for population. However, current long-term data does not indicate an increased risk regarding bone health.

All above-mentioned safety outcomes are being captured in the ongoing studies and routine pharmacovigilance activities.

3.6. Effects Table

Table 24: Effects Table for Vosoritde for the treatment of achondroplasia in patients aged between 0 and 60 month.

Effect	Short Description	Unit	Treatment Vosoritide N=32	Control (Placebo) N=32	Uncertainties / Strength of evidence	References
Favourable Effects						
Height Z-score at 52 weeks	age-specific reference (equivalent to 0)a for average stature children calculated using CDC or WHO	SDS to age specific average stature			Difference in LS mean change from baseline in Cohort 1-3: 0.25 (95% CI 0.02, 0.53) P=<0.07	CSR 111-206

<table>
<tr><th>Effect</th><th>Short Description</th><th>Unit</th><th>Treatment Vosoritide N=32</th><th>Control (Placebo) N=32</th><th>Uncertainties / Strength of evidence</th><th>References</th></tr>
<tr><td colspan="7">Analysis of Covariance of Height Z-Score at Week 52 (111-206 Cohort 2/3, 111-206 Cohort 1, 111-301 Overall)
<table>
<tr><th>Assessment</th><th colspan="2">Pooled Population 111-206 Cohorts 2 and 3 (≥3 to <24 months)</th><th colspan="2">111-206 Cohort 1 (≥24 to <60 months)</th><th colspan="2">111-301 Vosoritide-treated Participants (≥60 months)</th></tr>
<tr><th></th><th>Placebo</th><th>Vosoritide</th><th>Placebo</th><th>Vosoritide</th><th>Placebo</th><th>Vosoritide</th></tr>
<tr><td colspan="7">FAS [Randomized]</td></tr>
<tr><td>N</td><td>16</td><td>17</td><td>16</td><td>15</td><td>61</td><td>60</td></tr>
<tr><td>Baseline, mean (SD)</td><td>-3.43 (1.29)</td><td>-3.36 (0.91)</td><td>-5.13 (1.15)</td><td>-4.27 (0.81)</td><td>-5.14 (1.07)</td><td>-5.13 (1.11)</td></tr>
<tr><td>LSM change from baseline (95% CI)</td><td>-0.58 (-0.86, -0.30)</td><td>-0.32 (-0.65, 0.00)</td><td>-0.06 (-0.28, 0.16)</td><td>0.27 (0.04, 0.50)</td><td>-0.01 (-0.10, 0.09)</td><td>0.27 (0.18, 0.36)</td></tr>
<tr><td>Difference in LSM (95% CI) [a]</td><td colspan="2">0.26 (-0.16, 0.67)</td><td colspan="2">0.33 (0.00, 0.67)</td><td colspan="2">0.28 (0.17, 0.39)</td></tr>
<tr><td>p-value[b]</td><td colspan="2">0.2286</td><td colspan="2">0.0510</td><td colspan="2"><0.0001</td></tr>
<tr><td colspan="7">FAS</td></tr>
<tr><td>N</td><td>16</td><td>24</td><td>16</td><td>19</td><td colspan="2" rowspan="5">NA</td></tr>
<tr><td>Baseline, mean (SD)</td><td>-3.43 (1.29)</td><td>-3.53 (0.89)</td><td>-5.13 (1.15)</td><td>-4.32 (0.73)</td></tr>
<tr><td>LSM change from baseline (95% CI)</td><td>-0.55 (-0.82, -0.28)</td><td>-0.20 (-0.45, 0.05)</td><td>-0.03 (-0.24, 0.18)</td><td>0.26 (0.07, 0.45)</td></tr>
<tr><td>Difference in LSM (95% CI) [a]</td><td colspan="2">0.35 (-0.01, 0.71)</td><td colspan="2">0.29 (-0.01, 0.58)</td></tr>
<tr><td>p-value[b]</td><td colspan="2">0.0598</td><td colspan="2">0.0589</td></tr>
</table></td></tr>
<tr><td>Height at Week 52</td><td>LSM difference in Change in Height at Week 52 (cm</td><td>cm</td><td></td><td></td><td>LSM difference in Change in Height at Week 52 (cm)
0.77
95% CI:
-0.02, 1.56 (cm)
p=0.057</td><td>CSR 111-206</td></tr>
</table>

Effect	Short Description	Unit	Treatment Vosoritide N=32	Control (Placebo) N=32	Uncertainties / Strength of evidence	References

Analysis of Covariance of Height at Week 52 (111-206 Cohort 2/3, 111- 206 Cohort 1, 111-301 Overall)

Assessment	Pooled Population 111-206 Cohorts 2 and 3 (≥3 to <24 months)		111-206 Cohort 1 (≥24 to <60 months)		111-301 Vosoritide-treated Participants (≥60 months)	
	Placebo	Vosoritide	Placebo	Vosoritide	Placebo	Vosoritide
FAS [Randomized]						
N	16	17	16	15	61	60
Baseline, mean (SD)	62.30 (6.55)	63.07 (7.12)	79.38 (6.79)	79.77 (4.87)	102.94 (10.98)	100.20 (11.90)
LSM change from baseline (95% CI)	9.20 (8.49, 9.91)	9.85 (8.98, 10.73)	5.41 (4.72, 6.11)	6.38 (5.66, 7.10)	4.29 (3.97, 4.61)	5.86 (5.56, 6.17)
Difference in LSM (95% CI) [a]	**0.65 (-0.43, 1.73)**		**0.96 (-0.09, 2.02)**		**1.57 (1.21, 1.93)**	
p-value[b]	0.2377		0.0710		<0.0001	
FAS						
N	16	24	16	19	NA	
Baseline, mean (SD)	62.30 (6.55)	62.79 (6.89)	79.38 (6.79)	80.48 (4.98)		
LSM change from baseline (95% CI)	9.19 (8.48, 9.89)	10.15 (9.47, 10.82)	5.51 (4.84, 6.18)	6.38 (5.77, 6.99)		
Difference in LSM (95% CI) [a]	**0.96 (0.01, 1.90)**		**0.87 (-0.07, 1.81)**			
p-value[b]	0.0473		0.0689			

Effect	Short Description	Unit	Treatment Vosoritide N=32	Control (Placebo) N=32	Uncertainties / Strength of evidence	References
Annualized growth velocity (AGV at 52 weeks)	LSM difference in Change in AGV at Week 52 (cm/year) Key indicator of skeletal growth; well-documented over the paediatric age range; highly sensitive to factors that impact growth negatively or positively; and easily and objectively measurable in an accurate non-invasive manner.	Cm/ year			LS mean change from baseline: **FAS (random):** **0,77 cm/year** (95% CI: 0.02,1.54; with a two-sided p-value of p 0.0452) **FAS (+Sentinel):** **0.92 cm/year** (95% CI: 0.24, 1.59; with a two-sided p-value of p<0.0075) **Comparison** **>5 to 18 years:** 1.57 cm/year (95% CI: 1.22, 1.93; with a two-sided p-value of p<0.0001)	CSR 111-206 <u>>5 to 18 years compare-son:</u> CSR 111-301

Effect	Short Description	Unit	Treatment Vosoritide N=32	Control (Placebo) N=32	Uncertainties / Strength of evidence	References

Analysis of Covariance of AGV at Week 52 (111-206 Cohort 2/3, 111-206 Cohort 1, 111-301 Overall)

Assessment	Pooled Population 111-206 Cohorts 2 and 3 (≥3 to <24 months)		111-206 Cohort 1 (≥24 to <60 months)		111-301 Vosoritide-treated Participants (≥60 months)	
	Placebo	Vosoritide	Placebo	Vosoritide	Placebo	Vosoritide
FAS [Randomized]						
N	16	17	16	15	61	60
Baseline, mean (SD)	15.00 (7.65)	16.64 (6.18)	4.20 (1.78)	4.74 (1.68)	4.06 (1.20)	4.26 (1.53)
LSM change from baseline (95% CI)	-6.68 (-7.38, -5.97)	-5.95 (-6.82, -5.09)	0.89 (0.23, 1.55)	1.99 (1.31, 2.67)	0.13 (-0.18, 0.45)	1.71 (1.40, 2.01)
Difference in LSM (95% CI) [a]	**0.72 (-0.34, 1.79)**		**1.10 (0.13, 2.07)**		**1.57 (1.22, 1.93)**	
p-value[b]	0.1827		0.0276		<0.0001	
FAS						
N	16	24	16	19	NA	
Baseline, mean (SD)	15.00 (7.65)	16.87 (6.71)	4.20 (1.78)	5.07 (1.74)		
LSM change from baseline (95% CI)	-6.97 (-7.65, -6.29)	-6.02 (-6.68, -5.36)	0.77 (0.14, 1.40)	1.78 (1.20, 2.35)		
Difference in LSM (95% CI) [a]	**0.96 (0.04, 1.87)**		**1.00 (0.13, 1.88)**			
p-value[b]	0.0405		0.0256			

Upper to lower body segment ratio	Indicator of changes to body proportionality, whereby ratio falls to 1 by approximately 10 years of age in average stature children and never reaches 1 in untreated children with ACH	U:L body segment ratio	Results for the ANCOVA analysis in the FAS (randomized) showed a numerically larger decrease in upper to lower body segment ratio in the vosoritide group compared with placebo in the overall population (LSM difference of -0.07 [95% CI: -0.17, 0.04]), driven particularly by changes in Cohort 2 (LSM difference of -0.21 [95% CI: -0.43, 0.00]), with no worsening observed in Cohort 3 (LSM difference of -0.03 [95% CI: -0.27, 0.32]). **The LS mean difference was not consistent across the cohorts and the 95% CIs greatly increased in size from Cohort 1 to Cohort 3. They were also not statistically significant.**	CSR 111-206

Effect	Short Description	Unit	Treatment Vosoritide N=32	Control (Placebo) N=32	Uncertainties / Strength of evidence	References

Analysis of Covariance of Upper to Lower Body Segment ratio at Week 52 (111-206 Cohort 2/3, 111-206 Cohort 1, 111-301 Overall)

Assessment	Pooled Population 111-206 Cohorts 2 and 3 (≥3 to <24 months)		111-206 Cohort 1 (≥24 to <60 months)		111-301 Vosoritide-treated Participants (≥60 months)	
	Placebo	Vosoritide	Placebo	Vosoritide	Placebo	Vosoritide
FAS [Randomized]						
N	16	17	16	15	61	60
Baseline, mean (SD)	2.78 (0.28)	2.83 (0.42)	2.25 (0.19)	2.35 (0.17)	2.01 (0.21)	1.98 (0.20)
LSM change from baseline (95% CI)	-0.17 (-0.29, -0.05)	-0.27 (-0.38, -0.15)	-0.08 (-0.18, 0.01)	-0.14 (-0.24, -0.04)	-0.02 (-0.05, 0.01)	-0.03 (-0.06, 0.00)
Difference in LSM (95% CI) [a]	**-0.10 (-0.26, 0.07)**		**-0.06 (-0.20, 0.09)**		**-0.01 (-0.05, 0.02)**	
p-value[b]	0.2638		0.4253		0.5060	
FAS						
N	16	24	16	19	NA	
Baseline, mean (SD)	2.78 (0.28)	2.82 (0.41)	2.25 (0.19)	2.33 (0.21)		
LSM change from baseline (95% CI)	-0.17 (-0.28, -0.06)	-0.27 (-0.36, -0.17)	-0.08 (-0.17, 0.01)	-0.12 (-0.20, -0.04)		
Difference in LSM (95% CI) [a]	**-0.10 (-0.24, 0.05)**		**-0.04 (-0.16, 0.09)**			
p-value[b]	0.1942		0.5481			

Sleep apnoea polysomno-graphy	Change from baseline in Sleep Study Indices at Week 52	Indices for several polysomno-graphic parameters	Overall, a reduction in all the polysomnography parameters was observed at Week 52 in the vosoritide group, with the exception of Apnea Index in Cohort 3, while changes were mixed in the placebo group No worsening in the polysomnography parameters were observed with vosoritide at Week 52 compared to placebo. **Whilst directional positive change in all but one polysomnography parameters were seen with vosoritide in all cohorts, it is unclear whether these changes represent a clinically meaningful effect of treatment on sleep apnea.**	CSR 111-206

Effect	Short Description	Unit	Treatment Vosoritide N=32	Control (Placebo) N=32	Uncertainties / Strength of evidence	References
Change from baseline in Imaging assessments at Week 52 regarding change from baseline in facial volume, sinus volume and the area of foramen magnum	These parameters are of particular interest in ACH due to mid-facial hypoplasia, obstructive sleep apnea and foramen magnum stenosis, all characteristic features of the condition.	MRI parameters	On comparison of MRI parameters at Week 52, positive numerical changes were observed with vosoritide treatment compared to placebo, most notably in Cohort 3, including marked positive percentage. In Cohort 1 and Cohort 2, which recruited older children, changes in these parameters were less pronounced and variable, particularly in foramen magnum, reflecting the natural growth and premature closure of synchondroses in the base of the skull that impact development of foramen magnum in children with ACH.			CSR 111-206
Unfavourable Effects						
Type of Adverse Event		**Incidence** **Exposure adjusted event rate[a]**	**All Vosoritide N=43**	**Placebo N=32**	**Comment/ Explanation**	**Source**
Subjects with any AE		n (%)	43 (100) 8737 (204.5)	32 (100) 2357 (73.6)		CSR 111-206 and SCS
Subjects with any treatment-related AE		n (%)	37 (86.0) 8232 (192.7	17 (53.1) 1930 (60.3)		CSR 111-206 and SCS
Subjects with any SAE		n (%)	3 (7.0) 4 (0.1	6 (18.8) 8 (0.2)		CSR 111-206 and SCS
Treatment-related SAEs		n (%)	0 (0.0)	0 (0.0)		CSR 111-206 and SCS
Subjects with any AE of CTCAE grade ≥ 3,		n (%)	2 (4.7) 3 (0.1)	3 (9.4) 5 (0.2)		CSR 111-206 and SCS
Participants who died		n (%)	0 (0)	1 (2.3)	Sudden infant deaths (assessed as not treatment related)	CSR 111-206 and SCS
Injection sites reactions	AEs/person-year	n	37 (86.0) 8281 (193.8)	17 (53.1) 1939 (60.5)	Mostly erythema, rarely urticaria, more frequent in vosoritide	CSR 111-206 and SCS
Blood Pressure decrease		n (%)	2 (4.7) 2 (0.0)	2 (6.3) 2 (0.1)	Mild and asymptomatic	CSR 111-206 and SCS
Hyper-sensitivity events		n (%)	17 (39.5) 44 (1.0)	11 (34.4) 11 (0.3)	ADAs in about 30 -62 %, neutralizing Abs in 2 subjects only	CSR 111-206 and SCS

Effect	Short Description	Unit	Treatment Vosoritide N=32	Control (Placebo) N=32	Uncertainties / Strength of evidence	References
Avascular necrosis / osteonecrosis		n (%)	0	0 (0.0)	No events also in the pooled target population	CSR 111-206 and SCS
Slipped capital femoral epiphysis		n (%)	0	0 (0.0)	No events also in the pooled target population	CSR 111-206 and SCS

[a] Exposure-adjusted event rates were calculated by dividing the total number of events (n) by the total treatment exposure up to the last dose reported in each column. Multiple occurrences of an AE in the same category for a participant were counted for each occurrence for that category.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Subjects with ACH have markedly reduced endochondral growth leading to disproportionately short stature. Vosoritide can at least partially correct the consequences of the underlying pathophysiological defect by downregulating the FGFR3 signalling in chondrocytes and is currently approved for the treatment of children ≥2 years with ACH. The MAH is now applying for removal of the age restriction to allow starting treatment shortly after birth. The efficacy results from the placebo-controlled study 111-206 and its extension 111-208, including multiple comparative analyses using NH data, confirmed the beneficial effects of vosoritide in the paediatric population with ACH in the initially approved population aged ≥2 to 5 years and showed treatment benefit in patients <2 years of age.

However, the placebo-adjusted increase in length was considered relatively small in the patients below age of 2 years. This was surprising, since a significantly larger treatment effect was expected especially in the younger children due to their greater growth potential.

With their response, the MAH provided additional analyses including new outcome data after 10 additional months.

The applicant clarified that children with ACH typically exhibit a stable and predictable growth pattern, which is characterized by the largest decline in growth during the first 5 years, while the most rapid decline in growth velocity occurs from birth to 2 years of age. After 5 years and throughout the next decade, growth is more stable with only a gradual decline, notably with no pubertal growth spurt. In consequence, a small difference in the age below 2 years can have a big impact on growth measurements and may lead to unpredictable findings, particularly in very small populations as those included in the cohorts 2 and 3. The challenge in evaluation of growth in very young children is illustrated by the reported results for the annualized growth velocity (AGV) from Study 111-206 by cohort. Despite a very narrow and similar age range across both treatment arms in Cohort 3 (4.4 months to 6.5 months on Study Day 1), the variability in AGV is large ranging from 4.8 cm/year to 30.2 cm/year. Later, with increasing age, the variability in baseline AGV decreases significantly, ranging from 2.5 cm/year to 18.5 cm/year in Cohort 2, and 0.3 cm/year to 8.7 cm/year in Cohort 1 making it easier to identify treatment effects. Insofar, in small and very young populations, comparisons may be significantly biased by small differences in age, due to the high variability in growth, making it very difficult to show treatment benefit.

Using height Z-scores alleviates those concerns to some extent. Change in height Z-scores was indeed roughly similar across age cohorts.

In addition, in order to better characterise the beneficial effects, the applicant has compared the efficacy outcome in vosoritide subjects below the age of 2 years not only with the small number of placebo subjects included in trial 111-206, but also with a larger untreated AchNH external control group as well as an observational/placebo external control. Moreover, more mature data for the efficacy parameters were presented as mentioned above.

The additional data and analyses suggest a continuous increase in treatment gain in all cohorts but also show the impact of variability. Maintenance of efficacy over 3 years of follow-up can be derived from these data, although the effect size in the youngest patients cannot be precisely estimated from these comparisons.

There was still uncertainty with regard to the appropriate dose for children below age 4 months for whom no PK, efficacy or safety data are yet available and due to the uncertainties whether the popPK model is adequate to predict exposure in these patients. Therefore, the indication has been restricted to treatment of patients ≥4 months of age.

During the initial approval procedure, vosoritide had shown an acceptable safety profile and good tolerability based on the available clinical development safety data in children aged > 5 years as well as in 11 sentinel patients in the age range 24 and 60 months.

With respect to the mode of action and the non-clinical data, injection site reactions (ISRs), blood pressure decreases, hypersensitivity, fractures, and heart rate changes were identified as adverse events of special interest.

Vosoritide appeared to be well tolerated also in participants <2 years of age, with no treatment limiting adverse effects and a safety profile generally consistent with that seen in participants >2 years of age. While injection site reactions (ISRs) were reported at a higher event rate in participants <2 years of age and caused the observed increase in TEAEs, the nature, pattern and severity of those reactions were similar to older participants. The CHMP acknowledged that also some other events occurred at a higher rate in <2 years age group, however they may be attributed to common conditions specific to that age group. This notion was supported by the finding of similar rates of those events across treatment and placebo group.

Most treatment-related AEs were grade 1 and some were grade 2 injection site reactions (ISRs), which resolved without any treatment. AEs of Grade >3 were reported at a lower rate in the All Vosoritide than in the placebo group (V: 4.7% vs P:9.4%). In addition, there was no evidence of an exposure-safety relationship to vosoritide, amongst those events that occurred at a higher rate in participants below 2 years of age.

In general, no signals regarding new safety risks were identified; neither from the outcome of the placebo controlled trial 111-206 nor from the long-term data.

Moreover, assessment of the details regarding the case of death due to SIDS in one child below the age of 6 months, who suffered from significant ACH associated comorbidities confirmed the absence of evidence for causal association with vosoritide.

Potential long-term safety risk, particularly risk for bone and joint malformation that may lead to osteonecrosis and cartilage dysfunction after longer treatment durations can still not be finally assessed. However, the available data continue to be in line with the assumption that the improvement in growth is not associated with any detectable accelerated bone maturation, disproportionate skeletal growth or abnormal bone morphology. The long-term safety and efficacy are being assessed in the ongoing studies and the outcomes will be submitted for the committee’s review.

An updated popPK model to further support the posology will be developed by the applicant post-approval as recommended by the CHMP.

3.7.2. Balance of benefits and risks

The benefit of vosoritide in terms of height increase has been confirmed in patients with ACH for whom treatment with vosoritide is already approved (2 years and older) and has also been reasonably shown in patients below age of 2 years.

The new data support the previously established safety profile. No new safety issues arise from these data. Patients below age of 2 years experienced an increased frequency of usually mild and transient ISRs, which may potentially be caused by the increased dose and age-specific factors.

Taken together, the benefits of offering treatment with vosoritide to patients from an early age are considered to outweigh the risks. However, due to the absence of any data in patients below age 4 months and the uncertain exposure with the proposed dosage in these patients, the indication has been restricted to treatment of patients ≥4 months of age in line with the agreed indication: the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic.

3.8. Conclusions

The overall B/R of *Voxzogo* is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of children 4 months of age and older for Voxzogo, based on final results from the category 1 study BMN 111-206 and interim results from its open-label extension study 111-208. 111-206 is a phase 2 randomized, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy of BMN 111 in infants and young children with achondroplasia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 3.4 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the

Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that is deleted from the Annex II:

Description	Due date
PAES: In order to further evaluate the efficacy of vosoritide in patients aged 2-5 years, the MAH should submit the final results of the study 111-206, an ongoing Phase 2 randomized, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy of daily SC injections of vosoritide in younger children with achondroplasia.	September 2022

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

NA

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0060/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 16 October 2023. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 10 March 2023. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.