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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Voxzogo

International non-proprietary name: vosoritide

Procedure No. EMEA/H/C/005475/0000

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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
A_{280}	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	annualised 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
AUC_{0-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 programme
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 Organisation
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 organisation
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 normalised
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	
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 Recognised as Safe
H&E	Haematoxylin 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 hybridisation
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 Characterisation 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
$SK_{CA/KA}$	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-Sterilisation-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. Submission of the dossier

The applicant BioMarin International Limited submitted on 23 July 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Voxzogo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2019.

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

The applicant applied for the following indication Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older and whose epiphyses are not closed.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Voxzogo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/voxzogo.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 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 because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance vosoritide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

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 programme 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: Andrea Laslop

CHMP Peer reviewer(s): Natalja Karpova

The application was received by the EMA on	23 July 2020

The procedure started on	13 August 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	11 November 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	4 November 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 November 2020
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	27 November 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 December 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	31 March 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 April 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 April 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 April 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 June 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Voxzogo on	24 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant initially applied for the following indication:

Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older and whose epiphyses are not closed.

The applicant applied for the treatment of patients 2 years and older due to the limited availability of data in those younger than 2 years. However, the product is still under development and the aim is to finally treat all age ranges (before epiphyseal closure) once appropriate data are available.

2.1.2. Epidemiology and risk factors

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 characterised 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.

2.1.3. 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 dimerisation 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.

2.1.4. Clinical presentation, diagnosis and prognosis

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, 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 they possess an increased risk for hydrocephalus and its potential consequences). The children are not only uniformly motor delayed but 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.

2.1.5. Management

Current treatments for ACH are mainly limited to 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, while supportive care options are available to assist with activities of daily living via the use of adaptive devices, many young patients choose to undergo invasive limb-lengthening procedures with prolonged recovery as an attempt to ameliorate disproportionate short stature. While as much as 15 to 30 cm gain in standing height can be achieved, limb lengthening remains a controversial, long and arduous process. It is performed rarely in the US and with varied frequency in the EU. Growth hormone (GH) has been used in several different studies in subjects with ACH toimprove 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 and is rarely used by pediatric endocrinologists for this condition.

The applicant therefore states a clear unmet medical need for the condition.

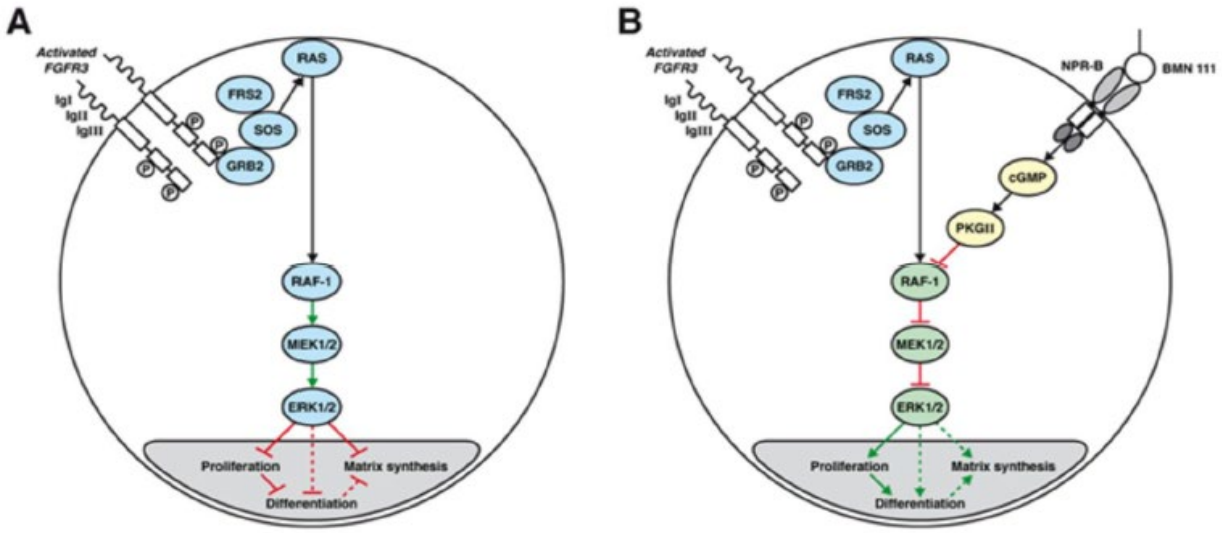
About the product

BMN111 (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.

The substance down-regulates Fgfr3 signalling and consequently promotes endochondral bone formation, such that with sufficient duration of treatment, has the potential to improve the phenotype of individuals with ACH. Vosoritide was designed to be resistant to neutral endopeptidase (NEP) degradation resulting in an extended half-life (t1/2) relative to endogenous CNP that 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 the following figure:

Figure 1: Fgfr3 and CNP/Vosoritide Signalling 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 analogue that inhibits Fgfr3 downstream signalling 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 annualised growth velocity (AGV). The applicant furthermore claims that height, in and of itself, is a factor of health-related quality of life (HRQoL). 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 far beyond the increased in stature alone.

2.2. Quality aspects

2.2.1. Introduction

The finished product Voxzogo is presented as a powder and solvent for solution for injection containing 0.4 mg/vial, 0.56 mg/vial, and 1.2 mg/vial of vosoritide as active substance.

Other ingredients in the lyophilised powder vial are citric acid monohydrate (E330), sodium citrate dihydrate (E331), trehalose dihydrate, D-mannitol (E421), L-methionine and polysorbate 80 (E433).

The product is available in 2 mL glass vials with rubber stopper (bromobutyl) and colour-coded flip caps, white (0.4 mg), magenta (0.56 mg), and grey (1.2 mg).

The solvent is sterile water for injection (sWFI) contained in a pre-filled glass syringe with plunger (bromobutyl) and tip cap with a luer lock and tamper evident seal containing 0.5 mL, 0.6 mL and 0.7 mL sWFI.

As per SmPC, prior to administration the powder in each vial must be reconstituted with the appropriate volume of solvent; 0.4 mg with 0.5 ml sWFI; 0.56 mg with 0.7 ml sWFI; and 1.2 mg with 0.6 ml sWFI.

One pack size of 10 contains 10 vials of Voxzogo, 10 pre-filled syringes of sterile water for injections, 10 individual single use needles (23 gauge, for reconstitution) and 10 individual single use administration syringes (30 gauge).

2.2.2. Active Substance

General information

The active substance vosoritide contained in the medicinal product Voxzogo is a truncated modified analogue of the native human C-type natriuretic peptide (CNP) expressed in E. coli. Recombinant vosoritide is a 39-amino acid peptide, comprising of 37 C-terminal residues of the native human CNP and two additional amino acids (Pro-Gly) on the amino terminus, as shown in **Figure 2** and **Figure 3**.

Figure 2: Chemical structure of vosoritide

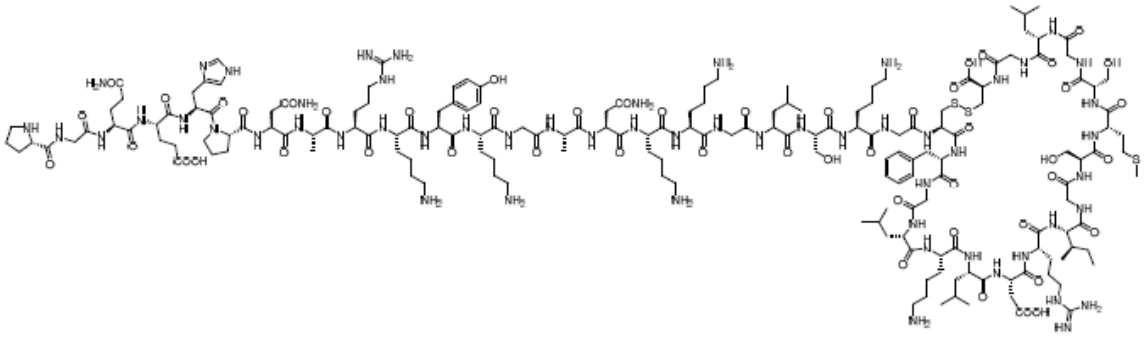


Figure 3: Amino acid structure of vosoritide

1
NH2-Pro-Gly-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-

Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-

Ser-Met-Ser-Gly-Leu-Gly-Cys-COOH .
39

Vosoritide has a molecular weight of 4.1 kDa. Two cysteine residues (Cys23 and Cys39) form a disulfide bond, creating a cyclic peptide, which is essential for biological activity by binding to the extracellular domain of natriuretic peptide receptor-b (NPR B). Due to the reduced size conferring resistance to zinc metallo-protease neutral endopeptidase (NEP), vosoritide has an extended half-life ($t_{1/2}$ 10-fold greater serum half-life) relative to endogenous CNP. This increases exposure to the target growth plate and allows for once daily subcutaneous administration to produce its desired pharmacologic effect.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Vosoritide formulated bulk active substance is manufactured by BioMarin Pharmaceutical Inc. (Novato, USA). EU GMP compliance is confirmed for all sites.

The vosoritide active substance manufacturing process has been adequately described. Main steps are fermentation, recovery and purification. The ranges of critical process parameters (CPPs) and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. No design space is claimed. The active substance manufacturing process is considered acceptable.

Vosoritide (BMN 111) is manufactured by expression of TAF-BMN 111 fusion protein in recombinant *E. coli* cells. The vosoritide upstream process starts with the thawing of one vial of the MCB or the WCB. Cell expansion is performed in a seed fermenter and cell production proceeds in a production fermenter. Cells are harvested and inclusion bodies (IBs) are recovered by homogenisation and subsequent centrifugation. The downstream process starts with the chemical cleavage of TAF-BMN 111 followed by clarification by centrifugation and filtration to yield the BMN 111 peptide. The clarified filtrate is purified by chromatography and filtration steps, followed by buffer exchange. The eluate is formulated using a formulation buffer concentrate, followed by pH and concentration adjustment to obtain the target BMN 111 concentration. The resulting formulated bulk active substance is filtered and aliquoted into bags for storage. The storage bags are sterilised and supplied to BioMarin ready for use. Sufficient detail is provided on the container closure system for storage of the active substance. Appropriate extractable and leachable studies have been performed.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. Information on quantitative compositions of media used for cell bank generation, seed operations and production fermentation, as well as the compositions of buffers used during downstream purification and formulation are provided.

The generation of the cell substrate is well described. Sufficient information on the host cell line *E. coli* has been provided and the expression plasmid has been adequately described. The amino acid sequence of TAF-BMN 111 have been provided. The DNA sequence as well as a schematic of the final expression plasmid are presented.

A two-tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. Genetic stability has been demonstrated for cells at and beyond the LCA. A dual storage system for the MCB and WCB is in place. A comprehensive protocol for the establishment of future WCBs has been provided following the same approach as used for the implementation of the current WCB.

The characterisation testing programme of MCB and WCB is considered adequate to identify relevant phenotypic and genotypic characteristics. Cell banks will be tested periodically to confirm viability and compare it to historical trends. This is considered adequate.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

The information on control of critical steps and intermediates comprises CPPs and critical performance attributes (CPAs; in-process controls) of the vosoritide formulated bulk active substance manufacture. The information on CPPs and CPAs along with their acceptance criteria (PAR or action limits, respectively) are in line with information provided in section 3.2.S.2.2. A comprehensive summary of critical quality attributes (CQAs) as defined for vosoritide formulated bulk active substance is also included in section 3.2.S.2.4 *Control of critical steps and intermediates*.

It is noted that control of product-related substances/impurities during vosoritide manufacture is limited to a chromatography step, the main reduction step of products variants as demonstrated by process validation. This approach is considered acceptable.

Microbial testing (bioburden and endotoxin) of process materials along with appropriate acceptance criteria/action limits are indicated. The hold times and storage condition for process intermediates stated in section 3.2.S.2.4 are adequately supported by process validation data

provided in section 3.2.S.2.5.

Process validation and/or evaluation

The active substance manufacturing process has been validated adequately. Consistency in production has been shown on four full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

According to EU guidelines, the process validation (PV) follows a three-stage life-cycle approach from development through confirmation of process consistency prior to approval of the MAA to post-marketing process monitoring. The proposed life-cycle approach is endorsed. However, the applicant states that adjustments to the manufacturing process and/or control scheme may be implemented during process verification (stage three) following completion of appropriate validation testing and/or justification. The applicant commits to introduce any changes in the manufacturing process and/or controls via an appropriate variation procedure application and that any changes will only be implemented following regulatory approval.

Consecutive representative PPQ batches were manufactured at commercial scale by the intended commercial 2a process at the intended manufacturing site. All PPQ runs operated at the established normal operating ranges (NORs); critical and key process parameters and performance attributes for the upstream /downstream process were found to be within the normal operating and expected ranges. Select non-critical, non-key process parameters that are considered most important with respect to the purpose of the step were also verified to be within the specified ranges. Each lot met in-process limits and batch record requirements, demonstrating consistent operations. Additional process monitoring was performed in particular with respect to the microbial control of the process intermediates. Some deviations occurred. Overall, deviations have been satisfactorily handled by the applicant. Microbial control of process intermediates is considered confirmed. In conclusion, the consistency and reproducibility of the vosoritide formulated bulk active substance manufacturing process has been adequately confirmed, supporting the proposed control strategy.

The process clearance capability for process-related impurities has been evaluated by monitoring these impurities during the manufacture of commercial scale PPQ batches after each purification step. Even though the number of commercial batches is limited, omission of routine testing of the aforementioned process-related impurities at vosortide formulated bulk active substance release is considered justified; acceptable log clearance capabilities could be demonstrated, and residual levels were consistently below limit of quantification and/or detection, as applicable, from early in the manufacturing process through formulated bulk active substance. Residual levels in formulated formulated bulk active substance

consistently met pre-defined acceptance criteria and were comparable to historical ranges. Overall clearance of HCPs and endotoxins has been sufficiently demonstrated. Of note, control of HCPs and endotoxins will remain as release tests in the vosoritide formulated bulk active substance release specification. As regards elemental impurities, the levels of Class 1 (Cd, Pb, As, Hg), 2A (Co, V, Ni), and Class 3 (Li, Sb, Cu) elements in formulated bulk active substance were all well within the permitted daily exposure (PDE) limits for parenteral medicines as listed in ICH Q3D. Reduction of product-related variants and multimers has been demonstrated to occur at a chromatography step. Main peak, product variant results and multimer levels consistently met the formulated bulk active substance release specification. Respective reports and a summary of the reports have been provided.

Process material hold times and storage conditions have been validated based on evaluation of commercial scale lots of each intermediate (microbial control capacity and chemical stability) and small-scale cumulative hold runs (chemical stability) at the maximum hold time. The studies sufficiently support the proposed hold times of process intermediates as stated in section 3.2.S.2.4.

Column resin re-use cycles have been sufficiently demonstrated in small-scale studies with downscaled conditions representative of the commercial manufacturing scale. Confirmation of resin use life will be performed at commercial scale. Acceptable validation protocol has been provided.

Validation of potential reprocessing has been conducted under scaled-down conditions and at commercial scale. This approach is considered acceptable.

Shipping qualification studies demonstrated suitability of the selected shipping configuration.

Manufacturing process development

The manufacturing process was developed in parallel with the clinical development programme following a traditional approach.

Analytical comparability of materials prior and post-change has been sufficiently demonstrated. Batches included in the comparability exercise derived from the development manufacturing processes and the proposed commercial process. Quality elements assessed for comparability included comparative analytical testing (release testing), comparative additional characterisation and forced degradation stress studies.

Overall, the proposed comparability exercise is considered acceptable.

CQAs were determined by a risk assessment of product quality attributes and their impact on safety and efficacy using information from clinical, nonclinical, toxicology studies and prior knowledge. CQAs have been categorised into (1) obligatory CQAs, (2) CQAs related to process-related impurities and product-related substances and impurities, and (3) raw material CQAs. Product-related substances, product-related impurities and process-related impurities were categorised based on potential impact on bioactivity/efficacy, pharmacokinetics, immunogenicity. Overall, the selection of CQAs is considered justified. Chromatography column resins and process filters used in the manufacture of vosortide formulated bulk active substance are automatically classified as critical raw materials in the applicant's Quality Management system, which is endorsed.

The process control strategy as proposed by the applicant is considered acceptable. Following principles of ICH Q8, the relationship between process controls and CQAs were systematically evaluated. A failure mode and effects analysis (FMEA) in combination with process and product knowledge (prior knowledge and experimentation) was used to identify potential failure modes and to link these to the manufacturing steps and parameters as well as to classify CPPs. Each process parameter was examined with regard to its potential effect on either process performance or the CQAs, then scored on its ability to affect a CQA, the ability to control that parameter in the manufacturing setting, and the likelihood that a deviation outside the accepted range could occur. An appropriate

control strategy for each CPP has been developed. Moreover, for each CPP, the PAR was tested experimentally and no impact on CQAs were observed. All CPPs together with the respective PAR are included in section 3.2.S.2.2 and section 3.2.S.2.4.

The overall control strategy is based on the identification CQAs and includes the control of materials, in-process controls, release and stability testing. The overall control strategy has been sufficiently described and is considered appropriate to ensure consistent product quality of vosoritide formulated bulk active substance.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure.

Recombinant vosoritide is a truncated analogue of native C-type natriuretic peptide (CNP) with 39 amino acids and a molecular weight of 4100 Daltons. The two existing cysteine residues (Cys23 and Cys39) form a disulfide bond, creating a cyclic peptide, which is essential for biological activity.

The majority of the characterisation studies have been performed using active substance manufactured with the proposed manufacturing process representative for the commercial manufacturing process. The primary structure of vosoritide was evaluated by appropriate analytical methods. The expected molecular weight and primary structure with complete coverage were confirmed. The correct intramolecular disulfide bond between the two cysteine residues of vosoritide was confirmed. The secondary structure investigation revealed a characteristic signature of a random coil, α helical or β sheet structure elements were not present. Higher order structure is not considered relevant due to the simple structure of vosoritide. The absence of secondary and tertiary structure is further supported by literature data for the closely related natriuretic peptide. The purity of vosoritide active substance commercial batches was determined by appropriate analytical methods. Extensive analyses were used to characterise numerous product related impurities of vosoritide active substance. To understand the potential degradation pathways for vosoritide stress studies employing different stress conditions and a panel of analytical methods including release tests have been performed. Vosoritide is predominantly degraded by known pathways. The biological activity was determined by a cell-based assay. Activity of product related substances was measured. Most related substances had reduced or only residual activities. Thus, the intact vosoritide and the trisulfide form (converted into the disulfide form *in vivo*) represent the biologically active peptide fraction.

Specification, analytical procedures, reference standards, batch analysis

The active substance specification of vosoritide includes tests for identity (peptide map, tryptic digest, RP-HPLC), appearance (visual), bacterial endotoxin (Ph. Eur.), bioburden (Ph. Eur.), purity-multimer content (SEC), purity-deamidation (SCX), purity-related substances (RP-HPLC), purity-host cell protein (ELISA), potency-active fraction (RP-HPLC), peptide concentration (UV), pH (Ph. Eur.), osmolality (Ph. Eur.), polysorbate 80 (RP-HPLC-CAD).

The active substance specification for release and shelf life covers the relevant quality attributes of vosoritide and the acceptance criteria are considered to be acceptable. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

As requested, the applicantapplicant has tightened the active substance release and shelf life specifications. The proposed specification limits are based on statistical analysis of batches used in the Phase 2 and/or Phase 3 studies and commercial active substance batches. The respective approach that resulted in the more stringent acceptance criterion has been used. The applicant has also

committed to further revise the limits once at least 20 batches manufactured with the proposed commercial process are available (see **REC1,** section 2.2.7).

The specification for general parameters like appearance, endotoxin, bioburden, pH, polysorbate, osmolality are considered adequate. It is also agreed that with the exception of HCPs, the specification contains no limits for other process-related impurities. Validation data sufficiently cover the removal of other process relate substances including residual DNA. The applicant commits to complete and submit the final study report on the Low Endotoxin Recovery (LER) study with the closing sequence (see **REC2,** section 2.2.7).

The formulated bulk active substance contains a number of product-related substances/impurities. The specification for purity includes acceptance criteria for multimer content (SEC), deamidation (SCX) and as measured by RP-HPLC main peak (desired product), total inactive fraction, identified and unidentified impurities. The specification for the active fraction is acceptable. The applicant proposes to replace the cell-based assay that was used for potency determination during development, by defining an active fraction by RP-HPLC. A comprehensive analysis has been provided to demonstrate the correlation between potency as determined by the cell-based assay and the active fraction by RP-HPLC. Considering the scientific rationale that vosoritide is a quite simple molecule without any significant secondary or tertiary structure, the proposal of the applicant to replace the cell-based potency assay by RP-HPLC is considered acceptable. Some analytical procedures (multimer content by SEC-HPLC, peptide content (strength), deamidation by SCX, polysorbate 80 by RP-HPLC-CAD, identity and purity by RP-U/HPLC and identity by peptide map) have been validated also for the finished product.

Batch analysis

Batch analyses data are available for the commercial, clinical and pre-clinical manufacturing processes. All results meet the specification at the time of measurement. All process verification lots met the proposed commercial specification and confirm consistency of the manufacturing process.

Reference Standard

The manufacturer has established an appropriately characterised in-house primary and working reference material, prepared from lots representative of the commercial manufacturing process.

Adequate qualification data for the reference material used to date including release as well as characterisation data have been submitted. An appropriate justification for the different acceptance criteria for certain quality attributes for qualification/requalification of the primary and working reference standard has been provided. A protocol for establishing reference materials is provided.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

Real time, real condition stability data on commercial scale batches formulated bulk active substance has been evaluated at both long-term and accelerated temperature conditions according to the ICH guidelines. The parameters tested are the same as for release.

All results of the stability study performed with two batches (primary stability batches on commercial scale) were found within the proposed acceptance criteria. Supplementary data of two development and four commercial active substance vosoritide batches has been provided. Structure characterisation and forced degradation studies also showed no differences between these batches. Therefore stability

results from development are considered as representative of the vosoritide formulated bulk active substance manufactured by commercial process.

Photo-stability results were presented. Photostability was confirmed, associated with increased oxidation, ring cleavage, deamidation, and overall degradation.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Vosoritide finished product is a single-use, sterile lyophilised powder in a Type I glass vial for reconstitution with sterile water for injection (sWFI) prior to use. It is intended for daily administration by subcutaneous injection. The vosoritide lyophilised powder is white to yellow in colour and is preservative-free and not intended for multi-use.

Vosoritide will be supplied in three strengths: 0.4 mg, 0.56 mg, and 1.2 mg.

The primary packaging is 2 mL vial (glass) with rubber stopper (bromobutyl) and white flip cap and pre-filled syringe (glass) with plunger (bromobutyl) and tip cap with a luer lock and tamper evident seal containing the solvent. The material complies with Ph. Eur. and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Ten lyophilised vosoritide single dose vials are co-packaged with ten diluent syringes pre-filled with sWFI for reconstitution (1.5 mL Type 1 glass syringe with integrated luer lock and polystyrene clear plunger rod) and two ancillary components.

The ancillary components comprise ten diluent needles (EasyPoint®Needle, 23 G, 1in, luer lock needle with safety device) and ten administration syringes (VanishPoint®Syringe, 1 mL long medical grade polypropylene syringe with a polypropylene plunger rod with attached 30 G 8 mm retractable needle). The medical devices in the co-package are considered appropriate for dilution and administration of vosoritide finished product. All devices are CE-marked and comply with relevant medical devices legislation.

Vosoritide finished product was shown to be compatible with the commercial administration components. Sterilisation of the diluent needle and administration syringe is performed according to ISO standards. The excipients are citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate D-mannitol, L-methionine and polysorbate 80.All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. No overage is added to vosoritide finished product.

Satisfactory and extensive data have been provided for pharmaceutical development. A comprehensive quality target product profile (QTPP) was presented.

The CQAs for vosoritide were determined based on a science and risk-based assessment of process-related impurities, product-related impurities, raw material residuals, as well as obligatory attributes. Defined as CQAs are identity, appearance, colour and clarity, moisture content, reconstitution time, particulate analysis, uniformity of dosage units, bacterial endotoxin, sterility (bioburden), container closure integrity, multimer content, deamidation, related substances and impurities, active fraction, total peptide concentration, pH, osmolality, and polysorbate 80 content. Preformulation studies were performed to develop the optimal composition of vosoritide finished product. Compatibility of vosoritide with the formulation excipients is considered proven and supported by long-term, accelerated stability data and in-use stability data. The composition of commercial and clinical formulation is the same.

During development the vial size was changed from 10 mL to 2 mL vial size. Forced degradation studies were performed. Photostability was tested according to ICH Q1B. The main changes during manufacturing process development are considered appropriately documented and comprehensible. The container closure system consists of 2 mL (2R) Type I untreated borosilicate, clear glass vial closed with fluorocarbon-coated bromobutyl rubber stopper and crimped sealed with flip-off aluminium cap. Each vosoritide finished product strength is differentiated by the cap colour of the vial. The container closure system is considered appropriate for lyophilised vosoritide finished product. Extractable and leachable studies were performed and the respective study report is provided. Stability studies underline the compatibility of the container closure with vosoritide finished product.

Manufacture of the product and process controls

BioMarin International Ltd. located in Ireland is responsible for EEA batch certification Valid GMP certificates were provided.

A detailed narrative description of the manufacturing process was provided and a flow-chart including in-process controls was provided. Manufacturing consists of dilution of thawed formulated bulk active substance by bioburden reduction filtered buffer solution. Subsequently, bioburden reduction filtration of vosoritide finished product solution is performed prior to (inline) sterile filtration through two consecutive 0.22 µm filters and aseptic filling into 2 mL vials followed by lyophilisation. A brief description of the batch numbering system and a clear batch definition including potential pooling of different active substance batches has been provided.

A control strategy for finished product has been implemented based on process and product understanding and risk management. Identified CPPs are consistent with the pre-defined CQAs in the development section. Acceptable ranges have been established for critical process parameters to adequately control the process. Further, appropriate ranges for in-process controls have been established. Relevant PPs and performance attributes along with their acceptance criteria/operating ranges and classification has been included in the process description.

Process validation was adequately performed using representative commercial batches for process validation of the finished product manufacturing process adequately covering different strengths and batch sizes. The maximum number of vials produced is limited by the lyophiliser load and was verified for a range. All processing steps were appropriately verified and validation and qualification reports are provided. All materials used in the manufacturing process were appropriately qualified and compatible with vosoritide finished product.

Relevant process holding times are provided. Process simulation media fills were appropriately conducted to validate aseptic processing and filling times for vosoritide finished product.

Shipping qualification confirmed adequate shipping of vosoritide finished product in vials and sWFI in pre-filled syringes.

Product specification, analytical procedures, batch analysis

The finished product release and shelf-life specifications include tests for identity (Immunoblot, RP-HPLC), appearance (visual), colour and clarity (Ph. Eur.), moisture (Ph. Eur.), reconstitution time, particulate analysis (Ph. Eur.), uniformity of dosage units (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), purity-multimer content (SEC), purity-deamidation (SCX), purity-related substances (RP-HPLC), potency-active fraction (RP-HPLC), peptide concentration (UV), intact vosoritide (RP-HPLC, UV), pH (Ph. Eur.), osmolality (Ph. Eur.), polysorbate 80 (RP-HPLC-CAD).

The majority of methods are used to control both the active substance and finished product. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Colour and clarity, moisture, particulate analysis, uniformity of dosage units, bacterial endotoxin, sterility and container closure integrity are compendial methods performed according to Ph. Eur. or USP monographs. The compendial method for particulate analysis is provided for subvisible particles. Visible particles are controlled within the visual assessment of appearance. Stability specifications are the same as release specifications, apart from identity, and polysorbate 80 content determination. As polysorbate 80 content was assessed during development and was found stable for the shelf-life duration it does not have to be included in the shelf-life specification.

Changes in acceptance criteria for main peak and purity testing were implemented for related substances. Altogether, the batch analysis results confirm batch-to-batch consistency and significantly improved impurity profiles for commercial batches with much lower impurity levels related substances compared to development batches. Impurity specifications include multimer content, deamidation and as measured by RP-HPLC main peak (desired product), total inactive fraction, identified and unidentified impurities. In line with the active substance specifications, the acceptance criteria of the finished product specifications are currently acceptable. The applicant proposes to determine potency by RP-HPLC, the same method that is used for purity and thus replace the cell-based assay that has been used for potency determination up to now. Considering the available data, the applicant´s approach to remove the cell-based potency assay and use a RP-HPLC method as potency assay is endorsed (please refer to the active substance section).

Justification of specification is based on the limits of the active substance, evaluation of clinical and commercial process batch data, and analytical variability and stability data of finished product. In line with the commitment for the active substance, a commitment has been provided to revise the finished product specification once data of at least 20 active substance batches will be available from the commercial process (see **REC1**, section 2.2.7).

It is stated that no additional impurities are introduced in the finished product compared to active substance.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested by CHMP, major objection) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Batch analysis data comprise comprehensive documentation of development and commercial batches. Satisfactory batch analysis data have been provided for all batches comprising identity, potency, purity testing, strengths and composition. Additional batch analysis data has been provided for related substances by RP-HPLC for commercial batches.

The same reference materials are used for active substance and finished product. For information on reference materials, refer to the active substance section.

Stability of the product

The proposed shelf-life of 24 months at 2-8°C including storage at 30±2°C for a single period up to 90 days for patient convenience is acceptable. In-use stability is indicated for 3 hours at 25°C and a statement is included in the SmPC.

Comprehensive data on ICH conforming stability studies have been provided. Adequate stability protocols (tests, methods, acceptance criteria, storage conditions, and pull schedule) are presented.

Real time/real condition stability data of finished product lots have been evaluated at long-term (5 ± 3°C), accelerated (25 ± 2°C / 60 ± 5% RH and 30 ± 2°C / 75 ± 5% RH) and stress (40 ± 2°C / 75 ± 5% RH) temperature, in line with ICH guidelines.

Real time data supporting the proposed shelf life were generated for finished product batches manufactured at the intended commercial site (lots with 0.4, 0.56, and 1.2 mg/vial). These primary stability batches are generally representative for commercial finished product manufacturing process using formulated bulk active substance manufactured with the commercial process and the commercial primary container closure system. Stability data are also generated for the PPQ/commercial finished product batches that used the formulated bulk active substance manufactured by the commercial process, not yet covering the proposed shelf life, but up to 18 months long-term storage. Finished product stability testing is performed according to the finished product shelf life specification at that time. Test methods employed in the stability studies are adequate and cover the stability profile of the product. The methods have been demonstrated to be stability indicating.

Forced degradation and photostability studies (as per ICH Q1B) showed stability of vosoritide finished product under kinetic agitation and extreme light exposure with minor degradation. As a precaution, seen as vosoritide active substance is sensitive to photolytic degradation, a warning to protect from light is added in the SmPC.

Stability upon reconstitution was assessed in the development section using representative commercial batches. A stability commitment stating annual testing and monitoring for at least one commercial lot for each dosage strength is given. Stability for ongoing commercial lots will continue to be monitored through 48 months with updated stability specifications.

2.2.4. Finished Medicinal Product – Diluent, sWFI

Description of the product and Pharmaceutical Development

The diluent syringe consists of a siliconised glass barrel, a siliconised stopper, and a closure system composed of a tip cap with a luer lock and a tamper-evident seal. The glass syringes are pre-filled with sterile water for injection. The diluent is available with three different filling volumes of 0.5 mL, 0.6 mL, and 0.7 mL. The label is colour coded to match with vosoritide finished product vial colours.

A platform and bracketing approach to prior manufacturing experience of other sWFI pre-filled syringes (PFS) of varying sizes and fill volumes by the manufacturer was used for the development of the diluent, sWFI. The container closure is considered appropriate for storage and application of the diluent sWFI. The stopper and tip cap comply with USP and Ph. Eur. requirements for elastomeric closures.

Manufacture of the product and process controls

The standard manufacturing process comprising of sWFI generation, in-line filtration and terminal sterilisation via steam sterilisation is described and validated. A flow-chart and brief description of the manufacturing process was provided, and in-process controls are depicted. IPCs and CPPs have been appropriately defined and included in the process description. Validation data is provided to cover the full range of diluent fill volumes needed for vosoritide commercial product.

Product specification, analytical procedures, batch analysis

The release and stability specifications for sWFI were set in accordance to Ph. Eur. monograph for sterilised water for injection. For other compendial tests method validation reports are provided. Batch analyses were performed. Batches of BioMarin's sWFI pre-filled syringes covering each configuration were analysed and met the requirements.

Stability

A shelf-life of 60 months for the sWFI PFS when stored at 2°C to 32°C is proposed. Stability data is provided and confirms stability for 60 months. Since the shelf-life of vosoritide finished product is proposed for 24 months, the co-packaged product will be assigned the shortest expiry of all components.

Adventitious agents

A comprehensive strategy has been employed to avoid, reduce or eliminate microbial and viral contamination in the vosoritide active substance manufacturing process. The strategy, in compliance with the ICH guidelines Q5A and Q5B pertaining to characterisation tests, ensures that the starting materials and process materials are free of microbial and bacteriophage contamination. The risk of introduction of contaminating microorganisms and bacteriophage into the manufacturing process is minimised by the use of a well characterised production cell substrate, the careful selection of raw materials and the use of a closed manufacturing system wherever possible.

Validation and evaluation of viral clearance capability of the manufacturing process is not applicable, since vosoritide is produced by a microbial fermentation process in *E. coli* cells. Adequate information has been provided concerning the TSE risk assessment.

Post approval change management protocol(s)

A post approval change management protocol (PACMP) is included for transfer of vosoritide analytical methods for release and stability testing of active substance and finished product. The PACMP is considered acceptable.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Active Substance

Overall, sufficient detail has been provided with regard to the active substance manufacturing process, process description and process controls. Thus, the active substance manufacturing process is considered adequately described. Process verification is satisfactory; the consistency and reproducibility of the vosoritide formulated bulk active substance manufacturing process has been adequately confirmed, supporting the proposed control strategy.

The peptide has been characterised in detail using state of the art methods. Due to the manufacturing process, the DS contains an unusually high number of product-related substances and impurities, which is quite unusual for such a relatively small molecule. As requested, the active substance specification has been considerably tightened. To determine potency the cell-based assay has been replaced by RP-HPLC for future batches. At this stage, based on the limited data provided, the specification is considered acceptable. Nevertheless, considering the relatively wide acceptance criteria for some parameters, further evaluation of the specification is requested once more batch data are available (see **REC1,** section 2.2.7). A PACMP was approved for transfer of vosoritide analytical methods for release and stability testing of active substance. The applicant also commits to complete and submit the final study report on the Low Endotoxin Recovery (LER) study with the closing sequence (see **REC2,** section 2.2.7).

Finished Product

Adequate quality of vosoritide finished product has been confirmed. Pharmaceutical development of the lyophilised finished product is described in detail. The aseptic manufacturing process and lyophilisation is appropriately documented and the control strategy adequately justified. Satisfactory validation data covering all strengths and batch sizes are provided. The finished product release and shelf life specifications are considered appropriate. As for the active substance specification, the finished product specification will be revised after at least 20 active substance batches are available. The major objection raised in relation to the lack of nitrosamine impurities risk assessment has been satisfactorily resolved. A PACMP was approved for transfer of vosoritide analytical methods for release and stability testing of finished product.

The container closure system is considered appropriate and compatible with vosoritide finished product. The proposed shelf-life of 24 months at 2-8°C including storage at 30±2°C for a single period up to 90 days for patient convenience can be accepted. In-use stability is indicated for 3 hours upon reconstitution.

The platform and bracketing approach applied for the development and manufacturing of the diluent sterile water for injection (sWFI) provided in pre-filled syringes is considered appropriately documented and validated.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.7. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to review the acceptance limits for active substance and finished product release and stability specifications once at least 20 active substance batches produced by the commercial process are available. (REC1)
2. The applicant commits to complete and submit the final study report on the Low Endotoxin Recovery (LER) study with the closing sequence. (REC2)

2.3. Non-clinical aspects

2.3.1. Introduction

This is a full application for a new substance. All non-clinical aspects (PD, PK and toxicology) were covered with own studies by the applicant. Since vosoritide is a peptide, related to endogenous C-Type Natriuretic Peptide (CNP), the PK and genotoxicity programme were adapted accordingly. Carcinogenicity studies of vosoritide have not been conducted. A carcinogenicity risk assessment for vosoritide was conducted, based on the known physiological properties of CNP and on the results of the repeated-dose toxicity studies and in consideration of the ICH S1A guideline.

2.3.2. Pharmacology

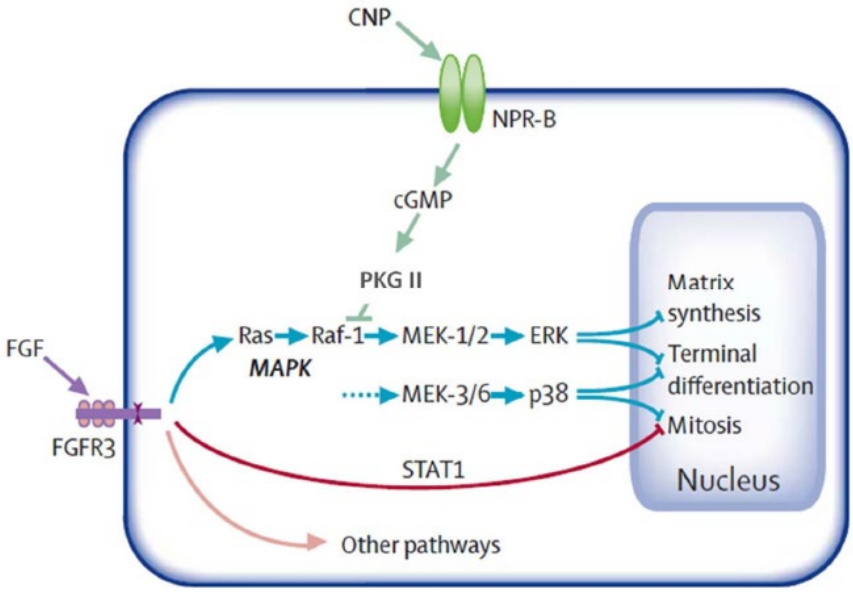
Primary pharmacodynamic studies

Vosoritide, also known as BMN111, is a stable analogue of the endogenous peptide CNP (C-type Natriuretic Peptide). CNP is a member of the NP family, together with ANP (Atrial Natriuretic Peptide) and BNP (Brain Natriuretic Peptide). It was recognised that CNP acts as a paracrine factor involved in endochondral bone formation. It also exerts actions in the cardiovascular system, brain and reproductive system.

Three receptors exist for the natriuretic peptides which are called NPR-A, -B and -C. The latter is thought to be a scavenger receptor. CNP mainly binds to NPR-B and -C whereas ANP has a high affinity to NPR-A. The primary action of NPR-A and -B is induction of formation of the second messenger molecule cyclic GMP (cGMP) by guanylyl cyclases.

Achondroplasia is caused by a gain-of-function mutation in the fibroblast growth factor receptor FGFR3. CNP is regarded as a functional antagonist of this receptor in chondrocytes. The signalling pathways involved in this interaction are shown in Figure 4.

Figure 4: Crosstalk between FGFR3 and CNP signalling pathways in chondrocytes



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

Based on the knowledge from the literature on CNP physiology, the applicant conducted a number of primary PD studies *in vitro* and *in vivo* to further elucidate the pharmacological properties of the CNP analogue vosoritide in respect to its action on chondrocytes and bone growth. Cell culture and animal models of disease, carrying a mutated FGFR3 gene, were also used.

Primary PD *in vitro*

Design and key results of the conducted *in vitro* or *ex vivo* studies to characterise primary PD are tabulated below.

Table 1: Overview of the *in vitro* / ex vivo studies

Study ID	Test system	Main results
BMN111-11-044	Cynomolgus monkey brain tissue	The amino acid sequence of the NP receptors NPR-A, -B and -C is highly homologous, at least 98%, across species (mouse, rat and cynomolgus monkey). In case of cynomolgus monkeys, the NPR sequences were determined by the applicant by RT-PCR amplification from brain tissue and consecutive nucleotide sequencing.
BMN111-10-110	NIH/3T3 fibroblasts	BMN111 dose-dependently increased cGMP production in the 3T3 murine fibroblasts similar to the positive control CNP22; ANP had a small effect only.
BMN111-11-028	HEK293T cells	HEK cells were transfected with the human receptors NPR-A, NPR-B and NPR-C, respectively. The activations of these receptors by different ligands (BMN111, CNP22 and ANP) was determined as intracellular cGMP production. BMN111 and CNP22 hardly activated NPR-A.
BMN111-18-002	HEK293T cells transiently expressing	The receptor NPR-B from rabbit, rat, mouse and human was expressed in HEK cells. EC50 of BMN111 was similar across these species and was in the low nanomolar range.

	NPR-B from several species	
BMN111-11-004	Human chondrocytes	BMN111 and CNP22 dose-dependently increased cGMP levels in primary normal human chondrocytes. BMN111 also increased cGMP in primary chondrocytes artificially expressing the achondroplastic mutation (G380R) of FGFR3
BMN111-10-086	Various human chondrocyte cell lines	Inhibition of FGF-dependent MAPK phosphorylation by BMN111 was determined by Western blotting in primary human fetal immortalised chondrocytes from growth plate, taken from normal fetuses and from fetuses carrying different FGFR3 mutations (G380R, Ach, or Y373C, TD). In all cases BMN111 partially prevented MAPK phosphorylation.
RS19-001	Rat chondrosarcoma (RCS) cells	BMN111 suppressed FGF2-induced MAPK phosphorylation in the rar chodrosarcoma cell line RCS. Furthermore, BMN111 partly counteracted the FGF2-depended suppression of proliferation in these cells; also BMN111 itself retarded proliferation
BMN111-10-002	Explants from $FGFR3^{Y367C/+}$ mice	Endochondral growth in response to BMN111 was determined in femur explants from embryonic TD mice (WT served as control). BMN111 increased femur length after six days' culture *in vitro*, for WT and TD.

The most important results of these studies are presented in more detail hereafter.

Study BMN111-18-002: Potency of vosoritide on NPR-B from different species assessed in HEK293T cells expressing cynomolgus monkey/human, mouse, rat, and rabbit NPR-B

Cells were stimulated with ascending vosoritide concentrations; the readout was intracellular cGMP production. A 22-amino acid fragment of CNP (CNP22) served as comparator. No relevant differences in potency between the species tested were observed for vosoritide (Table 2)

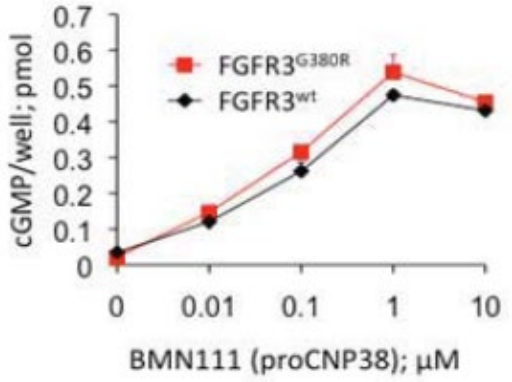
Table 2: NPR-B Potency (EC50)

NPR-B Species	**EC50 (nM CNP22)**	**EC50 (nM BMN111)**	**n**
Rabbit	75.4, 24.1	2.9, 4.4	2
Rat	5.6, 5.2	1.4, 2.2	2
Mouse	9.3, 7.0	2.8, 2.4	2
Human	5.3, 4.1	1.7, 1.7	2

Study BNM111-11-004: Vosoritide Induced cGMP Production in FGFR3G380R and wild type chondrocytes

Vosoritide was able to stimulate intracellular cGMP in normal chondrocytes as well as in chondrocytes carrying the Ach mutation of FGFR3 G380R (Figure 5)Primary human chondrocytes were used, from normal and from Ach donors.

Figure 5: Vosoritide Induced cGMP Production in FGFR3G380R and wild type chondrocytes



Study RS19-001: Evaluation of Dosing Frequency on Suppression of FGF2 Signalling and Restoration of Proliferation and Matrix Deposition by BMN111

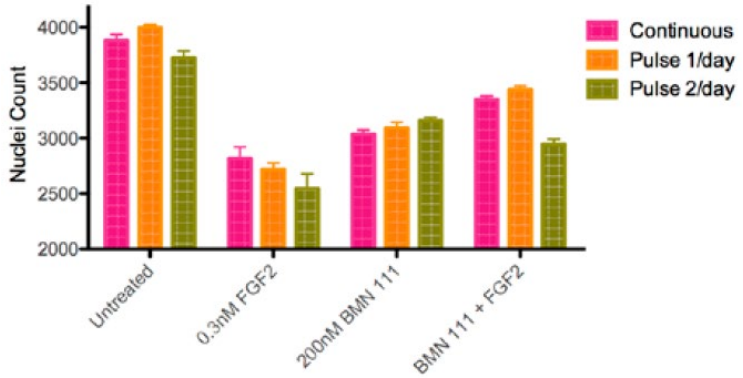
In this study, the effect of vosoritide on MAPK (ERK1 and ERK2) activation, proliferation and production of extracellular matrix material was tested in the RCS rat chondrosarcoma cell line. Vosoritide was able to attenuate FGF2-induced MAPK activation (measured as phosphorylation by Western blotting).

Proliferation of RCS cells was determined by counting the cells after cultivation for 72 hours (3 days) in the presence or absence of the test compounds. Vosoritide was present either continuously over the 72 hours or was added for 60 min each once or twice daily (labelled as pulse in Figure 6)

For each vosoritide treatment scheme (continuous, one pulse per day or two pulses per day) separate treatment controls (medium alone or FGF2 only) were defined since the procedures (e.g. frequency of medium change) were different. For this reason, three bars are shown in the figure also for untreated and FGF2-only treated cells.

It was observed that FGF2 decreased the proliferation rate of the RCS cells. Vosoritide also reduced proliferation, albeit to a lesser extent. When vosoritide was added to FGF2, the proliferation rate increased; i.e. vosoritide partly antagonised the FGF2 effect as desired. No principal differences between the different stimulation schemes of vosoritide were observed.

Figure 6: BMN111 partly rescues FGF2 suppression of RCS cell proliferation



The above results show that vosoritide alone does not induce cell proliferation, at least in the RCS cells used here. Vosoritide exerts its proliferative effect only in the presence of FGF signalling by counteracting the anti-proliferative effect of the latter.

Deposition of extracellular matrix material was determined quantitatively by alcian blue staining. Similar to the effects on proliferation, FGF2 suppressed matrix production and vosoritide largely counteracted this suppression.

Primary PD *in vivo*

The *in vivo* studies conducted are tabulated below. Key studies are presented in more detail hereafter.

Table 3: Overview of the *in vivo* studies

Study ID	Species/strain	Main results
BMN111-10-046	$FGFR3^{Y367C/+}$ mice	BMN111 (240 and 800 µg/kg for 10 d) dose-dependently increased body length and the length of certain bones by up to 6.6% (femur) in TD mice
BMN111-11-045	$FGFR3^{Y367C/+}$ mice	Similar to Study 046; 800 µg/kg BMN111 for 20 d; 17.5% increase in femur length by BMN111 compared to vehicle; one high-dose animal had impaired hind-limb motility and paw swelling
BMN111-11-001	FVB-$FGFR3^{ach}$ mice	Three doses (20, 80 and 280 µg/kg) of BMN111 were administered for 36 days in FVB mice carrying the human FGFR3 mutation. There was a small but statistically significant increase in body length (naso-anal) and some bones
BMN111-09-048	FVB mice	Different CNP analogues were tested. For BMN111 the results on body and bone length were in general in line with the findings of Study BMN111-11-001
BMN111-09-074	FVB mice	Different administration schemes of and durations of treatment with BMN111 were tested. Daily dosing appeared to promote preferentially appendicular growth. Laboratory markers of bone growth, histology of selected organs and anti-drug antibodies were also determined. Inflammation of the lungs was found in all groups; mild forms also in the vehicle group
BMN111-09-075	FVB mice	Two doses of BMN111 (80 and 280 µg/kg, QD for 5 weeks) were tested. There was a dose-dependent increase in body (naso-anal), tail and bone length
BMN111-11-017	rats (SD)	BMN111 (80, 240 and 800 µg/kg) was administered for 36 days in older rats (8 months old). Increase in body length was not statistically significant; curvature of the tail and reduced hind limb motility were observed in some animals of the mid- and high-dose group.
BMN111-09-072	cynomolgus monkeys, juvenile	This was a pilot study in 4 males per group receiving either vehicle or 9 or 33 µg/kg BMN111 QD for 6 months. BMN11 increased leg length, measured by callipers and tibia length measured by radiography; histologically, a widening of the growth plate (distal femur) was observed.

FVB mouse: An albino, inbred laboratory mouse strain that is named after its susceptibility to Friend leukaemia virus B
FGFR3ach mouse: A mouse model of ACH in which the endogenous mouse Fgfr3 gene was replaced with human FGFR3G380R, the most common mutation in human ACH

Study BMN111-10-046: Evaluation of Endochondral Bone Growth in FGFR3^{Y367C} (TD) Mice Following Multiple Subcutaneous Administrations of BMN111

The objective of this non-GLP study was to evaluate the effects of once-daily subcutaneous administrations of vosoritide on overall development including skeletal growth when administered for 10 days to 7-day-old TD mice. TD mice carry the heterozygous Y367C mutation in the FGFR3 gene, corresponding to the mutation leading to thanatophoric dysplasia in humans.

Seven-day-old TD mice and their WT littermates were administered vehicle or vosoritide at 240 or 800 µg/kg via subcutaneous injection once daily for 10 days. The duration of the study was 10 days due to the shortened lifespan of the TD mice and to eliminate the need for tooth trimming past 17 days of age.

Clinical signs and mortality were also recorded daily during the study. Body weights were reported twice weekly.

No unscheduled deaths occurred. No obvious changes in body weight were observed in the vosoritide treated TD mice in comparison to vehicle TD mice.

One female, administered vosoritide at 800 µg/kg, was observed to have a mild reduction in hind limb motility and contraction, in addition to paw swelling and/or mild curvature of the paw (motility and contraction normal).

In general, most mice at the 800 µg/kg dose level showed a transient reduced motor activity following drug administration for the first 5 days of treatment presumably due to vosoritide-related haemodynamic changes. Normal motor activity was resumed approximately 2 hours after drug administration.

Vosoritide increased the length of the bones assessed and whole body length dose-dependently by around 3% (low dose) and around 5% (high dose, Table 4).

Table 4: Increase in the Length of Bones and Naso-Anal Segment in BMN111-Treated TD Mice for 10 Days

	Femur	**Tibia**	**L4-L6**	**AP Skull**	**Naso-Anal**
WT + vehicle (mm)[1]	9.84 mm	12.99 mm	5.83 mm	20.25 mm	69.08 mm
TD + vehicle (mm)[1]	5.31 mm	5.41 mm	4.16 mm	14.18 mm	45.14 mm
BMN111, 240 µg/kg (%)[2]	3.41%*	3.69%	2.84%	2.88%	4.51%*
BMN111, 800 µg/kg (%)[2]	5.23%*	6.64%*	3.26%	4.77%*	5.29%*

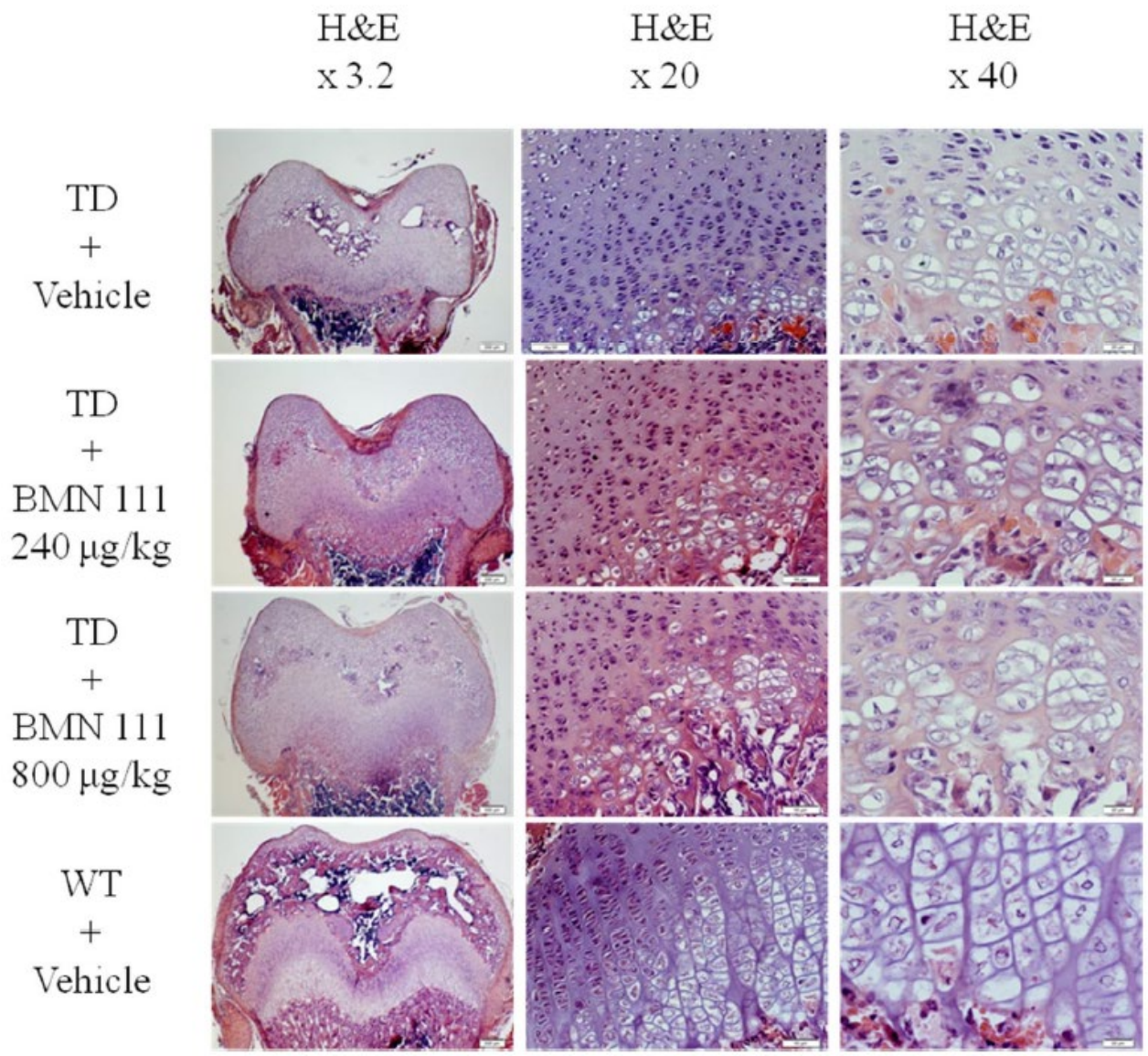
* $p<0.05$ using a one-way ANOVA (post hoc Tukey's) when compared to vehicle-treated TD mice.

1 Data presented are absolute measures and are expressed in mm.

2 Data presented are percentage of increase in comparison to vehicle-treated TD mice.

In comparison to vehicle-treated WT mice, the histological analysis of the distal femur of the TD mice revealed a marked decrease in the size of the epiphyseal head, delayed secondary ossification, reduced size of the growth plate, lack of pre-hypertrophic zone, lack of columnar arrangement and abnormal shape and small size of the hypertrophic cells. Vosoritide daily subcutaneous administrations for 10 days partially restored the mentioned defects; see figure below.

Figure 7: Histological Evaluation of the Effects of Vosoritide on the Growth Plate of TD Distal Femurs after 10 Days of Treatment.



In this mouse model of thanatophoric dysplasia, disordered arrangement of chondrocytes in the growth plate is observed. The applicant claimed that disordered chondrocytes also are a typical sign for achondroplasia in humans. Healthy animals treated with vosoritide revealed disarranged chondrocytes in the growth plate (see toxicology section). The applicant argues that any undesired bone changes observed in healthy animals after vosoritide treatment are due to more-than-normal bone growth. According to the applicant, undesired bone changes such as disordered chondrocytes with vosoritide should not occur when the bone growth is retarded by an FGFR3 mutation as in achondroplasia because even after vosoritide treatment the bone growth is not higher than normal. Unfortunately, the TD model is not helpful to confirm this assumption because in TD animals disturbed chondrocyte order already exists without vosoritide treatment.

Disordered arrangement of the chondrocytes in the growth plate is not established as a classical feature of Ach in humans. In a recent review on achondroplasia by Ornitz and Legeai-Mallet (Developmental Dynamics 246:291–309, 2017) it was stated that "with age, there is progressive

disorganisation of the skeletal growth plate", implying that at young age or during foetal development there is no disorganisation. The applicant has presented three publications in which histological images of growth plates from Ach subjects and healthy individuals are shown (Ponseti, J of Bone and Joint Surgery 1970, 52-A: 701-716; Rimoin et al., New Engl J Med 1970, 238: 728-735; Briner et al. 1991, Path Res Pract 187: 271-278). Some of the Ach subjects had nearly normal chondrocyte arrangement in the growth plates whereas in others the latter was markedly altered. Thus, disordered arrangement of chondrocytes obviously is not a common feature in Ach, although it may occur.

Study BMN111-11-001: Evaluation of Bone Growth in FGFR3^{ach} Mice Following Subcutaneous Administrations of BMN111 for 36 days

In this study, an animal model of Ach was used, carrying the heterozygous FGFR3 mutation G380R which corresponds to the human Ach mutation. The mutated FGFR3 gene was introduced into the mice as a transgene. Its expression was largely restricted to cartilage by using Type II collagen promotor and enhancer sequences for driving its expression. The mice have an FVB gene background, named after their susceptibility to Friend leukaemia virus B.

The Ach mice display a moderate decrease in the length of the appendicular and axial skeletons, a dome shape cranium, and smaller proliferative and hypertrophic zones with, nonetheless, overall intact architecture. Heterozygous animals had approximately 5-10 % shorter body length and ~24% shorter limb length when compared to the WT littermates. While Ach patients have a narrowing of the foramen magnum, increased foramen magnum area was observed in these mice.

Eight Ach mice (males only) per group (Groups 2 to 5) received a daily dose of vosoritide (0 [vehicle], 20, 80 or 280 µg/kg) for 36 days. A group (Group 1) of 10 wild-type FVB mice receiving vehicle was also included for comparison (Table 5).

Table 5: Groups in Study BMN111-11-001

Group	Genotype	Administered	Dose (ug/kg)	# Animals (Males)
1	wild-type	Vehicle	0	10
2	FGFR3^{ach}	Vehicle	0	8
3	FGFR3^{ach}	BMN111	20	8
4	FGFR3^{ach}	BMN111	80	8
5	FGFR3^{ach}	BMN111	280	8

Clinical signs:

The following observations were made, scored according to the scheme, 1, mild; 2, moderate; 3, severe; 4, extreme or complete:

Reduced hind limb movement
Animal 4289 (Group 2 [vehicle]) scored 3, 3, 1 on Days 15, 22, 36, respectively
Animal 4318 (Group 5 [280 µg/kg]) scored 2, 1, 1 on Days 22, 29, 36, respectively

Tail Kinking
Animal 4236 (Group 3 [20 µg/kg]) scored 1 on Day 29
Animal 4245 (Group 3) scored 1, 1, 1, 2 on Days 15, 22, 29, 36, respectively
Animal 4276 (Group 3) scored 1, 1, 1 on Days 15, 22, 29, respectively
Animal 4302 (Group 3) scored 1, 1 on Days 29, 36, respectively
Animal 4202 (Group 4 [80 µg/kg]) scored 1 on Day 15

Animal 4318 (Group 5 [280 µg/kg]) scored 1, 1, 1, 1 on Days 15, 22, 29, 36, respectively

Body weight:

The body weights of Ach animals were significantly lower than their WT littermates at the beginning of the study. Treatment with vosoritide resulted in an increase in body weight in vosoritide-treated Ach mice when compared to vehicle-treated Ach mice. After 18 days of treatment, body weights in Ach animals given 280 µg/kg were not statistically different from vehicle-treated WT mice.

Body/tail/bone length:

At the beginning of the treatment, Ach animals were shorter (naso-anal) than wt animals. After 36 days of treatment with vosoritide, a dose-dependent increase in mean body length compared to vehicle control was observed; the mean body length in the high-dose group slightly exceeded the mean length of the WT animals (**Table *6***).

Table 6: Naso-Anal Length (cm)

Group	Data	Day 1	Day 36
1 Vehicle (Wild Type)	Mean	7.38	*9.40*
	SD	0.30	0.24
	n	10	10
	stat	n.a.	n.a.
2 Vehicle FGFR3Ach	Mean	6.47	8.82
	SD	0.53	0.44
	n	8	8
	stat	c	c
3 BMN111 20 µg/kg FGFR3Ach	Mean	6.43	9.00
	SD	0.50	0.18
	n	8	8
	stat	c	c
4 BMN111 80 µg/kg FGFR3Ach	Mean	6.46	9.25
	SD	0.51	0.27
	n	8	8
	stat	c	b
5 BMN111 280 µg/kg FGFR3Ach	Mean	6.45	9.76
	SD	0.35	0.16
	n	8	8
	stat	c	b,c

b: $p < 0.05$ in ANOVA with Groups 3-5 (vs. 2)
c: $p < 0.05$ in ANOVA with Groups 2-5 (vs. 1)

Changes in tail length were similar to the changes in naso-anal length (**Table *7***).

Table 7: Tail Length (cm)

Group	Data	Day 1	Day 36
1 Vehicle (Wild Type)	Mean	6.21	*8.43*
	SD	0.51	0.25
	n	10	10

	stat	n.a.	n.a.
2 Vehicle FGFR3^{ach}	Mean	5.63	8.10
	SD	0.56	0.35
	n	8	8
	stat	n.s.	n.s.
3 BMN111 20 µg/kg FGFR3^{ach}	Mean	5.43	8.05
	SD	0.70	0.39
	n	8	8
	stat	c	c
4 BMN111 80 µg/kg FGFR3^{ach}	Mean	5.63	8.29
	SD	0.72	0.25
	n	8	8
	stat	n.s.	n.s.
5 BMN111 280 µg/kg FGFR3^{ach}	Mean	5.50	8.68
	SD	0.51	0.30
	n	8	8
	stat	n.s.	b

b: $p < 0.05$ in ANOVA with Groups 3-5 (vs. 2)
c: $p < 0.05$ in ANOVA with Groups 2-5 (vs. 1)

The applicant pointed out that the tail shortening caused by the Ach mutation was over-corrected with high-dose vosoritide, i.e. mean tail length in the high-dose group was higher than in WT animals.

Particularly in healthy animals used in the repeated-dose toxicology studies (see Section 2.3.4.), functional impairment of the hind limbs and abnormal shape of the femur were observed along with tail kinking. The applicant assumed that the reason for the irregular bone growth leading to these signs is a higher-than–normal growth rate which results from vosoritide treatment in animals with a normal growth rate before treatment. The applicant also referred to similar observations in FGFR3 knock-out mice which also show faster-than-normal growth.

The applicant further argued that in animals with FGFR3 mutations and in humans suffering from Ach the bone growth rate is reduced so that vosoritide treatment usually does not lead to a higher-than-normal growth rate. Consequently, irregular bone growth should not occur.

However, in this study tail-kinking was also observed in the low- and mid-dose group in which growth rate was not higher than in WT controls. Functional impairment of the hind limbs was observed in two Ach animals only, one of the vehicle and one of the high-dose group, so that no firm conclusions on the relationship between vosoritide dose, growth rate and hind limb impairment can be drawn from this study.

An early sign of irregular bone growth could be the disarrangement of the chondrocyte columns in the growth plate as observed in healthy animals treated with vosoritide (see section on repeated-dose toxicology). Histology of the growth plate was not reported in this study. Furthermore, the applicant claimed that in Ach the chondrocyte arrangement is disturbed as such. However, as discussed above (Study BMN111-10-046), disturbed chondrocyte arrangement is not a consistent finding in Ach.

Also the growth of the long bones was in line with the increase in body length; vosoritide dose-dependently increased the length of femur, tibia and ulna; there was virtually no effect on the humerus (**Table 8**).

Table 8: Bone Length Summary Data (Right/Left) (mm); Day 36

Group	ID #	L/R Femur	L/R Tibia	L/R Humerus	L/R Ulna
1 Vehicle (Wild Type)	Mean	14.91	18.24	12.04	14.16
	SD	0.26	0.44	0.25	0.30
	n	20	20	20	20
	stat	b	n.s.	n.s.	n.s.
2 Vehicle FGFR3Ach	Mean	14.36	17.91	12.17	13.81
	SD	0.86	0.77	0.68	1.09
	n	16	16	16	16
	stat	c	n.s.	n.s.	n.s.
3 BMN111 20 µg/kg FGFR3Ach	Mean	14.36	17.91	12.17	13.81
	SD	0.86	0.77	0.68	1.09
	n	16	16	16	16
	stat	b	B	n.s.	n.s.
4 BMN111 80 µg/kg FGFR3Ach	Mean	14.64	18.12	12.05	14.11
	SD	0.89	0.76	0.28	0.35
	n	16	16	16	16
	stat	n.s.	n.s.	n.s.	n.s.
5 BMN111 280 µg/kg FGFR3Ach	Mean	15.43	19.10	12.28	14.42
	SD	0.37	0.48	0.33	0.18
	n	16	16	16	16
	stat	b,c	b,c	n.s.	b

b: $p < 0.05$ in ANOVA with Groups 3-5 (vs. 2)
c: $p < 0.05$ in ANOVA with Groups 2-5 (vs. 1)

Regarding the skull, vosoritide dose-dependently increased the anterior-posterior length of the whole skull and decreased the dimensions (length and width) of the foramen magnum. In Ach animals the foramen magnum is larger than in WT animals; in the high-dose group the foramen became smaller than in WT animals.

Growth plate histomorphometry:

The heights of the three different zones of the femur growth plate were measured histologically. A clear dose-dependent increase in height was observed for the zone of multiplication, from 64.7 µm (vehicle) to 85.7 µm (high dose). In the other zones, zone of reserve cartilage and zone of hypertrophy, no or only small changes were observed.

Organ weights:

There was a dose-dependent increase in liver weight with vosoritide treatment, from 1.20 g (vehicle to 1.45 g (high-dose). No major changes were observed for other organs.

Secondary pharmacodynamic studies

In search for off-target effects of vosoritide, the applicant conducted an *in vitro* screen of a panel potential (off-)target structures (Study BMN111-11-026). Eight receptors were inhibited by BMN111 in low micromolar concentrations, most strongly the human apelin receptor (which mediates various CV effects). The observed IC50 values of vosoritide in that assay are by more than 3 orders of magnitude higher than the mean Cmax at week 52 in patients treated with 15 µg/kg vosoritide.

Safety pharmacology programme

The following table provides an overview of the safety pharmacology studies performed. Findings were made in the monkey CV safety study BMN111-11-040, transiently increased HR and decreased BP. The respective study is presented in more detail hereafter.

Table 9: Overview of the safety pharmacology studies

Study ID	Test system	Main results
BMN111-11-023	hERG-transfected HEK293 cells	No relevant inhibition of hERG current was detected
BMN111-11-021	SD rat	CNS effects were studied using a modified Irwin assessment after a single dose (0, 30, 100 and 300 µg/kg) of BMN111. No abnormal observations were made.
BMN111-11-022	SD rat	Respiratory safety was assessed using head-out plethysmography after a single dose (0, 30, 100 and 300 µg/kg) of BMN111. No changes in respiratory function were observed.
BMN111-09-060	FVB mouse	Pilot study testing different CNP analogues including BMN111 (single dose). BNM111 dose-dependently decreased mean arterial pressure (up to 25%) in anesthetised mice.
BMN111-09-067	Telemeterised cynomolgus monkey	Pilot study for dose finding (single and repeated [QWD for 7d]) in conscious and anesthetised monkeys. BMN111 MTD was defined as 28 µg/kg based on a ≤10% BP drop and ≤25% HR increase.
BMN111-11-041	Telemeterised cynomolgus monkey	Pilot study for determining the length of the washout period; 2 days washout were needed between 2 doses to achieve a naïve-like CV response after the second BMN111 injection.
BMN111-11-040	Telemeterised cynomolgus monkey	After a single dose (10, 50 or 200 µg/kg), BMN111 causes a dose-dependent increase in HR, lasting up to 4 hours. The decrease in mean blood pressure was less pronounced and clearly visible only with the high dose. After repeated daily dosing, BP excursions became smaller; no accommodation was seen for HR.

Study BMN111-11-040: Cardiovascular Safety Pharmacology Evaluation of BMN111 Administered by Rapid Subcutaneous Infusion to Male Telemetry Instrumented Conscious Nonhuman Primates

The purpose of this GLP study was to evaluate the potential CV effects of vosoritide in telemeterised male cynomolgus monkeys. Vosoritide was administered by rapid remote subcutaneous infusion to animals in a double Latin square dosing design (Phase I) and a 7-day repeat dose study design (Phase II).

In Phase I, eight male cynomolgus monkeys were 3.6 to 6 years of age at study initiation with body weights of 4.0 to 5.8 kg. Animals were telemeterised and permanently implanted with in-dwelling catheters in the abdominal aorta. Prior to dosing, catheters were introduced to the subcutaneous tissue in the lumbar region and sutured in place. An external pump was used to administer the test article. The dosing regimen for Phase I is presented in **Table 10**.

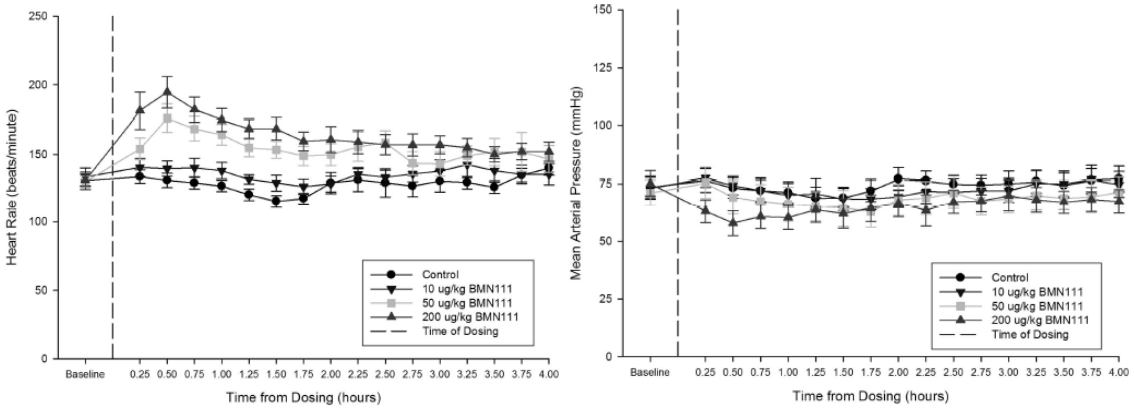
Table 10: Latin Square Crossover Design for the Cardiovascular Safety Pharmacology Study in Cynomolgus Monkeys (Phase I)

Animal ID	**Dose Level Designation on Specified Days (µg/kg)**			
(Male)	Day 1	Day 4	Day 8	Day 11
I09049	10	0	200	50
I09050	50	200	0	10
I09051	200	10	50	0
I09052	0	50	10	200
I09053	0	200	50	10
I09054	200	10	0	50
I09055	50	0	10	200
I09056	10	50	200	0

In Phase II, all animals were transferred from Phase I and given vosoritide at 200 µg/kg daily for 7 days at a dose volume of 1 mL/kg.

After a single vosoritide dose (Phase I), a dose-dependent transient increases in HR and decrease in blood pressure were noted, see figure below. Maximal effects were reached within 15 to 30 minutes of dosing for animals given 200 µg/kg, and within 1.75 or 2 hours for animals given 50 or 10 µg/kg, respectively. At the nadir, BP decrease was 6.8% and 12.2% in animals given 50 and 200 µg/kg respectively. Maximum HR increase was ~ 37% and ~ 49 % in animals given 50 and 200 µg/kg, respectively.

Figure 8: Mean Heart Rate and Mean Arterial Pressure in Phase I Animals



All ECG parameters evaluated were considered qualitatively normal. Some intervals were shortened (e.g. PR, QT, and QTcB) but the QRS duration was not affected.

In Phase II, i.e. with repeated dosing, vosoritide-related clinical observations were limited to idiosyncratic short and repeated bouts of sternal or lateral recumbency in 3/8 animals during the first hour post-dose in the repeat-dose portion of the study. This may be likely related to the haemodynamic effects of vosoritide, but it is unclear why the clinical observations of recumbency were only seen in Phase II. Vosoritide rapidly decreased arterial pressures and increased HR with similar timing and magnitude as seen in Phase I. Blood pressure effects on subsequent days were generally smaller in magnitude and appeared later. No apparent accommodation was seen for HR.

Pharmacodynamic drug interactions

No studies on PD interaction were conducted.

2.3.3. Pharmacokinetics

The following PK studies were performed:

Table 11: Overview of the PK studies

Study ID	Test system	Main results
Absorption		
BMN111-15-100	FVB mice and FVB FGFR3^{ach} mice	Overall, the PK of vosoritide was similar between wild-type FVB and FGFR3ACH FVB mice
BMN111-15-076	SD rats	Plasma exposure for the same dose level generally increased with age (7d to 13wk)
BMN111-17-048	Rats	Relative bioavailability of vosoritide is greater after IM administration compared to SC administration
BMN111-15-072	neonatal SD rats	Clearance and apparent volume of distribution were high in the young rats
Distribution		
BMN111-11-002	CD1 mice	cGMP production after a single vosoritide administration was demonstrated in several tissues, particularly bone and kidney
BMN111-11-003	CD1 mice	cGMP tissue levels after repeated vosoritide dosing (daily up to 7d) were determined; increased cGMP levels in distal femur were found
BMN111-17-027	SD rats	Tissue distribution of 124I-vosoritide was determined by PET scan after a single SC or IV administration. High levels were found in liver, kidney and stomach
BMN111-18-004	SD rats	Radiolabelled (I-124) vosoritide was determined in various tissues after a single SC administration by measuring radioactivity. High levels were found in the stomach and at the injection site.
Metabolism		
BMN111-18-101	Human liver microsomes	BMN111 is not metabolised by CYP enzymes
BMN111-10-109	In-vitro assay	In contrast to CNP22, BMN111 was virtually not degraded *in vitro* by neutral endopeptidase *in vitro* over around 2.5 hours
BMN111-16-024	Tissue from various species and animals of disease	Expression of the NP receptors NPR-B and –C was determined in various tissues from normal rats, mice and monkeys and in Ach mice by quantitative PCR. Age and sex were also considered. Expression was found in all tissues tested with some quantitative differences; no specific pattern could be derived
DDI		
BMN111-18-093	Human liver microsomes	BMN111 is not an inhibitor of CYP enzymes
BMN111-18-102	Human primary hepatocytes	BMN is not an inducer of CYP enzymes

Absorption

Vosoritide is a peptide intended for SC injection. Therefore, no studies for determining the mechanism of absorption were performed.

The most salient finding of absorption and TK studies was a strong increase of Cmax and AUC with dose which was markedly higher than proportional. An example (from rat toxicology study BMN111-11-052) is shown in **Table 12**. The mechanism underlying this phenomenon was not determined; however, there is a scavenger receptor (NPR-C) for CNP which also binds vosoritide. Saturation of this receptor with increasing vosoritide doses could retard elimination and thereby increase plasma levels and exposure.

Table 12: Vosoritide Gender Combined Dose Proportionality based on Plasma Pharmacokinetic Parameters Cmax and AUC0-t on Dose Days 1 and 182

Dose Day	Dose µg/kg	Cmax pg/mL	AUC0-t pg*min/mL	Dose Ratio	Cmax Ratio	AUC Ratio
1	10	1645	NC	1.0	1.0	NC
1	30	1597	NC	3.0	0.971	NC
1	90	3007	NC	9.0	1.83	NC
182	10	603	16488	1.0	1.0	1.0
182	30	2922	112208	3.0	4.85	6.81
182	90	21525	597397	9.0	35.7	36.2

Distribution

Distribution studies revealed the following results:

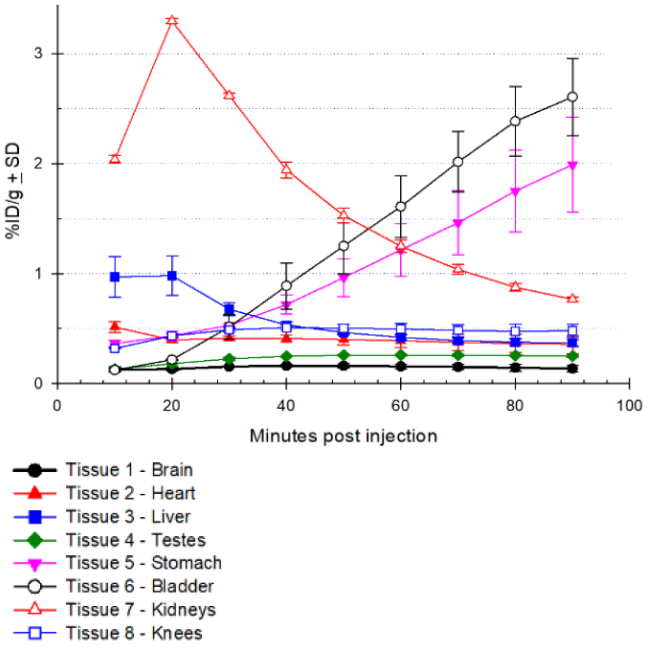
Study BMN111-17-027: Characterisation of the Biodistribution of ^{124}I-BMN111 using PET Imaging in Sprague Dawley Rats

Tissue distribution of vosoritide was determined in rats (Sprague Dawley) by PET imaging using vosoritide labelled with iodine-124 after a single SC injection of 90 µg/kg or a single IV injection of 50 µg/kg.

Following imaging, animals were euthanised and multiple tissue samples were collected for *ex vivo* analysis. *Ex vivo* gamma counts were obtained of the injection site, brain, lung, liver, stomach, intestines, kidneys, spleen, muscle, testicles, femur, tibia and for some animals also of the heart.

The results of the dynamic PET scan after IV injection are shown in Figure 9. Shortly after dosing, most activity is found in liver and kidney which declines over time. Simultaneously, activity in the stomach and in the bladder markedly increased. No change over time was observed in the brain. Static PET revealed a decline of activity in the stomach and testes from 4 hours after IV injection onwards. At 24 hours after injection, some residual radioactivity was still present in the stomach.

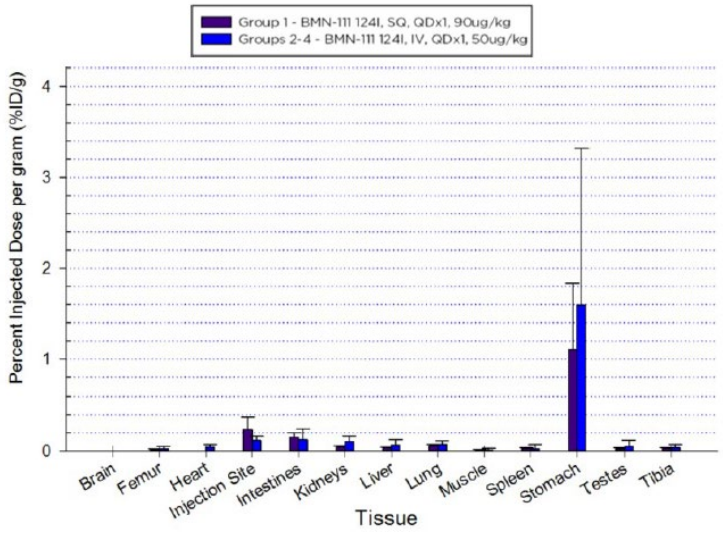
Figure 9: Dynamic PET after IV injection of 124I-vosoritide (50 µg/kg): % Injected Dose Per Gram with Std Deviation



After SC injection, dynamic PET mainly revealed activity at the injection site which declined over time.

The ex-vivo investigation (Figure 10) of tissues revealed radioactivity predominantly in the stomach and, to a much lesser extent, at the injection site and in the intestine. Virtually no activity was detected in the brain.

Figure 10: Ex Vivo % Injected Dose Per Gram and % Injected Dose with Std Deviation



Study BMN111-18-004: Biodistribution of ^{124}I-BMN111 after Subcutaneous Administration to Rats

Male Sprague Dawley rats received a SC administration of ^{124}I-vosoritide at a target dose level of 90 µg/kg, equivalent to a radioactive dose level of 500 µCi/kg. Necropsy was performed at three different time points after dosing, at 0.25, 0.5 and 1 hour(s) post-dose. At the time points 0.25 h and 1 h 3

animals were euthanised, and at the time point 0.5 h 2 animals; one animal was not evaluated due to a dosing error. Blood and tissues were analysed for radioactivity and the counts were corrected for radioisotope decay. The results are provided in **Table 13**. Most radioactivity was present at the injection site, followed by stomach. The lowest levels were found in the brain.

Table 13: Mean Concentrations of Radioactivity in Plasma and Tissues at Specified Times after a Single Subcutaneous Administration of 124I-Vosoritide to Male Sprague Dawley Rats (Group 1, 90 µg/kg); shown are ng Equivalents ^{124}I-BMN111/g

	0.25 hours		**0.5 hours**	**1 hour**	
Sample	**Mean**	**SD**	**Average**	**Mean**	**SD**
Plasma	101	33.4	140	191	1.34
Femur	27.9	8.07	48.9	49.0	7.01
Brain	11.1	1.60	19.6	18.5	1.25
Heart	45.8	12.4	65.4	61.0	8.29
Kidneys	202	63.0	259	112	10.2
Large intestine	26.4	4.06	34.7	37.0	5.11
Liver	34.6	4.18	51.8	39.8	9.90
Lungs	34.4	23.3	108	88.6	8.13
Muscle	25.4	6.35	41.1	42.5	4.94
Injection site	2740	2540	1120	1470	1010
Small intestine	25.3	3.51	41.6	54.5	14.7
Spleen	38.4	7.63	60.4	47.2	11.2
Stomach	35.8	14.1	98.8	236	91.1
Testicles	11.3	2.92	25.9	35.1	2.48
Tibia	27.7	8.38	45.8	45.9	4.17

Metabolism

Metabolism was not studied. Therefore, it is not known whether circulating biologically active fragments of vosoritide contribute to its effects.

Excretion

Excretion was not studied except for an *in-vitro* study with human live microsomes making excretion via CYP enzymes unlikely as expected for a peptide. A scavenger receptor, NPR-C, exists; furthermore, glomerular filtration of vosoritide is conceivable unless it is bound to plasma proteins (which is not known). Proteolytic degradation also will play a role in excretion.

DDI

In-vitro cytochrome P450 inhibition and induction studies showed that vosoritide is neither an inducer nor an inhibitor of CYP enzymes.

2.3.4. Toxicology

Single dose toxicity

Two single-dose studies were performed (**Table 14**).

Table 14: Overview of single-dose studies

Study ID	Species	Age	Doses [µg/kg]	Main results
BMN111-11-015	SD Rat; 10M, 10F	8 to 10 wk	0, 80, 240, 800 SC 0, 15 50, 150 IV	800 µg/kg SC: total alkaline phosphatase↑ Incidental finding: decrease in thymus ratio (relative to body weight) was observed in animals of the i.v. group. Thymus ratios relative to body weights decreased in a dose dependant fashion, reaching statistical significance at 150 µg/kg. Considered as incidental finding in the absence of change in mean thymus weight or mean thymus-to-brain weight ratio.
BMN111-11-006	Cynomolgus monkey; 3M, 3F	2 to 3.5 years	0, 20, 60, 200 SC 0, 2, 6, 20 IV	200 µg/kg IV: urine volume↑

Repeat dose toxicity

The applicant conducted seven repeated-dose studies (**Table 15**). Part of the studies were conducted in animals which were juvenile at least at the start of the study. In all repeated-dose studies, vosoritide's actions on bone were specially and extensively evaluated using several different methods. One rat study (BMN111-11-036) was conducted in rather old animals (8 to 9 months), assuming that bone effects are less pronounced in these slower growing animals so that other toxic effects would be easier to detect.

The studies in juvenile animals are also described in the respective subsection of the section on reproductive toxicology. The description here focuses on bone effects and provides comparison to the findings in adult animals. The pivotal toxicity studies in rats and monkeys (adult and juvenile) are presented in more detail hereafter.

Table 15: Overview of the repeated-dose studies

Study ID	Species	Age at initiation of dosing	Duration of study	Doses [µg/kg]	Main results
BMN111-11-029	SD Rat; 20M, 20F per group	7 to 8 wk	28d, 7d recovery	0, 50, 150, 500	50 µg/kg: increased growth plate thickness, infiltrate at injection site 150 µg/kg: as low dose plus swollen tarsal joints, degeneration/haemorrhage of growth plate 500 µg/kg: as mid dose plus reduced mobility of hind legs, femurs and tarsal joints abnormally shaped, disorganisation and reduced vascularisation of growth plate, periarticular fibromatous/myxomatous tissue alterations were partially reversible
BMN111-11-019	Cynomolgus monkey; 7M, 7F per control and high-dose group; 4M, 4F per low-and mid-dose group	2 to 3 years	28d, 7d recovery	0, 20, 90, 300	20 µg/kg: increased thickness of growth plate, increased thickness, necrosis and decreased vascular invasion of primary spongiosa 90 µg/kg: as low dose but more frequent and/or severe, disorganisation of the proliferative zone of the growth plate 300 µg/kg: as mid dose but more frequent and/or severe plus HR↑ post-dose alterations were partially reversible

BMN111-11-036	SD Rat; 20M, 20F per control and high-dose group; 15M, 15F per low-and mid-dose group	8 to 9 months	26 wk, 28 d recovery	0, 50, 150, 500	50 µg/kg: tail kinking, abnormal shape of bones, disorganisation of chondrocytes, growth plate dysplasia 150 µg/kg: as low dose but generally more frequent and/or severe plus altered ambulation, valgus, AP↑, sperm count↓ 500 µg/kg: as mid dose but generally more frequent and/or severe plus WBC↑, lymphocytes↑, serum phosphorus↑, lung weight (abs. and rel.)↑ alterations were partially reversible
BMN111-11-043	Cynomolgus monkey; 7M, 7F per control and high-dose group; 4M, 4F per low-and mid-dose group	4 to 5 years	44 wk, 13 wk recovery	0,25,75,250	75 µg/kg: limited use of hindlimbs (M), abnormal femoral heads and acetabula (M), bone length↑, cartilage erosion, presence of fibrocartilage, periarticular exostosis, thickened/fibrotic synovium, infiltrates at injection sites 250 µg/kg: as mid dose but generally more frequent and/or severe plus limited use of hindlimbs (M,F), abnormal femoral heads and acetabula (M,F), hypoactivity, HR↑ post-dose
BMN111-11-053	SD Rat, juvenile; 4M,4F per group	7 days	21 d	0, 90	non-GLP pilot study 90 µg/kg: body weight↓ (M), tail length↑, no difference vs. control in naso-anal length and femur length
BMN111-11-052	SD Rat, juvenile; 10M, 10F per main	7 days	26 wk, 6 wk recovery	0, 10, 30, 90	30 µg/kg: radiolucency of physes↑, BMC↓, BMD↓, changes in growth plates,

	study group; 16M, 16F per recovery group; 20M, 20F per reproductive group; 27M, 27F per TK group				joints and articular cartilage, serum phosphorus↑ 90 µg/kg: as mid dose but generally more frequent and/or severe plus altered use and appearance of hind paws and/or hindlimbs, crown-rump length↑, tail length↑, fractures, scoliosis, kyphosis, neutrophils↑, AP↑, creatinine↑
BMN111-11-035	Cynomolgus monkey, juvenile; 7M, 7F in control and high-dose group; 4M, 4F in low- and mid-dose group	2 to 3 years	26 wk, 28 d recovery	0, 20, 90, 300	Not all animals received the desired dose, probably due to uneven mixing of the test material during preparation of aliquots; variability was around 70% to 150% of the desired dose. 20 µg/kg: thickness of the proliferative and hypertrophic/calcified zones of physeal cartilage↑, height of growth plate↑, inflammation at injection sites 90 µg/kg: as low dose but generally more frequent and/or severe plus length of long bones↑, CTxII↑, disorganisation of chondrocyte columnar arrangement 300 µg/kg: as mid dose but generally more frequent and/or severe plus limited use of hips and/or decreased range of motion of hind legs, abnormal shape of femur head, degeneration of cartilage of acetabula alterations were partially reversible

Study BMN111-11-036: 26-Week Repeat-Dose Toxicity and Toxicokinetic Study by Subcutaneous Administration of BMN111 in Sprague Dawley Rats with a 28-Day Recovery

At study initiation, rats were at least 8 months of age to minimise vosoritide PD effects on bone.

Animals were assigned to 8 groups and were either given vehicle control or BMN111 at 50, 150 or 500 µg/kg daily for 26 weeks (183 doses total) as a single SC administration in the dorsal region. Main study animals were allocated to Groups 1 through 4 and toxicokinetics (TK) animals to Groups 5 through 8. Five animals/gender/group (main study dose groups 1-4) underwent a 28-day recovery period after the dosing phase.

	No. of Animals		**Dose Level (µg/kg)**
Group	**Male**	**Female**	
Toxicity Animals			
1 (Control)	20	20	0
2 (Low)	15	15	50
3 (Mid)	15	15	150
4 (High)	20	20	500
Toxicokinetic Animals			
5 (Control)	6	6	0
6 (Low)	9	9	50
7 (Mid)	9	9	150
8 (High	9	9	500

The dose volume was 1 mL/kg.

The following observations were made:

Mortality

In total, there were 17 unscheduled deaths. None was considered related to vosoritide.

Clinical observation

Administration of BMN111 resulted in limited use of hind legs (males given >150 µg/kg and females given 500 µg/kg), kinking tails (males given >50 µg/kg and females given >150 µg/kg), altered ambulation (males and females given >150 µg/kg) and valgus at joints (males given >150 µg/kg and females given 500 µg/kg). Severity of kinking tail was dose-dependent, with low-dose animals illustrating minor waved tail appearances and high-dose animals having corkscrew-like tail appearances.

Altered ambulation was observed mostly at the hind legs and was described as pigeon-toed with knees buckled inwards. Valgus was observed mostly at the front paws/legs and was categorised as outward angulations of carpal joints.

The observations persisted to the end of the recovery phase and correlated with macroscopic bone observations such as abnormal shapes of stifle and carpal joints, femur, and tail (coccygeal vertebra).

Body weight, food consumption

No test article-related alterations were observed.

DXA scan

No consistent changes in BMC or BMD were observed.

ADA

Antidrug antibodies (ADA) were measured in plasma by a bridging electrochemiluminescent (ECL) immunoassay.

Two sets of 5% pooled normal serum from the species to be tested (rat here) in Assay Buffer in duplicate and the Protein A-purified rabbit anti-C Type Natriuretic Peptide (CNP) IgG polyclonal antibody at three concentrations (250, 62.5, 31.3 ng/mL) were included on each plate as negative and positive controls, respectively. The positive control served to monitor the assay and had no clinical relevance. The negative control was used to establish a plate-specific cut point. The samples were screened at 1:20 and 1:100 in duplicate. Samples were evaluated relative to the cutpoint relative light units (RLU) of the plate, where the cutpoint RLU was defined as the mean RLU of the two sets of matrix controls plus the cutpoint constant established during validation.

Antibody results:

ADAs were detected in all dosage groups, the titre ranging from 20 to 2500. A clear dose-response relationship in ADA incidence or titre was not observed.

Due to the study design, and the fact the toxicokinetic concentration samples were not collected in these animals, the impact of positive ADA on the toxicokinetics of BMN111 could not be assessed.

The neutralising potential of ADA was not tested. Neutralising antibodies could mask effects of the test substance, but since exaggerated PD effects of vosoritide were observed in the toxicology studies, neutralising antibodies apparently are not considered as an issue.

Laboratory findings

A small increase in white blood cell count was observed in high-dose females.

Several serum chemistry parameters were mildly altered in mid-and high-dose animals, including cholesterol and triglycerides (lowered), inorganic phosphorus (higher) and alkaline phosphatase (higher). The latter two could be related to test article-related alterations of bone turnover.

The described changes were largely reversible at the end of the recovery period.

Macroscopic findings

Test article-related macroscopic findings related to the pharmacology of BMN111 were limited to bones, and were present in joint (stifle and carpal joints); tail (coccygeal vertebra); sternum; femur; and bone (tibia; thoracic vertebra; and spinal vertebrae, entire). These macroscopic findings generally correlated microscopically with increased bone growth plate thickness and/or growth plate dysplasia

Table 16: Incidence of Test Article-Related Macroscopic Findings - Dosing Phase - Scheduled and Unscheduled Necropsies

Sex	**Males**				**Females**			
BMN111 µg/kg	0	50	150	500	0	50	150	500
No. Animals Examined	15	15	15	15	15	15	15	15
Joint, Other								
Abnormal Shape	0	3	11	13	0	0	6	14
Tail								
Abnormal Shape	0	13	12	14	0	0	9	11
Bone, Other								
Abnormal Shape	0	3	6	6	0	0	0	2
Femur Bone								
Abnormal Shape	0	0	5	3	0	0	0	2
Sternum Bone								
Abnormal Shape	0	0	0	2	0	0	2	3

Microscopic findings

Test article-related microscopic findings were limited to expected pharmacologic targets for bone, and included femur; sternum; joint (stifle and/or carpal joint bones); bone (tibia; thoracic vertebra; and/or spinal vertebrae, entire); and tail (coccygeal vertebra). Males given >50 µg/kg and females given >150 µg/kg were affected. The findings included increased growth plate thickness and/or growth plate dysplasia (minimal to moderate severity) of bone. In the long bones (femur; tibia; and less frequently, radius), these changes often resulted in an abnormal angle of the distal bone that correlated to the in-life observations of valgus deformity, swollen limbs, limited use, and altered ambulation.

Increased growth plate thickness was characterised by increased number and disorganisation of chondrocytes in the growth plates of affected bones [femur, tibia, ulna, radius, vertebrae (tail, spine, and thoracic), and sternum]. The bones examined varied in individual animals depending on the depth of the section in areas sampled. In contrast to the well-organised, straight columns of chondrocytes in growth plates of control animals, affected growth plates were thicker with irregular contours and comprised of varying sized oval to circular clusters of chondrocytes, sometimes separated by a cellular cartilage matrix. The growth plate thickening was primarily characterised by increased layers of chondrocytes in the zones of multiplication, maturation, and hypertrophy.

Growth plate dysplasia was characterised by disorganised chondrocytes forming variably sized irregular-shaped aggregates of cells, often below the original growth plate, in the shaft of long bones, forming a continuous band of cartilage across the subphyseal bone, increases in endochondral ossification, increased subphyseal trabecular bone, and increased numbers of retained cartilage cores in subphyseal trabecular bone.

Bone growth

Bone growth data were not reported.

Vaginal cytology

No test article-related alterations were noted in the oestrous cycle.

Spermatogenesis

Administration of BMN111 to male rats at 150 or 500 µg/kg caused a significant decrease in sperm count at the dosing phase euthanasia. For details see section on reproductive toxicity.

TK

TK parameters for Day 176 are provided in **Table 17**. In the high-dose group, Cmax and AUC were markedly higher in males than in females. This was associated with strong increase in dose-normalised AUC in high-dose males. The reason for this observation is unclear. At the other study days where TK data were obtained (Day 1 and Day 85) AUC and Cmax in general were markedly higher in males than in females.

Table 17: PK Parameters in Plasma Collected from Rats Following Daily Subcutaneous Injection of Vosoritide; Day 176

Dose Level (µg/kg/ day)	Gender	Cmax (pg/mL)	DN Cmax	Tmax (min)	AUC_{0-t} (pg•min/ mL)	AUC_{0-180m} (pg•min/ mL)	DN AUC_{0-180m}	t1/2 (min)	CL/F (mL/min/kg)	Vz/F (mL/kg)
50	M	19830	397	15.0	592675	592675	11854	27.6	83.4	3318
	F	16800	336	15.0	635775	635775	12716	72.3	73.6	7675
	Comb.	18315	366	15.0	614401	614401	12288	43.8	79.2	4997
150	M	38067	254	15.0	1436808	1436808	9579	NC	NC	NC
	F	27817	185	15.0	1317208	1317208	8781	21.7	113	3550
	Comb.	32942	220	15.0	1377008	1377008	9180	NC	NC	NC
500	M	495667	991	15.0	25410983	25410983	50822	NC	NC	NC
	F	163333	327	5.00	8715225	8715225	17430	24.4	56.9	2000
	Comb.	356300	713	15.0	18369410	18369410	36739	NC	NC	NC

DN, dose normalised; CL/F, Apparent SC Clearance; Vz/F, Apparent SC Volume of Distribution

Study BMN111-11-043: 44-Week Repeat-Dose Toxicity and Toxicokinetic Study Following Daily Subcutaneous Administration of BMN111 in Cynomolgus Monkeys with a 13-Week Recovery

Male and female cynomolgus monkeys of Chinese origin (Covance Research Products Inc., Alice, TX, USA) were 4 to 5 years old with body weights ranging from 2.6 to 5.4 kg for males and 2.8 to 4.1 kg for females at study initiation. Animals were randomly assigned to four groups and were dosed with vehicle or 25, 75, or 250 µg/kg vosoritide once daily for 44 weeks by subcutaneous injection in the interscapular region in four rotating sites, with a fifth naïve site used for the final dose. The following observations were made:

Clinical observations

In the 250 µg/kg group, 6 animals (5M, 1F) and in the 75 µg/kg group 1 male displayed limited use of hindlimbs, beginning at Day 121 (around 20 weeks) of dosing. According to the applicant, this mainly resulted from decreased range of motion of the hip joint.

Body weights

No vosoritide-related effects were observed

Blood pressure, ECG

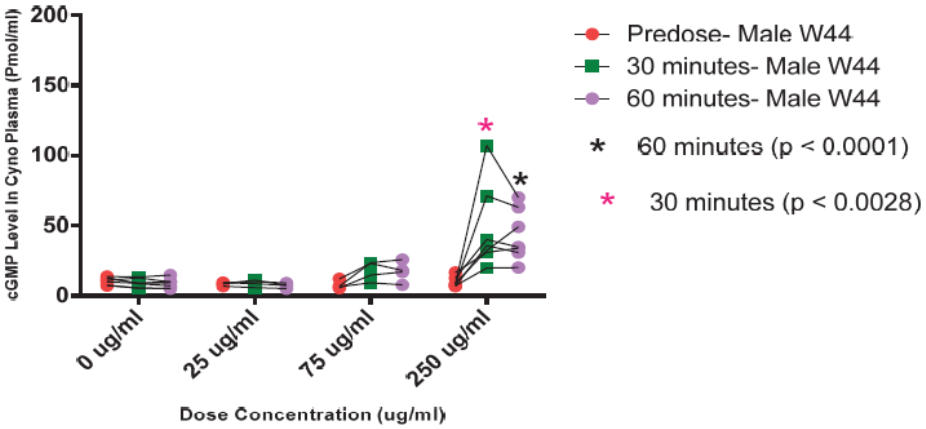
No vosoritide-related effects on blood pressure were observed

Heart rate (HR) was derived from ECG readings. HR was significantly higher post-dose compared to controls in the high-dose (250 µg/kg) group. HR excursion peaked on Day 305 with 155 bpm in mean in the high-dose group (males) vs. 122 bpm (mean) in the control group (males) and 193 bpm vs. 146 bpm in females.

cGMP levels

Levels of cGMP were determined in the blood plasma of the study animals by a commercial cGMP Enzyme Immunoassyay (EIA). The results are shown in Figure 11. In the mid-and high-dose group, a clear and dose-dependent cGMP increase over time is visible.

Figure 11: Levels of cGMP



ADA

The method of antibody detection was the same as used in Study BMN111-11-036.

No anti-drug antibodies (ADA) were detected in control animals. The number of ADA-positive vosoritide-treated animals increased during the study, but there was no dose-dependence of ADA incidence. At study end, 100%, 87.5% and 78.6% of the animals were ADA positive in the 25, 75 and 250 µ/kg group, respectively.

The neutralising potential of the antibodies was not tested.

Laboratory findings

There were no relevant haematology, coagulation or clinical chemistry findings.

Macroscopic findings

Except for bone, there were only few macroscopic findings in individual animals which can be considered incidental. Dose dependent bone changes mainly were noted in the femur (e.g. raised or depressed area, fracture) but also in the pelvis (shallow acetabulum), tibia, patella, humerus, scapula and ulna (depressed area and others). Depressed area can mean cartilage erosion.

Microscopic findings

In case of bones and joints, the macroscopic abnormalities were further examined microscopically.

Beside of incidental findings in individual animals, vosoritide-related changes were observed at the injection sites and in bones and joints; the latter included e.g. erosion of articular cartilage. Increased thickness of growth plate was noted in animals having received 250 µg/kg with more closely spaced chondrocyte columns, increased layers of chondrocytes and hypertrophic chondrocytes.

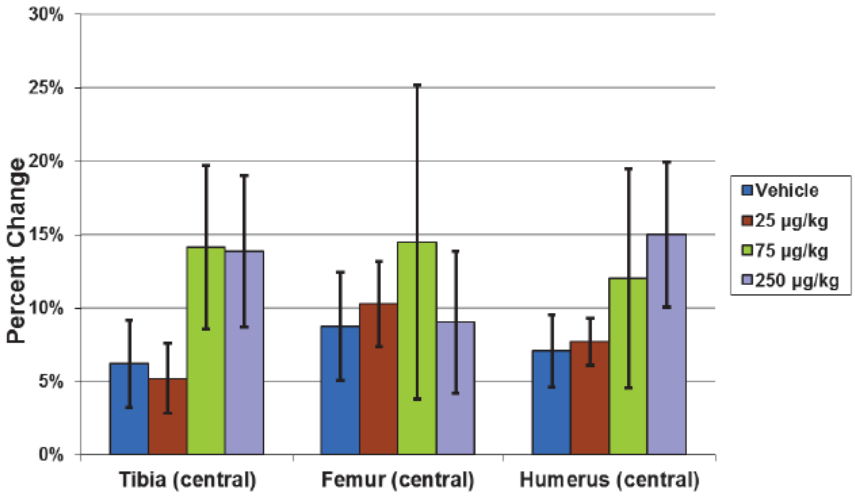
At the injection sites in the subcutis, a dose-dependent increase of perivascular infiltrates and fibrosis was observed.

Bone growth

Bone growth was still evident in these older animals. Mid and high dose vosoritide increased the length of long bones.

The per cent change in bone length (tibia, femur and humerus as depicted below) was up to around 15 in mid- or high-dose animals compared to around 5% to 10% in vehicle controls.

Figure 12: Percent change in bone length, Week 44 vs. predose



DXA

There were no vosoritide-related effects on BMC or BMD.

Serum bone/cartilage markers

The following markers were investigated:

- N-terminal propeptide of Type I collagen (PINP)
- C-telopeptide of collagen Type II (CTx II)
- C-telopeptide of collagen Type I (CTx I)
- Osteocalcin (OC)
- N-telopeptide (NTx)
- Bone-specific alkaline phosphatase (NTx)

Vosoritide-related changes were only observed for CTx II, a cartilage degradation marker. Levels were slightly increased compared to control during treatment in the mid- and high-dose group. Statistical significance was reached in high-dose females. At the end of the recovery period, CTx II levels remained increased in two high-dose females.

Biomechanical strength

Femora and L3 vertebrae were tested for mechanical stability (maximum load, stiffness, energy, ultimate strength [femora] or stress [vertebra], elastic modulus and toughness). No consistent and dose-dependent effects of vosoritide were observed.

Male reproductive assessment

No relevant abnormalities were detected.

TK

The obtained TK parameters are provided in **Table 18** for Week 12. Exposure was often but not always higher in males than in females. AUC and Cmax were generally higher in Week 12 than at Day 2. Variability (SD) was rather high. The increase of Cmax and AUC with dose was markedly higher than proportional.

Table 18: Toxicokinetic Parameters for Vosoritide in Monkey Plasma, Week 12

Dose Level			**Cmax**	**DN Cmax**	**Tmax**	**AUC_{0-6h}**	**DN AUC 0-6h**	**AUC_{0-t}**	**AR AUC 0-6h**	**t1/2**	**CL/F**	**Vz/F**
(µg/kg)	**Sex**		**(pg/mL)**		**(hr)**	**(pg·hr/mL)**		**(pg·hr/mL)**		**(hr)**	**(mL/hr/kg)**	**(mL/kg)**
25	M	Mean	1690	67.6	0.167	NA	NA	NA	NA	NA	NA	NA
		SD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	0	0	0	0	0	0	0
	F	Mean	2040	81.5	0.139	1270	50.7	1060	NA	NA	NA	NA
		SD	1340	53.5	0.0964	NA	NA	NA	NA	NA	NA	NA
		N	3	3	3	1	1	1	0	0	0	0
	MF	Mean	1900	76.0	0.150	1270	50.7	1060	NA	NA	NA	NA
		SD	1120	45.0	0.0915	NA	NA	NA	NA	NA	NA	NA
		N	5	5	5	1	1	1	0	0	0	0
75	M	Mean	30600	408	0.333	26500	353	24000	2.11	0.621	7700	7240
		SD	29300	391	0.144	20500	273	19200	2.10	NA	NA	NA
		N	3	3	3	3	3	3	3	2	2	2
	F	Mean	9160	122	0.208	11500	153	10600	3.37	0.780	7430	8870
		SD	5220	69.6	0.0835	11500	153	11400	1.33	0.266	4730	8070
		N	4	4	4	4	4	4	3	3	3	3
	MF	Mean	18300	245	0.262	17900	239	16300	2.74	0.716	7540	8220
		SD	20800	277	0.122	16400	219	15500	1.71	0.210	4810	6740
		N	7	7	7	7	7	7	6	5	5	5
250	M	Mean	99600	398	0.357	173000	694	171000	2.09	0.711	5620	5960
		SD	77500	310	0.283	194000	774	195000	1.30	0.299	8040	10700

		N	7	7	7	7	7	7	7	7	7	7
	F	Mean	274000	1100	0.286	312000	1250	311000	3.85	0.725	1340	1190
		SD	217000	867	0.0945	224000	896	225000	2.42	0.206	979	666
		N	7	7	7	7	7	7	7	7	7	7
	MF	Mean	187000	748	0.321	243000	972	241000	2.97	0.718	3480	3570
		SD	181000	723	0.206	214000	854	215000	2.08	0.247	5930	7700
		N	14	14	14	14	14	14	14	14	14	14

Study BMN111-11-052: A 26-week Subcutaneous Injection Toxicity Study of BMN111 in Juvenile Rats Followed by a 6-week Recovery

Rats were administered BMN111 from Days 7 to 188 post-partum (young adult) followed by a 6-week recovery period. In addition, the toxicokinetic characteristics of BMN111 were determined.

Table 19: Study Design: Toxicity and TK animals (Subset A, B, D)

Group	Compound	Dose µg/kg	Dosing Phase (Subset Ad): No. and Gender per Group	Recovery Phase Animals (Subset Bd): No. and Gender per Group	Toxicokinetic and ADA Phase Animals (Subset Dd): No. and Gender per Group
1	Vehicle	0	10M+10F	16M+16F	9M+9F
2	BMN111	10	10M+10F	16M+16F	27M+27F
3	BMN111	30	10M+10F	16M+16F	27M+27F
4	BMN111	90	10M+10F	16M+16F	27M+27F

Table 20: Study Design: Reproductive Phase animals (Subset C)

Group	Compound	Dose µg/kgc	No. and Gender per Group
1	Vehicle	0	20M+20F
2	BMN111	10	20M+20F
3	BMN111	30	20M+20F
4	BMN111	90	20M+20F

Due to the unexpected lack of pharmacologic effects noted at the high dose during the first 13 weeks of treatment, evaluation of the animals in respect to body length and food consumption measurements as well as clinical observation were transiently stopped. *In vivo* activities started again once the first pharmacologic effects were noted, approximately one week later. No relevant findings were made in the pre-weaning period. The observations in the post-weaning period are presented hereafter.

Mortality

There were several unscheduled deaths (mainly animals found dead) during the study, but none was considered related to treatment with BMN111 by the applicant.

Clinical observations

The clinical observations made predominantly were related to abnormal motoric functions as tabulated below. Motoric impairment only occurred in the high-dose group and consisted among others of abnormal hind paws, abnormal gait and hunched posture. Males were more frequently affected than females.

Table 21: Summary of Treatment-Related Clinical Observations – Main and Recovery Animals

Daily dose (µg/kg)	**0**		**10**		**30**		**90**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Swollen firm hind paws/limbs							22	9
Day pp from - to							84-231	98-231
Abnormal hindpaws							23	8
Day pp from - to							88-231	126-231
Abnormal gait							21	6
day pp from - to							91-231	105-231
Stiff hindpaws							24	14
Day pp from - to							91-231	98-231
Limited usage hindlimbs							13	3
Day pp from - to							98-231	140-231
Splayed foot							17	2
Day pp from - to							98-224	126-175
Skin red forepaws/forelimb or hindpaws							3	3
Day pp from - to							154-231	140-231
							8	4
Backbone Prominent							119-231	126-231
Day pp from - to								
Thin			-	1	-	3	12	12
Day pp from - to				231-231		140-231	112-231	119-231
Hunched posture							14	9
Day pp from - to							126-231	147-231
Tail bent							16	1
Day pp from - to							120-231	210-231

Body weight, food consumption

In high-dose males, reduced body weight gain and reduced food consumption were observed. No clear effects were seen in females.

Body length

Body (crown-rump) and tail length was increased in high-dose animals compared to vehicle controls, Figure 13, Figure 14.

Figure13: Summary of Crown to Rump Length Measurements – Males (left) and Females (right)

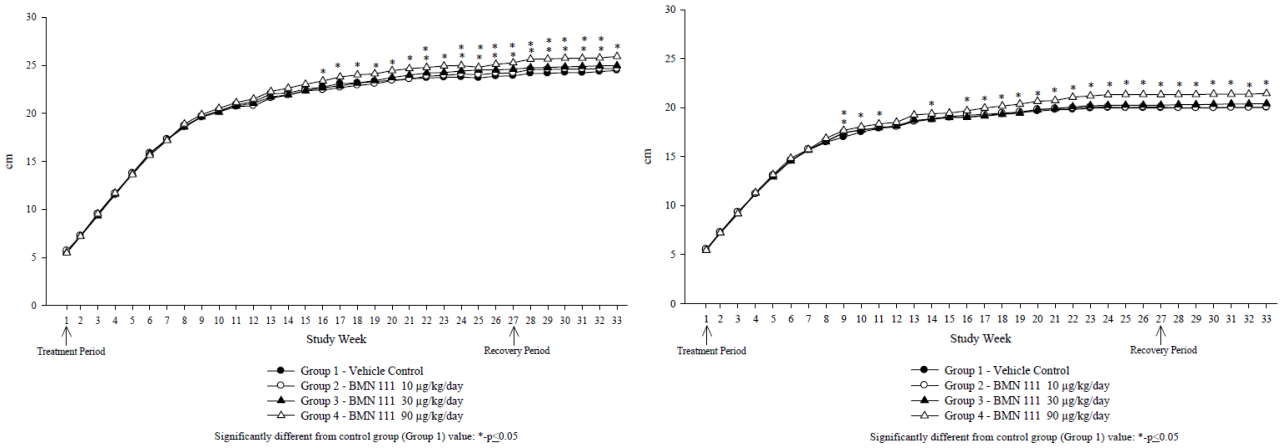
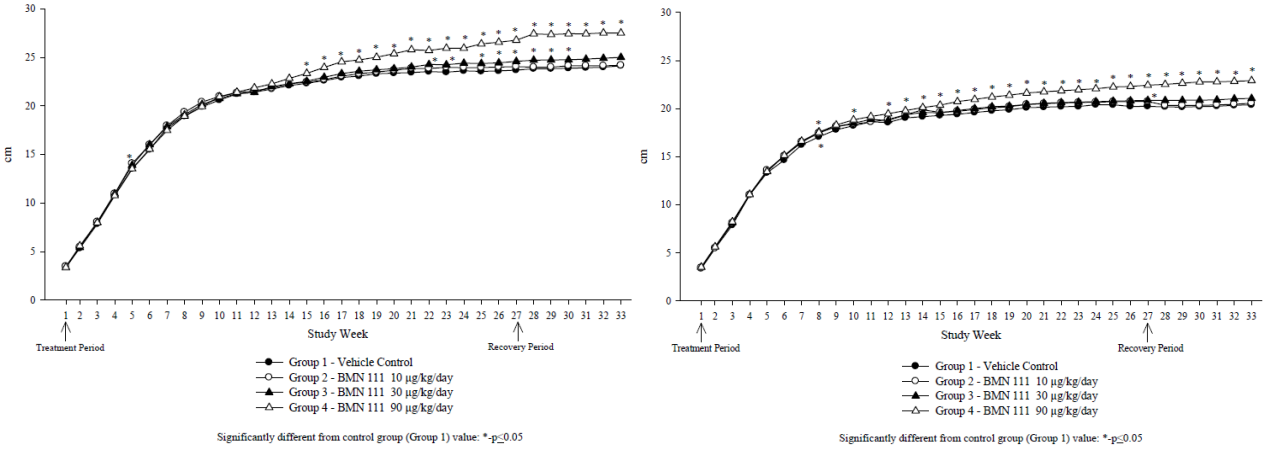


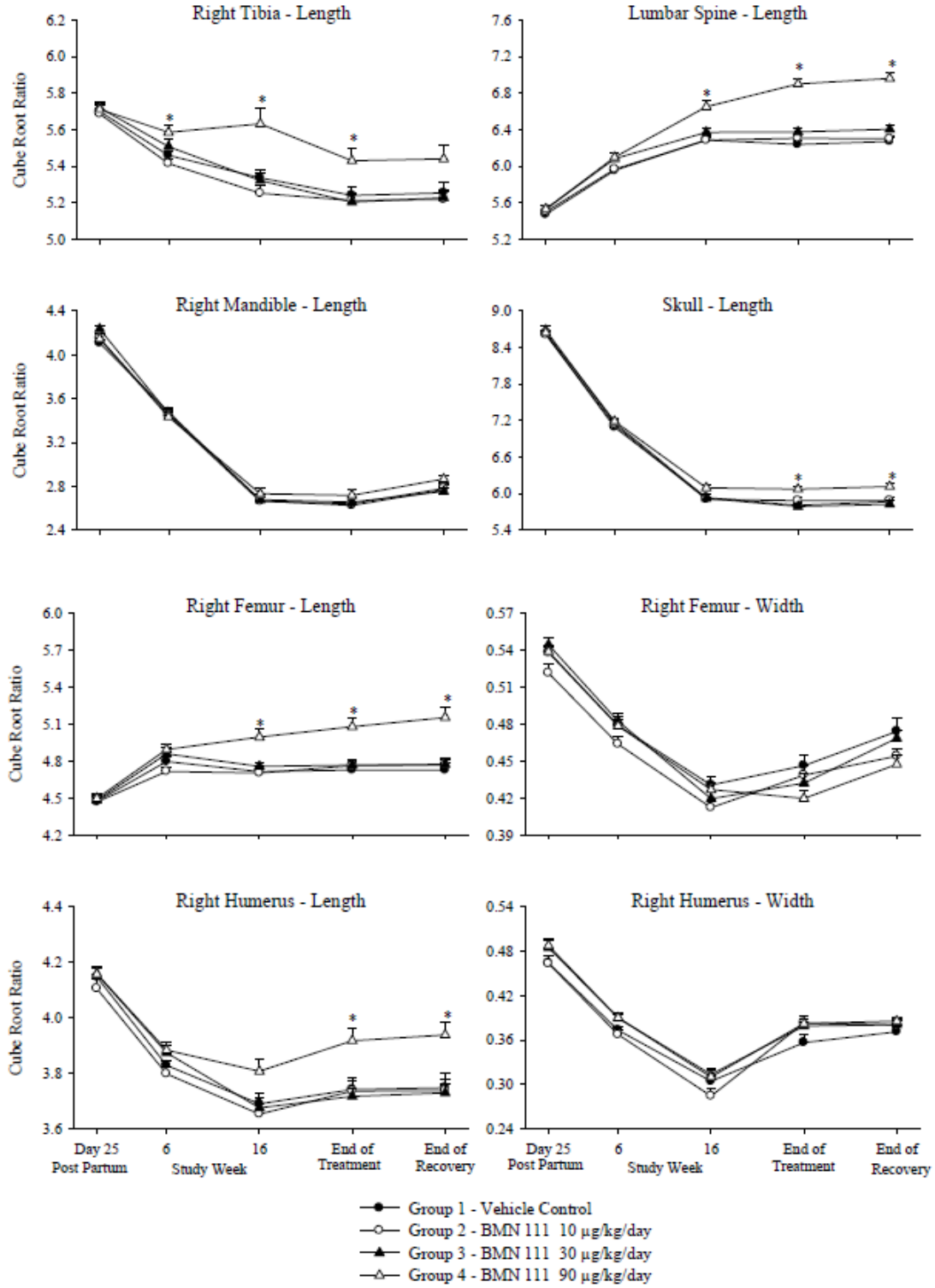
Figure14: Summary of Tail Length Measurements – Males (left) and Females (right)



Bone length

High-dose vosoritide increased the length of long bones and of the lumbar spine over time compared to vehicle controls. Width of the bone was not relevantly affected. Figure 15shows the results for male animals. The findings in females were similar but slightly less pronounced in general.

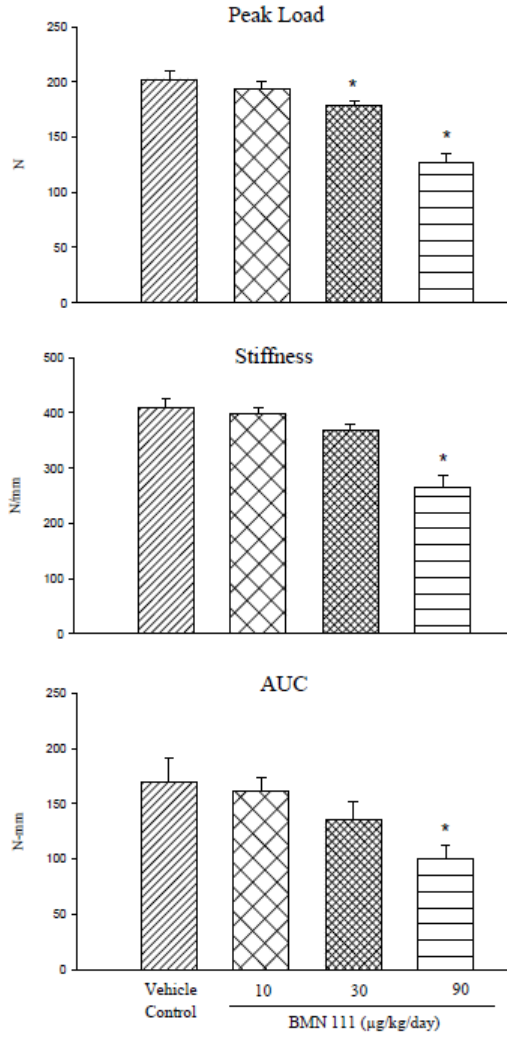
Figure 4: Radiographic Bone Measurements - Cube Root Ratio of BW - Males - Mean (SEM)



Biomechanical testing

As shown in **Figure *16***, there was a dose-dependent decrease in some parameters of mechanical stability of the femur in males, reaching statistical significance in the high-dose group (for peak load also in the mid-dose group). The effects in females were similar albeit slightly less pronounced.

Figure 5: Femur 3-point Bending - Treatment Period - Males - Mean (SEM); AUC means Area under the curve of force vs. distance (N [Newton] vs. mm).

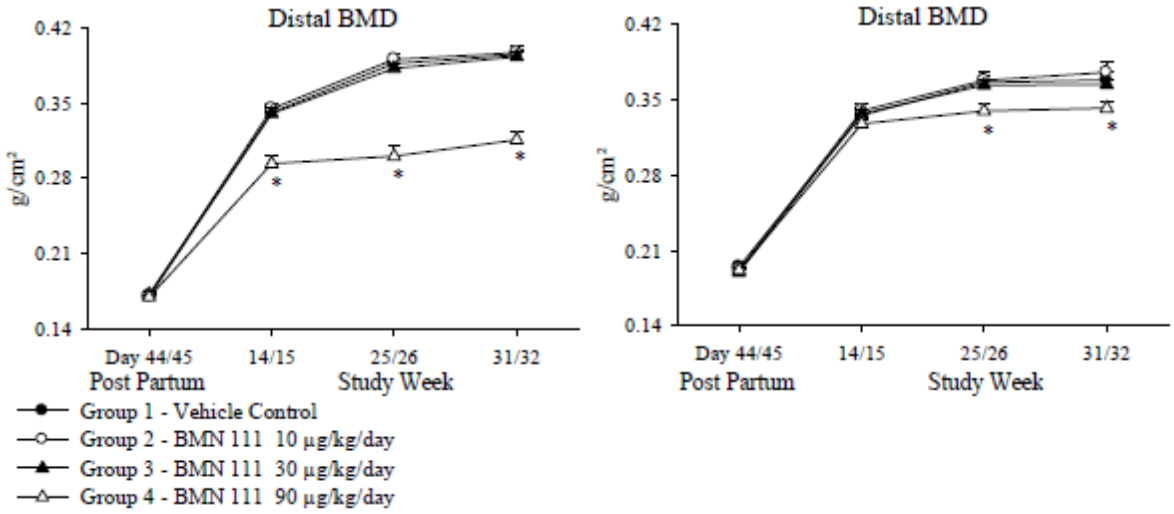


DXA

Starting at Study Week 14/15, males and females treated with BMN111 at 90 µg/kg/day were noted with decreased BMC and BMD at the femur and lumbar spine, compared to controls. In the high-dose males, femur BMD decreased by up to 19%.

Figure 17 shows the BMD results for the distal femur where the effects were most pronounced.

Figure 6: Bone Densitometry Values (Distal BMD, Mean [SEM]) by DXA - Femur - Males (left), Females (right)



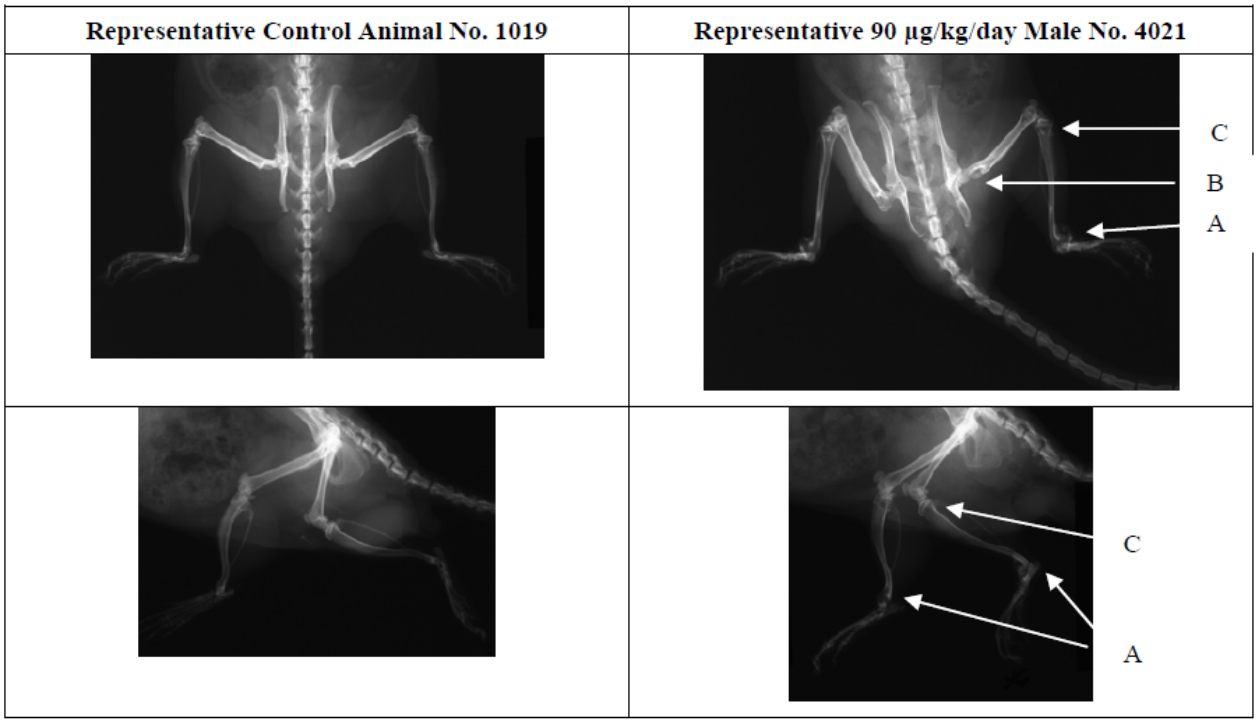
Serum bone/cartilage markers

PINP was decreased in high-dose females and in mid- and high-dose males during treatment. TRACP-5b were also increased during treatment, most pronounced in the high-dose group. CTx-II were increased in high-dose males.

Bone radiography

X-ray of the hind limbs revealed pathological changes in the distal tibia and proximal femur, mainly in high-dose animals. The changes included increased radiolucency, displacement of the physis and fractures (**Figure *18***, **Table *22***).

Figure 7: Selected Radiographs - Study Week 26



A: Distal tibia: Increased radiolucency, physis and metaphysis, with periosteal reaction and displacement/fracture; B Proximal Femur: Increased radiolucency, physis and metaphysis; C: Distal femur and proximal tibia: Increased radiolucency, metaphysis.

Table 22: Summary of Radiographic Findings - Treatment Period (Study Week 16)

Sex	Males				Female			
Dose	**0**	**10**	**30**	**90**	**0**	**10**	**30**	**90**
No. Animals	**26**	**26**	**26**	**24**	**26**	**23**	**25**	**25**
Calcaneum Proximal								
Increased radiolucency, metaphysis and/or	—	—	—	22	—	—	—	6
Femur Distal								
Increased radiolucency, metaphysis (R and/or L)	—	—	—	14	—	—	—	—
Femur Proximal								
Increased radiolucency, metaphysis and/or physis and/or head, and/or periosteal reaction and/or displacement	—	—	6	24	—	—	6	20

Laboratory findings

In 3 out of eight high-dose females, a small increase in neutrophil count was observed as compared to control. No relevant changes in coagulation parameters were observed. Serum phosphorus and alkaline phosphatase were slightly increased in mid- and high-dose males. The latter changes can be related to altered skeletal growth.

ADA

The method for detecting binding antibodies is described in Study BMN111-11-036; neutralising potential of the ADA was not determined.

ADA were observed at all three dose levels 10, 30, and 90 µg/kg. There were 0 of 12 (0%) ADA positive responses detected in vehicle treated rats (Group 1) on Days 188 and 230. The incidence of positive ADA responses on Day 188 in all three treatment groups was similar. For Group 2 (10 µg/kg), 12 out of 18 (67%) tested positive for ADA. For Group 3 (30 µg/kg), 10 out of 18 (56%) tested positive for ADA. For Group 4 (90 µg/kg), 11 out of 18 (61%) tested positive for ADA. On Day 188, the mean and median titres increased with increase in dose level. The mean/median titres were 138/20, 767/100, and 1368/300 for Groups 2, 3, and 4, respectively.

Macroscopic findings

Macroscopic, vosoritide-related findings were limited to bones and joints and were mainly found in high-dose males. Findings included thickening of acetabulum, raised or depressed areas and fractures of the femur and raised areas on the tibia.

Microscopic findings

Microscopically, vosoritide-related findings in animals euthanised on PND 189 were limited to skeletal structures attributed to exaggerated pharmacology of vosoritide in animals treated with ≥ 30 μg/kg, consistent with clinical, macroscopic, and radiologic findings. The bones affected were those of the appendicular skeleton (posterior and anterior), axial bones, and joints. The changes primarily affected the growth plate and associated metaphysis. Joints and articular cartilage were also secondarily affected. There were few gender differences noted. The changes consisted of enlargement and/or persistence of the physes of numerous bones related to pharmacologic effects on chondrocyte proliferation, degeneration and necrosis in the femoral head and neck and acetabulum, disorganised cartilage and bone growth in the tibia, and articular/periarticular inflammation of the tibiotarsal joint. These findings were described as degenerative joint disease or degenerative osteoarthritis and were attributed to exaggerated growth causing mechanical dysfunction and possibly vascular impediments leading to loss of tissue integrity. There were no microscopic findings in soft tissue structures related to treatment with vosoritide.

Behavioural Performance

The following tests were performed: Functional observation battery, motor activity, auditory startle habituation and Cincinnati water maze.

Treatment-related changes in functional observational battery and decreased motor activity were noted in the high-dose group. The changes in functional observation primarily affected the neuromuscular system domain (gait function, locomotor activity, arousal, body position, rearing and toe pinch). These as well as the reduced motor activity were attributable to the clinical conditions of the hind limbs/hind paws of these animals. In the water maze, swimming abilities were impaired, but learning was not affected.

Study BMN111-11-035: 26-Week Repeat-Dose Toxicity and Toxicokinetic Study of Subcutaneous Administration of BMN111 in Cynomolgus Monkeys with a 28-Day Recovery

Juvenile male and female cynomolgus monkeys (Macaca fascicularis) of Chinese origin were assigned to four groups and administered vehicle control or test article as indicated in the following table. At study initiation, the animals were 2-3 years of age, weighted 2.1-2.7 kg for the males and 2.1-2.9 kg for the females and were growing as assessed by the presence of open growth plates during the conduct of the study.

	No. of Animals		Dose Level	Dose Concentration
Group	**Male**	**Female**	**(µg/kg)**	**(µg/mL)**
1 (Control)e	7	7	0	0
2 (Low)	4	4	20	20
3 (Mid)	4	4	90	90
4 (High)	7	7	300	300

Dose analysis

All Day 141 female samples (when Lot No. CM050611-FBDS was used as reference standard for formulations prepared using Lot No. 2011-111-11-101711) had mean concentrations ranging between 143.3 and 146.5%. Analytical standards prepared using Lot No. CM050611-FBDS were injected as samples and quantified against analytical standards prepared using Lot No. 2011-111-11-101711. Results showed that CM050611-FBDS standards were approximately 70% of targeted concentrations when Lot No. 2011-111-11-101711 was used as reference standard, explaining the high recovery at this interval. Additionally, all Day 176 male and female samples (when Lot No. 2011-111-11-101711 was used as reference standard for formulations prepared using the same lot) had mean concentrations ranged between 66.3 to 69.8%. Re-analysed backup samples for Day 176 female samples showed similar results. The reanalysis and OOS investigations did not yield any definitive cause of the low recoveries. A possible cause for these OOS observations could be the uneven mixing of the test material after thawing during test material aliquot procedures. The presence of drug-related clinical signs during the study and the toxicokinetic analysis indicated that the animals may have received sufficient doses but possibly variable.

Mortality

All animals survived to their scheduled necropsy at the end of the dosing or recovery phase

Clinical observations

BMN111-related clinical signs included limited use of hips and/or decreased range of motion of hind legs in animals given 300 µg/kg (4M, 1F).

Decreased range of motion appeared as early as Day 88 of the dosing phase and limited use of hips appeared later in the dosing phase (after 21 weeks of dosing) and persisted through the end of recovery phase, or appeared with a delayed occurrence during the recovery phase. The four males with test article-related clinical signs had higher (approximately 2- to 15-fold) Cmax levels on Day 85 when compared with the other three males in the same group. The one high dose female with limited use of hips had similar Cmax to the rest of its group. Bilateral abnormal femoral heads were observed macroscopically in two animals at necropsy, corresponding to the clinical sign of limited use of hips.

Body weight, food consumption

No BMN111-related alterations in body weight and body weight change were noted for animals given up to 300 µg/kg. Qualitatively low or no food consumption was noted periodically and had no impact on weight gain.

Blood pressure, ECG

No BMN111-related alterations in blood pressure were noted for animals given up to 300 µg/kg when evaluated 30 minutes to 1.5 hours post dose using a tail cuff on unanesthetised animals.

Incidental, statistically significant QRS duration values were noted. The magnitudes of the differences in QRS duration relative to the control group were minimal. The statistical findings in QRS duration were inconsistent between sex and across collection intervals in the males. Therefore, the alterations in QRS duration were considered incidental by the applicant and not attributed to BMN111.

A dose-dependent increase in heart rate after dosing, lasting around 3 to 4 hours, was observed [table at p1065 of study report].

ADA

The method for detecting binding antibodies is described in Study BMN111-11-036; neutralising potential of the ADA obviously was not determined.

At Week 13, ADA incidence was 7/8 (88%), 2/8 (25%), and 5/14 (36%) for the low-, mid and high-dose group, respectively. All animals with positive ADA titres on Week 13 remained positive at Week 26.

Laboratory findings

There were few statistically significant changes in the haematology, clinical chemistry, and urinalysis data were of minimal magnitude, occurred during a predose interval, were not dose-related, likely represented individual variation, and/or were not different from the range of control or baseline values. Therefore, these changes were not considered toxicologically important by the applicant.

DXA

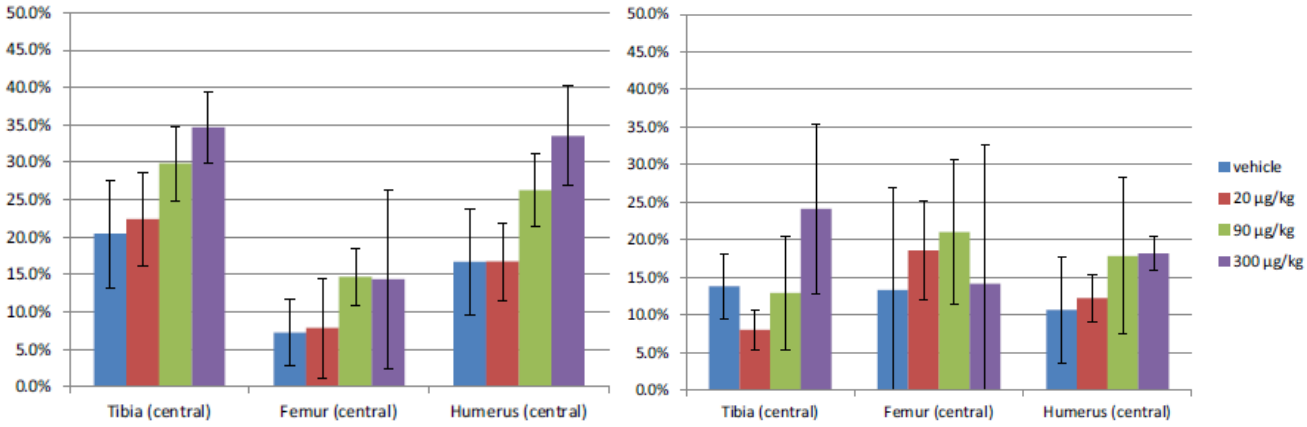
No relevant vosoritide-related changes in BMC and BMD were observed.

Bone growth

Increase in length over time for tibia, femur and humerus was observed. Although the growth rates were rather variable and the bone lengths at baseline often differed between groups, a more pronounced increase in bone length could be seen in general in the mid- and high-dose groups compared to vehicle control.

The per cent change in growth velocity from baseline to Week 13 and from Week 13 to Week 25 is depicted in the following figure. From baseline to Week 13, mid- and high-dose vosoritide numerically increased growth velocity of tibia, femur and humerus compared to vehicle control; statistical significance obviously was not reached, but this can be related to the low number of animals. From Week 13 to Week 25 the vosoritide effect on bone growth was less pronounced and more variable (longer error bars).

Figure 8: Percent Changes in Growth Velocity – Males - Week 13 vs. Pre-Dose (left); Week 25 vs. Week 13 (right)



Mechanical strength of the bone

Three-point bend test of the femur and compression of lumbar vertebra LV3 were performed. There were only small and inconsistent changes in the mechanical bone parameters (maximum load, stiffness, energy, stress, elastic modulus and toughness) with vosoritide treatment.

Serum bone/cartilage markers

The bone formation markers PINP, osteocalcin and alkaline phosphatase (bone-specific) displayed small changes in both directions (increase or decrease) in the different dose groups and at different time points. The same is true for the bone resorption markers CTx I and NTx and for the marker of cartilage degeneration, CTx II. Thus, taken together, there were no clear and consistent effects of vosoritide on bone turnover.

Macroscopic observations

Vosoritide-related macroscopic findings were limited to bones. The following observations were made: The shape of the proximal end of the femur (femoral head) was bilaterally abnormal in two animals of the high-dose group.

Microscopic observations

Vosoritide-related microscopic findings were limited to bones.

There were no vosoritide-related changes in the L1 to L4 vertebral length, foramen magnum dimensions, or skull measurements. At the end of the dosing phase, daily treatment with vosoritide resulted in dose-dependent increases in the area and height of proximal femur growth plate in all treatment groups when compared with the controls. Microscopic examination showed increased thickness of the proliferative and hypertrophic/calcified zones of physeal cartilage that was generally minimal to mild in all treatment groups. Disorganised chondrocyte columnar arrange in the proliferative zone was also observed in males and females treated with ≥90 µg/kg. Increased thickness of the primary spongiosa was also seen in all treatment groups. These findings had resolved in females by the end of the recovery period but were still present in 2/3 males treated with 300 µg/kg. These findings are consistent with pharmacologic effects of vosoritide on skeletal growth and previous observations in this species.

Genotoxicity

Vosoritide is a peptide containing only natural amino acids. In concordance with ICHS6 genotoxicity studies are not considered useful for natural peptides.

Carcinogenicity

No carcinogenicity studies have been conducted with vosoritide.

Reproduction Toxicity

Reproductive toxicity

In line with the initially proposed indication „treatment of achondroplasia in patients 2 years of age and *older and whose epiphyses are not closed*", a full range of reproductive and juvenile toxicity studies were conducted under consideration of the respective ICH guidelines. All pivotal studies were conducted in compliance with GLP regulations.

Rats were used for the assessment of possible vosoritide induced adverse effects on male and female fertility, as well as on prenatal and postnatal development. Rabbits served as second species for detection of possible drug-related impacts on prenatal development. Juvenile toxicity studies were performed in rats and cynomolgus monkeys covering the human age range from birth to young adulthood.

To address **fertility and early development**, a rat study was conducted. Male and female rats were treated daily prior to cohabitation for mating (28 days for males and 15 days for females) with 0, 90, 270, or 540 µg/kg/day vosoritide. Seminal vesicle weights with and without fluid were significantly decreased relative to the vehicle group in all test-article groups in a dose-response fashion. Slightly increased time to mate and significant decreases in sperm count and density were observed at least at 540 µg/kg, but these findings were not considered adverse by the study director due to lack of any impact on the fertility index.

Embryofetal development (EFD) studies were conducted in rats and rabbits, respectively. Vosoritide did not induce maternal toxicity or affect prenatal development in either species. In both studies, the maternal and developmental NOAELs were set at the top doses of 540 µg/kg/day in rats and 240 µg/kg/d in rabbits, respectively. This is agreed.

Dosages for the pivotal rabbit EFD study were selected on the results of the DRF study. In the DRF study, the high dose of 240 µg/kg/day affected fetal viability and fetal body weights. Such effects were not seen in the pivotal study despite identical doses as in the DRF study were administered. However, this is not a concern, as exposures were far above the human exposure.

In rats, **placenta transfer** of vosoritide appears to be minimal if at all, the concentrations of vosoritide on lactation day 14 in the milk were less than 5% of plasma.

A study of pre- and postnatal development revealed that treatment of pregnant rats did not adversely affect gestation, natural delivery, and maternal behaviour during lactation.

Prenatal development and postnatal development including assessment of learning and memory as well as reproductive capacity, was not affected by treatment of dams up to the highest dose tested.

In dams, mean plasma concentrations at 30 minutes post-dose on lactation day 14, increased with increasing dose from 90 to 540 µg/kg. In general, the concentrations of vosoritide on lactation day 14 in the **milk** were less than 5% of plasma. When estimable, the milk to plasma concentration ratios ranged from 0.0130 to 0.0473 at 270 µg/kg and from 0.0162 to 0.0502 at 540 µg/kg.

In all but one pup, no vosoritide was detected in blood samples collected on PND 1 and 14. However, one pup born to a high dose mother had a quantifiable concentration of 0.137 ng/mL, which is slightly above the lower limit of quantification (0.100 ng/mL).

The NOAEL for maternal toxicity and pre- and postnatal developmental toxicity in rats was 540 µg/kg/day, which corresponds to a plasma concentration range of 16.0 to 42.3 ng/mL at 30 minutes post-dose on lactation day 14.

Juvenile animal studies were conducted in rats and cynomolgus monkeys. Pivotal studies were preceded by preliminary toxicological assessments in a 21-day pilot feasibility study in juvenile rats and in an escalating dose range finding/7-day repeat dose toxicity and safety pharmacology study in telemeterised juvenile cynomolgus monkeys, respectively.

A 28-day toxicity/TK study was conducted in juvenile monkeys, while in both species 26-week toxicity / TK studies were carried out spanning the age from infancy (7-day-old rats) to pre/peripubescence (2-3-year-old cynomolgus monkeys) at study initiation. The selected age ranges at treatment start are considered adequate for the paediatric age group to be treated, and the subsequent treatments for 26 weeks cover all stages of development until the end of sexual maturation and attainment of reproductive capacity in rats, and at least into adolescence in monkeys. The treatment period does not include the time of closure of the growth plates, which is around an age of 11 months in rats, and around 57 months in female and 63 months in male cynomolgus monkeys, respectively (S. H. Kilborn et al, CONTEMPORARY TOPICS, 2002 by the American Association for Laboratory Animal Science, Volume 41, No. 5). However, this approach is fully in line with the initially proposed indication of *„treatment of achondroplasia in patients 2 years of age and older and whose epiphyses are not closed."*

Aside from standard toxicological assessment, skeletal changes were monitored through bone length measurement, radiological evaluations, and/or histological and histomorphometric analysis of the growth plates. Evaluation of possible drug related impact on reproductive development and capacity was part of the juvenile rat study, while cardiovascular effects were monitored in the course of the studies in cynomolgus monkeys using High Definition Oscillometry (HDO) for BP in combination with Jacketed External Telemetry (JET) for HR and ECG waveforms. Reversibility of any adverse finding was assessed in both species at the end of a recovery period.

The 26-week toxicity study in **juvenile rats** was quite extensive with almost 550 pups included. There were four subsets of animals, either allocated to the main or the recovery parts of the study or used for evaluation of TK and anti-drug antibodies levels, respectively. A fourth subset of rats was assessed for possible drug-induced adverse effects on reproductive capacity. Several developmental milestones were evaluated during the preweaning or post-weaning period.

Treatment of juvenile rats from postnatal day (PND) 7 to 188 by daily subcutaneous injection of 10, 30, or 90 µg/kg/day led to a dose-related increase in bone lesions, reductions of bone minerality and density, and reduced biomechanics that corresponded to *in vivo* observations of reduced limb and joint function and abnormal appearance of joints due to swelling and displaced articular surfaces. These changes were not observed *in vivo* during early development, with increases in growth (crown-rump and tail length), reduction of BMD/BMC, and clinical signs related to bone overgrowth largely not appearing until rats reached adolescence to adulthood (approximately 8-15 weeks of age). There was a sex difference in incidence and severity of skeletal effects on study, which was likely due to higher vosoritide exposures in males. There were no apparent effects on the behavioural or sexual development of juvenile rats related to treatment with vosoritide.

The NOAEL for juvenile rats treated for 26 weeks was determined to be 10 µg/kg/day due to the low prevalence and severity of findings at this dose level, which can be agreed. This dose corresponds to a Cmax of 680 pg/mL and AUC0-t of 22,842 pg*min/mL in males and a mean Cmax of 527 pg/mL and AUC0-t of 10,133 pg*min/mL in females on PND 188.

Bone changes are provided in the toxicology section. The main findings of the 26wk study in respect to reproduction are provided in **Table *23***.

Table 23: 26-Week Subcutaneous Injection Toxicity Study of BMN111 in the Juvenile Rats Followed by a 6-Week Recovery

Study ID GLP	Species Number/Group Age at treatment initiation	Dose Vehicle Route	Treatment period Recovery period	NOEL/ NOAEL (µg/kg/day)
BMN111-11-052 yes	Rats, Crl:CD(SD) *Note: prior to treatment, on PND 4, litters culled to 4 m + 4 f, cross-fostering with a maximum of 1 m + 1 f siblings / litter, no pup assigned to its biological mother)* Allocation to groups see below 7 days	0, 10, 30, 90 µg/kg/d citrate buffer solution SC	PND 7 – 188 (26 weeks) 6 weeks	10 µg/kg/day

Allocation to groups

Group	Compound	Dose (µg/kg)	Number of Litters per Group	Number and Gender per Group			
				Dosing Phase (Subset A)	Recovery Study (Subset B)	Reproductive Phase (Subset C)	Toxicokinetic and ADA Study (Subset D)
1	Vehicle	0	18	10M/10F	16M/16F	20M/20F	9M/9F
2	Vosoritide	10	19	10M/10F	16M/16F	20M/20F	27M/27F
3		30	19	10M/10F	16M/16F	20M/20F	27M/27F
4		90	19	10M/10F	16M/16F	20M/20F	27M/27F

Parameters evaluated

Mortality, clinical observations (cage side), body weights, food consumptions, growth (crown-rump + tail lengths), physical development (sexual maturation), ophthalmic exam, behavioural testing (FOB, motor activity, auditory startle, "Cincinnati" Water Maze (figure8maze)), clinical pathology (haematology, coagulation, clinical chemistry, urinalysis), anti-drug antibodies (ADA), TK, pathology, histopathology;

Bone measurements: biochemical markers of bone turnover, ex vivo radiography, bone mineral density (DXA), bone CT, biomechanical testing

Major findings

FOB	**90** m > f: ataxic gait, gait incapacity, bent tail, swelling of hindpaw/limb, lying on side / curled up, limited use of hindlimbs, stiff hindpaws, thin body conditions → ↓↓ extensor thrust, toe pinch, positional activity, hindlimb grip strength
Motor activity	**90** m: ↓↓ motor activity *due to physical condition of males' hind limbs + paws associated ambulatory difficulties without recovery*
Cincinnati Water Maze	**90** m: swimming performance affected by condition of hind paws and/or legs; time to complete each path ↑↑ without ↑ no. of errors → *considered unrelated to impaired learning + memory;* no recovery
Reproductive performance	no effects on oestrus cyclicity + uterine parameters (assessed on gd 13); fertility index at 90↓ (no. of animals that failed to mate ↑ (*possibly due to conditions of hindlimbs but within historical control);* ↑ preimplantation loss in Co compared to treated groups; however, with historical control range; no effects on sperm motility, morphology or concentration and spermatogenic cycle

Growth and bone parameters	See section on repeated-dose toxicity
Organ weights	**90** m: thymus weight ↓ with ↓ lymphoid cellularity no changes at end of recovery
NOAEL	**10 µg/kg/day**
Exposure on PND 188 at NOAEL	m: C_{max} of 680 pg/mL and AUC_{0-t} of 22,842 pg*min/mL f: C_{max} of 527 pg/mL and AUC_{0-t} of 10,133 pg*min/mL

m = male, f = female, PND = postnatal day, ↓ = decrease(d), ↓↓ = sign decrease(d), ↑ = increase(d), ↑↑ = sign increase(d), gd= gestation day, pQCT = Peripheral Quantitative Computed Tomography, TRACP5b = Tartrate-resistant acid phosphatase 5b, LD = low dose, MD = mid dose, HD = high dose

In **juvenile monkeys**, a dose range finding / dose escalating study in 3-year-old monkeys was conducted prior to the pivotal studies, one with 28 days of treatment and another one with 26 weeks of treatment, respectively. In both studies, recovery periods were included after the end of treatment.

Monkeys were 2 to 3 years old at treatment initiation, an age considered equivalent to preadolescence in humans. As in rats, subsequent treatment for 26 weeks covers preadolescence, and at least part of adolescence.

Drug-related effects were limited to skeletal overgrowth and subsequent functional changes in the joints, particularly at the head and neck of the femur and hip joint. Clinically significant effects in males included limited ambulation and posture changes, possibly due to higher C_{max} values on Day 85. No such relationship was apparent for the single affected female. Mild increases in reactogenicity at the injection site were attributed to treatment with vosoritide and likely related to or enhanced by immune responses to the test article. Due to the persistent bone and joint clinical effects observed in animals treated with 300 µg/kg, the NOAEL for daily chronic administration in juvenile cynomolgus monkeys is 90 µg/kg/day corresponding to mean C_{max} and AUC_{0-600m} values of 10984 pg/mL and 523098 pg• min/mL on Day 176. Design and results of the 26wk-study are provided in Table 24.

Table 24: 26-Week Repeat-Dose Toxicity Study of Subcutaneous Administration of BMN111 in Cynomolgus Monkeys with a 28-Day Recovery

Study design			
Study ID GLP	**Species (*Strain)* Age at dosing initiation Number/Group**	**Dose (µg/kg/d) Route**	**Duration**
BMN111-11-035 yes	Cynomolgus monkeys (*Macaca fascicularis)* 2 – 3 years *Main:* 4 m/4 f *Recovery*: 3 m/3 f in Co + HD	0, 20, 90, 300 (*3 different test article lots*) *dose selection based on expected cardiovascular effects at ≥ 90* Vehicle: citrate buffer solution SC	*Main*: 26 w *Recovery*: 28 d
Parameters			

Mortality, clinical signs, food consumption, body weight Cardiovascular system: BP, ECG TK + ADA Clinical pathology: haematology, coagulation, clin. chemistry, urine analysis + chemistry Organ weights Histopathology Spermatogenesis: staging **Bones**: DEXA (whole body) bone mineral content/density, long bone length, hips; ex vivo: length (vertebrae L1-L4, foramen magnum (2 dimensions)), mechanical testing (left femur, vertebra L3), skull (2 dimensions), histology + morphometry (right femur + skull bone calvarium) Bioanalytical analysis:, cyclic guanosine monophosphate (cGMP), atrial natriuretic peptide (ANP) + brain natriuretic peptide (BNP) Biomarker of bone turnover: N-Terminal propeptide of Type I collagen (P1PN), C-telopeptides of collagen type II (CTXII), C-telopeptides of collagen type (sCTx) (CTXI), osteoclacin, N-telopeptides (NTx), Bone specific alkaline phosphatase (BSAP)

Major findings	
Dose concentrations	↓ (only 70% of peptide conc.) Days 1-85 (m), 1-78 (f), *possibly due to uneven mixing, but based on TK, it was considered that animals may have received sufficient, but variable doses*
TK	20: Day 85 → 3 m + 2 f < BLQ (250 pg/ml); Day 176 → 3 m + 4 f < BLQ; 90: Day 176 → 1 m < BLQ → *TK not calculated for these animals on respective days* → BMN111 exposure ↑ greater than dose proportional → plasma concentrations highly variable (CV% > 30%) → sex differences < 2 x → 20 + 90: C_{max} + AUC_{0-600} Day 1 > Day 85 + 176; 300: C_{max} + AUC_{0-600} Day 1 < Day 85 + 176
Anatomical pathology	no findings
Growth and bone findings	See section on repeated-dose toxicity
NOAEL	**90 µg/kg/day**
Exposure on Day 176 at NOAEL Day 176.	C_{max} : 10984 pg/mL; AUC_{0-600m} :523098 pg·min/mL on

m = male, f = female, w = weeks, d = days, Co = Control, LD = low dose, MD = mid dose, HD = high dose, ↑ = increase(d), ↑↑ = sign increase(d), ↓ = decrease(d), ↓↓ = sig. decrease(d)

Exposure margins:

Exposure margins were calculated on the basis of the exposures at the NOAELs reported in the respective study reports and on comparison with human PK data obtained in Studies 111-202/205 and 111-301/302 with a dose of 15 µg/kg vosoritide SC QD for 52 weeks; subjects ≥5y of age: C_{max} of 4710 to 7180 pg/mL and $AUC_{0-\infty}$ of 244000 to 283000 pg*min/mL. For better comparison of animal with human values, human exposures values were expressed in ng/ml and ng*min/ml as well (C_{max}: 4.7 – 7.1 ng/ml, and AUC: 244 – 283 ng*min/ml).

In **Table *25***, the NOAELs set in the respective study reports were used for comparison with human exposure data. Exposure margins at the NOAELs in the 26-week repeated dose toxicity studies in juvenile animals are below 1 and around 2 in rats and monkeys, respectively.

The juvenile toxicity studies are considered crucial with regard to the paediatric population to be treated. However, the relevance of the findings obtained in healthy animals following long-term treatment for use of vosoritide in children born with achondroplasia is not known. The classic approach for risk assessment - comparing exposure margins at the NOAELs with the human exposure - reveals no or only small safety margins, but this approach might not be adequate, as the underlying exaggerated pharmacology can only partly be taken into account.

Table 25: Overview on the exposure margins at the NOAELs

Study / ID	**NOAEL (µg/kg/d**	**C_{max} at NOAEL (ng/ml)**	**AUC at NOAEL (ng*min/ml)**	**Ratio C_{max}**	**Ratio AUC**
FEED general toxicity (BMN111-14-060)	90	m: 13.6 f: 8.46	m: 411 f: 628	m: 1.9 – 2.9 f: 1.2 – 1.8	m: 1.5 – 1.7 f: 2.2 – 2.6
FEED reproductive toxicity (BMN111-14-060)	540	m: 86.1 f: 45.0	m: 4510 f: 3280	m:–12.0 - 18.3 f: 6.3 - 9.6	m: 15.9 - 18.5 f: 11.6 - 13.4
EFD rats (BMN111-14-061)	540	gd 6: 47.5 gd 17: 64.5	gd 6: 1520 gd 17: 3950	6.6 - 10.1 9.0 - 13.7	5.4 - 6.2 14.0 - 16.2
EFD rabbits (BMN111-14-081)	240	gd 7: 351 gd 19: 379	gd 7: 60300 gd 19: 58000	48.9 - 74.7 52.8 - 80.6	213.0 - 247.1 205.0 - 237.7
PPND	540	ld 14: 28.2		6.0 – 3.9	
Juvenile rats (BMN111-11-052)	10	PND 188: m: 0.68 f: 0.53	PND 188: m: 22.85 f: 10.13	m: 0.09 - 0.15 f:– 0.07 - 0.11	m: 0.08 - 0.09 f: 0.04
Juvenile monkeys 28 days (BMN111-11-019)	> 300	m: 132.07 f: 144.36	11646.61 10673.02	m: 6.8 – 18.5 f: 20.1 - 30.8	m: 41.2 - 47.7 f: 37.7 - 43.8
Juvenile monkeys 26 weeks (BMN111-11-035)	90	Day 176: 10.98	Day 176: 523.1	1.5 - 2.3	1.85 - 2.14

Local Tolerance

No specific studies were conducted.

Injection site reactions were assessed in the repeated-dose studies. Subcutaneous injection site findings observed in rats and monkeys suggest that vosoritide is slightly more irritating than vehicle alone.

Other toxicity studies

Not applicable.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a biotechnologically derived peptide analogue to the naturally occurring C-type Natriuretic Peptide, consisting of natural amino acids. Its use will not alter the concentration or distribution of the substance in the environment. Therefore, vosoritide is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Vosoritide is a stable analogue of the endogenous peptide CNP (C-Type natriuretic peptide) and is intended to stimulate chondrocyte proliferation in the growth plate via activation of the natriuretic peptide receptor NPR-B and consecutive intracellular cGMP production. Thereby, vosoritide is intended to counteract the FGFR3 signalling which leads to differentiation of the chondrocytes. In Ach, FGFR3 signalling is increased by a gain-of-function mutation of this receptor.

Primary PD studies *in vitro* demonstrated that vosoritide stimulates cGMP production and chondrocyte proliferation; the latter was due to counteracting the anti-proliferative effect of FGF2, a ligand of FGFR3.

The *in vivo* primary PD studies demonstrated that vosoritide treatment increases bone, tail and body length in normal animals and also in animals carrying gain-of-function mutations of FGFR3. Two different mouse models were used, each carrying another FGFR3 mutation. One mutation corresponds to human Ach and the other to human thanatophoric dysplasia (TD). Besides length measurements, vosoritide actions on bone were also measured using further parameters such as serum markers of bone and cartilage turnover, DXA scan, X-ray, histology and histomorphometry of the physis and mechanical strength. Not all of these parameters were obtained in the animal models of disease but in healthy animals within the frame of the repeated-dose toxicology studies.

The FGFR3 mutations were introduced into an unusual mouse strain called FVB which carries several defects unrelated to bone. It was reported that FVB mice carry a mutation in a certain cGMP-specific phosphodiesterase (PDE6B) so that increased cGMP levels could result in some tissues. Since the biological actions of vosoritide are mediated by intracellular cGMP production, the applicant was requested to discuss whether the reaction of FVB mice on vosoritide may differ from the reaction of other strains. The applicant explained that the unusual mouse strain was selected for technical reasons, because of easier handling of the oocytes for introducing the transgene. The defective gene PDE6B, which is involved in cGMP metabolism, is not expressed in the bone, but only in photoreceptive cells in mammals, according to published literature. Therefore, the known gene defects on PDE6B of this strain most likely do not affect vosoritide action on bone. This is agreed by the CHMP.

Particularly in healthy animals as tested in the repeated-dose toxicity studies, vosoritide at least in high doses caused undesired bone effects. These included altered shape, dislocation of physis, decreased BMD, reduced mechanical stability, altered histology of the growth plate and consecutive impairment of gait and hind limb use. The reason for these observations is not clear; the applicant suggested a faster-than-normal bone growth caused by vosoritide in these healthy animals and pointed out that FGFR3 knock-out mice, which also show increased bone growth, have a similar phenotype. However, it cannot be excluded that vosoritide directly leads to irregular bone growth, independent of growth velocity. In animals of disease, functional impairment of hind limbs was hardly observed. In the 5-week-study in Ach mice, tail kinking was observed already at vosoritide doses which did not cause a higher-than-normal growth rate.

The applicant pointed out that knock-out of the FGFR3 gene in mice as described in the publication by Colvin et al. 1996 (Nature Genetics 12: 390-397) also displayed increased bone growth that was

irregular and led to misshaped bones. The applicant therefore argued that irregular bone growth is a consequence of strong FGFR3 inhibition. This can be achieved by vosoritide in healthy animals but most likely not in Ach patients or animal models thereof because in this case the basal FGFR3 activity is much higher. Furthermore, it is not intended to suppress FGFR3 activity in Ach to levels less than normal. These arguments are understood by the CHMP. However, the applicant was requested to comment on three aspects. First, FGFR3 knock-out mainly affects other bones than those affected by vosoritide treatment (eE.g., FGFR3 KO leads to prominent kyphosis / scoliosis and curved femur and humerus). In contrast, vosoritide treatment affected hip and tibia, see toxicology section 2.3.4.). Second, disordered chondrocyte arrangement in the growth plate, a consistent finding with vosoritide, was obviously not observed in FGFR3 KO mice (Fig. 3d of the Colvin publication). Third, vosoritide is assumed to inhibit only one signalling pathway of FGFR3, the MAPK pathway. The STAT1 pathway remains unaffected. Further pathways can also couple to FGFR3, e.g. PI3K and PLC, but their role in chondrocytes is unknown (Ornitz and Legeai-Mallet 2017, Developmental Dynamics 246: 291-309). Thus, vosoritide cannot be expected to counteract all FGFR3 actions so that the peptide will cause findings which differ from complete FGFR3 inhibition or knock-out. Another aspect is that in case of FGFR3 KO animals the receptor is absent during the whole period of embryo-foetal bone development whereas vosorotide was administered later in life. The applicant discussed potential reasons for the observed morphological differences resulting from FGFR3 knock-out vs. vosoritide treatment. There is no clear explanation why the FGFR3 knock-out phenotype differs from the morphological changes induced by vosoritide treatment. No meaningful conclusions could be drawn and the issue of FGFR3-KO was not further pursued by the CHMP.

An early sign of irregular bone growth could be the observed disarrangement of the columnar order of the chondrocytes in the growth plate. According to the applicant, in TD mice the chondrocytes are disordered as such. For Ach, the situation is less clear. The applicant stated that disarrangement also occurs in Ach mice and in humans suffering from Ach. However, literature reports do not indicate that chondrocyte disarrangement in the growth plate is a typical sign of Ach in humans (Ponseti, J of Bone and Joint Surgery 1970, 52-A: 701-716; Rimoin et al., New Engl J Med 1970, 238: 728-735; Briner et al. 1991, Path Res Pract 187: 271-278). Published data indicate that in Ach the normal architecture of the growth plate, i.e. linear arrangement of the chondrocytes as columns or oblong clusters, is at least partly preserved; the cells and clusters are smaller and fewer in Ach than in healthy subjects. In contrast, in the TD mouse model used by the applicant, this architecture was largely destroyed; again, chondrocytes were smaller and fewer. Vosoritide was able to increase chondrocyte number and size but did not improve the linear, longitudinal ordering of the chondrocytes. On the other hand, vosoritide affected the normal chondrocyte ordering in the growth plates of normal animals, leading to functional impairment of the adjacent joints, probably due to irregular or asymmetric bone growth. Based on the above-mentioned findings, it cannot be excluded that vosoritide may exert adverse effects on bone and joint with long-term treatment. The applicant has agreed to follow up this issue post-marketing.

There was no strong correlation between disturbed chondrocyte arrangement in the hypertrophic zone and joint damage so that other factors probably have also contributed to joint degeneration. The applicant reported uneven growth of the acetabular cartilage as a likely reason for impaired hip function and hip joint degeneration. According to published literature (reviewed by Peake et al., Osteoarthritis and Cartilage 22, 2014: 1800-1807), CNP signalling not only plays a role in the growth plate but in chondrocytes in general. Therefore, the observed joint damage in the toxicology studies could be largely due to direct action of vosoritide on the articular cartilage. Exogenous CNP, especially at high doses, may disturb the delicate balance of endogenous factors that ensure normal chondrocyte function and proportional growth. In contrast to healthy animals, vosoritide can re-install the balance between CNP and growth factors in animal models of Ach and TD. This can explain why adverse joint effects were hardly observed in Ach and TD animals. If this assumed mechanism were true, vosoritide would be unlikely to cause adverse joint effects in Ach patients. However, uncertainties remain

regarding the possibility of damage and functional impairment of the large joints and will be followed-up postmarketing.

Beside its effects on chondrocytes in the growth plate, vosoritide also had cardiovascular effects as revealed in **safety pharmacology** studies. There was a transient increase in heart rate for a few hours after dosing and a – less pronounced – decrease in blood pressure. After repeated dosing the effect on blood pressure decreased; no such accommodation was observed in respect to heart rate. The cardiovascular effects of vosoritide can be explained by its relationship to atrial natriuretic peptide (ANP). In general, CV-related effects were observed in cynomolgus monkeys at dose levels in the range of the anticipated clinical dose in humans (15 µg/kg). The CV effects observed in cynomolgus monkeys are adequately addressed in Section 5.3 of the SmPC and precautions for use to reduce the risk of potential blood pressure decrease are included in Sections 4.2 and 4.4 of the SmPC.

Vosoritide's inhibitory effect on the hERG channel was studied *in vitro*. Due to technical issues, data from higher vosortide concentrations could not be evaluated. The calculated safety margins between the concentration tested in the hERG assay and the C_{max} values observed in the Phase 3 clinical study and in the Phase 2 clinical study as well as the highest plasma levels achieved in toxicology studies were at least 500-fold. Based on these safety margins, it is acceptable to the CHMP that data on high vosortide concentrations in the hERG assay are not available.

Secondary PD: Inhibitory effects were seen on eight receptors/channels, including NPR-A, in the SpectrumScreen® test. However, the observed IC50 values of vosoritide in that assay are by more than 3 orders of magnitude higher than the mean Cmax at week 52 in patients treated with 15 µg/kg vosoritide. No relevant off-target effects are thus expected in patients.

The applicant did not conduct PD interaction studies. However, based on vosoritide's mechanism of action (indirect inhibition of Fgfr3 downstream signalling), pharmacodynamic interactions with other drugs affecting this pathway or parts thereof are conceivable. The applicant discussed this possibility and identified potential interactions of vosoritide with drugs that bind to NPR-B or have a pharmacologic activity within the ERK1/2/MAPK pathway or drugs binding to the NPR-C receptor that could reduce vosoritide clearance via this mechanism. The applicant concluded that interactions with vosoritide are not relevant to the target population since the only approved drugs with potential interactions are authorised in Europe for use in adults only mainly for the treatment of decompensated heart failure, moderate to severe irritable bowel syndrome and certain cancer drugs, but none of these drugs are approved for use in children. This is agreed by the CHMP.

Pharmacokinetics: Plasma levels of vosoritide over time were obtained in several PK and toxicology studies for calculation of AUC, Cmax, t1/2 and related parameters in different species. AUC and Cmax increased with dose markedly more than proportionally. In general, the exposure following a given dose was higher in males than in females.

The applicant provided only limited information about absorption, distribution, metabolism and excretion. It is acceptable that the ADME programme is reduced for an injected peptide.

Absorption from the subcutaneous space was not further investigated. This is acceptable to the CHMP because vosoritide is not a depot formulation or anything else for which special mechanisms of deposition and absorption in the SC space play a role.

Plasma protein binding was not measured. According to the applicant, high plasma protein binding is unlikely due to the fact that vosoritide is extensively metabolised and rapidly eliminated from plasma. Plasma protein binding is thus not expected to play a significant role in the elimination of vosoritide. The issue was not further pursued by the CHMP since the potential influence was not considered clinically relevant.

For determination of distribution, vosoritide labelled with the radioactive isotope iodine-124 was injected. PET scans were performed thereafter in living animals to determine tissue distribution over time. In another study, radioactivity of I-124 was counted in selected tissues. Vosoritide mainly accumulated in the stomach after SC injection for unknown reasons. According to the applicant, this could be due to free iodine, liberated from labelled vosoritide. A sodium/iodide symporter is expressed in the stomach. The hypothesis was considered plausible to the CHMP, however, if the distribution pattern observed was indeed influenced by dissociation and subsequent accumulation of free iodine, it would have been expected that the thyroid would have been the primary source of radioactivity. This point could not be further elucidated since the thyroid was not investigated. The issue was not further pursued by the CHMP since the signals would not harbour vosoritide-relevant safety relevance. Low activity was found in the brain. CNS safety studies did not indicate CNS effects of vosoritide but their conduct was hampered by vosoritide-related impairment of motility after repeated dosing.

Biodistribution was only studied in male mice and rats. Biodistribution of vosoritide was primarily in the periphery, with most vosoritide remaining at the injection site, in plasma circulation, and in highly perfused organs. This is as expected for a peptide or small protein for which the major distribution mechanism is passive diffusion and most likely not influenced by sex. Further, biodistribution was only studied in adolescent (7 to 9 weeks-old rats) and young adult (8 to 10 weeks-old mice) animals, but not in juvenile or infant animals. The applicant argued that further to the vosoritide distribution pattern, the pharmacodynamics target tissues are the bones and that no soft tissue off-target toxicity was observed in the non-clinical studies. Finally, the applicant noted that growth velocity and tolerability of vosoritide in clinical studies were comparable across the investigated paediatric age subgroups. Therefore, although Ach patients are of younger age, the CHMP agreed that conducting non-clinical biodistribution in younger than juvenile animals is not expected to add to the overall understanding of vosoritide action.

Metabolism of vosoritide was not further characterised. It was shown that – as expected – vosoritide is not a substrate of CYP enzymes. Based on theoretical considerations, cleavage of amino acids from the C-terminus of vosoritide could lead to active metabolites. However, it remains unclear whether C-terminal cleavage takes place and – if yes – which amount of active metabolites is formed. Since vosoritide is a peptide, it is not expected that toxic metabolites are formed so that lack of metabolism studies is not a toxicological concern. Whether presence of active metabolites has to be taken into consideration when measuring plasma exposure and correlating this with the therapeutic action of vosoritide is a clinical problem. Thus, this issue was not further pursued by the CHMP from a non-clinical point of view, and was discussed as part of the clinical assessment (see Section 2.4.4. of the assessment report).

The applicant has not studied the route of excretion of vosoritide. A salient PK finding was a marked, higher than proportional, increase in Cmax and AUC with increasing dose. This could be due to saturation of the excretion mechanism. The applicant presented a possible explanation by noting that scavenger receptors for CNP (which also recognise vosoritide) are located in adipose tissue, i.e. close to the subcutaneous space and thereby close to the injection site. Thus, it is conceivable that vosoritide in lower doses largely becomes eliminated by these local scavenger receptors and that these receptors become saturated upon injection of higher doses. This proposed mechanism was not substantiated with data by the applicant. The applicant also did not provide information to which extent different routes of elimination (e.g. receptor-mediated scavenge and proteolytic degradation) are used. Thus, the reason for the salient more-than proportional increase in exposure with dose remains unclear. Finding of a suitable therapeutic dose in humans is addressed by clinical data, therefore the lack of respective non-clinical data was acceptable to the CHMP.

The involvement of glomerular filtration in excretion of vosoritide is also unknown. Based on theoretical considerations, the applicant concluded that glomerular filtration does not play a relevant role for the

excretion of vosoritide. Thus, non-clinical data did not allow to conclude whether there is a need for dose adjustment in case of renal insufficiency, this issue was addressed based on clinical data.

The potential for transporter inhibition by vosoritide has been excluded based on *in vitro* investigations. Literature data suggest that endogenous CNP is not a substrate or inhibitor of common transporter proteins.

The **toxicology** programme was considered adequate by the CHMP. **Repeated-dose** studies were performed in rodents (rats) and non-rodents (cynomolgus monkeys) for sufficiently long duration, up to 44 weeks (10 months) in monkeys and up to 26 weeks (6 months) in rats. Part of the repeated-dose studies were performed in juvenile animals.

Across all studies, the predominant findings were changes in long bones and joints. These were most pronounced in the high-dose groups of rats and monkeys but occasionally also present in the mid-dose group. The most salient effect was impaired function of the hind limbs. This was accompanied by morphological changes of tibia, femur and acetabulum, damage of articular cartilage, alterations in biomechanical strength testing and histological alterations in the growth plate, indicating irregular growth of the bone. The latter mainly consisted of disordering of the columnar chondrocyte arrangement. In rats, hind limb impairment was accompanied or preceded by the sign of kinked or bended tail. The latter signs could also be related to irregular bone growth, of the vertebrae of this case. The applicant claimed that the mentioned bone findings are related to exaggerated bone growth and are not expected when the basal growth rate is reduced by Ach. This issue is further discussed above, in the frame of the PD studies.

It is conceivable that, at least in healthy animals, CNP or vosoritide enhance chondrocyte proliferation in some undirected fashion so that the columnar arrangement in the growth plate becomes increasingly lost during growth. In consequence, growth could become irregular, resulting in misshaped bone and impairment of joints. Animal data cannot definitely answer the question whether this could also happen in Ach patients. Thus, this issue will be further investigated post-marketing, taking into account that Ach itself can lead to impaired function of extremities and joints.

According to a publication (Colvin et al. 1996, Nature Genetics 12: 390-397), complete loss of FGF3R by knock-out in mice led to inner ear defects and deafness. It appears likely that the inner ear defects come from absence of FGFR3 during embryo-fetal development. Thus, post-natal inhibition of FGFR3 signalling by vosoritide most likely does not affect the inner ear. This is also supported by the finding that the startle response was unaltered by vosoritide in the CNS safety pharmacology studies, indicating normal hearing of the animals.

Carcinogenicity studies were not performed, based on physiological consideration deriving from the knowledge on CNP. The applicant provided reasons why no further tissue evaluation in the disease model have been performed and notes that in the chronic toxicology studies with vosoritide in rat and cynomolgus monkeys no evidence for preneoplastic or neoplastic lesions was found. A carcinogenic risk assessment was performed by the applicant. The molecular mode of action with cross talk of FGFR3 and CNP/vosoritide is outlined with special focus on potential relations of FGFR3 signalling and cancer. It outlines that for inhibition of FGFR3 downstream signalling by NPR-B activation with CNP/vosoritide an effect similar to direct FGFR3 inhibition can be expected. FGFR3 inhibition is considered to have an inhibitory effect on urothelial carcinomas. Furthermore, studies in published literature were cited describing weak but inhibitory effects on tumour cell growth *in vitro*. In one study this was demonstrated to be connected to the generation of cGMP. The applicant notes that in CNP overexpressing mice no carcinogenic lesions were reported and also cites a report on inhibition of rhabdomyosarcoma xenografts growth in mice by CNP. In addition, publications were cited that families with heritable CNP receptor gain-of-function mutations do not show increased cancer

incidences over 3-4 generations. Taken together, the applicant concludes that a carcinogenic potential of vosoritide is not expected. This is endorsed by the CHMP.

All aspects of **reproduction** were evaluated in animal studies in line with current guidelines. Vosoritide did not affect reproductive parameters except male fertility parameters. Slightly increased time to mate, significant decreases in sperm count and density, and significant reductions in seminal vesicle weights were observed at least at the top dose of 540 µg/kg, but these findings were not considered adverse by the study director due to lack of any impact on the fertility index. The applicant submitted historical control data. Based on these data, it was shown that all, except the high dose value for the time to mating, were within the historical control range. The CHMP agreed that the delay to mating was due to significant effects of treatment on skeletal overgrowth, which affected the ambulation of the males and the ability to complete the mating act successfully. In addition, no effects on sperm count or other male reproductive parameters were observed in sexually mature nonhuman primates treated with up to 250 µg/kg/day vosoritide for 26 and 44 weeks, respectively.

The observed dose-dependent decreases in seminal vesicle weights in the fertility and early development study in rats were within normal historical ranges for Sprague-Dawley rats for all treatment groups. No similar observations were noted in any other non-clinical studies. Therefore, this observation is not considered biologically meaningful.

In rats, placenta transfer of vosoritide appears to be minimal if at all, and concentrations of vosoritide on lactation day 14 in the milk were less than 5% of plasma.

Juvenile toxicity studies were conducted in normal rats and monkeys. The selected age ranges at treatment start are considered adequate for the pediatric age group to be treated, and the subsequent treatments for 26 weeks cover all stages of development until the end of sexual maturation and attainment of reproductive capacity in rats, and at least into adolescence in monkeys. In both species, the treatment period does not include the time of closure of the growth plates, which is fully in line with the proposed indication of „*treatment of achondroplasia in patients 2 years of age and older and whose epiphyses are not closed*." Aside from standard toxicological assessment, skeletal changes were monitored through bone length measurement, radiological evaluations, and/or histological and histomorphometric analysis of the growth plates. Evaluation of possible drug related impact on reproductive development and capacity was part of the juvenile rat study, while cardiovascular effects were monitored in the course of the studies in cynomolgus monkeys. Adverse findings were limited in both species to the skeletal system and were considered due to exaggerated activity characterised by clinical observations of bent tails and reduced hind limb mobility and/or disorganisation and reduced vascularisation of growth plate microscopically.

Especially the 26-week juvenile toxicity studies are considered crucial with regard to the paediatric population to be treated. However, the relevance of the findings obtained in normal animals following long-term treatment, for the use of vosoritide in children born with achondroplasia is not known. The classic approach for risk assessment - comparing exposure margins at the NOAELs with the human exposure - reveals no or only small safety margins, but this approach might not be adequate, as the underlying exaggerated pharmacology can only partly be taken into account. Vosoritide's effect on chondrocyte clustering and alignment and on growth plate histology observed in toxicology studies in healthy animals is discussed in more detail in the paragraphs on primary PD. The available information indicates that vosoritide would be unlikely to cause adverse joint effects in Ach patients. However, uncertainties remain regarding the possibility of damage and functional impairment of the large joints and this will be followed-up post-marketing.

ANP increased in a dose-dependent manner in one repeated dose toxicity study in cynomolgus monkeys. No consequences of the increasing ANP levels on diuresis or natriuresis were observed. Such increases in ANP levels were only observed in adult cynomolgus monkeys, but not in juvenile ones.

This was identical to humans, in which ANP increases were observed in adult subjects of the conduct phase I study, but not in paediatric patients of later clinical studies. According to the applicant, the potential molecular mechanisms could include competition of endogenous ANP and vosoritide for the natriuretic peptide clearing receptor NPR-C. This is agreed by the CHMP.

No standalone local tolerance studies were conducted, as the respective endpoints were included in repeated dose toxicity studies. This is acceptable to the CHMP. Inefficient recovery of injection site lesions was observed in the cynomolgus monkey repeated dose toxicity Study BMN111-11-043, the applicant noted that mononuclear cell inflammatory responses can be self-perpetuating due to chemokine-release and subsequent recruitment of additional cells to the site, according to published literature (Shi, 2011). This explanation is supported by the CHMP.

Thymic changes were observed in some non-clinical studies. The thymus is known to be sensitive towards – among others - severe stress, poor nutrition and thin body condition. Thus, the observed thymus weight decreases probably were caused by increased stress levels due to test-article related exaggerated pharmacological adverse effects and therefore are considered of little relevance. This is agreed by the CHMP.

2.3.7. Conclusion on the non-clinical aspects

It was demonstrated that vosoritide increased bone growth in healthy animals and in disease models. However, bone growth was somewhat irregular, leading to kinked tails in rats and to impaired function of the hind limbs in rats and monkeys, at least in healthy animals. In animal models of disease, the picture was less clear since Ach itself can impair joint and limb function. With the non-clinical data presented including literature data and mechanistic considerations, it is not possible to fully exclude irregular bone growth with consecutive functional impairment in human Ach patients upon vosoritide treatment. As Ach itself leads to functional impairment, care has to be taken to distinguish effects of the underlying disease and vosoritide effects. The applicant has agreed to follow-up this issue post-marketing through additional pharmacovigilance activities (see Section 2.7. on Risk Management Plan).

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

Efficacy data in the submitted application was based on one observational study and five interventional studies up to data (cut-offs between May and September 2019). An overview is provided in **Table *26***:

Table 26: Summary of Clinical Studies in the Vosoritide Clinical Development Program

Study Identi-fier	Primary Objectives	Study Design and Type of Control	Dosage Regimen	Sub-jects En-rolled	Study Population	Duration of Follow-Up	Date of Study Initia-tion	Status at time of MA	Report data included in MA
111-101	To evaluate the safety and tolerability of single and escalating, and multiple and escalating SC injections of	Phase 1, double-blinded, placebo-controlled	Part 1: Single SC doses of vosoritide at 5, 10, or 15 µg/kg Part 2: Multiple SC doses	48	Healthy male volunteers	Part 1: 9 days Part 2: 25 days	14FEB 2012	Completed	Full final CSR
111-901	To collect consistent baseline growth measurements on pediatric subjects being considered for subsequent enrollment in 111-202, 111-301, and 111-206	Prospective, non-interventional	NA	342	Pediatric subjects with ACH from birth to <17 years of age	Observation period of up to 7 years	20APR2012	Ongoing	Interim full CSR Data cut- off date: 31MAY2019)
111-202	To evaluate the safety and tolerability of daily SC injections of vosoritide administered to children with ACH	Phase 2, open-label, sequential cohort dose-escalation, global, multicentre	Daily SC dose of vosoritide at 2.5, 7.5, 15, or 30 µg/kg	35	Pediatric subjects 5-14 years old with ACH	Up to 24 months (initial 6-month and optional 18 months extension)	13JAN 2014	Completed	Full final CSR
111-205	To assess the long-term safety, tolerability, and efficacy of daily SC injections of vosoritide in children with ACH	Phase 2 open-label extension of 111-202	Daily SC dose of vosoritide at 15 or 30 µg/kg	30	Subjects with ACH who completed 2 years of vosoritide treatment in 111-202	5 years, or until subject attains NFAH (evidence of growth plate closure and 6 month interval AGV <1.5 cm/year),	26JAN 2016	Ongoing	Interim full CSR Data cut- off date: 20NOV2019)

Study Identifier	Primary Objectives	Study Design and Type of Control	Dosage Regimen	Subjects Enrolled	Study Population	Duration of Follow-Up	Date of Study Initiation	Status at time of MA	Report data included in MA
111-301	To evaluate the efficacy and safety of daily SC injections of vosoritide in children with ACH	Phase 3, randomised, double-blinded, placebo-controlled, global multicentre	Daily SC dose of vosoritide at 15 µg/kg	121	Pediatric subjects 5-<18 years old with ACH	60 weeks (4 weeks screening 52 weeks of treatment with an additional 4 weeks of safety follow-up)	24NOV 2016	Completed	Full final CSR
111-302	To assess the long-term safety, tolerability, and efficacy of daily SC injections of vosoritide in subjects with ACH	Phase 3 open-label extension of 111-301	Daily SC dose of vosoritide at 15 µg/kg	119	Subjects with ACH who completed 111-301	5 years, or until subject attains NFAH (evidence of growth plate closure and 6-month interval AGV <1.5 cm/year), which ever comes later	11DEC 2017	Ongoing	Interim full CSR Data cut- off date: 31OCT2019
111-206	To assess the safety and efficacy of daily SC injections of vosoritide in younger children with ACH	Phase 2, randomised, double-blind, placebo-controlled, global, multicentre	≥ 2 to <5 years: daily dose of vosoritide 15 µg/kg ≥ 6 months to < 2 years: daily dose of vosoritide 30	Approx. 70 (44 enrolled)	Pediatric subjects from birth to <60 months old with ACH	60 to 72 weeks (4 weeks screening 52 weeks of treatment with an additional 4 weeks of safety follow-up; Cohort 3 had a 12 week	13JUN2018	Ongoing	Interim full CSR Data cut- off date: 12SEP2019
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	≥ 2 to <5 years: daily dose of vosoritide 15 µg/kg ≥ 6 months to < 2 years: daily dose of vosoritide 30 µg/kg	Approx. 70 (4 enrolled)	Pediatric subjects with ACH who completed 111-206	Until subject attains NFAH (evidence of growth plate closure and 6 month interval AGV <1.5 cm/year)	13JUN2019	Ongoing	Interim full CSR Data cutoff Date: 12SEP2019

2.4.2. Pharmacokinetics

The human pharmacokinetic properties of vosoritide were assessed in 3 *in vitro* studies performed using human biomaterials and 7 clinical studies.

Bioanalytical methods:

Samples from PK/PD studies were analysed at BioMarin using two assay approaches, a quantitative enzyme-linked immunosorbent assay (ELISA), used in the earlier studies, and an electrochemiluminescence assay (ECLA) designed to improve sensitivity and range of quantitation (in the later studies). Overall, the presented data demonstrate suitability of the assays.

Assay validation data were also presented for several biomarkers, as well as for anti-drug antibodies (ADAs), which were overall considered acceptable.

Absorption

Studies conducted:

No absolute bioavailability and human absorption, distribution, metabolism, and excretion (ADME) studies have been performed for vosoritide.

Pharmacokinetics evaluations were part of the designs of 7 interventional clinical studies (111-101, 111-202, 111-205, 111-206, 111-301 and 111-302) and were conducted in healthy volunteer adult male subjects, and children with a confirmed diagnosis of ACH.

In **Study 111-101**, the only study in healthy subjects, daily SC administrations of vosoritide 15 µg/kg were rapidly absorbed, reaching a median Tmax of 15 to 30 min. Increase in Cmax with dose was approximately greater than dose proportional from 2.5 to 15 µg/kg and increase in AUC0-t was approximately greater than dose proportional from 5 to 15 µg/kg. At 15 µg/kg, the mean ± SD of CL/F and Vz/F at 15 µg/kg was 20.3 ± 11.3 mL/min/kg and 1500 ± 530 mL/kg, respectively. The mean t1/2 was 69.5 min. Overall changes in vosoritide exposure (Cmax and AUC0-t) were minimal with repeat dosing out to 10 days.

While full PK profiles were determined in the HVs **study 111-101**, all other studies were conducted in the target population, and hence rather restricted PK sampling was applied. Due to the vulnerability of the population, and the properties of the substance with rapid clearance, the applied sampling schedule appears nevertheless appropriate.

In **Studies 111-202/205** and **111-301/302**, daily SC administrations of vosoritide 15 μg/kg were rapidly absorbed in ACH subjects aged ≥5 years, reaching a median Tmax of 15 min. At 15 µg/kg, over a treatment period of 52 weeks, mean t1/2 ranged from 21.0 to 27.9 minutes. Mean Cmax, and AUC0-∞ ranged from 4710 to 7180 pg/mL and 244000 to 283000 pg-min/mL respectively. Mean CL/F and Vz/F ranged from 79.4 to 104 mL/min/kg and 2880 to 3020 mL/kg, respectively. Increase in exposure (Cmax and AUC0-t) was greater than proportional with dose from 2.5 to 30 µg/kg.

In **Study 111-301**, PK parameters at 15 µg/kg were consistent throughout the 12 months of treatment. The mean (± SD) peak concentration (C_{max}) and area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) observed after 52 weeks of treatment was 5,800 (±3,680), and 290,000 (± 235,000) pg-min/mL respectively.

In the single-dose part of **study 111-202**, the PK parameters Cmax and AUC0-t increased greater than proportional to the increase in dose across the dose range of 2.5 to 30.0 µg/kg.

In **Studies 111-202** and **111-205**, PK parameters at 15 and 30 µg/kg were consistent up to 60 months. There was no evidence of accumulation observed following a once daily injection. Furthermore, population PK results indicated that body weight is the only significant covariate for vosoritide clearance and volume of distribution which supports dosing by weight.

In **Study 111-206**, over 52 weeks of treatment at 15 µg/kg daily, the mean Cmax and AUC0-∞ of ACH subjects aged 2 to 5 years were generally consistent with 15 µg/kg in older ACH subjects (aged 5-18 years), ranging from 3810 to 6860 pg/mL and 118000 to 350000 pg-min/mL, respectively. Median Tmax ranged from 14.0 to 15.5 minutes, and mean t1/2 ranged from 15.2 to 29.3 minutes. Mean CL/F and Vz/F ranged from 82.1 to 150 mL/min/kg and 2650 to 3800 mL/kg respectively.

Distribution

The mean volume of distribution in the Phase III **Study 111-301** conducted in ACH patients aged 5 to 18 years ranged from 2880 to 3020 mL/kg. This was comparable to the volume of distribution observed in patients dosed 15 µg/kg in the Phase II study 111-202.

The mean (± SD) apparent volume of distribution in **Study 111-301** after 52 weeks of treatment was 2,910 (± 1,660) mL/kg.

Elimination

Beside protease-mediated catabolism and NPR-C receptor mediated uptake, the applicant presumes that renal excretion is one of the elimination pathways for vosoritide.

The mean half-life of vosoritide in subjects aged 5-18 years ranged from 21.0 to 27.9 minutes. The mean clearance in **Study 111-301** ranged from 79.4 to 104 mL/min/kg. The mean (± SD) apparent clearance after 52 weeks of treatment was 79.4 (53.0) mL/min/kg. The mean (± SD) half-life was 27.9 (9.9) minutes.

It is noted that the compound is rapidly absorbed, has a very short half-life, which is under 1 hour in all cases in patients (and only slightly above in healthy volunteers), and the compound is also rapidly cleared from circulation. The pathways for elimination itself have not been elucidated in detail due to the character of the molecule and its rapid elimination from circulation. Only theoretical considerations on pathways of elimination are therefore available, but this can be accepted. Based on the character of the substance, data from animals, and theoretical considerations (including the clinical relevance in the target population) it is also finally accepted that no data are available in patients with hepatic and renal impairment. An influence is, however, not expected. The only special population addressed is, of course, children, which is the target population of the compound.

Dose proportionality and time dependencies

Overall, the PK of the compound has not been found to be linear (only for Cmax in healthy volunteers), but greater than proportional increases were found with higher doses, both for Cmax and AUC. Based on the sparse sampling data, dose-non-proportionality has also been confirmed after multiple administration based on data from **study 111-202**.

Findings suggest that there is an increase in bioavailability over time, for which it is most likely that it relates to weight gain over time. Accumulation as potential reason for this phenomenon has been

excluded due to the rapid clearance of the substance from circulation. The applicant has implemented an improved weight-band based dosing, considering the increase of bioavailability with weight/time. The weight-band based dosing regimen is acceptable, despite the dosing ranging partly outside the dose administered throughout the clinical study at the extremes of the weight range due to the fact that it provides a consistent exposure over the full range of weight categories. Due to potential safety concerns at the lower end of the weight categories, the submission of the final results for the cohort of the very young children (which is treated with a 30µg/kg dose) will be relevant for the final confirmation of safety.

Intra- and inter-individual variability

The inter-individual variability for the PK parameters observed in the Phase II **study 111-202** and the Phase III **study 111-301** was moderate to high. According to the Pop PK report, the inter-individual variability for CL/F was 33.6%.

Pharmacokinetics in target population

With the exception of **study 111-101**, the PK of vosoritide has mainly been documented in the target population of ACH patients. Therefore, the studies contributing to the description of pharmacokinetics have already been described in detail above.

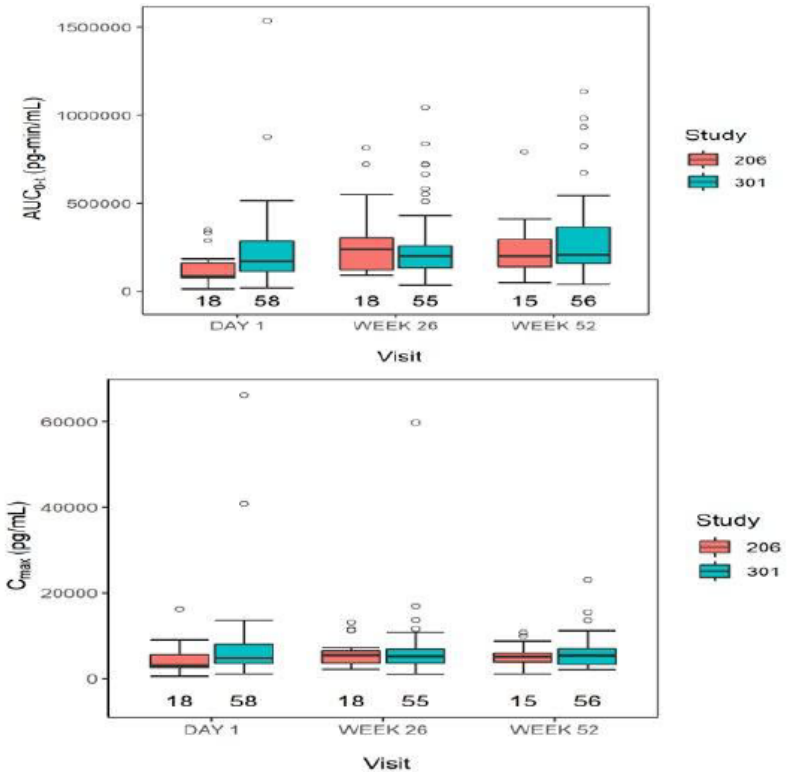
As a consequence of the intended target population, for which treatment after closure of the bone growth plates does not make sense, no adult or even elderly patients were included in the development programme.

Special populations

The results of the individual studies did not raise concerns. However, the PK documentation submitted, does overall not contain a consistent cross-study comparison of results. The influence of demographic factors on PK has additionally been presented. This showed that PK is not influenced by gender and race or ethnicity (with a caveat based on the low number of black patients included), but is dependent on age and weight, with increased plasma concentrations in higher weight bands, which is likely to be responsible also for the age effect. The concentration of the compound in the ranges provided in the product to be commercialised (0.8 mg/ml and 2.0 mg/dl) did not influence PK in relevant manner. The applicant has also evaluated intrinsic/demographic factors for their influence on PK only in the modelling exercise, and has similarly found body weight and in addition the concentration of the compound being the only significant factors influencing PK. The apparent clearance and volume of distribution of vosoritide increased with increasing body weight in patients with achondroplasia (9 to 74.5 kg). However, the influence of concentration was only applicable for the low concentration of 0.2 mg/ml used in early development.

Only limited data on PK were available for the age group below 5 years of age, for which only 4 "sentinel" subjects had been evaluated for PK in the initial submission. Additional data have been submitted, and the PK data now include a total of 18 sentinel and randomised Cohort 1 subjects up to 52 weeks. The updated results provided sufficient evidence suggesting that at 15 µg/kg, exposure from **study 111-206** Cohort 1 subjects aged 2 to < 5 years was similar to that from subjects aged 5 to 18 years in **study 111-301** (**Figure *20***).

Figure 9: Comparison of Vosoritide AUC0-t and Cmax at 15 µg/kg between 111-206 Cohort 1 and 111-301



Pharmacokinetic interaction studies

Drug-drug interactions:

The applicant has conducted only a limited number of in-vitro studies in order to evaluate the potential of the compound for causing drug-drug interactions. The studies conducted are considered sufficient to rule out a relevant potential for cytochrome-, as well as transporter-based interactions. The in-vitro studies conducted have also made unlikely that metabolic (cytochrome) based degradation plays a relevant role in the elimination of the compound. Degradation of the compound itself has only been addressed in theoretical manner. As a small peptide, vosoritide is expected to be cleared primarily by protease-mediated catabolism, receptor mediated clearance via NPR-C and renal elimination. The enzymes responsible for degradation have not been finally characterised. However, this can be accepted based on the rapid clearance of the compound. The potential for genetic differences (of the target-receptor) or endopeptidases have also not been assessed, but theoretical considerations considerations on dual mutations or potential mutations of the metabolising enzymes have made it very unlikely that mutations of that kind would occur concomitantly with the FGF3R mutation responsible for ACH.

Pharmacokinetics using human biomaterials

Bioequivalence

The applicant has presented evidence that no relevant changes to the formulation have occurred during the development, and that after early development, the proposed formulations used in phase 2 and 3 of the development are not relevantly or not at all different from the to-be-marketed formulation

in terms of qualitative and quantitative composition. In addition, the two strengths to be marketed have both been included in the clinical phase 3 trial programme. Differences between formulations are therefore not expected. An additional investigation of PK (based on sparse sampling) of two of the proposed injection sites have not revealed differences between two of the injection sites (buttock and thigh). The alteration of injection sites was also included in the clinical administration schedule during the phase 2 and phase 3 trials, no further concern arises.

The impact of injection site locations on exposure were evaluated in the population PK analysis. The results for the influence of the location of administration indicate a very similar mean rate and extent of exposure, both for single dose, as well as for steady state.

Impact of antibody formation on PK:

The applicant has also undertaken an analysis of the impact of antibody formation on the PK of vosoritide. While a considerable part of patients (but none of the healthy subjects) included in the programme developed at least transient antibodies, all analysis conducted did not show an impact of antibody formation on the PK of the compound.

PPK-Modelling

A population pharmacokinetic analysis for vosoritide was performed with data from 158 ACH patients (4741 observations finally included from 6181 observations in total) from **studies 111-202, 111-205, 111-206, 111-301 and 111-302**. Data from **study 111-101**, a study with 22 healthy male adults was not included because PPK parameters were too different.

The PPK database included data from patients ranging in age from 0.95 to 15 years (mean age was 8.43 years). Weight ranged from 9 kg to 74.5 kg (mean baseline weight was 23.8 kg). Actual daily doses included 2.5 µg/kg/day (6 patients), 7.5 µg/kg/day (12 patients), 15 µg/kg/day (151 patients) and 30 µg/kg/day (11 patients). By race there were 114 White, 6 Black or African American, 28 Asian and 10 Other or Unknown.

Two different analytical assays were used to determine vosoritide concentrations ELISA for studies 111-202 and 111-205, and ECLA for studies 111-206, 111-301, and 111-302. Therefore, two different residual errors were estimated. PK data were fit using a log transform both sides approach with an additive error model.

Model development revealed that vosoritide PK was best described by a 1-compartment model with first order absorption and first order elimination, when administered by the subcutaneous route. A time-dependent change-point for the absorption rate constant was estimated, a fast absorption phase was followed by a slower absorption.

Methodology of model development was appropriate; estimation of PK parameters was precise (except for effect of WT on CL/F SE 25.1); goodness-of-fit plots did not reveal any model-misspecification. Overall, VPCs showed that concentrations were adequately predicted.

For the final model sex, race, age, location of injection, ADA status and NAB status were tested as covariates, but were not significant within the respective dataset. Evaluation of possible simpler models was provided. The applicant justified the high unexplained variability with the low bioavailability (1.23 % at 20 µg/kg) of vosoritide and the comparably higher residual error for the ELISA compared to the ECLA.

The applicant argues that no maturation factor is needed because body size fully accounts for clearance differences even in younger children. This is acceptable for children > 2 years, for younger children this should be substantiated that renal function and enzyme function is described adequately with a weight function.

A covariate effect of time on bioavailability was used to describe the increasing plasma concentrations occurring during long-term treatment. Vosoritide clearance in children was not sufficiently described in children not by allometry, even with a time effect on bioavailability. The underlying confounding effect of weight on clearance was addressed in the proposed weight band posology.

In the PPK-Model, an allometric coefficient was used. Consequently, for dosing allometric scaling is as well considered appropriate. Increased weight and dose of patients (and decreasing clearance per bodyweight) over time during the studies could rather be an explanation for higher plasma concentrations over time.

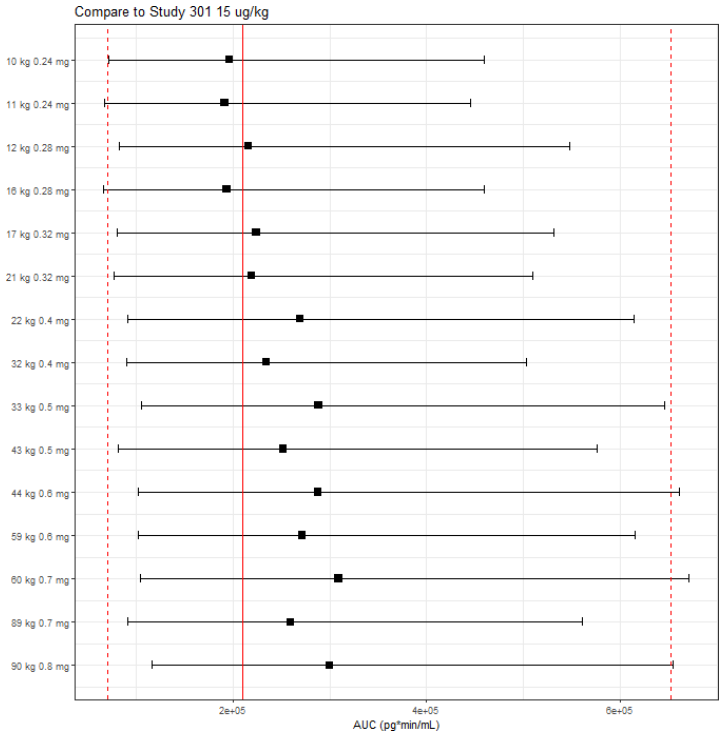
To address the need for a lower per kilogram dose for older patients (higher bodyweight) and for a higher per kilogram dose for younger patients (lower bodyweight) a Weight-band based posology was proposed.

Table 27: Proposed Weight-band Dosing for Vosoritide

Body Weight (kg)	SKU 1 Concentration: 0.8 mg/mL (0.50 mL)	SKU 2 Concentration: 0.8 mg/mL (0.70 mL)	SKU 3 Concentration: 2 mg/mL (0.60 mL)
10-11	0.24 mg/0.30 mL (22-24 µg/kg)		
12-16		0.28 mg/0.35 mL (18-23 µg/kg)	
17-21		0.32 mg/0.40 mL (15-19 µg/kg)	
22-32		0.40 mg/0.50 mL (13-18 µg/kg)	
33-43			0.50 mg/0.25 mL (12-15 µg/kg)
44-59			0.60 mg/0.30 mL (10-14 µg/kg)
60-89			0.70 mg/0.35 mL (8-12 µg/kg)
>=90			0.80 mg/0.40 mL (⩽9 µg/kg)

A comparison between the simulated exposure metrics of the updated weight-band dosing regimen and the observed exposure metrics at 15 µg/kg from 111-301 is provided in **Figure 21** and **Figure *22***.

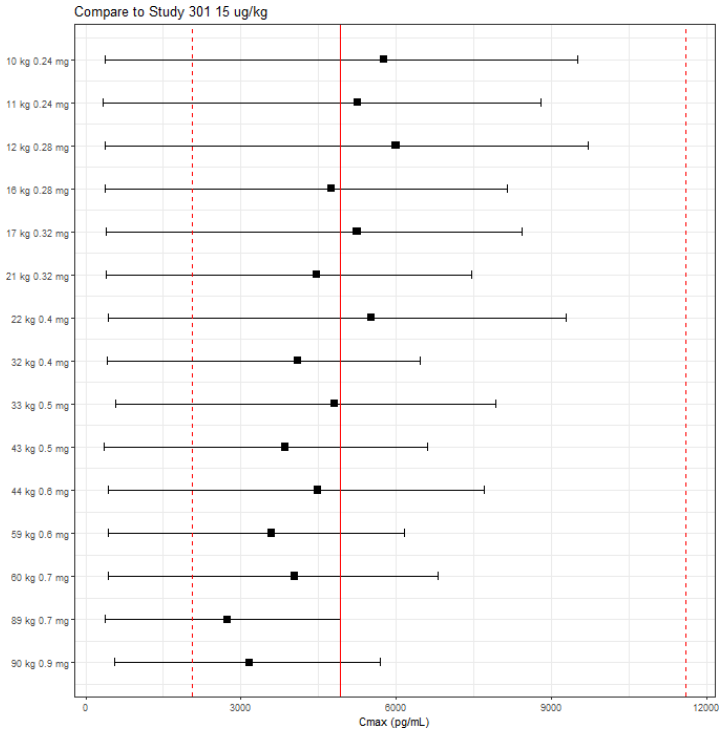
Figure 10: Simulated Vosoritide AUC Values as Compared to Observed AUC Values at 15 µg/kg from 111-301



AUC, area under the plasma concentration-time curve.

Note: Black squares represent the median exposure metrics for each weight, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of exposure. The red dashed lines represent the lower 5th and upper 95th percentiles of observed metrics from the comparison study. The red solid line represents the median of observed metrics from the comparison study.

Figure 22: Simulated Vosoritide C_{max} Values as Compared to Observed C_{max} Values at 15 µg/kg from 111-301



C_{max}, area under the plasma concentration-time curve.

Note: Black squares represent the median exposure metrics for each weight, the upper and lower whiskers represent the lower 5th and upper 95th percentiles of exposure. The red dashed lines represent the lower 5th and upper 95th percentiles of observed metrics from the comparison study. The red solid line represents the median of observed metrics from the comparison study.

2.4.3. Pharmacodynamics

Mechanism of action

PD properties of vosoritide were assessed in 3 *in vitro* studies performed using human biomaterials (BMN111-18-101, BMN111-18-093, and BMN111-18-102) and in 7 clinical studies (111-101, 111-202, 111-205, 111-206, 111-208, 111-301 and 111-302). The *in vitro* studies are discussed in pre-clinical section.

Only limited data are available from **study 111-206** that is still ongoing and targets investigation of vosoritide treatment in younger ACH population of age below 5 years. PK/PD data from **study 111-208** were not available at the time of this MAA, and are thus not included in the application.

Various biomarkers including cGMP, collagen X biomarker (CXM), bone-specific alkaline phosphatase (BSAP), N-terminal pro-peptide of pro-collagen I (PINP), cross-linked C- terminal telopeptides of type II collagen (CTXII), atrial natriuretic peptide (ANP) and N- terminal pro-peptide of CNP (NT-proCNP) were assessed. However, cGMP and CXM, were evaluated in more detail across the studies, as these parameters were considered the most reliable and sensitive. Annualised growth velocity (AGV) was also utilised as additional PD and efficacy parameter.

Primary and Secondary pharmacology

Primary pharmacology

In **study 111-101** (healthy volunteers) dose-dependent increases in plasma cGMP (mean values) were observed following both single (2.5 – 15 µg/kg) and multiple daily doses of vosoritide (up-to 10 days only for 2.5 and 5 µg/kg doses). No effects on cGMP were observed on placebo. There was no correlation with the ANP or NTproCNP levels.

In **study 111-202** (≥5 years old children with ACH), similarly dose-dependent increases (at dose levels of 2.5, 7.5, 10, 15 and 30 µg/kg) were observed in urine cGMP/Cr and serum CXM, which were sustained over 2-year treatment period for 15 and 30 µg/kg (lower dose levels were not evaluated). However, CXM increase plateaued at the 15 and 30 µg/kg doses. There was no correlation between the plasma exposure of BMN111 and serum BSAP levels.

AGV estimated after 6 months of vosoritide treatment showed similar differences as CXM with more pronounced changes on higher doses of 15 and 30 µg/kg vosoritide, when compared to the lower dose groups.

In **study 111-205**, similar trends in changes of the key PD parameters were maintained as in **study 111-202**.

Study 111-301 tested PD effects of the single proposed therapeutic dose of 15 µg/kg vosoritide against placebo in ACH children aged 5 to < 18 years.

The PD marker analysis showed an increase in urine cGMP after vosoritide treatment compared to placebo that was sustained over 52 weeks. However, the results for the PD marker BSAP were inconclusive. Although there seemed to be a slight increase at certain time-points with vosoritide

treatment compared to placebo, the data were highly variable. On the other hand, there was also an increase in the PD marker CXM with vosoritide treatment over the 52 weeks period.

Data from **study 111-302**, an ongoing extension study to 111-301, are limited, but similar to those from study **111-301**.

Limited data were submitted from **study 111-206***,* which is an ongoing study in infants and younger children (max. age of 5 years). At the time of data cut-off, PD information (plasma cGMP and serum CXM) in 4 sentinel subjects and 33 randomised subjects (aged ≥ 24 to < 60 months) receiving 30 µg/kg vosoritide was available.

Increases in post-dose plasma cGMP concentrations were observed, which remained constant over the time period of 52 weeks and were similar to the changes observed in older age group. CXM (mean and median) on vosoritide was increased in serum throughout the study (over up-to 39 weeks) compared to baseline and placebo. However, values overlapped considerably between vosoritide and placebo. High variability was noted in the measured parameters.

An updated blinded analysis in Cohort 1 subjects (19 vosoritide-treated subjects and 16 placebo-treated subjects aged ≥ 24 to < 60 months) showed that levels in serum CXM (averaged across all visits and per treatment) were roughly similar to those observed in older children (i.e. study 111-301) for the respective treatment. High variability in CXM values are noted.

Secondary pharmacology

Evaluations including exposure-response relationship for safety relevant parameters, such as HR, BP (systolic and diastolic) suggest a potential weak correlation between BMN111 exposure and increase in HR with a shallow, but significant ($p < 0.05$), positive slope, in subjects given daily doses between 2.5 µg/kg and 30 µg/kg. No significant correlations between BMN111 plasma exposure and systolic and diastolic blood pressure (as measured in sitting position) was detected.

Regarding possible off-target effects of vosoritide on diuresis, in **study 111-301** no effects on fluid or electrolyte balance were seen. No apparent clinical effects have been observed to suggest modulation of blood-brain barrier permeability.

Impact on QT interval/ECG parameters

A dedicated thorough QT study with vosoritide was not conducted.

The hERG-cell-based assay (BMN111-11-023) did not detect any inhibition of hERG using up to 13.4 µM vosoritide (50 µg/mL). Non-clinical *in vivo* studies also did not reveal any relevant findings which would raise safety concerns. Non-clinical data is presented in Sections 2.3.2. and 2.3.6. of this assessment report.

In **study 111-101**, the PD markers cGMP, ANP and NT-proCNP were evaluated. While there was a dose-dependent increase of cGMP levels both in the plasma and urine of the subjects, there was no correlation with the ANP or NTproCNP levels.

Analysis of the ECGs in **study 111-301** study showed, that in the by-visit analysis using statistical modelling, mean change-from baseline QTcF (ΔQTcF) was larger in the vosoritide group than in the placebo group and the maximum mean ΔΔQTcF of 5.4 ms (90% UCI 8.5 ms) was reported.

The relationship between the individually observed vosoritide plasma concentrations and estimated placebo-adjusted ΔQTcF (i.e., ΔΔQTcF) showed that the 90% CI widened with increased concentrations, but the 90% upper confidence bound of the estimated ΔΔQTcF remained below 10 ms.

The estimated slope of vosoritide plasma concentration in the concentration-QTc relationship was positive and not statistically significant. The effect on ΔΔQTcF was predicted to be 3.7 ms (90% CI: 1.41 to 6.03) for 15 µg/kg vosoritide.

Categorical analysis (pooled patient population) detected 7 patients with increased QTcF by >30 msec <60 msec on vosoritide and 3 on placebo. None of the cases had QTcF > 450 msec. Increases in QTcF were episodic. Majority of the patients had non-baseline pre-treatment values of QTcF, which were higher than the baseline and closer to the on-treatment peak QTcFs. High intra-subject variability in QTcF was observed in part of the patients.

PD interactions with other medicinal products

No clinical PD interaction studies were conducted.

Exposure-response analyses

The relationship between dose and improvement in AGV was assessed across Phase 2 and Phase 3 studies. In **study 111-202**, vosoritide was administered in ACH subjects aged 5 to 14 years in daily doses ranging from 2.5 µg/kg to 30 µg/kg. At 6 months, a positive dose-dependent response in AGV was observed from 2.5 up to 15 µg/kg daily, which reached plateau at the 15 µg/kg and 30 µg/kg doses (Cohorts 3 and 4) with no clinically significant difference in mean change from baseline AGV between these two cohorts. After 6 months, when Cohorts 1 and 2 subjects were dose titrated from 2.5 and 7.5 µg/kg, respectively, to the 15 µg/kg daily dosing, an improvement in baseline AGV was observed similar to that seen in Cohorts 3 and 4, persisting through the 24-month duration of the trial. In the ongoing extension **study 111-205**, Cohorts 3 and 4 had similar improvement in AGV up to 48 months (the longest duration available).

The relationships between vosoritide plasma exposure and changes in activity biomarker cGMP and bone metabolism biomarkers CXM have been evaluated in ACH subjects across different clinical studies and consistent exposure-response relationships were observed. Furthermore, the relationship between vosoritide plasma exposure and changes in AGV from baseline had been analysed in Phase 2 and Phase 3 studies. Overall, the exposure response analyses consistently show that changes in AGV from baseline have reached the plateau of the exposure-response curve at exposures obtained at 15 µg/kg and there are no additional meaningful improvements in AGV at 30 µg/kg compared to 15 µg/kg.

The exposure-response relationship between CXM and the investigated exposure metrics for vosoritide (AUC0-∞, AUC0-60min and Cmax) showed flat exposure-response curves for **study 111-206** (2 - <5 years old) as well as for **study 111-301** (>5 years old).

Effects of intrinsic/extrinsic factors on PD

Effects of intrinsic/extrinsic factors on PD were not investigated in dedicated analyses due to the high variability observed in PD.

However, with respect to efficacy parameters, effects of sex, age group, Tanner stage, strata, baseline height Z-score, and baseline AGV on efficacy of vosoritide were studied in **Study 111-301**.

Analysis of AGV by baseline age group (>= 5 to < 8 years, >= 8 to < 11 years, >= 11 to < 15 years) did not show any apparent differences on treatment with vosoritide at week 52.

Analysis of AGV by baseline Tanner stage (I vs >I), and baseline AGV category (<= 3.5 cm/yr, > 3.5 to <= 4.5 cm/yr, > 4.5 cm/yr) suggest that the patients with younger age (i.e. 5-8 y/o), with Tanner stage I, and lower baseline AGV (<= 3.5 cm/yr and > 3.5 to <= 4.5 cm/yr) benefited from vosoritide treatment the most. The patients with baseline AGV of > 4.5 cm/yr (N=27 at week 52 of the treatment) did not seem to have any improvement in baseline AGV at all.

In the subgroup analysis by baseline z-score for height (<= -6, > -6 to <= -5, > -5 to <= -4, > -4), lowest change in AGV was observed in the subgroup with baseline z-score of <= -6. The remaining subgroups did not differ considerably in respect to the AGV. However, sample size of the subgroups was very small and the conclusions are difficult to draw on potential impact of baseline z-score for height on efficacy of vosoritide.

2.4.4. Discussion on clinical pharmacology

The applicant has presented a limited investigation on clinical pharmacokinetics partly owing to the nature of the compound (being a protein), the orphan nature of the disease to be treated, and the difficulties in investigating PK in healthy subjects, with hypotensive effects preventing the administration of higher doses. This is acknowledged by the CHMP.

The absolute bioavailability of vosoritide is unknown, as only the SC route was investigated in the clinical studies. While basic parameters of PK (absorption, distribution etc.) have been adequately investigated, several aspects of PK investigations and characterisations have been omitted or are partly deficient. The compound has been found to be non-proportional with increased plasma levels at higher doses. Demographic factors appear to play a role with regard to age and weight, however, this is thought to be attributable to weight only, which is likely to also explain the time-related effect of increase bioavailability over time (in long-term observation).

Only minor changes to formulation were made during the development, therefore no relevant changes in bioavailability are expected, and no comparison between formulations has been conducted. This is agreed by the CHMP. The interchangeability of administration sites has only partly been investigated, but no relevant differences were detected, and the proposed alteration of administration sites was also mirrored in the development programme, the CHMP therefore considers that no clinically relevant deviation is expected and the proposed dosing/administration site is agreed.

With regard to interactions, the potential for cytochrome - as well as transporter - based interactions has been excluded based on *in vitro* investigations. In addition, theoretical considerations on metabolism were provided since, as a small peptide, vosoritide is expected to be cleared primarily by protease-mediated catabolism, receptor mediated clearance via NPR-C and renal elimination. Due to the nature of the compound and its rapid clearance, it is agreed by the CHMP that no further investigations are carried out with regard to identification of further degradants/metabolites and their PD activity.

The applicant was requested to justify why vosoritide has a prolonged half-life in comparison to endogenous CNP. The applicant clarified that endogenous CNP has a short half-life of 2.6 minutes in humans (Potter, 2011: 2.6 minutes, Lorget, 2012: 2 minutes). The structural modification of vosoritide confers resistance to proteolysis by neutral endopeptidase (Wendt, 2015) such that its half-life is extended almost 10-fold (mean t1/2 of 27.9 minutes at Week 52 of study 111-301) in comparison to endogenous CNP. Furthermore, the applicant explained that the longer half-life observed during the trials in healthy volunteers might be explainable by the higher body weight of the healthy adult volunteers compared to the paediatric ACH patients. The increased total dose administered to adult healthy volunteers might have saturated clearance and prolonged the elimination half-life. This is accepted by the CHMP.

Antibody formation (although overall frequent; see below) has not shown to have an influence on PK.

The compound is intended for the use in children and adolescents only, and hence, no data on adults and elderly patients are available which is acceptable to the CHMP. The data available for young children proposed for treatment between 2 and 5 years of age have been updated from the available

results of study 206 and are considered sufficient to be included in the posology. The proposed weight bands are finally considered acceptable.

The MAH was requested to revise the proposed posology since it was regarded to give an overall higher exposure, as well as higher dosing outside an acceptable range around 15 µg/kg at least for most of the smaller children (lower weight bands). The applicant has revised the proposed posology (**Table *27***). The simpler posology which provides advantages for application in children is acknowledged by the CHMP. The concern of higher exposure is alleviated with the revised proposal, which proposes a weight band dosing which does not include the 15 µg/kg, namely with a 22-24 µg/kg and a 18-23 µg/kg dose, only for those children of 10-11 and 12-16 kg body weight, respectively. However, since most of the children reaching the age of 2 fall in a weight above the two lowest bands and considering the background of higher clearance (per kg bodyweight), the dosing in the children under the lowest weight bands is agreed by the CHMP. The remaining theoretical safety concerns based on the relatively high doses used in the smallest children will be addressed with the provision of final data of the study 111-206 which is imposed as a condition to the marketing authorisation. The revised posology which addressed the nonlinear effect of weight on clearance is endorsed by the CHMP.No studies have been conducted in patients with renal or hepatic impairment, and this is agreed by the CHMP based on the nature of the compound and the fact that patients in the intended indication (and age) will rarely suffer from impairment of renal or hepatic function. The missing of data is adequately reflected in section 4.2. the SmPC.

PD and exposure-response analyses

There were no designated PD studies, but PD markers were assessed as secondary and exploratory endpoints in the clinical studies. This is acceptable to the CHMP.

To test PD effects of vosoritide cGMP (as measured in plasma and urine normalised to creatinine) and CXM (measured in serum) were selected as key biomarkers. Additionally, a clinical PD/efficacy parameter – annualised growth velocity (AGV) was evaluated.

Based on the mechanism of action of vosoritide, the selected 2 biomarkers for PD/primary pharmacology analysis appear scientifically justified, as cGMP reflects activation of the target receptor (NPR-B) of vosoritide in the target (growth plate/bones) and off-target (e.g. vasculature) tissues, and as CXM is thought to reflect endochondral ossification/bone growth (Coghlan et al., 2017). The AGV parameter is broadly acknowledged and clinically relevant as it directly measures effects of vosoritide on growth; AGV was the key efficacy clinical parameter in all vosoritide studies in ACH patients.

No background information on e.g., validation in monitoring of treatment effects, clinically relevant changes, etc. was submitted on cGMP and CXM, neither it seems that such data are available. However, given that clinically relevant and reliable efficacy parameter - AGV - was also used as a PD parameter, this parameter can be utilised as a reference, and lack of biomarker validation and respective uncertainties are regarded not critical.

There were additional biomarkers analysed in the clinical data package, which showed inconsistent results. The controversial findings were explained by limited sensitivity of some markers to detect small changes in growth that occur over a short time frame.

Descriptive analysis of cGMP over the dose range of 2.5 to 30 µg/kg vosoritide suggests that the interaction between vosoritide and NPR-B receptors in various tissues takes place quickly after the substance becomes systemically available, is dose-dependent, and sustained during repeated use throughout the 2-year treatment, suggesting rapid and durable drug activity at receptors.

Serum CXM and AGV showed a dose-dependent increase, that plateaued at 15 and 30 µg/kg doses suggesting saturation of vosoritide effects at 15 µg/kg. These data support the assumed mechanism of action of vosoritide, suggesting that vosoritide affects bone growth. Further, while, additional activation of NPR-B receptors seem to be achieved with 30 µg/kg vosoritide (as indicated by cGMP) no additional PD effects on bone (as indicated by CXM and AGV) were achieved with this dose. This suggests that greater systemic pharmacological activity of vosoritide at this dose does not translate solely into the effects on the on-target tissue.

Model-based exposure-response analyses showed PK/PD dependencies which were consistent with the descriptive PD analysis. All 3 PD parameters showed correlation between the exposures and effects at the dose levels up-to 15 µg/kg. But no correlations were noted at 15 and 30 µg/kg dose levels, that supports the assumption, that there is a saturation of PD effects 15 µg/kg dose.

An Emax-Model with hill coefficient was used to describe the relationship between Cmax or AUC vs. different PD endpoints (cGMP, CXM, AGV). Estimated values for E0, EC50 and Emax had broad confidence intervals and include highly negative values for the E0-Plateau, which can hardly be explained physiologically and questions the validity of the estimated EC50 values. However, since consistent dose- and exposure-dependent changes were observed across various PD parameters (biomarkers, i.e., cGMP, CXM and clinical parameter - AGV) and across the studies, the observed findings are considered reliable and support the use of 15 µg/kg dose of vosoritide in the ACH population ≥ 5 years old.

In patients 2-<5 years of age only very limited data have been submitted due to the fact, that the study is still ongoing and blinded. Study or age-related differences (2-<5 years olds vs. older age groups) regarding the exposure-response relationship could neither be determined nor excluded based on the presented data.

Limited PD data in 2-<5-year-olds and their comparison to older patients suggest that PD effects of vosoritide are similar across various age groups.

The applicant has not conducted dedicated secondary pharmacology studies, however, evaluations including exposure-response relationship for safety relevant parameters, such as HR, BP, hypotension and injection site reactions were conducted and showed no or weak correlation with vosoritide exposure. In **study 111-301,** no effects on fluid or electrolyte balance were seen and there are also no effects indicating a modulation of the blood-brain barrier permeability.

In the **study 111-101** conducted in healthy volunteers, there was a dose-dependent increase of cGMP levels (indicating binding of BMN111 to NPR-B) both in the plasma and urine of the subjects. However, there was no correlation with the ANP (biomarker of natriuretic peptide homeostasis) or NTproCNP (marker for CNP biosynthesis) levels. The results suggest activity of the target receptor, while the endogenous CNP production does not seem to be influenced. This is acceptable to the CHMP.

Thorough QT study was not conducted. Non-clinical data on vosoritide did not suggest clinically relevant effects on cardiac repolarisation/length of QT. As to the clinical data, the applicant analysed ECGs in the patients with ACH on the exposures corresponding to a single therapeutic dose of 15 µg/kg in the pivotal **study 111-301** and its open-label extension **study 111-302**. Cases of QTcF prolongation (by >30 and < 60 msec) were reported on treatment with vosoritide. However, these changes were episodic/transient, not associated with a cardiac AE, and are assumed not to be drug-related. Vosoritide is a peptide analogue of an endogenous substance and, thus, less likely to have any impact on QT. Overall, based on the data available, there are no concerns raised in regard to potential effects of vosoritide on QT.

The applicant did not provide clinical data on drug-drug interactions. This is acceptable to the CHMP, since as discussed in the non-clinical Section 2.3.6. of the assessment report, the only approved

medicines with potential drug-drug interactions are not expected to be used in children. Furthermore, the *in vitro* investigations did not indicate potential influence on cytochromes or on transporter-based interactions.

Effects of intrinsic/extrinsic factors on PD were assessed as subgroup analyses (sex, age group, Tanner stage, strata, baseline height Z-score, and baseline AGV) in **study 111-301.** The results from the subgroup were overall consistent with the main analysis. It was noted that the lowest change in AGV was observed in the subgroup with baseline z-score of <= -6; however, no conclusions could be drawn due to the limited sample size.

2.4.5. Conclusions on clinical pharmacology

The information on vosoritide pharmacokinetics is overall sufficient. The posology is agreed by the CHMP. There are remaining theoretical safety concerns based on the relatively high doses used in the smallest children that will be addressed with the provision of final data of the study 111-206 which is imposed as a condition to the marketing authorisation. The dosing recommendations, especially with regard to the proposed weight bands, may be re-discussed when the PASS results are available.

The presented data package for testing of PD and PK/PD is overall acceptable and is considered supportive for the targeted indication and therapeutic approach.

2.5. Clinical efficacy

Four different types of comparative controls were used to support the assessment of efficacy in this application:

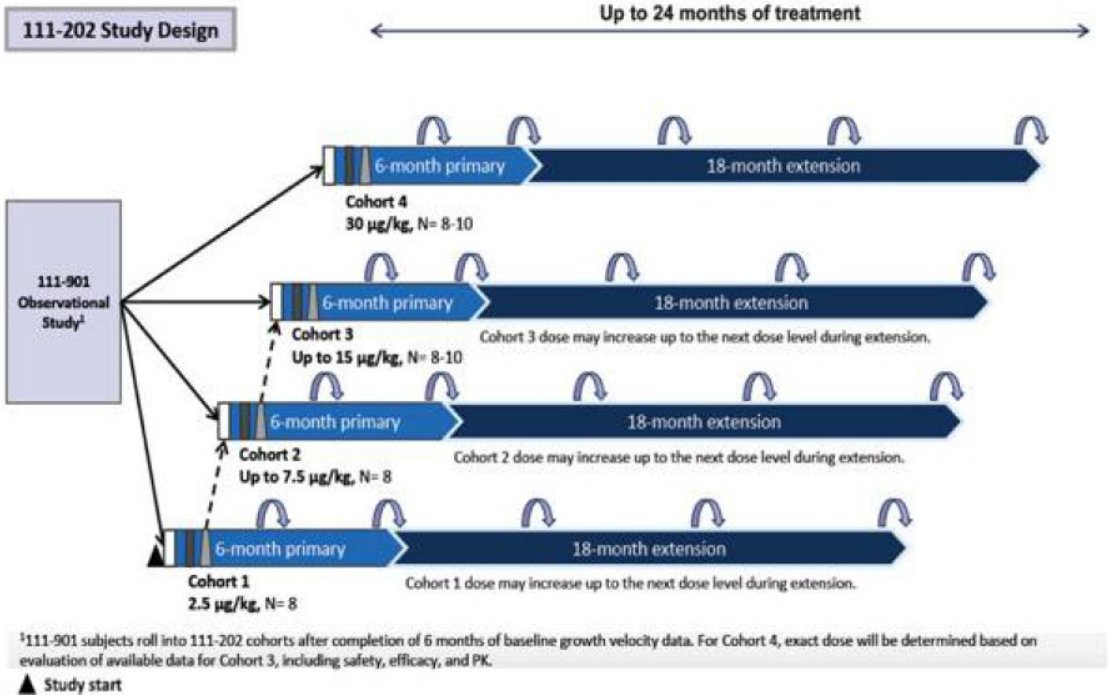
- **Placebo** – inherent with the study design of **study 111-301** including 60 subjects randomised to the vosoritide arm and 61 subjects randomised to the placebo arm;
- **Observational/placebo** – established by extending the 52-week follow-up placebo arm in **study 111-301** to include ≥6 months of pretreatment growth data from **study 111-901**;
- **External control** – subjects from the NH sources (primarily AchNH and supported by pooled 111-901, LIAISE and KAISER) were matched to the vosoritide subjects by sex and integer age at the time of the height assessment; this matching process resulted in a one to many matching with a different number of NH subjects matched to each vosoritide subject;
- **Intra-subject (baseline) control** – inherent with the designs of the Phase 2 and 3 studies assessing intra-subject comparisons of change from baseline for each variable every 6 months, whereby pretreatment growth data were collected in 111-901 for baseline AGV calculations (the number of subjects per treatment arm are presented for each individual study. The Phase 2 and 3 studies also allowed evaluation of changes in AGV prior to, and then after, either dose increases (111-202), or switching from placebo to active vosoritide (111-302).
- The applicant conducted also **Study 111-206** and the extension **Study 111-208** in patients 0 to 60 months, similarly designed as those for the older age cohort (111-301 and 302) described above.

2.5.1. Dose response study(ies)

Study 111-202

Study 111-202 was a paediatric, Phase 2, open-label dose-escalation study to assess the safety and tolerability of daily BMN111 administered to 35 subjects with a clinical diagnosis of ACH. Subjects who were 5 to 14 years of age inclusive, with documented ACH confirmed by genetic testing, had at least a 6-month period of pretreatment growth assessment in study 111-901 immediately before study entry, and who met the study eligibility criteria were selected to participate in this study. BMN111 was to be administered SC once daily provided none of the protocol-defined stopping or safety criteria occurred. On days of scheduled clinic visits, BMN111 administration was to be performed in the clinic relative to the scheduled assessments and procedures defined in the Schedule of Events. Subjects were to participate in the study as shown in ***Figure 23***.

Figure 23: Flow of participants in study 111-202



During the study, subjects received BMN111 in one of the following daily dosing regimens:

Cohort 1: daily morning dose 2.5 µg/kg

Cohort 2: daily morning dose 7.5 µg/kg

Cohort 3: daily morning dose 15.0 µg/kg

Cohort 4: daily morning dose 30.0 µg/kg

Initial treatment duration was 6 months with an optional 18-months extension study.

Efficacy Summary on dose finding from study 111-202

Initial 6-month Treatment Period

At 6 months, an increase in AGV was observed with BMN111 at 7.5, 15 and 30 µg/kg. The changes in AGV were dose dependent and achieved a plateau with 15 µg/kg. There was no additional benefit in effect on AGV seen with 30 µg/kg daily dose compared with 15 µg/kg.

Consistent dose-dependent increases of post-dose urine cGMP/Cr concentrations at 7.5 to 30 µg/kg BMN111 demonstrate systemic ligation of target NPR-B receptors and downstream systemic pharmacological activity that is durable over 24 months. The analysis of correlation between plasma PK and urine cGMP suggests that at 30 µg/kg, BMN111 activity as assessed by urine cGMP is near maximal or saturated). Based on the dose-dependent increase in AGV with 2.5 µ/kg, 7.5 µg/kg and 15 µg/kg doses, after 6-months, subjects initially treated with 2.5 µg/kg (Cohort 1) and 7.5 µg/kg (Cohort 2) were dose titrated to 15 µg/kg. Subjects on 15 µg/kg (Cohort 3) or 30 µg/kg (Cohort 4) remained on their initial doses.
Sustained dose-dependent increases in pre-dose CXM biomarker concentrations up to 15 μg/kg BMN111 suggest durable dose-dependent increases in endochondral bone formation up to 15 μg/kg BMN111. No additional CXM response was observed at 30 μg/kg BMN111, suggesting increased pharmacological activity at 30 μg/kg BMN111 indicated by post-dose urine cGMP changes was not in the target tissue and/or did not result in additional endochondral bone formation.
Together, AGV, cGMP, and CXM data support selection of the 15 µg/kg dose as the minimum dose that yields maximum on-target activity and subsequent potential treatment benefit.

Long-term Treatment Period (6-month Initial +18-month Extension)
The level of increase in AGV observed in Cohort 3 (15 μg/kg) and Cohort 4 (30 μg/kg) was maintained over a long-term treatment period, up to 24 months after the initiation of BMN111. There was no improvement in AGV with the 30 μg/kg dose versus the 15 μg/kg dose over the long-term period. At the 15 μg/kg dose, the mean AGV was maintained at approximately 6 cm/yr identical to the mean yearly growth velocity for US children for the age group recruited. This increase was maintained from 6 months to the end of the 24-month treatment period, with no evidence of tachyphylaxis.
Consistent with the observation of increase in AGV, a persistent improvement in height Z-scores was observed over the 2-year duration of the study, with an overall 0.88 SDS scores increase in height, suggesting an increase in linear growth compared with the matched non-ACH general population.
There was no evidence of worsening in body proportion ratios, implying proportional growth effect of BMN111 across upper and lower body segments and upper and lower limb segments. There was very small but statistically significant decrease in the upper to lower body segment ratio over the 2-year duration of the trial.
X-ray of the left hand to evaluate potential anatomic abnormalities and to evaluate the progression of skeletal development revealed no abnormal acceleration of skeletal maturity.
The mean maximum increase in urine cGMP was dose-dependent and sustained over 24 months of daily SC dosing. The analysis of plasma PK and urine cGMP over the 2-year duration of the study suggests that at 30 μg/kg, BMN111 activity as assessed by urine cGMP is near maximal or saturated.
There was no significant correlation between BMN111 plasma exposure and mean CXM through 24-months of daily dosing across the plasma exposure range with daily doses between 15 μg/kg and 30 μg/kg, suggesting the exposures obtained at these dose levels yield a maximal response.

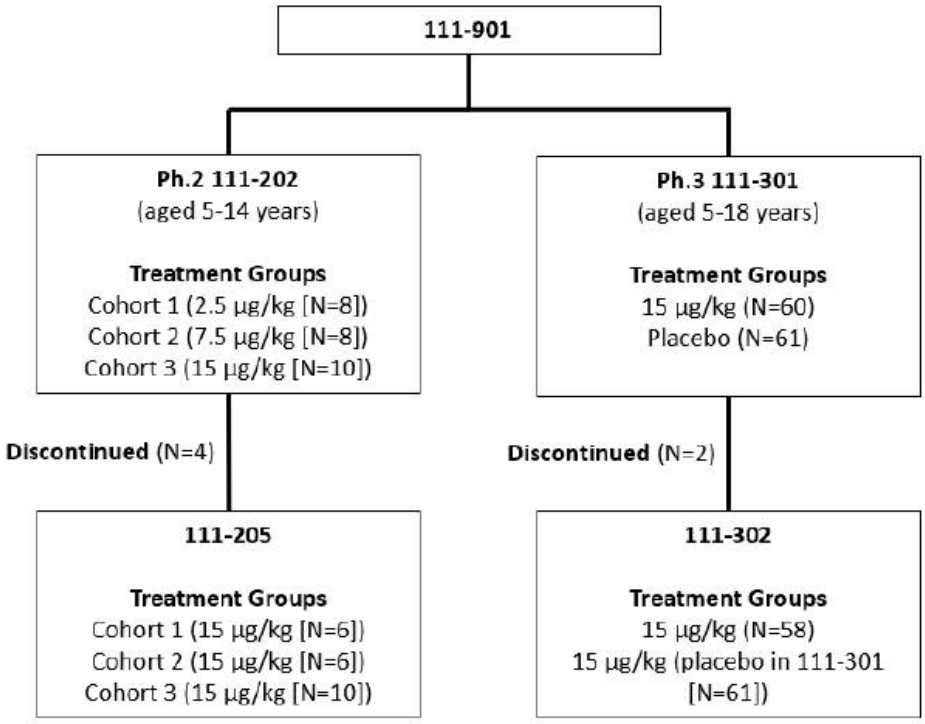
Once daily administration-justification:
The once-daily regimen was selected because it was expected to yield a maximal treatment effect based on nonclinical evidence. In the ACH mouse model, once-daily dosing with vosoritide was sufficient to restore growth in ACH mice to the levels achieved in wild type mice. Furthermore, *in vitro* studies demonstrated a once-daily regimen resulted in a similar extent of chondrocyte proliferation relative to twice daily or continuous exposure. This finding is consistent with evidence that suggests the target receptor (NPR-B) undergoes transient desensitisation following prolonged activation (Potter 2009).

2.5.2. Main studies

The efficacy analyses in this application focused on subjects who received an intended therapeutic daily dose of vosoritide 15 µg/kg. Pre-treatment growth measures collected in observational study 111-901 were used to calculate baseline AGV in studies **111-202**, **111-206** and **111-301** (pivotal study).

Pivotal trial in subjects in the age between ≥5 to ≤ 18 years contributing to the Efficacy of Vosoritide 15 µg/kg daily
Figure *24* provides an overview:

Figure 11: Overview of clinical efficacy studies in children ⩾5 to ⩽ 18 years contributing to the Efficacy of Vosoritide 15 µg/kg daily



Study 111-301: a multicentre, randomised, double-blind, placebo-controlled Phase 3 study to evaluate 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

Methods

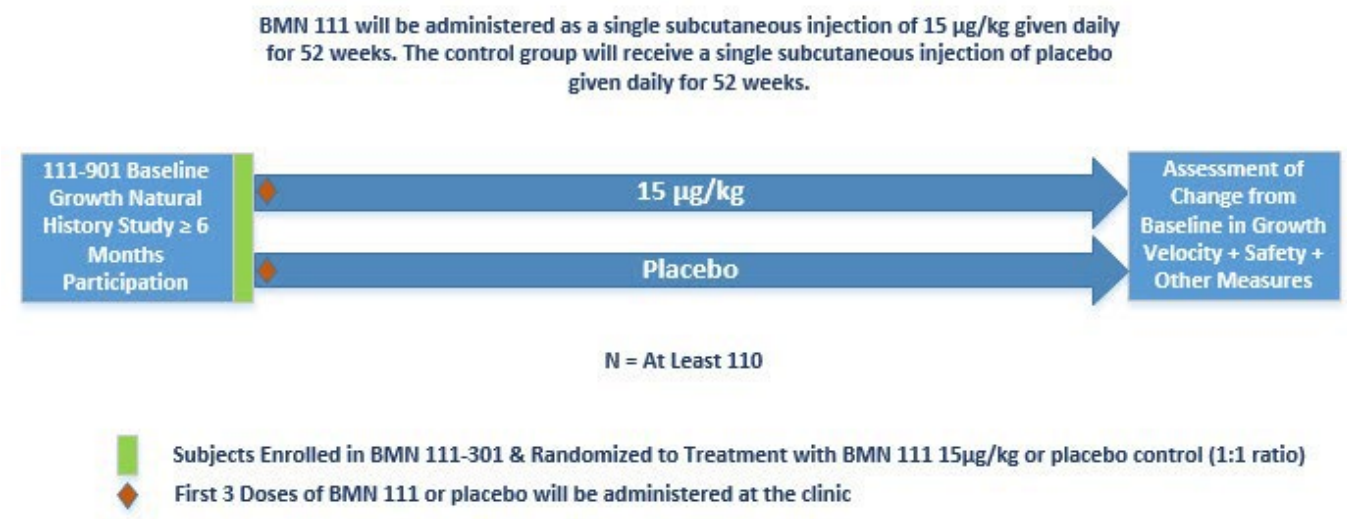
Study 111-301

The completed multicentre, randomised, double-blind, placebo-controlled Phase 3 study (111-301) 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.

Randomisation 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 randomised 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 (1 subject discontinued study due to an AE [anxiety about injections] and 1 subject discontinued study due to subject request [subject was experiencing pain during injections]). Figure 25 provides an overview about the study design:

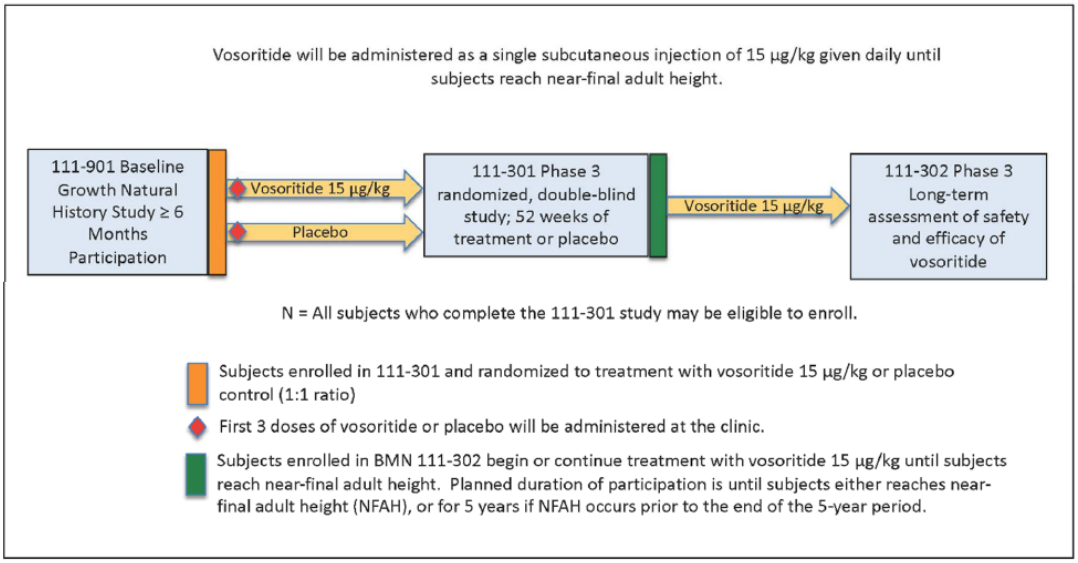
Figure 25: Study Design



Study 111-302 – extension of Study 111-301

Subjects who completed 1 year of vosoritide or placebo treatment in study 111-301 were eligible to enrol in the 111-302 extension study and continue to receive vosoritide 15 µg/kg daily (if randomised to vosoritide in study 111-301) or start vosoritide 15 µg/kg daily for the first time (if randomised to placebo in study 111-301). Subjects are followed either until they reach near-final adult height (NFAH) or for 5 years if NFAH occurred prior to the end of the 5-year period. The study was still ongoing during the marketing authorisation procedure. The initial submission included data up to a cut off of 31 October 2019. Updated data were provided during the procedure up to a cut off of 02 November 2020. A total of 119 subjects entered the study and received vosoritide 15 µg/kg daily: 58 from the vosoritide arm in 111-301 and 61 from the placebo arm in 111-301. The design for study 111-302 is presented in Figure 26.

Figure 26: Design of Study 111-302



Study Participants

Inclusion Criteria

Individuals eligible to participate in this study met all of the following criteria:

1. Parent(s) or guardian(s) willing and able to provide written, signed informed consent after the nature of the study had been explained and prior to performance of any research-related procedure. Also, subjects under the age of majority willing and able to provide written assent (if required by local regulations or the IRB/IEC/REB) after the nature of the study had been explained and prior to performance of any research related procedure. Subjects who reached the age of majority while the study was ongoing were asked to provide their own written consent.

2. 5 to < 18 years old at study entry.

3. Had ACH, documented by clinical grounds and confirmed by genetic testing.

4. Had at least a 6-month period of pre-treatment growth assessment, including standing height, and were currently active participants in 111-901.

5. Females ≥ 10 years old or who had begun menses must have had a negative pregnancy test at the Screening Visit and were willing to have additional pregnancy tests during the study.

6. If sexually active, willing to use contraception as specified in Section 9.3.3 of the protocol, Appendix 16.1.1 (for Protocol Amendment 4) or willing to use a highly effective method of contraception while participating in the study (for Protocol Amendment 3).

7. Ambulatory and able to stand without assistance.

8. Willing and able to perform all study procedures.

9. Caregivers willing to administer daily injections to the subjects and complete the required training.

Main Exclusion Criteria for Enrolment:

Individuals who met any of the following exclusion criteria were not eligible to participate in the study:

1. Had hypochondroplasia or short stature condition other than ACH (e.g., trisomy 21, pseudoachondroplasia).

2. Had any of the following:

- Hypothyroidism or hyperthyroidism.
- Insulin-requiring diabetes mellitus.
- Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others).
- Inflammatory bowel disease.
- Autonomic neuropathy.

3. Had a history of any of the following:

- Renal insufficiency defined as serum creatinine > 2 mg/dL.
- Chronic anaemia.
- Baseline systolic blood pressure (SBP) < 70 mmHg or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms ie, dizziness, fainting) or recurrent symptomatic orthostatic hypotension.
- Cardiac or vascular disease (Cardiac dysfunction, abnormal echocardiogram including abnormal left ventricle mass at Screening Visit, hypertrophic cardiomyopathy, pulmonary hypertension, congenital heart disease, cerebrovascular disease, aortic insufficiency or other clinically significant valvular dysfunction, clinically significant atrial or ventricular arrhythmias.

4. Had a clinically significant finding or arrhythmia on screening ECG that indicated abnormal cardiac function or conduction or Fridericias corrected QT interval (QTc-F) > 450 msec.

5. Had an unstable condition likely to require surgical intervention during the study (including progressive cervical medullary compression or severe untreated sleep apnoea).

6. Evidence of decreased growth velocity (AGV < 1.5 cm/year) as assessed over a period of at least 6 months or of growth plate closure (proximal tibia, distal femur) through bilateral lower extremity X-rays including both anterior-posterior (AP) and lateral views.

Moreover, a documented Vitamin D deficiency, any other investigational agent prior to completion of the study period or within 6 months before the screening Visit, current chronic therapy with antihypertensive medications or any treatment with growth hormone , insulin-like growth factor 1, or anabolic steroids in the previous 6 months or treatment greater than 6 months at any time were excluded.

Treatments

Subjects received either vosoritide 15 µg/kg or placebo, as allocated, for the duration of the 52-week treatment period. The dosing schedule was a **single daily SC injection** given 7 days a week. Vosoritide or placebo was initially administered by site staff in the clinic. After subjects were tolerating

vosoritide or placebo well and specified criteria had been met, caregivers were able to administer vosoritide or placebo at home.

Objectives

Table *28* provides an overview of the study objectives in Study 111-301:

Table 28: Overview of the objectives in Study 111-301

Primary objective
• Evaluate change from baseline in annualised growth velocity (AGV) at 52 weeks in subjects treated with vosoritide compared with control subjects in the placebo group
Secondary objective
• Evaluate change from baseline in height Z-score in subjects treated with vosoritide compared with control subjects in the placebo group at 52 weeks
• Evaluate change from baseline in upper to lower segment body ratio in subjects treated with vosoritide compared with control subjects in the placebo group at 52 weeks
• Evaluate change from baseline in body proportion ratios of the extremities
• Evaluate the effect of vosoritide on bone morphology and pathology by X-ray and dual X-ray absorptiometry (DXA)
• Evaluate potential changes in HRQoL as measured by the Quality of Life in Short Stature Youth (QoLISSY) and Pediatric Quality of Life Inventory (PedsQL) questionnaires
• Evaluate potential changes in functional independence as measured by the Functional Independence Measure for Children (WeeFIM) clinician-reported outcome
• Evaluate safety and tolerability of vosoritide in children with ACH
• Evaluate the pharmacokinetics (PK) of vosoritide
• Evaluate the immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures
• Evaluate change from baseline in bone metabolism biomarkers
Exploratory objective
• Evaluate sleep study scores by polysomnography in a subset of subjects
• Evaluate biomarkers of vosoritide activity
• Evaluate genomic biomarkers

Outcomes/endpoints

Table *29* provides an overview of the endpoint assessment in Study 111-301:

Table 29: Overview of the Endpoint Assessment in Study 111-301

Primary Endpoint/Assessment
Change from baseline in AGV at Week 52. The primary estimand was the difference between the vosoritide group and the placebo group in the mean change from baseline in AGV at the 52-week time point determined from a covariate adjusted ANCOVA model that includes all subjects in the Full Analysis Set (FAS).
Second Endpoint/Assessment
Change from baseline in height Z-score at Week 52. This was a key secondary endpoint for which Type I error was controlled allowing for confirmatory testing.

Change from baseline in upper to lower body segment ratio at Week 52. This was a key secondary endpoint for which the Type I error was controlled allowing for confirmatory testing.
Change from baseline to Week 52 for: Upper Arm Length to Lower Arm (Forearm) Length Ratio Upper Leg Length (Thigh) to Knee to Heel Length Ratio Upper Leg Length (Thigh) to Tibial Length Ratio Arm Span to Standing Height Ratio
Bone age, bone age Z-score, bone mineral density (BMD), BMD Z-score, and bone mineral content (BMC).
QoLISSY and PedsQL domain and total scores
WeeFIM domain and total scores
Incidence, severity and relationship to study drug of all treatment-emergent adverse events (TEAEs). Procedures/intervention/surgery, imaging assessments, clinical laboratory assessments, Child Behavior Checklist (CBCL), vital signs, electrocardiogram (ECG), and clinical hip assessment
AUC0-∞, AUC0-t, Cmax, Tmax, t1/2, CL/F, Vz/F
Anti-vosoritide total antibody (TAb) Anti-vosoritide antibody cross-reactivity with endogenous CNP, ANP, and BNP (TAb) Anti-vosoritide neutralizing antibody (NAb)
Collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP)
Exploratory Endpoint/Assessment
Presence and severity of sleep-disordered breathing overnight by measurement of blood oxygen saturation, pulse rate, and airflow (optional)
Urine cyclic guanosine monophosphate (cGMP) normalised by creatinine concentration
Exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signaling

Sample size

With 55 subjects planned in each of the two randomised groups (vosoritide and placebo), the power to detect a difference of 1.75 cm/year between the vosoritide group and the placebo group in change from baseline in AGV at 12 months was approximately 90%, assuming the pooled standard deviation (SD) of the change from baseline in AGV is 2.80, using a two-sided two-sample t-test at the 0.05 significance level. The power calculation was based on data from study 111-202 (a Phase 2, open-label, sequential cohort dose-escalation study of vosoritide in children with ACH) and 111-901.

Randomisation

Subjects were randomised 1:1 to vosoritide 15 µg/kg or placebo, using an interactive voice/web response (IXRS) system. In the original protocol, the randomisation was stratified by sex and age (< 11, ≥ 11 years). In Amendment 2 (dated 27 April 2017), the randomisation was updated and stratified (4 strata) by Tanner stage (Stage I or Stage > I, with no greater than 20% of subjects Stage > I) and sex (50% of each sex was to be enrolled, with neither to exceed 55%). Two subjects were enrolled according to the strata in the original study protocol.

Blinding (masking)

Vosoritide and placebo were packaged and labelled in the same way, with the study number and a unique identification number. Vosoritide placebo was designed to be comparable in appearance to vosoritide, was reconstituted in the same way, and contained all of the components of the drug product (except vosoritide) including commercially sourced sterile WFI. An independent third-party vendor developed the randomisation schedule so that BioMarin and site personnel did not know the treatment assignment. Subjects and the participating site members were blinded to study treatment.

Statistical methods

All efficacy analyses were performed on the Full Analysis Set (FAS) which included all randomised subjects. The Per-Protocol (PP) population was determined consistent with the ICH E9 Guideline and was defined as a subset of the FAS population who were compliant with the protocol. Safety analyses were performed on the Safety Population, defined as a subset of the FAS who received at least one dose of double-blinded vosoritide or placebo.

Analysis of covariance (ANCOVA) models were used to determine the treatment difference between vosoritide and placebo at 52 weeks. Unless otherwise specified, all models included the following baseline covariates: Treatment group, Stratum (Male Tanner Stage I, Female Tanner Stage I, Male Tanner Stage > I, Female Tanner Stage > I), age at baseline, AGV at baseline, Height Z-score at baseline.

The following primary hypothesis was tested (two-tailed):

H_0: Difference in mean AGV change from baseline at Week 52 between vosoritide group and the placebo group = 0

H_a: Difference in mean AGV change from baseline at Week 52 between vosoritide group and the placebo group ≠ 0

The study was considered positive if the two-sided p-value in favour of vosoritide was < 0.05.

Results of the statistical analyses were provided in separate tables, including the least-squares (LS) mean change from baseline at Week 52 for each treatment group, the treatment difference in LS means (calculated as vosoritide – Placebo), the 95% confidence interval (CI) for the treatment difference, and corresponding 2-sided p-value.

Height Z-score and upper to lower body segment ratio were analysed using the same methods and estimand formulation as the primary analysis.

The overall type I family-wise error rate for testing the primary and key secondary efficacy endpoints was controlled at the two-sided 0.05 significance level using a 3-step serial gatekeeping multiple comparison procedure (MCP). Following this MCP, advancement to the next step occurred only if the null hypotheses within a step and the previous step(s) were all rejected at the significance level of 0.05 in favour of vosoritide.

Subjects who discontinued from study drug were encouraged to remain in the study and their non-missing height measurements were then used in calculating their AGV. In the event that missing data did occur despite all efforts, the missing standing heights were imputed.

The proposal was to apply multiple imputation (MI) techniques with pattern-mixture models. In order to apply this method, each imputation required at least 5 subjects in the same treatment group who also discontinued treatment prematurely at a similar time point and had standing height assessments post treatment discontinuation. In the situation where insufficient data from patients discontinuing

treatment but not study was available, an alternative imputation technique was proposed in the SAP, whereby the missing standing height values at Week 52 (ie, Day 365) were imputed by applying the baseline AGV (cm/year) to the last available height assessment. This method was applied.

Results

Participant flow

Subject disposition is presented in Figure 27 and **Table *30***. A total of 121 subjects were enrolled into the study; 61 subjects were randomised to receive placebo and 60 subjects to receive 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.

Figure 12: Subject Disposition - Full Analysis Set

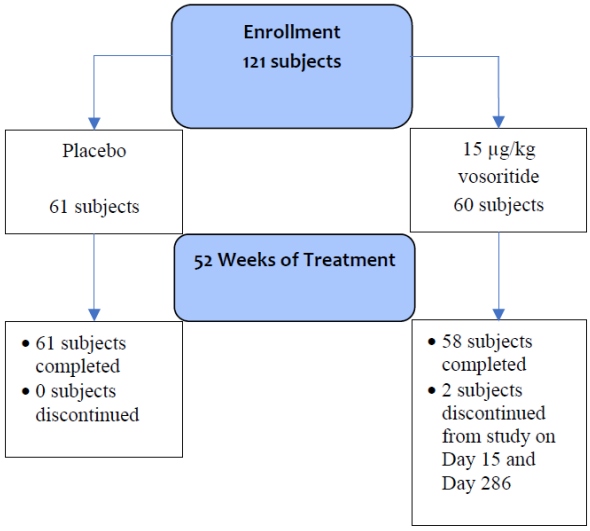


Table 30: Subject Disposition - Full Analysis Set

Category	Placebo (N = 61)	15 µg/kg Vosoritide (N = 60)	Overall (N = 121)
Subject's treatment / study status, n (%)[a]			
Randomized but not treated	0	0	0
Treated	61 (100.0)	60 (100.0)	121 (100.0)
Completed treatment	61 (100.0)	58 (96.7)	119 (98.3)
Completed study	61 (100.0)	58 (96.7)	119 (98.3)
Discontinued from study	0	0	0
Discontinued from treatment	0	2 (3.3)	2 (1.7)
Completed study	0	0	0
Discontinued from study	0	2 (3.3)	2 (1.7)
Subject's study status, n (%)[a]			
Completed study	61 (100.0)	58 (96.7)	119 (98.3)
Discontinued from study	0	2 (3.3)	2 (1.7)

[a] Percentages were calculated using the total number of subjects in the full analysis set (N for each treatment group) as the denominator

Recruitment

Study Start Date: 24 November 2016

Study End Date: 30 October 2019

Date of Study Report: 21 April 2020

The study was conducted by 24 principal investigators at 24 study centres in 7 countries (US (11 centre) , Australia (2 centre),Germany (2 centre), UK (2 centre), Japan (3 centre), Spain (3 centre), Turkey (1 centre).

Conduct of the study

There were four amendments during the trial conduct (**Table *31***).

Table 31: Summary of 111-301 Protocol Amendments – Key changes

Amendment 1 28 November 2016
Addition of Section 9.3.3 Use of Birth Control During and After Study Participation
Amendment 2 27 April 2017
Upper limit of age range increased from less than 15 years old to less than 18 years old
Stratification /randomisation to be conducted by Tanner stage rather than by age group Criterion for removing subjects from treatment or assessment, "Subject has reached near adult height in the judgment of the investigator…" revised to be more specific
ISR photo language has been revised
Inclusion criterion #1, regarding informed consent, revised to state the subjects who reach age of 18 years while study is ongoing are asked to provide their own written consent

Inclusion criteria #4 revised to elaborate on requirements for entering 111-301 from 111-901
New section, Procedures due to Achondroplasia added
Pregnancy Testing, language added stating that start date of menses is captured
New section, Events of Special Interest, added
Statistical Methods and Determination of Sample Size, has been substantially revised.
Amendment 3 05 January 2018
Evaluation of change from baseline in bone metabolism biomarkers moved from exploratory to secondary objectives
Exclusion criterion #6 revised to include evidence of decreased growth velocity (AGV < 1.5 cm/year) as assessed over a period of at least 6 months
Exclusion criterion #15 revised to state that subjects with previous bone-related surgery may enroll if surgery occurred at least 6 months prior to screening, rather than 12 months, excluding tooth extraction
Salivary cortisol, serum prolactin, FSH/LH, and cognitive assessment with the CBCL added as safety assessments
Section 9.3.3, Use of Birth Control During and After Study Participation, progestogen-only hormonal contraception removed
DXA scans to no longer include tibia scans
Section 9.12.5.9, Hip Clinical Assessment, requirement to be completed by a physician, ie, the investigator or sub-investigator changed to assessment by an appropriately qualified health care professional
Amendment 4 01 February 2019
The following exploratory objectives moved to secondary: Change from baseline in body proportion ratios of the extremities, Effect of vosoritide on bone morphology and pathology by X-ray and DXA Changes in HRQoL and functional independence
Contraception in inclusion criteria and birth control during and after the study updated
Duration of subject participation updated to account for 4-week safety follow-up after Week 52
Primary and secondary efficacy variables separated so that new secondary variables are incorporated
Replaced "18 years of age" with "age of majority"
Inserted "In Japan, subject enrollment was staggered initially, with a minimum of a 2-week window between the first 4 subjects enrolled"

Baseline data

An overview of demographics at baseline is provided in **Table *32***.

Table 32: Demographics - Full Analysis Set

Demographic Variable	Placebo (N = 61)	Vosoritide 15 µg/kg (N = 60)	Overall (N = 121)
Age at Day 1 (years)			
n	61	60	121
Mean (SD)	9.06 (2.47)	8.35 (2.43)	8.71 (2.47)
Median	9.31	7.78	8.99
Min, Max	5.1, 14.9	5.1, 13.1	5.1, 14.9
Age at Day 1, n (%)[a]			
≥ 5 to < 8 years	24 (39.3)	31 (51.7)	55 (45.5)
≥ 8 to < 11 years	24 (39.3)	17 (28.3)	41 (33.9)
≥ 11 to < 15 years	13 (21.3)	12 (20.0)	25 (20.7)
Sex, n (%)[a]			
Male	33 (54.1)	31 (51.7)	64 (52.9)
Female	28 (45.9)	29 (48.3)	57 (47.1)
Race, n (%)[a]			
White	41 (67.2)	45 (75.0)	86 (71.1)
Asian	13 (21.3)	10 (16.7)	23 (19.0)

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

a Percentages were calculated using the total number of subjects in the full analysis set (N for each treatment group) as the denominator.

Baseline Disease Characteristics

A summary of baseline characteristics for the FAS is presented in Table ***33***. Weight and BMI Z-scores were derived using age-sex specific reference data (mean and SDS) for average stature children per the CDC. Data is presented as SDS above or below the age-specific reference (which is equivalent to 0).

Table 33: Baseline Characteristics - Full Analysis Set

Characteristic Variable	Placebo (N = 61)	Vosoritide 15 µg/kg (N = 60)	Overall (N = 121)
Tanner Stage[a], n (%)[b]			
I	48 (78.7)	48 (80.0)	96 (79.3)
> I	13 (21.3)	12 (20.0)	25 (20.7)
Weight (kg)			
n	61	60	121
Mean (SD)	24.62 (9.07)	22.88 (7.96)	23.76 (8.55)
Median	23.00	21.33	21.50
Min, Max	11.6, 68.9	13.6, 53.0	11.6, 68.9
Weight Z-Score			
n	61	60	121
Mean (SD)	−1.62 (1.44)	−1.49 (1.19)	−1.56 (1.32)
Median	−1.52	−1.27	−1.45
Min, Max	−5.1, 2.6	−4.8, 1.6	−5.1, 2.6
BMI (kg/m^2)			
n	61	60	121
Mean (SD)	22.64 (5.43)	22.22 (3.44)	22.43 (4.54)
Median	21.88	21.56	21.78

BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation.

[a] Tanner Stage (I, > I) is determined using the genitalia and breast Tanner Stage for males and females respectively.

[b] Percentages were calculated using the total number of subjects in the full analysis set (N for each treatment group) as the denominator.

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

Numbers analysed

Table 34: Analysis Populations - Full Analysis Set

Analysis Population	Placebo (N = 61)	Vosoritide 15 µg/kg (N = 60)	Overall (N = 121)
Subjects randomized, n (%)[a]	61 (100.0)	60 (100.0)	121 (100.0)
Full Analysis Set, n (%)[a]			
Included	61 (100.0)	60 (100.0)	121 (100.0)
Per-Protocol population, n (%)[a]			
Included	57 (93.4)	56 (93.3)	113 (93.4)
Excluded	4 (6.6)	4 (6.7)	8 (6.6)
Reason for exclusion			
Did not complete allocated treatment[b]	2 (3.3)	4 (6.7)	6 (5.0)
Assigned to incorrect strata	1 (1.6)	0	1 (0.8)
Major protocol deviation[c]	1 (1.6)	0	1 (0.8)
Failed inclusion/exclusion criteria	0	0	0
Safety population, n (%)[a]			
Included	61 (100.0)	60 (100.0)	121 (100.0)
Pharmacokinetic population, n (%)[a]			
Included	0	60 (100.0)	60 (49.6)
Immunogenicity population, n (%)[a]			
Included	61 (100.0)	60 (100.0)	121 (100.0)

a Percentages were calculated using the total number of subjects in the full analysis set (N for each treatment group) as the denominator.

b Subject who did not complete the treatment originally allocated (ie, did not receive the assigned treatment [vosoritide or placebo]), did not have a Week 52 visit within the defined visit window and were not at least 90% compliant with study drug).

c Subject took growth hormone or gonadotropin-releasing hormone, or had limb lengthening on-study.

Outcomes and estimation

a.) <u>Primary Endpoint</u>: Change from Baseline in AGV at Week 52 (ANCOVA Model) – Full Analysis Set in Pivotal trial 111-301

The primary efficacy variable in **study 111-301** was the annualised growth velocity which is a 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.

Table 35: Outcome in Primary Endpoint: Change from Baseline in AGV at Week 52 (ANCOVA Model) – Full Analysis Set in Pivotal trial 111-301

Annualised Growth Velocity (cm/year)	Placebo (N = 61)	Vosoritide 15 µg/kg (N = 60)
Baseline		
n	61	60
Mean (SD)	4.06 (1.20)	4.26 (1.53)
Median	4.13	4.14
Min, Max	1.5, 6.7	−0.1, 6.9
Week 52		
n	61	60c
Mean (SD)	3.94 (1.07)	5.61 (1.05)
Median	3.97	5.75
Min, Max	1.3, 6.5	2.3, 8.4
Change from baseline		
n	61	60
Mean (SD)	−0.12 (1.74)	1.35 (1.71)
Median	−0.37	1.44
Min, Max	−3.6, 4.5	−2.1, 6.5
LS mean change from baseline (95% CI)	0.13 (−0.18, 0.45)	1.71 (1.40, 2.01)
Difference in LS mean change from baseline (95% CI)[a]		1.57 (1.22, 1.93)
P-value[b]		<0.0001

AGV, annualised growth velocity; ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; LS, least-square; Max, maximum; Min, minimum; SD, standard deviation

[a] Difference is 15 µg/kg vosoritide minus placebo.

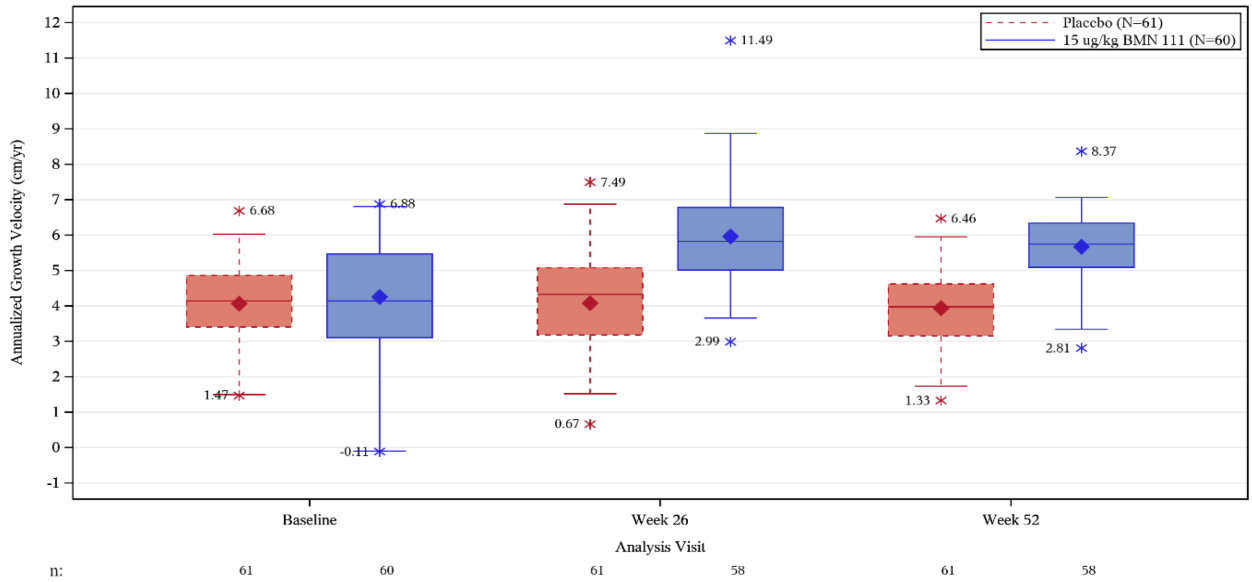
[b] Two-sided p-value.

[c] Two subjects in the vosoritide group discontinued from the study before Week 52. The values for these 2 subjects were imputed for this analysis.

LS means and difference in LS means were obtained from an analysis of covariance model. Model terms included stratum defined by sex and Tanner stage, treatment, baseline age, baseline AGV and baseline height Z-score. AGV at a Post-baseline Visit is defined as [(Height at Post-baseline Visit - Height at Baseline)/(Date of Post-baseline Visit - Date of Baseline Assessment)] x 365.25. Missing assessments at Week 52 were imputed as described in the SAP

A box plot of AGV over time is presented in Figure 28.

Figure 28: Box Plot of AGV over Time in study 111-301– Full Analysis Set



AGV, annualised growth velocity; FAS, full analysis set Box plot displays the 25th and 75th quartiles (box edges), the median (midline), the mean (diamond symbol) and the 2.5th and 97.5th percentiles (whiskers). Asterisks represent outliers. AGV at a Post-baseline Visit is defined as [(Height at Post-baseline Visit - Height at Baseline)/(Date of Post-baseline Visit - Date of Baseline Assessment)] x 365.25.

In the **PP population**, the results were similar to the FAS ANCOVA analysis with a LS mean change from baseline of 0.22 cm/year (95% CI: −0.16, 0.59) in the placebo group and 1.80 cm/year (95% CI: 1.45, 2.16) in the vosoritide group.

The difference in LS mean change from baseline was statistically significant in favor of vosoritide (1.58, 95% CI: 1.22, 1.95; p<0.0001). The difference in effect on AGV between placebo and vosoritide was observed already at Week 26 and was maintained to Week 52.

b.) <u>Key secondary outcome</u>: Change from Baseline in Height Z-score at Week 52 (ANCOVA Model) – Full Analysis Set in study 111-301

The key secondary efficacy variable in **Study 111-301** was height Z-score. Data are presented as SDS above or below the age-specific reference (equivalent to 0) for average stature children calculated using CDC or WHO, as applicable.

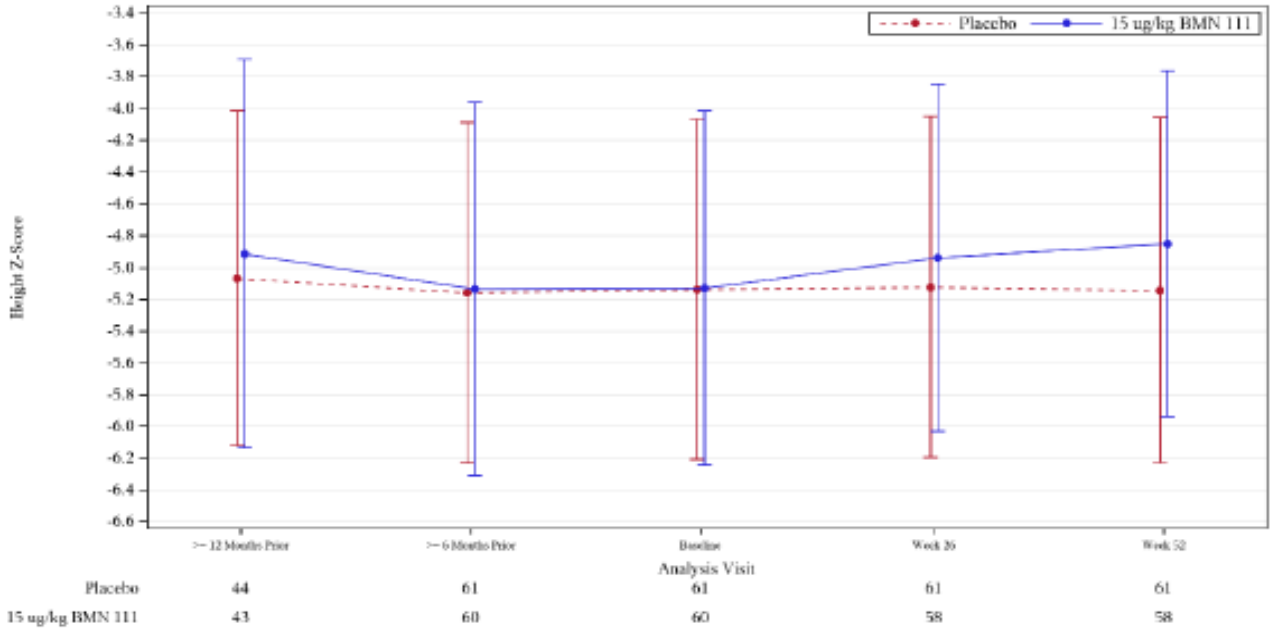
Table 36: Change from Baseline in Height Z-score at Week 52 (ANCOVA)

	Placebo	Vosoritide
Baseline		
n	61	60
Mean (SD)	−5.14 (1.07)	−5.13 (1.11)
Median	−5.1	−5.27
Min, Max	−7.9, −2.7	−7.7, −1.1
Week 52		
n	61	60
Mean (SD)	−5.14 (1.09)	−4.89 (1.09)
Median	−5.1	−4.86
Min, Max	−7.8, −2.8	−7.5, −1.1
Change from baseline		

n	61	60
Mean (SD)	0.00 (0.28)	0.24 (0.32)
Median	0.00	0.19
Min, Max	−0.8, 0.5	−0.4, 1.0
LS mean change from baseline (95% CI)	**−0.01 (−0.10, 0.09)**	**0.27 (0.18, 0.36)**
Difference in LS mean change from baseline (95% CI)[a]	**-**	**0.28 (0.17, 0.39)**

AGV, annualised growth velocity; ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; LS, least-square; Max, maximum; Min, minimum; SD, standard deviation a Difference is 15µg/kg vosoritide minus placebo. b Two-sided p-value. LS means and difference in LS means were obtained from an analysis of covariance model. Model terms included stratum defined by sex and Tanner stage, treatment, baseline age, baseline AGV and baseline height Z-score. Z-Scores were derived using age-sex specific reference data (means and SDS) for average stature children per the Centers for Disease Control and Prevention. Missing assessments at Week 52 were imputed as described in the SAP.

Figure 29: Mean (SD) Height Z-scores Over Time in 111-301– Full Analysis Set



FAS, full analysis set; SD, standard deviation; Z-Scores were derived using age-sex specific reference data (means and SDS) for average stature children per the Centers for Disease Control and Prevention

c.) Key secondary outcome: Upper to Lower Body Segment Ratio

A key secondary efficacy variable in **Study 111-301** was the upper to lower body segment ratio. This is an 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.

Table 37: Change from Baseline in Upper to Lower Body Segment Ratio at Week 52 (ANCOVA Model) – Full Analysis Set in trial 111-301

Upper to Lower Body Segment Ratio	Placebo	Vosoritide 15 µg/kg
Baseline		
N	61	60
Mean (SD)	2.01 (0.21)	1.98 (0.20)
Median	1.99	2.01
Min, Max	1.5, 2.6	1.3, 2.3
Week 52		
N	61	60
Mean (SD)	1.98 (0.18)	1.95 (0.20)
Median	1.96	1.97
Min, Max	1.6, 2.4	1.3, 2.3
Change from baseline		
N	61	60
Mean (SD)	−0.03 (0.09)	−0.03 (0.11)
Median	−0.01	−0.04
Min, Max	−0.4, 0.1	−0.2, 0.6

	−0.02 (−0.05, 0.01)	−0.03 (−0.06, 0.00)
Difference in LS mean change from baseline (95% CI)a		−0.01 (−0.05, 0.02)
P-valueb	-	0.5060

ANCOVA, analysis of covariance; CI, confidence interval; LS, least-square; SD, standard deviation Source: Table 14.2.3.2

a Difference is 15µg/kg vosoritide minus placebo.

b Two-sided p-value.

LS means and difference in LS means were obtained from an analysis of covariance model. Model terms included stratum defined by sex and Tanner stage, treatment, baseline age, baseline AGV, baseline height Z-score and baseline upper to lower body segment ratio.

The LS mean change from baseline to Week 52 in upper to lower body segment ratio was −0.02 (95% CI: −0.05, 0.01) in the placebo group and −0.03 (95% CI: −0.06, 0.00) in the vosoritide group. The difference in LS mean change from baseline was −0.01 (95% CI: −0.05, 0.02; p<0.5060) indicating that there was no evidence of a difference between treatment groups.

In the PP population, the results were similar to the FAS ANCOVA analysis, with a LS mean change from baseline of −0.03 (95% CI: −0.07, 0.01) in the placebo group and −0.04 (95% CI: −0.07, −0.01) in the vosoritide group. Again there was no evidence of a difference between treatment groups in LS mean change from baseline was not statistically significant (−0.01, 95% CI: −0.05, 0.02; p<0.5291).

d.) <u>Secondary Outcome</u>: Standing Height

Standing height was a secondary endpoint. A positive, consistent and durable effect on AGV will ultimately result in a meaningful incremental increase in standing height, standing height was thus used to quantify treatment benefit on growth over the long-term period.

The results of the ANCOVA model analysis of change from baseline in standing height at Week 52 is presented in Table 38.

Table 38: Change from Baseline in Standing Height at Week 52 (ANCOVA Model) – Full Analysis Set

Standing Height (cm)	Placebo (N = 61)	Vosoritide 15 µg/kg (N = 60)
Baseline		
n	61	60
Mean (SD)	102.94 (10.98)	100.20 (11.90)
Median	104.63	98.58
Min, Max	79.9, 129.3	80.1, 136.8
Week 52		
n	61	60
Mean (SD)	106.87 (10.84)	105.80 (12.03)
Median	108.07	104.88
Min, Max	84.9, 134.0	85.5, 142.3
Change from baseline		
n	61	60
Mean (SD)	3.93 (1.08)	5.59 (1.06)
Median	3.97	5.72
Min, Max	1.3, 6.6	2.3, 8.2
LS mean change from baseline (95% CI)	4.29 (3.97, 4.61)	5.86 (5.56, 6.17)
Difference in LS mean change from baseline (95% CI)[a]	-	1.57 (1.21, 1.93)
P-value[b]	-	<0.0001

ANCOVA, analysis of covariance; CI, confidence interval; LS, least-square; Max, maximum; Min, Minimum; SD, standard deviation

[a] Difference is 15µg/kg vosoritide minus placebo.

[b] Two-sided p-value. LS means and difference in LS means were obtained from an analysis of covariance model. Model terms included stratum defined by sex and Tanner stage, treatment, baseline age, baseline AGV, baseline height Z-score and baseline standing height.

Missing assessments at Week 52 were imputed as described in the SAP.

Spaghetti plots of individual standing height data plotted over time by treatment group and sex for average stature age-sex-specific reference data and ACH reference age-sex specific reference data from Hoover-Fong 2017 were shown in addition regarding this outcome, which indicate that growth for the majority of subjects prior to treatment was according to expected growth for untreated ACH. Post-baseline height trajectories show an incline for the vosoritide group compared to placebo subjects whose growth tracks continues to track according to children with untreated ACH.

e.) <u>Secondary Endpoint outcomes</u> on Quality of life and functional independence assessment in Study 111-301

Activities of daily living and functional independence were assessed using the:

- **Functional Independence Measure for Children (WeeFIM) instrument** - an assessment tool that measures functional performance across three domains (self- care, mobility and cognition) assessed by the clinician, and with input from the parent/caregiver

The WeeFIM instrument measures functional performance across 3 domains from the parent/caregiver's perspective (self-care [score range 8 to 56], mobility [score range 8 to 35], and cognition [score range 8 to 35]) and provides a total score between 18 and 126. Higher scores reflect greater functional independence in self-care, mobility, and social cognitive skills (WeeFIM Clinical Guide v6.0 2006). At Week 52, no difference was observed in change from baseline between the vosoritide and placebo groups in any of the domains.

- **The Pediatric Quality of Life Inventory (PedsQL) 4.0-generic score scales** - a generic tool to measure HRQoL in children and adolescents (child self-report and parent-report versions) consisting of questions across four domains
- Median change from baseline to Week 52 for PedsQL score (caregiver and self-reported) **at Week 52 shows no difference** in change from baseline between the vosoritide and placebo groups in any of the PedsQL domains for caregiver or self-reported. **The Quality of Life in Short Statured Youth (QoLISSY) questionnaire** – a disease-specific patient-reported outcome tool designed for short-stature youth (child self-report and parent report versions) consisting of questions across seven domains.

At Week 52, no difference was observed in change from baseline between the vosoritide and placebo groups in any of the caregiver reported QoLISSY domains.

Long term efficacy – available results from ongoing Study 111-302

During the procedure, the applicant provided analyses of the ongoing extension study 111-302 performed with a 02 November 2020 data cut-off to assess key efficacy endpoints, AGV, height Z-score, standing height, and upper to lower body segment ratio.

117 out of 121 subjects from Study 111-301 were continuing in Study 111-302. A total of 56 subjects had been treated for at least 2 years (initially randomised to vosoritide in 111-301), and 61 subjects had been treated with vosoritide for 1 year (initially randomised to placebo in 111-301). By the data cut-off date, 14 subjects completed 130-weeks on treatment with vosoritide, with 2 subjects reaching 156 weeks and 1 subject reaching 182 weeks.

In summary, the analyses of the 52-week data from Study 111-302 showed that the effect on growth, observed in the first 52 weeks of treatment with vosoritide in Study 111-301, is maintained in the second year of treatment.

In subjects on continuous vosoritide treatment after 2 years, the improvement in AGV observed at 52 weeks (mean AGV 5.67 cm/year) was maintained after 104 weeks (mean AGV 5.64 cm/year). The maintenance of positive effect on AGV resulted in a continuous improvement in height Z-score, with a change from baseline of +0.24 SDS after 52 weeks of treatment and to +0.45 SDS after 104 weeks of treatment. Improvement in the upper to lower body segment ratio was also observed, with a change from baseline of -0.03 after 52 weeks and -0.09 after 104 weeks of treatment. Furthermore, the treatment effect continued to be maintained beyond 2 years as observed for 14 subjects with 130 weeks on-treatment data with vosoritide.

Efficacy of vosoritide was also confirmed in subjects with one year on-treatment data, after switching from placebo to vosoritide treatment in 111-302, who showed a similar improvement in growth velocity after switching from placebo compared to those originally randomised to vosoritide and treated for one year in 111-301.

In a comparative analyses of growth data from the first year versus the second year of treatment with vosoritide, there was no difference in the LS mean change from baseline in study 111-302 to Week 52 for height, height Z-score, and upper to lower body segment ratio, demonstrating the treatment effect in Year 1 was maintained in Year 2.

For the 24-month analyses, which compared the untreated versus treated subjects over a 2-year period, the results were consistent with the conclusion that the treatment effect was maintained in the second year. The LS mean difference for AGV in the second year of treatment was similar to the difference observed in the first year. For height Z-score, and upper to lower body segment ratio, the LS mean difference in Year 2 was approximately twice of that observed in Year 1.

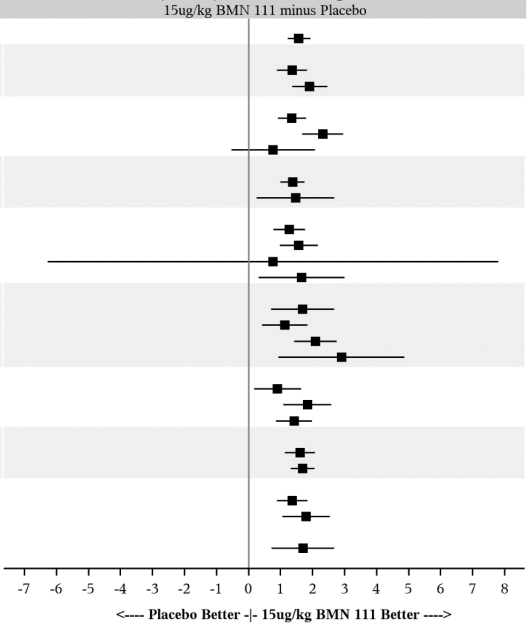
Ancillary analyses

Prespecified subgroup analyses were conducted whereby the ANCOVA model used in the primary analyses was applied to the following subgroups: sex, age group, Tanner stage, strata, baseline height Z-score, and baseline AGV. The difference between treatment group LS means within these subgroups (estimated as vosoritide − placebo), and the 95% CI for the treatment difference, at Week 52 are presented in **Table *39***.

The benefit of improvement in AGV in favour of Voxzogo was consistent across all predefined subgroups analysed including sex, age group, Tanner stage, baseline height Z-score, and baseline AGV. In the subgroup of males Tanner Stage >I, the point estimate of treatment effect was in favour of vosoritide however there were only 8 subjects in this subgroup (3 and 5 subjects in vosoritide and placebo arms, respectively).

Table 39: Forest Plot of Difference in Mean Change from Baseline in Annualised Growth Velocity at Week 52 by Subgroup - Full Analysis Set (111-301)

Subgroup	No. of Subjects (%)		LS Mean Change from Baseline	Difference (95% CI) in LS Mean Change from Baseline
	15ug/kg BMN 111	Placebo	Difference (cm/yr)	15ug/kg BMN 111 minus Placebo
Overall	60 (100.0)	61 (100.0)	1.57	
Sex				
Male	31 (51.7)	33 (54.1)	1.36	
Female	29 (48.3)	28 (45.9)	1.91	
Age Group				
>= 5 to < 8 years	31 (51.7)	24 (39.3)	1.35	
>= 8 to < 11 years	17 (28.3)	24 (39.3)	2.32	
>= 11 to < 15 years	12 (20.0)	13 (21.3)	0.77	
Tanner Stage				
I	48 (80.0)	48 (78.7)	1.38	
> I	12 (20.0)	13 (21.3)	1.47	
Strata				
Male Tanner Stage I	28 (46.7)	28 (45.9)	1.27	
Female Tanner Stage I	20 (33.3)	20 (32.8)	1.57	
Male Tanner Stage > I	3 (5.0)	5 (8.2)	0.76	
Female Tanner Stage > I	9 (15.0)	8 (13.1)	1.65	
Height Z-Score Category				
<= -6	15 (25.0)	10 (16.4)	1.69	
> -6 to <= -5	18 (30.0)	24 (39.3)	1.14	
> -5 to <= -4	22 (36.7)	19 (31.1)	2.09	
> -4	5 (8.3)	8 (13.1)	2.90	
AGV Category				
<= 3.5 cm/yr	19 (31.7)	19 (31.1)	0.90	
> 3.5 to <= 4.5 cm/yr	14 (23.3)	18 (29.5)	1.84	
> 4.5 cm/yr	27 (45.0)	24 (39.3)	1.42	
Race				
White	45 (75.0)	41 (67.2)	1.61	
Non-White	15 (25.0)	20 (32.8)	1.69	
Region				
North America	27 (45.0)	26 (42.6)	1.37	
Europe	18 (30.0)	18 (29.5)	1.80	
Japan	3 (5.0)	4 (6.6)	Non-Est	
Rest of World	12 (20.0)	13 (21.3)	1.70	



Pivotal trial in subjects in the age 0 to 60 months contributing to the Efficacy of Vosoritide 15 µg/kg daily

A separate study to include younger children was deemed appropriate due to possible pharmacokinetic differences, and due to differential growth patterns in younger children. Therefore, the applicant conducted **Study 111-206** and the extension **Study 111-208**, similarly designed as those for the older age cohort (111-301 and 302) fully described above. Available evidence for efficacy is presented here since both studies are ongoing. Interim Study report was available with a data cut-off of 12.09.2019 in the initial submission.

The applicant provided additional open label efficacy data (as of 20 March 2021) during the procedure in 4 sentinel subjects from Cohort 1, aged 2 to 5 years, supported by data in 4 sentinel subjects in Cohort 2, aged 6 months to 2 years.

Study 111-206: a Phase 2 Randomised, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months

and

Study 111-208: a Phase 2 Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of BMN111 in Children with Achondroplasia"

Methods

Study 111-206

Study 111-206 is an ongoing 52-week multicentre, Phase 2 randomised, open label un-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. The target number of subjects to be enrolled in 111-206 is 70 at 16 clinical centres worldwide.

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

Cohort 1 - children aged ≥ 24 to < 60 months (n ≥ 30 total: three sentinel subjects who receive vosoritide, and at least 27 additional subjects randomised 1:1 to treatment or placebo control), stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months). All subjects Cohort 1: 15 µg/kg/day subcutaneous injection (all subjects)

Cohort 2 - children aged ≥ 6 to < 24 months (n ≥ 20 total: three sentinel subjects who receive vosoritide, and at least 17 additional subjects randomised 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months). All subjects in this cohort are treated with 30 µg/kg/day adjusted to 15 µg/kg/day when subjects reach 2 years of age

Cohort 3 - children aged 0 to < 6 months (n ≥ 20 total: three sentinel subjects receive vosoritide, and at least 17 additional subjects randomised 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation. (At the time of the data cut for the interim report initially submitted, enrollment in Cohort 3 had not commenced yet).

Study Participants

Individuals eligible to participate in study 111-206 must meet all of the following criteria:

1. Diagnosis of ACH, confirmed by genetic testing. If subjects had previous genetic testing, subjects must have a lab report from a certified laboratory with the study specific mutation documented

2. Age 0 to <60 months, at study entry (Day 1)

3. Cohort 1 and 2 subjects must have at least a 6-month period of pre-treatment growth assessment in study 111-901 immediately before screening, and have one documented measurement of height/body length a minimum of 6 months prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrolment in 111-901 or (2) via enrolment in this 111-206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment

4. Parent(s) or guardian(s) (and the subjects themselves, if required by local regulations or ethics committee) are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure

5. Willing and able to perform all study procedures as physically possible.

6. Parent(s) or caregiver(s) are willing to administer daily injections to the subjects and complete the required training

Individuals eligible to participate in Cohort 3 of Study 111-206 need to meet all of the following criteria:

1. Parent(s) or guardian(s) willing and able to provide written, signed informed consent after the nature of the study is explained and prior to performance of any research related procedure. Also, willing and able to provide written assent (if applicable) after the nature of the study is explained and prior to performance of any research-related procedure

2. Birth to ≤3 months of age at study entry

3. Have ACH, documented by genetic testing

4. Are willing and able to perform all study procedures as physically possible

After completing the observation period, subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug.

Treatments

Duration of Treatment: 52 weeks of treatment in study 111-206 (followed by long-term treatment in 111-208 (until subjects reach NFAH).

Cohorts start enrolling sequentially starting with the eldest group (Cohort 1). Each cohort includes at least 3 sentinel subjects receiving vosoritide to evaluate the short-term safety and PK of vosoritide before initiating the rest of the cohort for randomised subjects. The goal is to achieve exposures similar to that characterised to be safe and effective in children with ACH aged ≥ 5 years old enrolled in study 111-202 at the 15 µg/kg/day dose.

Cohort 1 sentinel subjects received vosoritide as a single daily dose of 15µg/kg. Analysis of PK data showed that their exposure was comparable to the exposure range of 15 µg/kg/day in Study 111-202. Additional subjects were randomised to receive either vosoritide as a single daily dose of 15 µg/kg/day or placebo. The dosing schedule was a single daily SC dose.

The same dose of 15 µg/kg was used for Cohort 2 sentinels. Analysis of PK data for Cohort 2 indicated that the appropriate dose to achieve the desired exposure is 30 µg/kg/day, subsequent for 3 sentinels were increased to 30 µg/kg/day until the subjects reach 2 years where they were returned to 15 µg/kg dosing. Cohort 3 will be evaluated the same way.

Objectives

Table *40* provides an overview of the study objectives in Study 111-206:

Table 40: Overview of the objectives in Study 111-206

Primary Objective
Evaluate the safety and tolerability of vosoritide in children age 0 to < 60 months with ACH
Evaluate the effect of vosoritide on change from baseline in length/height Z-score
Secondary Objective
Evaluate the effect of vosoritide on change from baseline in 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 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 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
Secondary Objective
Evaluate the effect of vosoritide on bone metabolism and vosoritide pharmacodynamic biomarkers
Evaluate the effect of vosoritide on growth parameters and body proportions, including change from baseline in upper to lower body segment ratio
Evaluate the effect of vosoritide on sleep apnea
Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

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

Outcomes/endpoints

Table 41: Overview of the objectives in Study 111-206

Primary Endpoint/Assessment
Adverse events (AEs), SAEs, and clinically significant changes in vital signs, physical examination, electrocardiogram (ECG), imaging, and laboratory test results (urinalysis, chemistry, haematology).
Length/height Z-score at Week 52.
Secondary Endpoint/Assessment
AGV at Week 52
Bilateral X-rays of lower extremities Lumbar spine X-rays DXA of whole body and spine
AUC0-∞, AUC0-t, Cmax, Tmax, t1/2, CL/F, Vz/F
Hip monitoring clinical assessments
Hip monitoring clinical assessments
Bayley-III, WeeFIM, and ITQOL scores CBCL scores
Anti-vosoritide total antibody (TAb) Anti-vosoritide antibody cross-reactivity with endogenous CNP, ANP, and BNP (TAb) Anti-vosoritide neutralizing antibody (NAb)
Secondary Endpoint/Assessment
CXM and bone-specific alkaline phosphatase Collagen type II (CTX-II) Cyclic guanosine monophosphate (cGMP)
Anthropometric measurements Upper to lower body segment ratio Upper arm length to lower arm (forearm) length ratio Upper leg length (thigh) to knee to heel length ratio Upper leg length (thigh) to tibial length ratio Arm span to standing height ratio
Sleep study to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation pulse rate, and airflow during overnight monitoring. Apnea/Hypopnea Index
Magnetic resonance imaging (MRI) to define skull and brain morphology
Concomitant procedures/interventions/surgeries

Exploratory Endpoint/Assessment
Clinical photography of the full body, face, spine, and extremities
Exploratory genomics including, but not limited to, NPR-2, BRAF, and other genes associated with CNP signaling

Sample size

No formal sample size calculations were performed. Approximately 70 subjects age 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.

Randomisation

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

Subjects are being 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 randomisation schedule so that BioMarin and site personnel are 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 randomisation schedule so that BioMarin and site personnel did not know the treatment assignment. Subjects and the participating site members are blinded to study treatment.

Statistical methods

Efficacy data were analyzed using descriptive statistics.

Each measurement of standing height was converted to age- and sex-appropriate standard deviations score (SDS), also referred to as a height Z-score, by comparison with reference data available for average stature children from the Centre for Disease Control (CDC). Height Z-score, and its changes from baseline at Week 26 and Week 52 was summarised and presented for sentinel subjects by cohort and overall.

AGV, upper to lower body segment ratio, and standing and sitting height were summarised similarly to height Z-score. Results were summarised for sentinel subjects by cohort and overall. Other anthropometric measures (sitting height, head circumference, etc.) were summarised at each time point and were evaluated for changes from baseline). For younger subjects, body length was measured

and used in the analyses instead of standing height. Similarly, crown-to-rump was measured instead of sitting height.

Results

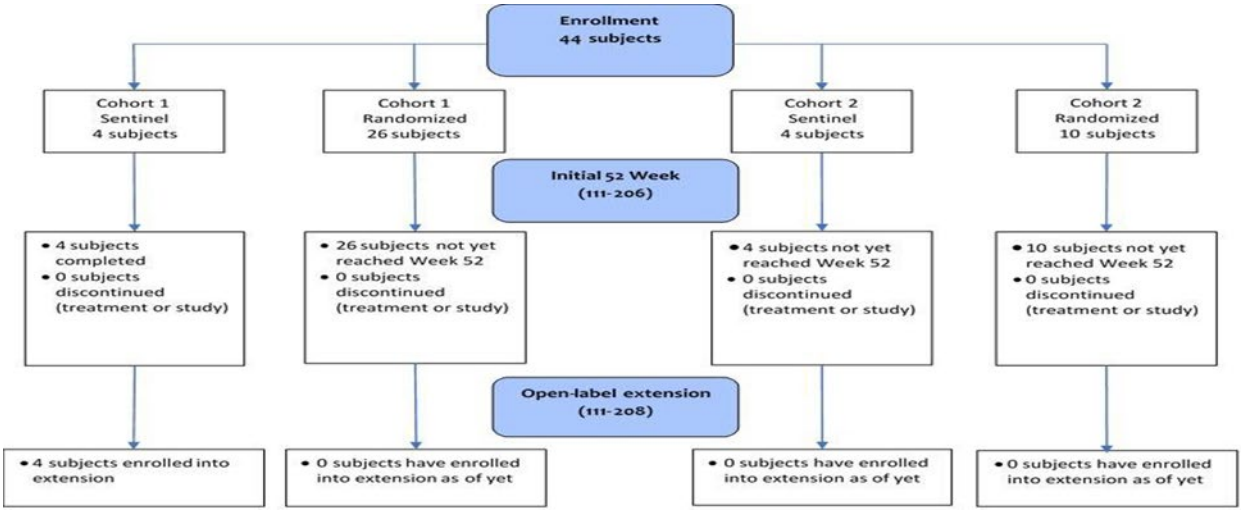
Participant flow

Disposition: At the time of the data-cut for the interim CSR (cut-off 12 Sep 2019), 44 subjects had enrolled into the study 111-206 and received treatment, four sentinel subjects and 26 randomised subjects in Cohort 1, and 4 sentinel subjects and 10 randomized subjects in Cohort 2.

In Cohort 1, **four sentinels subjects have completed 52 weeks of treatment**, while all 26 randomized subjects have completed the Week 13 visit and nine randomized subjects have completed the Week 39 visit.

In Cohort 2, **two sentinel subjects have completed the Week 26 visit**. No subjects had discontinued from the study drug or the 111-206 study at the time of the data-cutoff date.

Figure 30: Disposition of Subjects (Analysis Population: Full Analysis Set, interim report 12 September 2019)



Recruitment

Study Start Date: 13 June 2018

Date of Interim Study Report: 12 September 2019

Conduct of the study

The study is conducted at 16 study centres in 4 countries (United States, Australia, United Kingdom and Japan).

The original protocol for 111-206 was finalized and approved on 06 December 2017. The protocol was amended two times.

Baseline data

Table *42* shows the demographics of the currently included population in the trial:

Table 42: Demographics (Analysis Population: Full Analysis Set, interim report 12 September 2019)

Demographic Variable	Cohort 1 (Age ≥ 24 to		Cohort 2 (Age ≥ 6 to		Overall	
	Sentinel	Randomized	Sentinel	Randomized	Sentinel	Randomized
Age at Day 1, months						
n	4	26	4	10	8	36
Mean (SD)	48.45	42.63 (11.33)	15.79	17.62 (5.31)	32.12	35.68
Median	52.11	40.49	15.39	17.92	25.41	36.58
25th, 75th percentile	39.15,	31.11,	13.04,	11.93,	15.39,	23.52,
Min, Max	29.8, 59.8	25.4, 59.8	11.3, 21.0	9.7, 23.7	11.3,	9.7, 59.8
Sex, n (%)[a]						
Male	3 (75.0)	12 (46.2)	4 (100.0)	6 (60.0)	7 (87.5)	18 (50.0)
Female	1 (25.0)	14 (53.8)	0	4 (40.0)	1 (12.5)	18 (50.0)
Race, n (%)[a]						
White	4 (100.0)	21 (80.8)	3 (75.0)	8 (80.0)	7 (87.5)	29 (80.6)
Asian	0	4 (15.4)	0	1 (10.0)	0	5 (13.9)
Other	0	4 (15.4)	0	1 (10.0)	0	5 (13.9)
Native Hawaiian or	0	0	0	1 (10.0)	0	1 (2.8)
Multiple	0	1 (3.8)	1 (25.0)	0	1 (12.5)	1 (2.8)
Ethnicity, n (%)[a]						
Not Hispanic or Latino	4 (100.0)	23 (88.5)	4 (100.0)	9 (90.0)	8 (100.0)	32 (88.9)
Hispanic or Latino	0	2 (7.7)	0	0	0	2 (5.6)
Not Reported	0	1 (3.8)	0	1 (10.0)	0	2 (5.6)

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

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

Numbers analysed

Efficacy outcome – sentinel subjects (up data cut-off of 07 September 2020):

Height Z-score Change from Baseline

For Cohort 1 sentinel subjects the mean (SD) baseline height Z-score was -4.51 (0.33). For Cohort 1 sentinel subjects (N=4), the mean (SD) change from Baseline in height Z score at Week 26 was +0.15 (0.19) and at Week 52 was +0.34 (0.27). At Week 104, two of the three sentinel subjects showed an improvement in the height Z-scores of +0.77 SDS and +0.86 SDS, while an improvement of +0.27 SDS (at Week 78) and +0.20 SDS was noted in the other two subjects.

For Cohort 2 sentinel subjects the mean (SD) baseline height Z-score was -4.72 (0.53). For Cohort 2 sentinel subjects (N=4), mean (SD) change from Baseline at Week 26 was +0.43 (0.69) and at Week 52 was +0.84 (0.25).

Annualised Growth Velocity Change from Baseline

Baseline AGV was 6.21 cm/year for Cohort 1 sentinel subjects and 11.93 cm/year for Cohort 2 sentinel subjects. In Cohort 1 sentinel subjects (N=4), following 26 weeks of treatment, there was a mean (SD) increase in AGV from Baseline of 0.69 (1.70) cm/year and after 52 weeks of treatment there was a mean (SD) increase of 0.57 (0.91) cm/year in AGV from Baseline. The AGV at Week 104 in 2 subjects and Week 78 for 1 subject was higher than the AGV at Baseline; with only a slight decline noted in the fourth subject at Week 104. The subject with the decline in the AGV had a high baseline AGV and was youngest in the Cohort; the decline in the AGV is likely due to the subject being in the steeper curve of the growth decline.

In four Cohort 2 sentinel subjects, following 26 weeks of treatment, there was a mean (SD) decrease of 1.53 (3.03) cm/year in AGV from Baseline and of 2.75 (1.65) cm/year in AGV from Baseline at Week 52.

Upper to Lower Body Segment Ratio

There was no change in upper to lower body ratio over time in both cohorts. In Cohort 1 sentinel subjects (N=4), mean (SD) change in upper to lower body segment ratio from Baseline to Week 26 was -0.04 (0.06) and -0.02 (0.12) to Week 52. At week 104, a consistent reduction was noted in upper to lower body segment ratios in each of the subjects.

For Cohort 2 sentinel subjects (N=2), the mean (SD) change in upper to lower body segment ratio from Baseline to Week 26 was -0.07 (0.05) and -0.19 (0.28) cm at Week 52.

Standing Height and Sitting Height

In Cohort 1 sentinel subjects (N=4), mean (SD) change in standing height from baseline was 3.38 (0.82) cm at Week 26 and 6.78 (1.12) cm at Week 52. A consistent improvement was noted in standing height over 2 years of treatment in each of the subjects. Mean (SD) change in sitting height from baseline was 1.98 (1.12) cm at Week 26 and 4.69 (0.43) cm at Week 52.

In the Cohort 2 sentinel subjects (N=2), mean (SD) change in standing height from baseline was 5.15 (1.01) cm at Week 26 and 9.22 (0.98) cm at Week 52. Mean (SD) change in sitting height from baseline in 2 sentinel subjects was 3.70 (0.19) cm at Week 26.

Body Proportion Ratios of the Extremities Change from Baseline

There were no clinically significant changes in body proportions at Weeks 26 and 52.

Growth Measures Change from Baseline

Across all growth measures (head circumference, arm span, upper arm length, lower arm length, lower body length, upper leg length, knee to heel length, and tibial length) there were consistent positive improvements in growth in both Cohort 1 and 2.

Updated efficacy results (cut-off of 20 March 2021)

As of the data cut-off date of 20 March 2021, subjects in Cohort 1 (N=4) have received vosoritide for a median of 978 days (range: 921 to 1012 days) and in Cohort 2 (N=4) for a median of 733.5 days (range: 706 to 741 days). All sentinel subjects in Cohort 1 had treatment follow up for at least 130 weeks across the two studies 111-206/208 and in Cohort 2 up to Week 104; of note, one subject in Cohort 2 did not have a height assessment at the Week 104 visit as the visit was scheduled post the data cut-off date.

Height Z-Score

In Cohort 1 sentinels, the reduction in height deficit as evaluated by the height Z-score was sustained with vosoritide treatment over 2.5 years, with mean (standard deviation [SD]) change from baseline at Week 52 (N=4) of +0.34 (0.27) standard deviation score (SDS), at Week 104 (N=3) of +0.62 (0.36) SDS, and at Week 130 (N=4) of +0.49 (0.34) SDS. For Cohort 2 sentinels, the mean (SD) change from baseline in height Z-score at Week 52 (N=4) was +0.84 (0.25) SDS and was sustained at Week 104 (N=3) with a mean (SD) change from baseline of +0.69 (0.55) SDS.

AGV

In Cohort 1 sentinels the mean (SD) AGV at baseline was 6.21 (1.73) cm/year. The mean (SD) AGV in the first year of treatment in 111-206 remained at 6.78 (1.00) cm/year and in the second year of treatment in 111-208 was 5.85 (0.39) cm/year. In the Cohort 2 sentinels, the mean (SD) AGV at baseline was 11.93 (1.32) cm/year, in the first year of treatment was 9.17 (1.06) and was 6.55 (0.38) in the second year of treatment. This decline in AGV is not as pronounced as would be expected in the untreated children with ACH of this age range, thus illustrating positive effect of vosoritide on growth velocity.

Standing Height/Body Length

For Cohort 1 sentinels, the mean (SD) increase in standing height from baseline at Week 52 was 6.78 (1.12) cm, at Week 104 was 12.91 (1.61) and at Week 130 was 15.28 (1.39). In Cohort 2 sentinels, mean (SD) change in standing height from baseline was 9.22 (0.98) cm at Week 52 and at Week 104 was 15.76 (1.42).

Upper to Lower Body Ratio

In Cohort 1 sentinels, there was a reduction in the upper to lower body segment ratio over time with treatment with mean (SD) change in the ratio from baseline at Week 52 of -0.02 (0.12), at Week 104 (N=3) of -0.19 (0.10), and at Week 130 (N=4) of -0.19 (0.14). In Cohort 2 sentinels, the mean (SD) reduction in the upper to lower body segment ratio at Week 52 (N=4) was -0.19 (0.28) with further decline observed at Week 104 (N=3), showing a mean (SD) change from baseline of -0.33 (0.20).

Ancillary analyses

No subgroup analyses are available at present for Study 111-206/208.

Summary of main study

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 43: Summary of Efficacy for trial 111-301

Title: *A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Efficacy and Safety of BMN111 in Children with Achondroplasia*		
Study identifier	111-301 (EudraCT Number: 2015-003836-11)	
Design	Phase 3, randomised, double-blind, placebo-controlled, multicentre	
	Duration of main phase:	60 weeks (up to 4 weeks of screening, 52 weeks of treatment with an additional 4 weeks of safety follow up)

	Duration of Run-in phase:		At least 6 months in trial 901
	Duration of Extension phase:		After end of this trial subjects were transferred to Extension trial 111-302
Hypothesis	Superiority		
Treatments groups	Vosoritide		Vosoritide 15 µg/kg. 52 weeks, 60 subjects
	Placebo		Placebo. 52 weeks, 61 subjects
Endpoints and definitions	Primary endpoint	AGV	Change from baseline in annualised growth velocity (AGV) at Week 52
	Key Secondary	Height Z-score	Change from baseline in height Z-score at Week 52. This was a key secondary endpoint for which the Type I error was controlled allowing for confirmatory testing
	Key Secondary	U:L body segment ratio	Change from baseline in upper to lower body segment ratio at Week 52. This was a key secondary endpoint for which the Type I error was controlled allowing for confirmatory testing
	Other Secondary	Standing height	Change from baseline in standing height at Week 52
Database lock	31 October 2019		

Results and Analysis

Analysis description	**Primary Analysis - Change from baseline in AGV (ANCOVA model)**		
Analysis population and time point description	Full Analysis Set (FAS): ITT, all randomised, consented subjects included. After Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo (N=61)	Vosoritide (N=60)
	AGV (cm/year)		
	Number of subjects	61	60a
	Mean	-0.12	1.35
	Standard deviation	1.74	1.71
	Median	-0.37	1.44
	Min, Max	-3.6, 4.5	-2.1, 6.5
Effect estimate per comparison	Primary endpoint AGV	Comparison groups:	Vosoritide versus placebo
		Difference in LS mean change from baseline	1.57
		95% confidence interval (CI)	1.22, 1.93
		p-value[b] (ANCOVA)	<0.0001
Analysis description	**Secondary analysis (pre-specified) – Change from baseline in height Z-score (ANCOVA model)**		
Analysis population and time point description	Full Analysis Set (FAS) After Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo (N=61)	Vosoritide (N=60)
	Height Z-score (SDS)		

	Number of subjects	61	60[a]
	Mean	0.00	0.24
	SD	0.28	0.32
	Median	0.00	0.19
	Min, Max	-0.8, 0.5	-0.4, 1.0
Effect estimate per comparison	Key Secondary endpoint	Comparison groups	Vosoritide versus placebo
		Difference in LS mean change from baseline	0.28
		95% CI	0.17, 0.39
		p-value[b] (ANCOVA)	<0.0001
Notes	Each measurement of standing height was converted to an age-and sex-appropriate standard deviation score (SDS), also referred to as a Z-score, by comparison with reference data available for average stature children from the Centers for Disease Control and Prevention (CDC). ANCOVA model was used to determine the treatment difference between vosoritide and placebo at Week 52. Model terms included randomisation stratum defined by sex and Tanner stage, treatment, baseline age, baseline AGV, and baseline height Z-score. [a:] Two subjects in the vosoritide group discontinued from the study before Week 52 (1 due to an AE [anxiety about injections] and 1 due to subject request [subject was experiencing pain during injections]). The values for these 2 subjects were imputed for this analysis.		
Analysis description	**Secondary analysis (pre-specified) – Change from baseline in upper to lower body segment ratio (ANCOVA model)**		
Analysis population and time point	Full Analysis Set (FAS) , after Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo (N=61)	Vosoritide (N=60)
	U:L body segment ratio		
	Number of subjects	61	60[a]
	Mean	-0.03	-0.03
	SD	0.09	0.11
	Median	-0.01	-0.04
	Min, Max	-0.4, 0.1	-0.2, 0.6
Effect estimate per comparison	Key Secondary endpoint	Comparison groups	Vosoritide versus placebo
		Difference in LS mean change from baseline	-0.01
		95% CI	-0.05, 0.02
		p-value[b] (ANCOVA)	0.5060

Notes	ANCOVA model was used to determine the treatment difference between vosoritide and placebo at Week 52. Model terms included randomisation stratum defined by sex and Tanner stage, treatment, baseline age, baseline AGV, baseline height Z score, and baseline upper to lower body segment ratio. [a]: Two subjects in the vosoritide group discontinued from the study before Week 52 (1 due to an AE [anxiety about injections] and 1 due to subject request [subject was experiencing pain during injections]). The values for these 2 subjects were imputed for this analysis. [b:] Two-sided p-value.		
Analysis description	**Other secondary analysis (pre-specified) – Change from baseline in standing height (ANCOVA model)**		
Analysis population and time point description	Full Analysis Set (FAS) After Week 52		
Descriptive statistics and estimate variability	Treatment group	Placebo (N=61)	Vosoritide (N=60)
	Standing height (cm)		
	Number of subjects	61	60[a]
	Mean	3.93	5.59
	SD	1.08	1.06
	Median	3.97	5.72
	Min, Max	1.3, 6.6	2.3, 8.2
Effect estimate per comparison	Other Secondary endpoint	Comparison groups	Vosoritide versus placebo
		Difference in LS mean change from baseline	1.57
		95% CI	1.21, 1.93
		p-value[b] (ANCOVA)	<0.0001
Notes	ANCOVA model was used to determine the treatment difference between vosoritide and placebo at Week 52. Model terms included randomisation stratum defined by sex and Tanner stage, treatment, baseline age, baseline AGV, baseline height Z score, and baseline at standing height. a: Two subjects in the vosoritide group discontinued from the study before Week 52 (1 due to an AE [anxiety about injections] and 1 due to subject request [subject was experiencing pain during injections]). The values for these 2 subjects were imputed for this analysis. b: Two-sided p-value.		

Table 44: Study 111-302 Summary of efficacy

Title: *A Phase 3, Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of BMN111 in Children with Achondroplasia*		
Study identifier	Protocol number: 111-302 (EudraCT number: 2017-002404-28)	
Design	Phase 3 open-label, multicentre extension study to 111-301	
	Duration of main phase:	Until subjects have either reached near-final adult height, or for 5 years if near-final adult height occurs prior to the end of the 5-year period

	Duration of run-in phase: Duration of extension phase:		Not applicable Not applicable
Hypothesis	Not applicable		
Treatments groups	**NOTE:** Day 1 is considered as the first day subjects received vosoritide treatment. For subjects in the vosoritide arm in 111-301 (referred to as vos/vos), this will be the first day of treatment in 111-301 and for subjects who received placebo in 111-301 (referred to as plc/vos), this will be the first day of treatment in 111-302. Baseline is defined as the last assessment before the first dose of vosoritide. Therefore, for vos/vos subjects, their baseline assessment is the same as in 111-301. For plc/vos subjects, their baseline assessment is immediately prior to 111-302.		
	Plc/vos (For subjects who received placebo in 111-301)		Vosoritide 15 µg/kg daily, 61 subjects Mean (SD) duration of treatment in days 135.6 (121.7)
	Vos/vos (For subjects on the vosoritide arm in 111-301)		Vosoritide 15 µg/kg daily, 58 subjects Mean (SD) duration of treatment in days 498.3 (119.3)
Endpoints and definitions	Primary efficacy endpoint	AGV	Cumulative change from baseline in annualised growth velocity (AGV) (cm/year)
	Secondary efficacy endpoint	Height Z-score	Change from baseline in height Z-score
	Secondary efficacy endpoint	U:L body segment ratio	Change from baseline in upper to lower body segment ratio
Data cut-off date	31 October 2019 for interim analysis / **updated 02.Nov.2020**		
Results and Analysis			
Analysis description	**Primary efficacy analysis – Change from baseline in AGV**		
Analysis population and time point description	Full analysis set Defined according to the intention-to-treat principle and includes all enrolled subjects with a signed informed consent for 111-302. Time point description Week 26: Subjects treated with vosoritide for 26 weeks (in 111-302 study for plc/vos group and in 111-301 study for vos/vos group)		
Descriptive statistics and estimate variability	Treatment group	Plc/vos (N=61)	Vos/vos (N=58)
	Number of subjects who completed Week 26	14	58
	AGV, cm/year mean	+2.15	+1.70
	SD	1.35	2.45
	Median	+1.87	+1.45
	Min, Max	+0.3, +5.2	-2.7, +9.2
	95% CI	1.38, 2.93	1.06, 2.34
Effect estimate per comparison	Primary endpoint	Not applicable	
	Updated result (Cut-off: 02.Nov2020)		

	Treatment group	A total of 56 subjects had been treated for at least 2 years (initially randomised to vosoritide in 111-301), and 61 subjects had been treated with vosoritide for 1 year (initially randomised to placebo in 111-301).	
	Number of subjects who completed Week 130	14 (with 2 subjects reaching 156 weeks and 1 subject reaching 182 weeks)	
	AGV, cm/year mean	+ 5.67 cm/2years	
	SD	NR	
	Median	NR	
	Min, Max	NR	
	95% CI	NR	
Notes	None		
Analysis description	**Primary efficacy analysis – Change from baseline in AGV**		
Analysis population and time point description	Full analysis set Defined according to the intention-to-treat principle and includes all enrolled subjects with a signed informed consent for 111-302. Time point description Week 78: Subjects treated with vosoritide for 78 weeks		
Descriptive statistics and estimate variability	Treatment group	Plc/vos (N=61)	Vos/vos (N=58)
	Number of subjects who completed Week 78	1	13
	AGV, cm/year mean	+1.63	+1.37
	SD	NA	1.87
	Median	+1.63	+0.69
	Min, Max	+1.6, +1.6	-0.7, +4.8
	95% Confidence Limits	NA, NA	0.24, 2.50
Effect estimate per comparison	Primary endpoint	Not applicable	
Notes	None		
Analysis description	**Secondary efficacy analysis – Change from baseline in height Z-score**		
Analysis population and time point description	Full analysis set Defined according to the intention-to-treat principle and includes all enrolled subjects with a signed informed consent for 111-302. Time point description Week 26: Subjects treated with vosoritide for 26 weeks (in 111-302 study for plc/vos group and in 111-301 study for vos/vos group)		
Descriptive statistics and estimate variability	Treatment group	Plc/vos (N=61)	Vos/vos (N=58)
	Number of subjects who completed Week 26	14	58

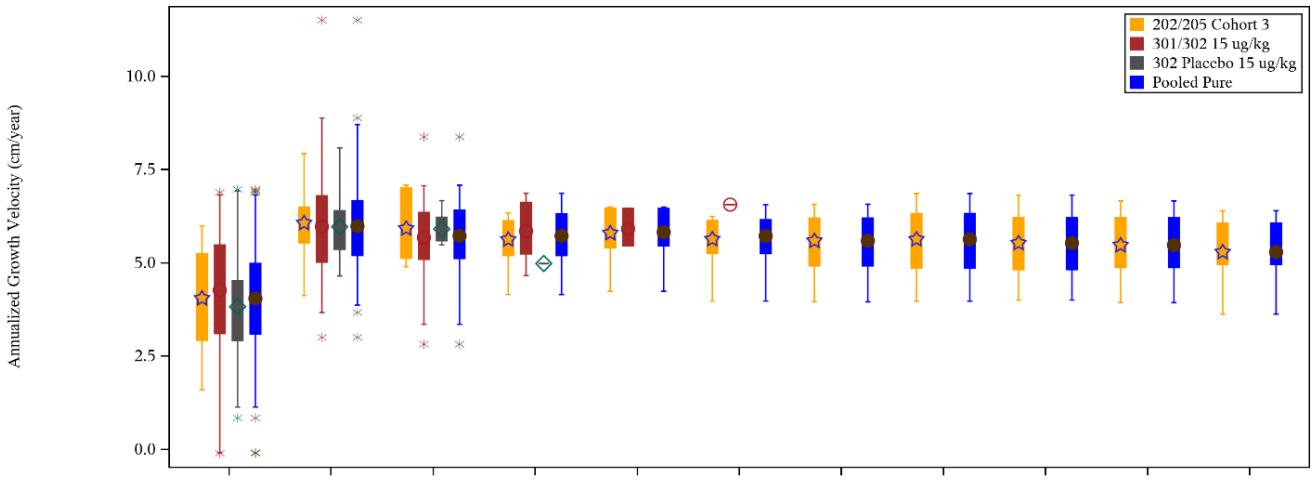
	Height Z-score mean	+0.16	+0.15
	SD	0.14	0.20
	Median	+0.13	+0.14
	Min, Max	-0.1, +0.5	-0.2, +0.6
	95% Confidence Limits	0.08, 0.24	0.10, 0.20
Effect estimate per comparison	Secondary endpoint	Not applicable	
Notes	**Update 02.Nov.2020: The maintenance of positive effect on AGV resulted in continuous improvement in height Z-score, with change from baseline of +0.24 SDS after 52 weeks of treatment to +0.44 SDS after 104 weeks of treatment**		
Analysis description	**Secondary efficacy analysis – Change from baseline in upper to lower body segment ratio**		
Analysis population and time point description	Full analysis set Defined according to the intention-to-treat principle and includes all enrolled subjects with a signed informed consent for 111-302. Time point description Week 26: Subjects treated with vosoritide for 26 weeks (in 111-302 study for plc/vos group and in 111-301 study for vos/vos group)		
Descriptive statistics and estimate variability	Treatment group	Plc/vos (N=61)	Vos/vos (N=58)
	Number of subjects who completed Week 26	14	58
	U:L body segment ratio mean	-0.05	-0.04
	SD	0.06	0.09
	Median	-0.05	-0.05
	Min, Max	-0.2, +0.0	-0.4, +0.2
	95% Confidence Limits	-0.08, -0.01	-0.06, -0.01
Effect estimate per comparison	Secondary endpoint	Not applicable	
Notes	None		
Analysis description	**Secondary efficacy analysis – Change from baseline in height Z-score**		
Analysis population and time point description	Full analysis set Defined according to the intention-to-treat principle and includes all enrolled subjects with a signed informed consent for 111-302. Time point description Week 78: Subjects treated with vosoritide for 78 weeks		
Descriptive statistics and estimate variability	Treatment group	Plc/vos (N=61)	Vos/vos (N=58)
	Number of subjects who completed Week 78	1	13
	height Z-score mean	-0.20	+0.49

	SD	NA	0.34
	Median	-0.20	+0.42
	Min, Max	-0.2, -0.2	-0.1, +0.9
	95% Confidence Limits	NA, NA	0.28, 0.70
Effect estimate per comparison	Secondary endpoint	Not applicable	
Notes	None		
Analysis description	**Secondary efficacy analysis – Change from baseline in upper to lower body segment ratio**		
Analysis population and time point description	Full analysis set Defined according to the intention-to-treat principle and includes all enrolled subjects with a signed informed consent for 111-302. Time point description Week 78: Subjects treated with vosoritide for 78 weeks		
Descriptive statistics and estimate variability	Treatment group	Plc/vos (N=61)	Vos/vos (N=58)
	Number of subjects who completed Week 78	1	13
	U:L body segment ratio mean	-0.02	-0.09
	SD	NA	0.07
	Median	-0.02	-0.09
	Min, Max	+0.0, +0.0	-0.2, +0.0
	95% Confidence Limits	NA, NA	-0.13, -0.05
Effect estimate per comparison	Secondary endpoint	Not applicable	
Notes	**Update 02.Nov.2020: Improvement in the upper to lower body segment ratio was also observed, with change from baseline of -0.03 at 52 weeks and -0.08 after 104 weeks of treatment**		

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

Cumulative annualised growth velocity for the 15 µg/kg pooled group across studies 111-202/205 and 111-301/302 is provided in Figure 31. In the Pure 15 µg/kg pooled group, mean (SD) change from baseline in AGV to Year 1 was 1.49 (1.62) cm/year and to Year 5 (Month 60) was 1.34 (1.31) cm/year.

Figure 13: Box Plot of Cumulative Annualised Growth Velocity Over Time by pooled group (Full Analysis Set)



Mean:	202/205 Cohort 3	301/302 15 ug/kg	302 Placebo 15 ug/kg	Pooled Pure							
202/205 Cohort 3	10	10	10	10	10	10	9	9	9	9	9
301/302 15 ug/kg	60	58	58	14	3	1	0	0	0	0	0
302 Placebo 15 ug/kg	60	14	4	1	0	0	0	0	0	0	0
Pooled Pure	130	82	72	25	13	11	9	9	9	9	9

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Baseline-growth assessment

Study 901 (ongoing, observational growth study in children from birth to <7 years): *A Multicentre, Multinational Clinical Assessment Study for Paediatric Patients with Achondroplasia*

With respect to the real world situation, it is noted that all patients included in the clinical development programme of vosoritide were initially enclosed in **Study 901**, which contribute also significantly to an adequate assessment of baseline in all trial subjects later included in the other trial. This study mainly intended to collect baseline growth measurements on paediatric subjects with ACH over 6 months in order to generate external comparisons and to demonstrate that the intended target population reflects the real clinical situation.

Study 111-901 is a prospective, multicentre, multinational study that collects specific growth measurements on paediatric subjects with ACH being considered for subsequent enrolment in future studies sponsored by the applicant. Approximately 500 subjects from birth to ≤ 17 years of age at study entry were to be enrolled, with approximately equal numbers of boys and girls.

Enrolled subjects underwent growth measurements at baseline and then subsequently at 3-month intervals until completion of the study (reaching the end of the protocol or enrolment in another BioMarin study), discontinuation of participation, or termination of the study. Subjects who did not enrol in a subsequent BioMarin drug-treatment study could choose to continue participating in Study 111-901 for up to 7 years. No study drug was administered. Actually, 342 of the planned 500 subjects were included (Cut-off: as of 31 May 2019). The objectives of this study are to collect baseline growth

measurements on paediatric subjects with ACH. Subjects with at least 6 months of growth data were considered for possible participation in future drug-treatment studies sponsored by BioMarin (for subjects aged 0 to < 3 months at study entry, a minimum of 3 months of data were required).

Growth parameters and analyses:

- Endpoints were presented according to the study that the subject enrolled into: Study 111-202, 111-206, or 111-301. Subjects who did not/or had not yet entered another vosoritide study were presented as "not enrolled". Summary outputs also included an overall category.
- Annualised growth velocity (AGV), height Z-scores, and upper to lower body ratio were presented by study visit.

  All growth parameters were categorised by age (0, 1, 2 to maximum year of age) at the time of the assessment and were presented by sex and overall.
- HRQoL, functional independence, and ADL questionnaires: The scores in HRQoL questionnaires, functional independence, and ADL questionnaires (including PedsQL, QoLISSY, and WeeFIM) were summarised by age at the time of the assessment. CBCL, BSID-III, and ITQoL were listed due to limited available data.

Patient population: Of the 342 subjects enrolled , 190 (55.6%) enrolled in a subsequent drug study: the majority (121subjects, 35.4%) enrolled in **study 111-301**; 35 subjects (10.2%) enrolled in **study 111-202**, 34 subjects (9.9%) enrolled in **study 111-206** and 152 subjects (44.4%) did not enroll in a subsequent drug study; enrollment into **study 111-206** was ongoing.

Of the 152 subjects who did not enroll in a subsequent drug study, 3 (2.0%) have completed **study 111-901**, 71 (46.7%) remain on study, and 78 (51.3%) have discontinued from the study. The mean (standard deviation [SD]) duration of follow-up overall in 111-901 was 19.32 (13.90) months (ranging from 0 to 75 months); this was equivalent to 550.6 patient-years.

Baseline demographics, growth characteristics, medical history, and use of concomitant medication reflected the epidemiology of ACH and the geographic distribution of recruiting countries. Across all groups by subsequent enrollment, including those not enrolled into a drug study, there was a balance of male and female subjects and the majority were Caucasian. Overall, at the study 111-901 baseline, subjects were aged from newborn to 13.5 years, with a mean age of 5.45 years. Most subjects were Tanner Stage I. Overall, 95.3% of subjects had a medical history condition reported at baseline and 89.8% had an ACH-related medical history condition reported at baseline. In general, the incidence by SOC of ACH-related medical histories were similar across all groups by subsequent enrolment, including those not enrolled into a drug study. Most subjects were receiving concomitant medication at entry to study 111-901 (87.7% overall), with those enrolling later in study 111-206 (the youngest age group) generally having the highest use of concomitant medications at baseline as well as concomitant medications initiated on-study.

Results:

AGV: Median (inter-quartile range [IQR]) AGV in subjects aged <1 year with ACH enrolled in study 111-901 was 11.25 (5.53, 12.98) cm/year for females and 14.39 (14.10, 14.73) cm/year for males. By 1 year of age, median (IQR) AGV decreased to 7.21 (6.50, 7.80) cm/year in females and 7.81 (7.09, 9.02) cm/year in males. AGV subsequently demonstrated a stable pattern by age, with a slow decline from the ages of 2-3 years to 10 years: median (IQR) AGV in subjects aged 2-10 years ranged from 5.59 (4.18, 7.32) to 3.46 (2.40, 4.51) cm/year in females and 5.87 (4.98, 6.54) to 3.53 (3.29, 3.90) cm/year in males. Median AGV remained approximately 4 cm/year for females and males aged 11 and 12 years. Median AGV for subjects enrolled in 111-901 was lower across all ages compared

with average stature children of a similar age, with the greatest difference observed between birth and 1-2 years of age.

Height Z-score: Compared with average stature children of a similar age, as measured by Z-scores, mean length/height deficit in both females and males with ACH enrolled in study 111-901 was high from birth (mean [SD] Z-scores of -3.68 [0.89] SDS for females and -3.88 [1.16] SDS for males) and the height deficit increased in subjects up to 5 years of age (Z-scores of -5.31 [1.08] SDS for females and -4.62 [0.78] SDS for males). Despite increasing variability after 5 years of age, the height deficit remained high in all age groups throughout the study.

Standing and sitting height: Median (IQR) length for subjects aged <1 year for females was 54.87 (52.50, 58.55) cm and for males was 58.37 (56.57, 61.40) cm. Median length/standing height gradually increased by age on study. For subjects aged 13 years the median (IQR) standing height for females was 122.83 (105.60, 126.25) cm and for males was 117.20 (114.90, 124.68) cm.

As expected, and reflecting the Z-score values, the standing and sitting height values in study 111-901 subjects with ACH are lower compared to average stature age-sex-specific reference data (CDC 2019) and are consistent with published data in ACH (Hoover-Fong 2017, Merker 2018) supporting the close resemblance of subjects in study 111-901 according to gender and age with the overall ACH population. For subjects with at least 36 months of data, individual standing height data plotted over time against average and short-stature reference data demonstrate that female and male subjects enrolled in study 111-901 are consistent with the ACH population, based on the published data (Hoover-Fong 2017), with standing height below average stature age-specific reference data.

Upper to lower body segment ratio: study 111-901 data show disproportionality in upper to lower body ratio and are consistent with the published data in ACH children. Due to the limited growth of their extremities, the ratio of the upper to lower extremities in subjects with ACH never reaches 1 (Hoover-Fong 2008).

Other body proportion ratios and growth measures: Data reflected those presented above and demonstrated that subjects enrolled in study 111-901 have disproportionate short stature, shortening of upper to lower body segment, and rhizomelic shortening of arms and legs, which is consistent with the overall ACH population. In this study and consistent with those reported in the literature in ACH (Hoover-Fong 2008), BMI Z-scores in ACH subjects were higher than in average stature children.

Supportive data with respect to long-term efficacy and safety outcome

Study 111-205 (ongoing, interim CSR available, trial includes relevant information regarding long term efficacy and safety for this application)

Study 111-205 is an ongoing multicentre, open-label, Phase 2 extension study to evaluate the long-term safety and efficacy of BMN111 treatment in children with ACH who had completed Study 111-202. Nine sites worldwide are participating in this study. This interim study report includes BMN111 efficacy and safety data from all subjects enrolled in Study 111-205, from the time of their first dose of BMN111 received in Study 111-202, which was available up to the data cut-off of 20 November 2019.

In Study 111-202, subjects were sequentially enrolled into 4 cohorts to receive the different daily dosing regimens (please refer for details in Section 2.5.1. Dose response study of this assessment report).

Eligible subjects who then completed 2 years of BMN111 treatment in Study 111-202 were enrolled in the 111-205 extension study to continue receiving the same stable dose of BMN111 received upon completion of 111-202 (15 or 30 µg/kg daily). The Baseline visit for Study 111-205 was the same day as the final treatment visit and study completion visit (Month 24) for Study 111-202, during which subject consent was obtained. Ongoing AEs from Study 111-202 are collected in the Study 111-205 medical history. In the event of a delay in starting Study 111-205, AEs were also reported in medical history. This information was included in the overall reporting of AEs.

Subjects are to be followed either until they reached near-final adult height (NFAH) or for 5 years if NFAH occurred prior to the end of the 5-year period. At least 6 months of baseline growth data for all subjects who entered 111-202 was required to be collected in Study 111-901.

111-Natural History Integrated Analyses

The primary NH source (AchNH) was a retrospective, protocol-driven study to primarily characterize growth in subjects with ACH. It was conducted at four highly specialised US skeletal dysplasia centres, which systematically and comprehensively collected data. It is a large data source with a wealth of height data over the age range of subjects enrolled in the vosoritide studies, with a substantial number of assessments collected in a longitudinal manner. An assessment of potential bias of the database confirmed its validity and reliability.

While height data were retrospectively collected, the data were highly concordant and comparable to prospectively designed study 111-901 across all ages and sexes as well as published data.

The supportive NH data sources (111-901, LIAISE and KAISER) provided important data to corroborate the results of the primary analyses.

The comparative analyses included comparisons between the vosoritide group (consisting of several treatment groups from studies 111-202/205 and 111-301) and the external control group (untreated ACH subjects from the NH sources). The subjects included in the external control group for most comparative analyses were selected by a sex and age matching process to each subject in the vosoritide group.

Primary Analysis: The pre-specified primary analysis was a 5-year cross-sectional analysis to compare the difference between height at 5-year follow-up and at baseline between the vosoritide group (Cohort 3 [15 µg/kg] of 111-202/205) versus the sex and age matched external control group from the Primary NH Descriptive Population. In addition, sensitivity and supportive analyses were performed to assess the robustness of the results.

The comparative analyses included comparisons between the vosoritide group (consisting of several treatment groups from studies 111-202/205 and 111-301) and the external control group (untreated ACH subjects from the NH sources). The subjects included in the external control group for most comparative analyses were selected by a sex and age matching process to each subject in the vosoritide group.

Results:

Table 45: Goodness of Matching for Cohort 3 of 111-202/205 versus External Controls (Analysis Population: 5-Year Comparative Analysis)

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

	Cross-Sectional Analyses		Longitudinal Analyses	Cross-Sectional Analyses	
	External Control (Primary at Year 5)	External Control (Primary at Baseline)	External Control (Primary)	External Control (Pooled at Year 5)	External Control (Supportive Pooled at Baseline)
	(N = 360)	(N = 559)	(N = 98)	(N = 84)	(N = 236)
Duration of follow-up (month)					
n	-	-	98	-	-
Mean (SD)	-	-	59.87 (1.51)	-	-
Median	-	-	59.81	-	-
25th, 75th Percentile	-	-	58.80, 61.02	-	-
Min, Max	-	-	57.1, 63.0	-	-

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

The difference in demographic and baseline growth characteristics is between each subject from the external control group of the NH source and their matched vosoritide subject. Height Z-Scores were derived using age sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

5-Year Cross-Sectional Comparative Analyses (Cohort 3 111-202/205) on Height (Primary Analysis)

The results of the pre-specified primary analysis are summarised in **Table *46***.

Table 46: TTEST of Height Difference at Year 5 and at Baseline (Cross-Sectional) (Analysis Population: 5-Year Cross-Sectional Comparative Analysis (111-205/202 versus Primary and Supportive Pooled External Controls)

	Primary Analysis		Supportive Pooled	
	Vosoritide 15 µg/kg	External Control (Primary)	Vosoritide 15 µg/kg	External Control (Supportive Pooled)
Height (cm) at Year 5				
N	10	360	10	84
Mean (SD)	130.94 (10.77)	116.90 (5.44)	130.94 (10.77)	117.88 (5.32)
Median (min, max)	130.53 (115.8, 158.0)	116.76 (110.2, 126.6)	130.53 (115.8, 158.0)	117.08 (111.9, 129.2)
25th, 75th percentile	124.65, 131.70	112.16, 119.29	124.65, 131.70	112.98, 121.11
Means difference (95% CI)	14.04 (7.29, 20.79)		13.06 (6.49, 19.62)	
2-sided p-value	**0.0011**		**0.0015**	
Height (cm) at Baseline				
N	10	559	10	236
Mean (SD)	104.61 (8.75)	99.64 (6.53)	104.61 (8.75)	100.29 (6.33)
Median (min, max)	103.95 (93.6, 126.1)	99.44 (90.8, 110.7)	103.95 (93.6, 126.1)	100.37 (91.2, 112.3)

25th, 75th percentile	100.90, 106.55	95.91, 102.77	100.90, 106.55	96.72, 104.00
Means difference (95% CI)	4.97 (0.19, 9.74)		4.32 (0.13, 8.51)	
2-sided p-value	0.0431		0.0447	
Height (cm) Difference (Year 5 – Baseline)				
Means (95 CI)	**9.08 (5.77, 12.38)**		8.74 (5.37, 12.11)	
2-sided p-value	**0.0002**		**0.0002**	

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

There was a statistically significant difference in height between the two groups at baseline (4.97 cm; p = 0.0431); this is principally due to one subject in Cohort 3 who had limb-lengthening prior to entry into the vosoritide study. At Year 5, there was a statistically significant difference in height between the two groups (14.04 cm; p = 0.0011).

The baseline-adjusted mean difference at 5-year follow up was a statistically significant mean (95% CI) difference in height in favor of vosoritide (9.08 [5.77, 12.38] cm; two-sided p = 0.0002) compared the external control group of untreated ACH subjects. This analysis was consistent with the results using a sex and age matched external control group from the pooled other NH sources (8.74 [5.37, 12.11]; two-sided p = 0.0002).

5-Year Longitudinal Comparative Analyses (Cohort 3 of 111-202/205) on Height

An ANCOVA model, with fixed effects for treatment and indicator variables for matching factors of sex and age, was applied for the 5-year longitudinal analyses to compare the change in height from baseline at Year 5 between the 10 subjects from Cohort 3 of 111-202/205 to sex and age matched subjects from the Primary NH Descriptive Population with 5 years follow-up (**Table *47***).

The estimated mean difference in height between subjects in the vosoritide group and untreated ACH subjects in the external control was 8.40 cm with 95% CI (6.13, 10.67), p < 0.0001, in favour of vosoritide.

Table 47: Longitudinal Analysis of Covariance of Change from Baseline in Height for Cohort 3 of 111-202/205 (Analysis Population: 5-Year Longitudinal Comparative Analysis versus Primary External Control)

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

CI, confidence interval; LS, least square; max, maximum; min, minimum; SD, standard deviation.
Results were based on an ANCOVA model with fixed effects of treatment and indicator variables for matching.

Potential Height at age of 16 years

To understand the potential treatment effect on final height, individual subject's height was extrapolated from the last height assessment at the data cut-off to the time when the subject reaches 16 years of age. At the time of the data cut off the 10 subjects ages ranged from 11 to 16 years. Extrapolated mean results were compared to the mean height of 16-year-old males and females from the Primary NH Descriptive Population. Different assumptions were applied for the extrapolated growth ranging from the best case scenario that subjects continued to grow at the same rate at the time of the data cut to the worst case scenario that the subjects grew no more after the time of the data cut off. Height differences of up to 20 cm could be observed in favor of subjects in the vosoritide group at the age of 16 years compared with the external control (**Table *48***), and in the worst case scenario where the subjects no longer grew (last observed carried forward [LOCF]), there was a difference of 8.71 cm compared between subjects in the vosoritide group to the external control.

Table 48: Summary of Extrapolated Near Final Adult Height at Age of 16 Years Old (Analysis Population: 111-202/205 Cohort 3 and Primary NH Descriptive Population)

	Vosoritide 15 µg/kg (N = 10)	External Control (N = 72)
Mean based on active AGV (95% CI)	142.86 (137.73, 147.98)	122.69 (120.78, 124.59)
Difference in mean based on active AGV (95% CI)	20.17 (14.70, 25.64)	
Mean based on 50% of active AGV (95% CI)	137.12 (132.16, 142.08)	122.68 (120.84, 124.53)
Difference in mean based on 50% of active AGV (95% CI)	14.44 (9.14, 19.73)	

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

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

2.5.3. Discussion on clinical efficacy

Achondroplasia and rationale behind the clinical development of vosoritide

The applicant developed vosoritide, a modified recombinant human CNP, for the treatment of ACH in the paediatric population. Vosoritide is a disease modifier.

The primary deficit in subjects with ACH is a constitutively active mutated FGFR3 that negatively affects skeletal growth and development through inhibition of mitosis and cellular differentiation of chondrocytes, as well as matrix deposition in active growth plates. Since CNP activates NPR-B with inhibitory effects downstream in the Fgfr3 signalling cascade and thereby counteracts the effect of constitutive Fgfr3 activation on chondrocyte function, the product was developed for the treatment of ACH. The applicant applied for the *treatment of achondroplasia in patients 2 years of age and older and whose epiphyses are not closed.*

Design and conduct of clinical studies

The applicant provided a comprehensive clinical data package with results from 7 prospective clinical studies including one study in healthy volunteers (**111-101-**FIM) and 6 in genetically confirmed ACH subjects: [**111-202(+111-205)** dose-finding, **111-301 (+111-302)** pivotal phase 3 RCT (≥5-≤18 years) and **111-206 (+111-208)** pivotal phase 2 RCT (0-≤5 years). In order to optimise disease

characterisation of the untreated population at baseline and for further comparisons of the long-term outcome, the applicant has performed one observational study **(111-901)** and generated real world evidence (RWE) from different natural history (NH) sources.

The CHMP acknowledged the strength of the clinical development programme since, although ACH is a rare orphan disease, the applicant has performed double-blinded placebo controlled randomised clinical trials to define efficacy (and safety) adequately. Since benefits and risks may differ, younger children below the age of 5 years were separately investigated after sufficient evidence was generated in those above 5 years of age. Moreover, the CHMP acknowledged that the endpoints as well as their assessment during all clinical trials was rather similar, which allows to prove consistency of the outcome and facilitate reliable pooling. The efficacy assessment is based mainly on anthropometric measurements. Primary endpoint was the AGV, which was validated and already accepted for the approval for several other growth-promoting products. The key secondary endpoints include Height Z-score in order to demonstrate robustness of the primary outcome, as well as "upper to lower body segment ratio" and "standing height" as very important endpoints with respect to long-term outcome. In addition, several QoL scores and many other endpoints of interest in the target population were included and assessed. Regarding the endpoints assessment, the Type I error was adequately controlled by hierarchical testing.

The trials' objectives and endpoints are acceptable to the CHMP and were also agreed in a previous CHMP's scientific advice. The inclusion and exclusion criteria, used are also agreed by the CHMP to characterise the target population of ACH patients. Upon the CHMP's request, the MAH agreed to revise the therapeutic indication to indicate that the diagnosis of ACH should be confirmed by appropriate genetic testing.

Most recommendations provided from the scientific advices were adequately considered or -in the case not followed- the reasons were comprehensible justified.

All patients in the clinical programme were initially included in the baseline observational growth study (**111-901**) at least for 6 months until they could be recruited for one of three studies (and their corresponding extension trials):

a.) Dose-finding study:

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 study 111-202, the 30 subjects could be rolled over in the long-term **extension study 111-205**. Subjects were followed until reaching near final adult height or a minimum of 5 years. Subjects in the low dose cohorts were transferred after completion of 111-202 into the 15 μg/kg dose cohort to increase the information about the selected posology.

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

Study 111-301 is a completed multicentre, randomised, 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. Randomisation (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 randomised 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 **extension study 111-302,** in which patients were treated with vosoritide until they either attain NFAH 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.

c.) Pivotal trial(s) for subjects from 0 to 60 months of age:

Study 111-206 is an ongoing 52-week multicentre, phase 2 randomised, 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 or will be enrolled into three age cohorts based on age [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 eldest population. Subjects in the extension trial 111-208 will receive vosoritide until they reach reached NFAH. However, this trial was started in June 2018, at the time of data cut-off in September 2019 only 44 of the planned 70 subjects could have been included and enrollment in Cohort 3 has even not commenced yet. Only 6 patients finalised the 52 weeks period and could be evaluated regarding efficacy; they were transferred to the **extension trial 208**. Since the study is still ongoing and blinded, only very limited results are currently available. At the latest data cut-off, the applicant reported that the study is now fully enrolled with completion (last patient/last visit) expected by March 2022.

Efficacy data and additional analyses

a.) Dose finding study

In the dose finding **study 202** at 6 months, a significant increase in AGV was observed with vosoritide at 15 and 30 µg/kg. The changes in AGV were dose dependent and achieved plateau with 15 µg/kg, (AGV-Median 2,5µg: -0.146; 7,5 mg: 1.348; 15µg: 2.652 and 30 µg: 2.899). Since no additional benefit in effect on AGV was seen with 30 µg/kg daily dose compared to 15 µg/kg, the CHMP agreed that the selected dose is adequately justified. The selected dose was further supported by the observed increase in AGV maintained over long-term treatment period for Cohorts 3 and 4 in the extension **study 205**. Moreover, participants initially receiving lower doses in Cohorts 1 (2.5 µg/kg dose) and Cohort 2 (7.5 µg/kg dose) transitioned to 15 µg/kg as the selected therapeutic dose during extension and their AGV increased over time, to the level observed with 15 µg/kg. These findings were consistent also if the key secondary endpoint Height Z-score was used for assessment.

The once-daily regimen was selected because it was expected to yield a maximal treatment effect based on nonclinical evidence. *In vitro* studies demonstrated that a once-daily regimen resulted in a similar extent of chondrocyte proliferation relative to twice-daily or continuous exposure. This finding is consistent also with respect to the outcome of further pharmacodynamics parameters evaluated.

b.) Target population in the age from 5 to <18 years of age

The initially presented short term analyses of AGV, based on the primary efficacy endpoint in **study 111-301** demonstrates a highly statistically significant improvement in AGV from baseline to Week 52 (1-year) in favour of vosoritide with a least squared (LS) mean difference of 1.57 cm/year (95% confidence interval [CI] 1.22, 1.93, two-sided p <0.0001). The improvement in AGV observed at 52 weeks (mean AGV 5.67 cm/year) was maintained after 104 weeks (mean AGV 5.64 cm/year). The maintenance of positive effect on AGV resulted in a continuous improvement in height Z-score, with a change from baseline of +0.24 SDS (LS mean difference of +0.28 (95% confidence interval [CI] 0.17, 0.39)) after 52 weeks of treatment and to +0.45 SDS after 104 weeks of treatment. Improvement in

the upper to lower body segment ratio was also observed, with a change from baseline of -0.03 after 52 weeks and -0.09 after 104 weeks of treatment.

The consistency of vosoritide treatment effect in AGV from baseline to Week 52 (1-year) was demonstrated in the pre-specified subgroup analyses for the following subgroups of interest: sex, age group, Tanner stage, strata, baseline height Z-score, and baseline AGV. In addition, these analyses were repeated with the subgroups of race and region showing also a consistent treatment effect.

The comparative analyses on AGV, with follow-up of 18 months and 2 years using an observational/placebo and external control, demonstrated that treatment effect of vosoritide on AGV observed at 1 year is maintained with continued treatment through Month 18 and 2 years, as indicated by the consistency of the results. The CHMP agrees that the magnitude of the effect of vosoritide on AGV (mean difference of 1,57 cm / year) represents restoration of a substantial proportion of the estimated 2 cm/year AGV deficit observed between children with ACH and those with average stature in this age range (Hoover-Fong 2008, Kelly 2014). In the 15 µg/kg analysis population, which allows to assess additional children with longer observation periods are available from all trials the mean (SD) change from baseline in AGV to Year 1 was 1.49 (1.62) cm/year and to Year 5 (Month 60) was 1.34 (1.31) cm/year. Considering the 95% confidence intervals, these results allow to presume the absence of clinically relevant tachyphylaxia. Compared to baseline, the improvement in AGV with vosoritide, was sustained year-by-year over 5 years of treatment, in reference to the untreated subjects with ACH at the studied age range, in whom a natural downward trend in AGV is observed (estimated to be 0.2 cm/year) according the Natural history database available. The robustness of these results is demonstrated also by the outcome regarding the Height Z-Score: Short-term analyses of improvements in height Z-score in terms reported a LS mean difference of +0.28 SDS (95% CI: 0.17, 0.39, p <0.0001) with reference to average stature children and thereby demonstrate consistency to the AGV outcome. In the updated efficacy analysis from **study 111-302** provided during the procedure, consistency of efficacy was demonstrated both, in the initially vosoritide treated population as well as in the newly treated former placebo-receiving subjects.

Similarly, the durability of the effect of vosoritide was also shown regarding the outcome on height Z-scores in the long-term analyses was assessed using NH comparative analyses on height Z-score at 5 years, in subjects treated in **study 111-202/205**. The relative improvement to placebo in standing height was observed after 1-year of treatment (LS mean change: 1.57 cm [ANCOVA model; 95% CI:1.21, 1.93, p < 0.0001, Study 111-301] in favour of vosoritide. The long-term increase in height gain, quantifying the sustained and durable effect of vosoritide after 5 years of treatment versus untreated children with ACH, has been confirmed using an external control in cross-sectional and longitudinal analyses using multiple sensitivity methods. These analyses report a baseline-adjusted mean difference at 5-year follow-up in cumulative height gain of 9.08 cm (95% CI [5.77, 12.38], P=0.0002) in favour of vosoritide. Although long-term data about efficacy during 4 to 5 years is currently restricted on 31 patients from **study 111-205**, including 10 patients treated only with vosoritide 15 µg/kg, the CHMP acknowledges that the incremental gain in height over 5 years of treatment was consistent with an approximate 5-time multiple of the gain in height observed in the pivotal **study 111-301** over a 1-year period. This allows concluding that the positive effect on growth with vosoritide is maintained year-by-year. However, although the attempts to generate comparative efficacy data for time periods beyond the 1-year time horizon of the randomised study is methodologically acknowledged and overall reasonable, it needs to be considered that due to inevitable limitations of the underlying data the analyses are considered to be highly exploratory. More comparative data from the ongoing trials and also final height data will become available post-marketing.

The effect on growth has not been associated with accelerated bone maturation, suggesting that final height may indeed be improved. In addition, improvement in linear growth was not associated with an unfavourable effect on body proportion. In fact, the 18-month comparative analysis of upper to lower body segment ratio indicates a trend for a greater decrease in ratio in the vosoritide arm compared to observational/placebo group, suggesting a small positive treatment effect.

The ultimate endpoint for medicines used in childhood for improvement of growth is the final adult height. This information (height velocity, standing height, height Z-score changes, and upper to lower body segment ratios) will be available from the ongoing open label studies 111-205 and 111-302, which are Category 3 studies in the agreed RMP.

Upon the CHMP's request, criteria for stopping treatment have been amended in the Section 4.2 of the SmPC in alignment with the criteria for treatment discontinuation in the open label study 111-302, as follows: *Treatment with this medicinal product should be stopped upon confirmation of no further growth potential, indicated by* ***a growth velocity of <1.5 cm/year and*** *closure of epiphyses.* Since there are differences across countries in the EU in standard of care to assess closure of the epiphyses, criteria to assess closure of the epiphysis is not included in the SmPC, this is agreed by the CHMP.

c.) ACH Population younger than 5 years:

Efficacy data in the population from 2 to <5 years of age from the phase 2 trial 111-206 is currently available only for 4 sentinel subjects in cohort 1 at time of data cut-off in September 2020. From baseline to 52-weeks of treatment, these patients experienced a mean (median) increase in height Z-score of 0.34 (0.27), which appears encouraging. At Week 104, two of the three sentinel subjects showed an improvement in the height Z-scores of +0.77 SDS and +0.86 SDS, while an improvement of +0.27 SDS (at Week 78) and +0.20 SDS was noted in the other two subjects. AGV at Week 104 indicated that vosoritide treatment reverted the decline in AGV expected in most of the subjects, with consistent improvement observed over 2 years of treatment. In addition, the effect appears to be greater in the population younger compared to those older than 5 years, which is biologically plausible since the maximum growth deficit in children with achondroplasia is accrued before 5 years of age. There was no worsening in upper to lower body segment ratio, which is clinically important as it indicates that the observed increase in growth is occurring proportionally in both the spine and the lower limbs.

Additional data with a cut-off on 20 March 2021 were provided for sentinel subjects from Cohort 1. Subjects in Cohort 1 have received vosoritide for a median of 978 days (range: 921 to 1012 days) and the available efficacy data continue to show positive trends across outcome measures.

In addition to the efficacy results available in patients 2 to 5 years, the applicant argued that the extrapolation of efficacy from older to younger children is further supported based on the following elements:

1) the pathophysiology of ACH which is a genetic disorder caused by a single mutation with the underlying pathophysiology of the disease being similar in all age groups

2) the mechanism of action of vosoritide that directly targets the underlying pathophysiology of ACH by down regulating Fgfr3 signalling

3) vosoritide pharmacology, bone-specific biomarker response, based on PD marker cGMP and bone-specific biomarker serum CXM, showing the time course and pattern of changes consistent with changes seen in the older children treated with vosoritide (see Discussion on Clinical Pharmacology).

The applicant's argumentation is agreed, the efficacy in children as of 2 years of age is considered sufficiently demonstrated. However, since uncertainties remain in children 2 to 5 years of age, the ongoing study 111-206 in this subgroup is important for the collection of additional efficacy data. Submission of final results for study 111-206 is an imposed condition to the marketing authorisation (category 1 study).Health related Quality of Life evaluation outcomes of vosoritide treatment in the target population remains inconclusive, since no difference was detected between the vosoritide and the placebo groups in the pivotal trial after 52 weeks of treatment. However, it is agreed with the applicant's argumentation, that it is likely that signals for any change in Quality of life scores may only occur after significantly longer treatment duration than currently assessable. Nevertheless, it is noted that the QoL assessment was adequately included in all ongoing extension studies.

2.5.4. Conclusions on the clinical efficacy

Vosoritide has been shown to be efficacious in children with ACH children from 5 to <18 years of age. Data from the pivotal placebo-controlled phase 3 studies 111-301/302, together with the already available long-term data in studies 202/205, demonstrate a consistent statistical significant and clinical relevant efficacy for the primary endpoint AGV. Results are robust as indicated by a consistent outcome for the key secondary endpoints Height Z-Scores as well as standing height. This is illustrated by the highly statistically significant improvement in AGV from baseline to Week 52 (1-year) in favour of vosoritide with a least squared (LS) mean difference of 1.57 cm/year (95% confidence interval [CI] 1.22, 1.93, two-sided p <0.0001). This suggests that about 75% of the normal growth in the corresponding age could be restored.

Although long-term data about efficacy during 4 to 5 years is currently restricted to 31 patients from study 111-205, it seems important that the incremental gain in height over 5 years of treatment was consistent with an approximate 5-time multiple of the gain in height observed in the pivotal study 111-301 over a 1-year period. This might allow concluding that the positive effect on growth with vosoritide is maintained long term.

For patients between 2 to 5 years in the pivotal RCTs 111-206/208, growth data from 4 (8) sentinel patients are encouraging. Efficacy in the lower age group is also based on extrapolation of efficacy from older (5 to <18 years) to the younger children (2 to 5 years) based on the pathophysiology of ACH, vosoritide mechanism of action and vosoritide pharmacology. Therefore, and because early treatment is likely to maximise patient benefit, CHMP agrees to include patients from the age 2 years in the authorised indication.

The CHMP considers the following measures necessary to address issues related to efficacy:

- 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 randomised, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy of daily SC injections of vosoritide in younger children with achondroplasia.

2.6. Clinical safety

Safety data from seven interventional studies are included in this application: 111-101 (up to 15 µg/kg vosoritide); 111-202 (2.5, 7.5, 15 or 30 µg/kg vosoritide); 111-205, 111-206 and 111-208 (15 or 30 µg/kg vosoritide), and 111-301 and 111-302 (15 µg/kg vosoritide).

In the non-clinical studies, the toxicity in animals was rather low and off-target toxicities seemed to be nearly absent.

The Phase 2 and 3 clinical studies were considered generally similar in design to justify pooling of the data to facilitate evaluation of long-term safety of vosoritide on the maximum number of ACH subjects exposed to vosoritide for the longest duration. Three pooled populations were defined to evaluate the safety profile of vosoritide in ACH subjects:

- **All Treated population** (pooled) – all ACH subjects treated with daily vosoritide irrespective of the age or dose received (N=164)
- **Maximum 15 µg/kg population** - all ACH subjects treated with at least one dose of, and no higher than, vosoritide 15 µg/kg daily (N=148)
- **Pure 15 µg/kg population** - all ACH subjects aged ≥5 years treated exclusively with vosoritide 15 µg/kg daily (N=131)

Patient exposure

Vosoritide is intended for the use in an orphan disease population. In COMP's orphan disease designation a frequency of ~1: 25000 is reported. This explains the comparable low number of patients exposed, which may affect the reliability of safety assessment regarding rare events. From the 164 subjects included in the pooled safety population 96 (58.5%) have longer exposure to vosoritide than 1 year and in 15 subjects (9.1%) exposure is longer than 5 years (**Table *49***).

Table 49: Extent of Vosoritide Exposure in Phase 2 and 3 Studies (Safety Population)

Exposure of Treatment	**All Treated Subjects (N=164)**
By duration, n (%)	
< 6 months	58 (35.4)
≥ 6 months	106 (64.6)
≥ 1 year	96 (58.5)
≥ 1.5 years	42 (25.6)
≥ 2 years	33 (20.1)
≥ 3 years	29 (17.7)
≥ 4 years	29 (17.7)
≥ 5 years	15 (9.1)
Total exposure, person-years	255.13

- In the **placebo-controlled phase 3 trial 111-301**, a total of **60 subjects received vosoritide** and **61 received placebo**. The mean (SD) duration of treatment was comparable between the vosoritide (353.0 [65.6] days) and placebo (364.8 [4.38] days) groups, with a total treatment exposure of 57.99 and 60.93 person-years, respectively. A mean (SD) total of 348.8 (65.1) and 359.6 (9.5) doses were administered in the vosoritide and placebo groups, respectively, over the 52-week study duration, with similar number of mean (SD) doses missed (4.4 [7.0] and 5.3 [10.1], respectively).
- In the **All Treated population**, as of the data cut-off for the MA, a total of 164 subjects in the Phase 2 and 3 studies have been exposed to any dose of vosoritide. Of these, 148 subjects have received at least one dose of, and not higher than 15 µg/kg vosoritide, and 131 subjects have exclusively received 15 µg/kg vosoritide.

- At the time of data cut-off, subjects in the All Treated population had been exposed to any dose of vosoritide for a duration ranging from 1 day to 69.3 months (> 5 years), with a **median duration of 13.7 months**, corresponding to **255.13 person-years** of treatment exposure. The **maximum duration of 69.3 months** was largely driven by the treatment duration in 111-202/205 studies.

At the time of MA submission, data in children below the age of ≤5 years at the time of treatment start (as well as ≥ 15 years) was very limited and restricted to 8 (or 11) patients. The study 111-206 had recruited at the time of MA cut-off 44 patients (~ planned about 70 patients) and considering the duration of 52 weeks in trial 111-206 more mature data regarding safety should be available post authorisation.

During the MA procedure, the applicant provided the updated safety from 8 sentinel subjects that seemed not to indicate a different safety in younger children.

In addition, updated safety data after initial submission including 102 weeks data from the initial population of the pivotal trial 111-301 now included in the extension trial 111-302 (including former placebo subjects) was provided (30 June 2020).

Adverse events

In the pooled safety data population (all treated population) a slightly lower number of patients (82.3%) experienced at least 1 AE during the studies with an overall exposure adjusted event rate of 79.01 AEs/person-year. Serious AEs were experienced by 9 (5.5%) subjects; none were considered related to study treatment or led to study drug or study discontinuation.

The majority of AEs reported during the studies were Grade 1 (mild) or 2 (moderate), with 10 (6.1%) subjects in the All Treated group reporting a Grade 3 (severe) event.

No Grade 4 AEs or deaths were reported. A total of 3 (1.8%) subjects discontinued treatment due to an AE, including 1 subject treated with 30 µg/kg due to Wolff-Parkinson syndrome (Grade 1), and 2 subjects treated with 15 µg/kg due to AEs of procedural anxiety (Grade 1) and transaminases increased (Grade 2) each. **Table *50*** and **Table *51*** provide an overview:

Table 50: Overall Summary of Adverse Events for the all safety populations

AE Category	**Pure 15 µg/kg (N=131)**	**Maximum 15 µg/kg (N=148)**	**All Treated (N=164)**
Subjects with any AE, n (%)[a]	**102 (77.9)**	**119 (80.4)**	**135 (82.3)**
AEs leading to dose reduction	0	0	0
AEs leading to dose interruption	22 (16.8)	29 (19.6)	33 (20.1)
AEs leading to study drug discontinuation	2 (1.5)	2 (1.4)	3 (1.8)
AEs leading to study discontinuation	0	0	0
AEs leading to study drug or study discontinuation	2 (1.5)	2 (1.4)	3 (1.8)
Subjects with any SAE, n (%)[a]	**6 (4.6)**	**8 (5.4)**	**9 (5.5)**
SAEs leading to dose reduction	0	0	0
SAEs leading to dose interruption	4 (3.1)	5 (3.4)	6 (3.7)
SAEs leading to study drug discontinuation	0	0	0
SAEs leading to study discontinuation	0	0	0

SAEs leading to study drug or study discontinuation	0	0	0
Subjects with any treatment-related AE, n (%)[a,b]	**69 (52.7)**	**84 (56.8)**	**99 (60.4)**
Treatment-related SAEs	0	0	0
Subjects with any AE of CTCAE grade ≥ 3, n (%)[a]	**5 (3.8)**	**9 (6.1)**	**10 (6.1)**
Subjects who died, n (%)[a]	**0**	**0**	**0**
Subjects with any EOI, n (%)[a]			
Injection site reactions during first year of treatment	61 (46.6)	75 (50.7)	89 (54.3)
Injection site reactionsd	25 (19.1)	30 (20.3)	38 (23.2)
Blood pressure decreases	16 (12.2)	23 (15.5)	28 (17.1)
Heart rate change	1 (0.8)	2 (1.4)	2 (1.2)
Hypersensitivity (SMQ Narrow)	29 (22.1)	37 (25.0)	44 (26.8)
Avascular necrosis or osteonecrosis	0	0	0
Slipped capital femoral epiphysis	0	0	0
Fractures	1 (0.8)	2 (1.4)	2 (1.2)

AE, adverse event; EOI, event of interest; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; N: total number of subjects in treatment group; n, number of subjects with event; 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 22.0 and graded for severity using NCI CTCAE version 4.0.

[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects with more than one AE of the same category were counted only once for that category.

[b] Relationship to study drug was assessed by the Investigator.

Table 51: Overall Summary of Adverse Events –comparison to Placebo from trial 111-301

	Placebo	**15 µg/kg Vosoritide**
Subjects with any AE, n (%)[a]	**60 (98.4)**	**59 (98.3)**
AEs leading to dose reduction	0	0
AEs leading to dose interruption	10 (16.4)	10 (16.7)
AEs leading to study drug discontinuation	0	1 (1.7)
AEs leading to study discontinuation	0	0
AEs leading to study drug or study discontinuation	0	1 (1.7)
Subjects with any SAE, n (%)[a]	**4 (6.6)**	**3 (5.0)**
SAEs leading to dose reduction	0	0
SAEs leading to dose interruption	2 (3.3)	2 (3.3)
SAEs leading to study drug discontinuation	0	0
SAEs leading to study discontinuation	0	0
SAEs leading to study drug or study discontinuation	0	0
Subjects with any treatment-related AE, n (%)[a,b]	**51 (83.6)**	**53 (88.3)**
Treatment-related SAEs	0	0
Subjects with any AE of CTCAE grade ≥ 3, n (%)a	**3 (4.9)**	**3 (5.0)**
Subjects who died, n (%)[a]	**0**	**0**
Subjects with any EOI, n (%)a		
Injection site reactions	50 (82.0)	51 (85.0)
Blood pressure decreases	3 (4.9)	8 (13.3)
Heart rate change	0	0
Hypersensitivity (SMQ Narrow Terms)	7 (11.5)	16 (26.7)
Avascular necrosis or osteonecrosis	0	0

Slipped capital femoral epiphysis	0	0
Fractures	0	1 (1.7)

AE, adverse event; EOI, event of interest; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; N: total number of subjects in treatment group; n, number of subjects with event; 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 22.0 and graded for severity using NCI CTCAE version 4.0.

[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects with more than one AE of the same category were counted only once for that category.

[b] Relationship to study drug was assessed by the Investigator.

Common adverse events

In the placebo-controlled population of study 111-301, in both treatment groups, AEs were most frequently reported in the SOC of general disorders and administration site conditions (90.0% in the vosoritide group versus 82.0% for placebo), followed by infections and infestations (63.3% versus 75.4%). Similarly, the highest event rates were reported in the general disorders and administration site conditions SOC (120.8 AEs/person-year for vosoritide versus 29.7 AEs/person-year for placebo) followed by infections and infestations SOC (1.7 AEs/person-year in both groups). Event rates for the remaining SOCs were <1 AE/person-year in both treatment groups. The higher event rate for the general disorders and administration site conditions in the vosoritide group was largely driven by incidence of AEs related to injection site reactions (**Table *52***).

Table 52: Adverse Events Reported in ≥ 10% Subjects in Any Treatment Group by System Organ Class – 111-301 (Safety Population)

System Organ Class	Placebo (N=61)		15µg/kg Vosoritide (N=60)	
	Incidence n (%)[a]	Event Rate m (rate) [b]	Incidence n (%)[a]	Event Rate m (rate) [b]
Total treatment exposure, person-years	**-**	**60.93**	**-**	**57.99**
Subjects with any AE, n (%)	**60 (98.4)**	**2121 (34.8)**	**59 (98.3)**	**7345 (126.7)**
General disorders and administration site conditions	50 (82.0)	1811 (29.7)	54 (90.0)	7003 (120.8)
Infections and infestations	46 (75.4)	102 (1.7)	38 (63.3)	101 (1.7)
Nervous system disorders	21 (34.4)	42 (0.7)	22 (36.7)	35 (0.6)
Gastrointestinal disorders	24 (39.3)	47 (0.8)	20 (33.3)	46 (0.8)
Musculoskeletal and connective tissue disorders	13 (21.3)	20 (0.3)	16 (26.7)	24 (0.4)
Injury, poisoning and procedural complications	13 (21.3)	22 (0.4)	15 (25.0)	24 (0.4)
Respiratory, thoracic and mediastinal disorders	16 (26.2)	30 (0.5)	14 (23.3)	32 (0.6)
Ear and labyrinth disorders	8 (13.1)	13 (0.2)	11 (18.3)	23 (0.4)
Skin and subcutaneous tissue disorders	8 (13.1)	8 (0.1)	9 (15.0)	13 (0.2)
Investigations	3 (4.9)	3 (0.0)	8 (13.3)	30 (0.5)
Metabolism and nutrition disorders	8 (13.1)	8 (0.1)	3 (5.0)	3 (0.1)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; m, number of events; N, total number of subjects in treatment group; n, number of subjects with event; 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 22.0.

[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects 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 in each treatment group. Multiple occurrences of an AE with the same SOC for a subject were counted for each occurrence for that SOC.

Adverse events reported in the pivotal trial 111-301 with a ≥ 5% difference between the vosoritide group compared to placebo and in ≥ 5 subjects are provided in **Table 53**.

Table 53: Adverse Events Reported with ≥ 5% Incidence in Vosoritide Group Compared to Placebo – 111-301 (Safety Population)

Preferred Term	Placebo (N=61)		15 µg/kg Vosoritide (N=60)	
	Incidence n (%)	Events m (rate)	Incidence n (%)	Events m (rate)
Injection site reaction	29 (47.5)	229 (3.8)	44 (73.3)	2280 (39.3)
Injection site swelling	6 (9.8)	53 (0.9)	23 (38.3)	322 (5.6)
Vomiting	12 (19.7)	16 (0.3)	16 (26.7)	25 (0.4)
Arthralgia	4 (6.6)	7 (0.1)	9 (15.0)	11 (0.2)
Injection site urticaria	2 (3.3)	5 (0.1)	8 (13.3)	71 (1.2)
Blood pressure decreased	3 (4.9)	3 (0.0)	7 (11.7)	10 (0.2)
Diarrhoea	2 (3.3)	2 (0.0)	6 (10.0)	8 (0.1)
Ear pain	3 (4.9)	3 (0.0)	6 (10.0)	11 (0.2)
Influenza	3 (4.9)	3 (0.0)	6 (10.0)	8 (0.1)
Dizziness	1 (1.6)	1 (0.0)	4 (6.7)	4 (0.1)
Fatigue	0	0	4 (6.7)	4 (0.1)
Gastroenteritis viral	1 (1.6)	1 (0.0)	4 (6.7)	4 (0.1)
Injection site mass	1 (1.6)	1 (0.0)	4 (6.7)	34 (0.6)
Seasonal allergy	1 (1.6)	1 (0.0)	4 (6.7)	4 (0.1)
Dry skin	0	0	3 (5.0)	3 (0.1)
Injection site rash	0	0	3 (5.0)	5 (0.1)

In the larger pooled safety population, which includes 104 additional patients to those investigated in the pivotal trial 111-301, the frequency of the most commonly reported adverse events (AEs) were rather similar: ISR (49.4%), injection site erythema (47.0%), nasopharyngitis (28.7%), injection site swelling (24.4%), cough (20.1%), headache (20.1%), pyrexia (23.2%), and vomiting (22.6%). Most AEs were Grade 1 (mild) in severity. Assessment of the details results not in identification of any relevant or clinically meaningful difference. In the limited data of subjects received a higher dose of 30 µ/kg, no evidence is seen for a clear dose dependency of any of these events.

With respect to pharmacodynamically reasoned adverse events of injection site reaction and blood pressure, also a slightly more pronounced incidence of arthralgia might be seen as clearly drug related.

Table 54: Adverse Events by CTCAE Grade – 111-301 (Safety Population)

CTCAE Grade	Placebo (N=61)		15 µg/kg Vosoritide (N=60)	
	Incidence n (%)[a]	Event Rate m (rate)[b]	Incidence n (%)[a]	Event Rate m (rate)[b]
Subjects with any AE, n (%)	60 (98.4)	2121 (34.8)	59 (98.3)	7345 (126.7)
Grade 1	59 (96.7)	2059 (33.8)	58 (96.7)	7294 (125.8)
Grade 2	24 (39.3)	57 (0.9)	19 (31.7)	46 (0.8)
Grade 3	3 (4.9)	5 (0.1)	3 (5.0)	5 (0.1)
Grade > 3	0	0	0	0

AE, adverse event; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; m, number of events; N, total number of subjects in treatment group; n, number of subjects with event; 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 22.0 and graded for severity using NCI CTCAE version 4.0.

[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects 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 in each treatment group. Multiple occurrences of an AE with the same SOC/PT/CTCAE grade for a subject were counted for each occurrence for that SOC/PT/CTCAE grade.

Table 55: Adverse Events by CTCAE Grade – Pooled Safety Population

CTCAE Grade	Pure 15 µg/kg (N=131)		Maximum 15 µg/kg (N=148)		All Treated (N=164)	
	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 exposure, person-years	**-**	**149.86**	**-**	**217.88**	**-**	**255.13**
Subjects with any AE, n (%)	102 (77.9)	10345 (69.03)	119 (80.4)	15293 (70.19)	135 (82.3)	20158 (79.01)
Grade 1	93 (71.0)	10175 (67.90)	110 (74.3)	14968 (68.70)	125 (76.2)	19791 (77.57)
Grade 2	47 (35.9)	132 (0.88)	61 (41.2)	257 (1.18)	68 (41.5)	279 (1.09)
Grade 3	5 (3.8)	7 (0.05)	9 (6.1)	11 (0.05)	10 (6.1)	12 (0.05)
Grade > 3	0	-	0	-	0	-
Missing	12 (9.2)	31 (0.21)	18 (12.2)	57 (0.26)	23 (14.0)	76 (0.30)

AE, adverse event; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; m, number of events; N, total number of subjects in treatment group; n, number of subjects with event; 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 22.0 and graded for severity using NCI CTCAE version 4.0.
[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects 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 in each treatment group. Multiple occurrences of an AE with the same SOC/PT/CTCAE grade for a subject were counted for each occurrence for that SOC/PT/CTCAE grade.

Grade 3 (severe) TEAEs were less frequent (vosoritide: 5.0% versus placebo: 4.9%) and overall balanced in the pivotal study. The absence of any grade ≥4 AEs and deaths also in the pooled safety population illustrate a rather low toxicity which is accordance with the non-clinical safety findings. Only one subject discontinued the study treatment (vosoritide arm) due to Grade 1 anxiety to injections.

During the evaluation, the applicant provided upon the CHMP's request **updated safety information (Data cut-off date 30 June 2020)**.

As of the 30 June 2020, 3 new subjects were included in the safety analyses (all 3 subjects in 111-206 Cohort 3 aged < 6 months of age), and a total of 167 subjects had been treated with vosoritide for a total exposure of 358.46 patient-years (an increase of 101.60 patient-years when compared to the initial marketing authorisation application [MAA]) (**Table *56***) in the pooled safety population. A total of 6 new subjects discontinued study treatment, of which 3 discontinued due to withdrawal of consent and 3 subjects reached NFAH as defined in the protocol. None of the subjects withdrew due to AEs during this period.

Table 56: Patient exposure (cut-off date of 30 June 2020)

Duration of Treatment	
Exposure, patient years	358.46
At least one dose of vosoritide, N	167
>1 year of treatment, n (%)	124 (74.3)
>2 years of treatment, n (%)	58 (34.7)
>3 years of treatment, n (%)	30 (18.0)
>4 years of treatment, n (%)	29 (17.4)
>5 years of treatment, n (%)	19 (11.4)
>6 years, n (%)	3 (1.8)

Exposure to treatment was derived from first dose to treatment discontinuation or data cut-off date of 30 June 2020. Source: Module 5.3.5.4, Day 120 Safety Update Report, Table 6.1.4.

As of 30 June 2020, a total of 17 SAEs were reported in 14 (8.4%) subjects overall in the pooled population in the All Treated population (**Table *57***). Six subjects reported a total of 7 new SAEs in the All Treated population since the data cut-off date for individual studies for the MAA submission. In addition, 5 SAEs were reported in 5 randomised subjects in the 111-206/208 studies. The most common SAEs were reported in the SOC of Congenital, familial and genetic disorders (developmental hip dysplasia and syringomyelia in one subject each) and musculoskeletal and connective tissue disorders (lumbar spinal stenosis and spinal stenosis in one subject each). None of the SAEs were assessed as related to vosoritide and were consistent with common medical conditions in childhood or with complications of ACH and were reported at expected frequencies in the ACH population.

Four new Grade 3 AEs were reported in 3 subjects, and 1 subject had a Grade 4 AE; none of the Grade 3 and higher events were assessed as related to study drug by the investigator (**Table *57***).

Table 57: Serious AEs and ≥Grade 3 AEs

Adverse Events	**All Treated Population N=167**
Grade 3 AEs All Treated population	**4**
Spinal stenosis	1

Developmental hypoplasia	1
Syringomyelia	1
Spinal cord injury	1
Grade 4 All Treated population	**1**
Appendicitis	1
Serious AEs in All Treated population	**6**
Developmental hip dysplasia	1
Syringomyelia	1
Lumbar spinal stenosis	1
Spinal stenosis	1
Spinal cord injury	1
Sleep apnoea syndrome	1
Appendicitis	1
Serious AEs in randomised subjects in 111-206/111-208	**5**
Petit mal epilepsy	1
Vomiting	1
Gastroenteritis	1
Intracranial pressure increased	1
Cervical cord compression	1

As of 30 June 2020, transient injection site reactions (ISRs) were the most commonly reported AE. A total of 84.9% of subjects (90/106 subjects from 111-202, 111-301, and 111-206 sentinels) reported ISRs in the first year of treatment with an exposure adjusted event rate of 142.53 AEs/person-year. Of note, all ISRs, irrespective of severity and duration, were reported in the first year of treatment in 111-301, 111-202, and 111-206, and the denominator (n=106) includes subjects from these 3 studies only. The majority of ISRs were transient, non-serious, mild (Grade 1) in severity, and resolved without medical intervention. No subjects interrupted or discontinued from treatment due to ISR-related events. The pattern and severity of ISRs did not change or worsen over time.

New events of blood pressure decreases were reported in 3 subjects (Grade 2 hypotension in two subjects and Grade 1 blood pressure decrease in 1 subject). Of these three events, documented symptomatic hypotension was reported in 2 subjects, both with Grade 2 hypotension. Both events resolved without medical intervention within an hour. None of the subjects reported events of slipped capital femoral epiphysis, avascular necrosis or osteonecrosis, or fractures changes post MAA data cut-off date. All hypersensitivity AEs (HAEs) were ≤ Grade 2 in severity and the type of HAEs were similar to events reported in the initial MAA.

There have been no reported AEs suggestive of off-target effects with long-term exposure including effects on the hepatic, kidney, central nervous system, respiratory, or reproductive systems.

Serious adverse event/deaths/other significant events

A total of 10 SAEs were reported in 9 subjects across all Phase 2 and 3 vosoritide studies. These events are reported as sleep apnoea syndrome [2subjects], tonsillar hypertrophy, thyroglossal cyst, syringomyelia, influenza, adenoidal hypertrophy, radius fracture, otitis media chronic, generalised tonic clonic seizure). The types of events reported as SAEs were consistent with common childhood illnesses

or with events expected in children with ACH. None of the SAEs were assessed as related to study treatment or led to study drug discontinuation.

No deaths occurred in the clinical development of vosoritide.

Adverse events of special interest (AESI):

According the non-clinical and secondary pharmacology data injection sites reactions (ISR), blood pressure decreases, hypersensitivity (SMQ narrow terms), fractures, and heart rate changes as well as slipped capital femoral epiphysis or avascular necrosis or osteonecrosis were defined as adverse events of special interest.

Injection sites reactions: Although similar number of subjects were reported with injection sites reactions in the vosoritide (51 (85.0%) subjects) and placebo arm (50 (82.0%) subjects) groups, the total number of events reported were higher in the vosoritide group (6983 events with an event rate of 120.4 AEs/person-year) compared to placebo (1776 events with an event rate of 29.2 AEs/person-year). Mean (SD) number of ISRs experienced per-subject with daily SC injections over the 52-week treatment period, in the vosoritide group compared to placebo, were 136.9 (137.9) versus 35.5 (70.0) events, with a median of 76.0 (range 1 to 365) versus 7.5 (range 1 to 355) events. This identifies ISR as a drug related adverse event, which could be expected for an active injectable peptide product associated with immunisation to some degree over time. The ISR PTs reported in ≥ 10% of subjects in vosoritide group, were injection site reaction (73%), injection site erythema (68%), injection site swelling (38%) and injection site urticaria (13%). Injection site reactions were Grade 1 (mild) in severity at the exception of 5 Grade 2 (moderate) events described in the vosoritide arm in two subjects probably reflecting immunisation (2 events of injection site urticaria, and 1 event of injection site vesicles while further 2 events were summarised as injection site reaction only).

The majority of ISRs resolved in < 24 hours; those lasting ≥ 24 hours in the vosoritide group compared to placebo, were injection site reactions (V:15 versus Plc:6 events) and injection site bruising (V: 15 versus Plc:10 events).

Data submitted regarding the pooled safety population seemed to be overall in line with the findings in the trial 111-301 population, but due to slightly different mode of reporting, the lower incidence of 53 % may be less reliable compared with the data from the pivotal RCT.

Blood pressure decreases: Consistent with the biological effects of CNP on vascular function (cGMP release) transient decreases in DBP could be expected and were observed in the non-clinical trials. Insofar, it is not surprising that blood pressure decreases were described under the most common ADRs. A decreased blood pressure was observed in 8 (13.3 %/ 11 events) patients treated with vosoritide compared to 3 (4.9%/ 3 events) in the placebo arm of the pivotal trial 111-301. The median time to onset from injection was 31 (18 to 120) minutes, except for 1 event in the vosoritide group that resolved within 2 hours, all remaining events resolved within 1 hour, (mean [SD] duration, 37.0 [28.6] minutes; median duration, 31.0 [range 5 to 90] minutes).

All events were Grade 1 (mild), and no subject discontinued treatment due to an AE of decrease in BP. A numerically slightly higher rate of 28 (17.1%) events is reported in the All Treated Population. However, there were no Grade 3 or 4 events, and none of the events were serious or led to discontinuation of study treatment. With one exception, the events with BPD were asymptomatic and the severity of the only symptomatic case was Grade 1 (post-dose SBP decrease of <20 mmHg/ DBP decrease of <10 mmHg). The reported events were identified predominantly during periods of frequent vital signs monitoring at clinical visits after dosing over a 52-week treatment period. No patients in the whole safety population needed any specific treatment and the only symptomatic episode observed was short-lasting (< 5 minutes with dizziness and vomiting after sitting up quickly) and self-limiting.

In addition to the above symptomatic hypotension reported by the Investigator, the Sponsor evaluated all AEs, using a pre-defined list of PTs, to identify symptoms that could potentially be associated with blood pressure decrease, which identified the following AE PTs (excluding the symptomatic ones already described above): **fatigue** (4 [6.7%] subjects [4 events] for vosoritide versus none for placebo), **nausea** (3 [5.0%] subjects [3 events] for vosoritide versus 4 [6.6%] subjects [6 events] for placebo), **presyncope** (without associated fall in BP) (2 [3.3%] subjects [2 events] for vosoritide versus none for placebo), and **dizziness** (4 [6.7%] subjects [5 events - 4 dizziness, 1 procedural dizziness] for vosoritide versus 1 [1.6%] subject [1 event] for placebo). Many of these events in the vosoritide group occurred at home without corresponding BP measurements, and hence due to the lack of BP values at the time of the event, no causality could be associated between these reported AEs with a reduction in BP. The adverse reactions of syncope, pre-syncope, dizziness and fatigue are considered clinically relevant as ADR.

Syncope was added as an ADR based on occurrence of 2 events of syncope in 1 subject (3%) in relation to blood draws during the Phase 2 open-label study 111-202 (N = 35); no events of syncope were reported in 111-301.

Tachycardia is reported in two subjects in the pooled safety population. No case was reported from the pivotal trial. In the two cases in the pooled safety population, no interventions were needed and the reasons for the tachycardia remain unknown in spite of cardiological diagnostic.

Hypersensitivity reaction: Please refer to the section on **Immunological events**

Slipped capital femoral epiphysis or avascular necrosis or osteonecrosis: An increased **risk for bone and joint malformation** probably leading to **osteonecrosis** and **cartilage dysfunction** was observed in healthy animals. Although the relevance of the observed findings in animal for the human ACH target population is uncertain, events like spontaneous or fractures due to inadequate trauma are of special interest. Similarly, events indicating growth associated impairment of bone and cartilage composition, which may lead to avascularnecrosis/osteonecrosis or slipped capital femoral epiphysis are relevant. Overall, two fractures, both events followed an adequate trauma and did not occur spontaneously, are reported in the pooled safety population. Both fractures healed without complications. The events were assessed as not related to vosoritide treatment. No events of avascular necrosis or osteonecrosis or slipped capital femoral epiphysis occurred in any of the treatment groups.

Drug interruptions:

In the placebo controlled pivotal trial 111-301, the proportion of subjects experiencing AEs and SAEs that led to study drug interruption was similar between the vosoritide (10 [16.7%] and 2 [3.3%] subjects, respectively) and placebo (10 [16.4%] and 2 [3.3%] subjects, respectively) groups.

Laboratory findings

With respect to the haematological parameter in the laboratory AEs interpretation of slight differences between vosoritide and placed in favour for placebo were noted. There were some shifts from baseline to a worsened severity for some parameters such as lymphocytes increased/decreased or shifts to grade 2 for neutrophils decreased (**Table *58***). The majority of shifts that occurred were self-limiting, resolved on or before the next scheduled visit.

Table 58: Shifts in CTCAE Grade of Haematology Laboratory Results from Baseline to Worst Post- Baseline Values – 111-301 (Safety Population)

Laboratory Abnormality, n (%)[a]	Normal to Grade 1		Normal to Grade 2		Grade 1 to Grade 2	
	Placebo (N=61)	15 µg/kg Vosoritide (N=60)	Placebo (N=61)	15 µg/kg Vosoritide (N=60)	Placebo (N=61)	15 µg/kg Vosoritide (N=60)
Anaemia	3 (4.9%)	5 (8.3%)	1 (1.6%)	0	0	0
Haemoglobin increased	8 (13.1%)	13 (21.7%)	0	0	0	0
WBC decreased	27 (44.3%)	20 (33.3%)	0	1 (1.7%)	2 (3.3%)	1 (1.7%)
Platelets decreased	11 (18.0%)	6 (10.0%)	0	0	0	1 (1.7%)
Neutrophils decreased	22 (36.1%)	16 (26.7%)	3 (4.9%)	3 (5.0%)	4 (6.6%)	9 (15.0%)
Lymphocytes decreased	1 (1.6%)	4 (6.7%)	1 (1.6%)	2 (3.3%)	0	0
Lymphocytes increased	0	0	5 (8.2%)	11 (18.3%)	0	0

CTCAE, common terminology criteria for adverse events; N, total number of subjects in treatment group; n, number of subjects with event, NCI, National Cancer Institute; WBC, white blood cell.

Laboratory abnormalities were graded for severity using NCI CTCAE version 4.0.

Baseline was the last measurement prior to the initiation of study drug. Laboratory results after the initiation of study drug and up to 30 days after study drug discontinuation were included.

[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator

Table 59: Shifts in CTCAE Grade of Clinical Chemistry Laboratory Results from Baseline to Worst Post-Baseline Values – 111-301 (Safety Population)

Laboratory Abnormality, n (%)[a]	Normal to Grade 1		Normal to Grade 2		Grade 1 to Grade 2	
	Placebo (N=61)	15 µg/kg Vosoritide (N=60)	Placebo (N=61)	15 µg/kg Vosoritide (N=60)	Placebo (N=61)	15 µg/kg Vosoritide (N=60)
Alkaline phosphatase	4 (6.6%)	10 (16.7%)	0	0	0	0
ALT increased	11 (18.0%)	13 (21.7%)	0	0	0	0
AST increased	4 (6.6%)	6 (10.0%)	0	0	0	0
Hypoglycaemia	2 (3.3%)	1 (1.7%)	0	1 (1.7%)	0	0
Hyperglycaemia	8 (13.1%)	6 (10.0%)	0	1 (1.7%)	0	0
Hyponatraemia	12 (19.7%)	7 (11.7%)	0	0	0	0
Bilirubin increased	1 (1.6%)	1 (1.7%)	2 (3.3%)	0	0	1 (1.7%)

ALT, alanine aminotransferase, AST, aspartate aminotransferase, CTCAE, common terminology criteria for adverse events; N, total number of subjects in treatment group; n, number of subjects with event, NCI, National Cancer Institute.

Laboratory abnormalities were graded for severity using NCI CTCAE version 4.0.

Baseline was the last measurement prior to the initiation of study drug. Laboratory results after the initiation of study drug and up to 30 days after study drug discontinuation were included.

[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator

Neither in the pivotal trial 111-301 nor in the pooled safety population clinically meaningful changes in the mean values for any of the clinical chemistry parameters over time were identified with respect to vosoritide. According to the data, no clinically significant changes in any chemistry parameters at any time in the total study population is reported. Smaller changes observed in laboratory testing return to normal values in almost all patients within the time to the next visit. The difference in ALP in comparison has to be seen as an indication for a higher osteoblastic activity (efficacy) rather than as hepatic safety signal.

Vital signs

Blood pressure (BP)

There were no notable differences between the vosoritide and placebo groups in overall mean change from baseline of pre-dose SBP, DBP, or HR at Week 26 or Week 52. Overall, the median values of SBP, DBP, and HR were comparable between the two treatment groups, and no clinically significant change in mean pre-dose SBP, DBP, or HR from baseline was noted in either group at any visit. However, a slightly more negative change in DBP and a slight compensatory increase in HR from pre-dose to post-dose values was observed in the vosoritide group, on Study Day 1, Week 26 and Week 52, when compared with the placebo group.

Electrocardiogram

No formal thorough QT (TQT) study was performed, based on 1) the sequence homology between vosoritide and endogenous CNP peptide; 2) the large size of this biologic peptide, such that an effect on cardiac ion channels is very unlikely; 3) the low QT prolongation potential characterised in the nonclinical program; 4) a negative hERG assay; and 5) lack of any signal in early phase clinical development (ECG data from 111-101 and 111-202).

An integrated cardiac safety report was prepared by an independent 3rd party including the exposure-response modelling for subjects in the Phase 3 studies 111-301 and 111-302. The data indicate no clinically significant effect of vosoritide on cardiac repolarisation, and a QT prolonging effect of ≥ 20 msec at clinically relevant exposures was excluded. A small, but clinically unimportant effect on PR interval was noted. The mean placebo-corrected ΔPR (ΔΔPR) ranged from −10.9 msec (Week 52) to −7.0 (Day 10) in study 111-301. No clinically relevant effect on QRS was observed, and no significant treatment-related morphology changes were observed.

There were no meaningful changes in mean ECG intervals over the study period (up to Month 66).

Imaging Assessments

To monitor for any potential adverse effect on skeletal growth, imaging assessments were included in 111-301/302 and 111-202/205 studies. These included X-rays of 1) the lower extremities to assess growth, 2) the lumbar spine to assess bone morphology and pathology and 3) the left hand and wrist to assess bone age. In studies 111-301/302, bone mineral density and bone mineral content were also assessed by dual X-ray absorptiometry (DXA), whilst in 111-202/205 quantitative computed tomography (QCT) was performed.

Data were not pooled across studies due to differences in imaging service provider between 111-301/302 and 111-202/205 studies. Data from the placebo-controlled data over 52 weeks from 111-301 followed by data up to Month 48 from 111-202/205 studies were provided.

In summary, there has been no evidence of disproportionate skeletal growth, accelerated bone age, abnormal bone morphology or negative changes in bone mineral density or content with vosoritide treatment over time.

Bone Age

Bone age was assessed using the Greulich and Pyle Atlas method using X-rays of the left hand and wrist (Greulich 1971; Tanner 1976). The improvements in growth have not been associated with premature bone maturation as assessed by the effect of vosoritide on bone age.

Study 111-301

Bone age at baseline was approximately 8 years in both the placebo and vosoritide treatment arms. At Week 52, mean (SD) change from baseline was approximately 1 year in both treatment arms (1.02 years [0.83] and 1.14 years [0.82] in the vosoritide and placebo groups, respectively) showing normal skeletal maturity over the 52-week period. This was similar in both males and females.

Study 111-202/205

Consistent with the observations in 111-301 study, the assessment of bone age using Greulich and Pyle method, did not show any abnormal acceleration or abnormal changes in skeletal maturity with vosoritide up to Month 48.

Lower Limb X-Rays

X-rays were performed to assess growth of the lower extremity long bones, status of their growth plates and tibial bowing.

There was no evidence to suggest an imbalance in the growth of long bones in the lower extremities; both tibia and fibula increased in length in a proportional manner over time. There was no worsening in manifestations of genu varum (tibial bowing).

Study 111-301

For left and right tibia bowing angle, there was no clear or consistent change from baseline in either treatment group at Week 52, suggesting that there was no worsening in manifestations of genu varum with consistent growth rates between tibia and fibula.

For left and right tibia distance between ankle joint and distal growth plate of fibula, there was no clear or consistent change from baseline in either treatment group at Week 52, suggesting that there was no imbalance in growth rates between tibia and fibula.

Study 111-202/205

An increase in both tibia and fibula length was observed over time with a 1:1 ratio.

There was no clinically meaningful change from baseline in the tibia bowing angle by age group. The long-term positive effect on growth was not associated with findings indicative of pathological changes in bones of lower extremities during prolonged treatment with vosoritide.

Lumbar Spine X-Rays

There was no evidence to suggest any adverse effect on growth of the vertebral bodies or spinal canal with no treatment-related worsening in ACH-related skeletal abnormalities such as lordosis and kyphosis.

Study 111-301

Sagittal width of the spinal canal, interpedicle distances, and vertebrae heights were measured for each of the lumbar vertebrae. Anterior height to medial height, anterior height to posterior height and medial height to posterior height ratios were calculated for each individual vertebra (L1 to L5). Angles of sacral tilt, lordosis (inward curve of the spine) and kyphosis (convex curvature of the spine) were also assessed.

A proportional increase in the height of the vertebral bodies was observed in both the vosoritide and placebo treatment groups; there was no obvious change in any of the ratios by Week 52.

At Week 52, there was no change from baseline in interpedicle distance in lumbar vertebrae or change from baseline in the width of spinal canal in either treatment arm within each age category.

The change from baseline in mean sacral tilt, lordosis and kyphosis angle were numerically small and similar between treatment groups and age categories; no obvious trend by age was observed.

Study 111-202/205

No notable change was observed in the vertebrae height ratios, interpedicular distance of the lumbar vertebrae or width of the spinal canal through Month 48. There were no consistent or notable change in thoracolumbar kyphosis or lumbosacral lordosis angles over time with exception of one subject in Cohort 2. This male subject (age 11 years at baseline) had pre-existing thoracolumbar kyphosis at baseline (angle of 38 degrees). Over the first 2 years of the study, there was no significant change in the kyphosis angle. At Month 48, his kyphosis worsened to 55 degrees, he was asked to wear a brace but was not compliant; corrective surgery is planned. This was captured as an AE.

Bone Mineral Density and Bone Mineral Content

In 111-301, dual energy X-ray absorptiometry scans were performed to collect relevant bone mineral content (BMC) and bone mineral density (BMD) data for whole body less head and the lumbar spine.

All DXA data was summarised separately for each scanner manufacturer (GE - Lunar Prodigy or Hologic – Discovery Horizon).

Compared to placebo, there were no notable differences in BMC or BMD at any of the sites studied over 52 weeks with vosoritide.

Safety in special populations

Subgroup analyses were performed for the pooled safety population (All Treated pooled group). In these analyses, differences in safety outcome regarding sex, ages, race/ethnicity groups and geographical regions were not observed. It is agreed that in the small paediatric population analysed, no clinically significant differences were observed in the profile of AEs by any of these parameters. However, the conclusions on these analyses are limited by the low number of patients.

Due to the paediatric indication, no data in elderly patients can be expected and the age subgroup analysis is restricted. It is acknowledged that the overall incidence of AEs, and type and nature of events reported in the small number of subjects in the age of 2 to <5 years was no different to those reported for subjects older than 5 years in the pooled analyses; the commonly reported AEs were mostly ISR-related events. There have been no SAEs assessed as related to study drug, no Grade 3 or higher AEs, and no symptomatic decreases in BP reported in younger subjects in 111-206 as of the data cut-off date.

Immunological events

Since vosoritide is a peptide, immunisation and potential hypersensitivity adverse events (HAE) are of special interest with respect to safety. The incidence and the effect of anti-vosoritide antibodies was evaluated in the context of reported ISRs, HAEs, and safety impact associated with cross-reactive antibodies.

In the pooled safety analysis (Phase 2 (111-202/205) and 3 (111-301/302) studies), ADA responses were detected in approximately 34% to 63% of subjects across studies with the incidence being 38% (59/156) in the All Treated population and earliest time to ADA development being Day 85. The magnitude of TAb titers ranged from 14 to 18,500 with 35% of the TAb-positive subjects showing a decline in titers back to baseline levels by the end of the treatment duration in the study. **Neutralising antibodies (NAb**) were detected in 2% (3/156) of All Treated subjects at a single visit after which they reverted to NAb negative status at the next time point and remained negative for all subsequent study visits. According to the information available, the presence of neutralising antibodies in the 3 subjects had no negative impact on the AVG observed. Cross -reactive binding of anti-vosoritide TAbs to ANP, BNP or CNP *in vitro* was detected in 30% (47/156), 3% (4/156) or 19% (30/156), respectively, of All Treated subjects at one or more visits. However, TAb cross-reactivity was not correlated with safety signals in any of the studies. The immunogenicity risk assessment strategy in the Phase 2 and Phase 3 studies includes continuing to closely monitor safety signals associated with antibody cross-reactivity to natriuretic peptides.

In the placebo controlled pivotal trial 111-301 (N=131) the incidence for HAEs was higher in vosoritide group (16 [26.7%] subjects with 81 events) compared to placebo (7 [11.5%] subjects with 13 events). This difference was largely driven by a higher incidence and event rate for injection site urticaria in the vosoritide group. Since only moderate 2 Grade events of injection site urticaria were observed, both in the same subject treated with vosoritide and all other HAEs were Grade 1 (mild), the

risk derived from HAEs seems to be moderate and higher compared with that in placebo treated subjects. It is reassuring that no Grade 3 or higher events were reported and no subjects experienced events meeting NIAID/FAAN criteria for anaphylaxis. The event rates for HAEs in the pooled safety population with a significantly longer observation period: 44 (26.8%) of All Treated subjects (N=164) is in line with the results of the pivotal trial 111-301. For HAEs with an event rate of 1.54 AEs/person-year is calculated. In conclusion, the risk for the target population due to HAEs can be assessed as mild to moderate, probably also during longer treatment periods as needed.

Safety related to drug-drug interactions and other interactions

In vitro microsome stability study and CYP inhibition and induction studies were conducted for vosoritide. The microsome stability study suggested that CYP-mediated phase I metabolism was not the major clearance mechanism for vosoritide. The *in vitro* CYP inhibition and induction studies suggested that vosoritide did not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, nor induce CYP 1A2, 2B6, or 3A4/5. Based on the results from these studies, CYP mediated drug-drug interactions for vosoritide are unlikely.

Discontinuation due to adverse events

In the main pivotal RCT trial 111-301 two subjects in the active arm discontinued treatment early with only 2 and 6 days on treatment (followed by study discontinuation on Study Days 15 and 286, respectively). One (1) subject treated with 30 µg/kg due to a Wolff-Parkinson syndrome (Grade 1), and 2 subjects treated with 15 µg/kg due to AEs of procedural anxiety (Grade 1) and transaminases increased (Grade 2) each.

In the pooled safety population, 3 (1.8%) subjects discontinued treatment due to an AE. One (1) subject treated with 30 µg/kg due to a Wolff-Parkinson syndrome (Grade 1), and 2 subjects treated with 15 µg/kg due to AEs of procedural anxiety (Grade 1) and transaminases increased (Grade 2) each. With respect to the case of increased transaminase, an independent paediatric hepatologist presumed after evaluation that "the event is likely to be attributable to mild hepatitis with a possible infectious etiology including parasitic infections, e.g. Toxocara, or community-acquired infections such as parvo B19, adeno or hepatitis E virus".

Post marketing experience

Vosoritide is not available as a marketed drug in any country. All data included in this marketing application are from clinical studies conducted with vosoritide.

2.6.1. Discussion on clinical safety

Vosoritide is intended for use in the rare paediatric orphan disease population of Achondroplasia for which a frequency of ~1: 25000 is reported. It is acknowledged that the safety evaluation is limited by the small size of the database and non-clinical safety data is of particular interest.

Across all non-clinical toxicology studies, the predominant findings were changes in long bones and joints. The most salient effect was impaired function of the hind limbs. This was accompanied by morphological changes of tibia, femur and acetabulum, damage of articular cartilage and histological alterations in the growth plate, indicating irregular growth of the bone. The latter mainly consisted of disordering of the columnar chondrocyte arrangement. It is acknowledged that the bone findings may

be related to exaggerated bone growth and are not expected when the basal growth rate is reduced by Ach. The growth rate with vosoritide treatment is not expected be higher than normal (i.e. higher than in healthy subjects/animals), such adverse effects are therefore not expected in patients with ACH. However, no conclusion can be made in view of the limited human data currently available. Long-term safety including skeletal effects is listed as missing information in the RMP, additional information will be collected post marketing from the completion of the ongoing long-term studies in ACH patients (111-208 and 111-302) and the planned PASS.

The non-clinical data indicate no significant off-target toxicity of vosoritide (See Discussion on non-clinical Section 2.3.6. 2.4.4.).

Exposure

Clinical safety data is available from seven interventional studies **111-101** (up to 15 µg/kg vosoritide); **111-202** (2.5, 7.5, 15 or 30 µg/kg vosoritide); **111-205**, **111-206** and **111-208** (15 or 30 µg/kg vosoritide), and **111-301** and **111-302** (15 µg/kg vosoritide).

Safety can be assessed from 164 ACH subjects treated (pooled safety population of all treated subjects) of whom 60 were included in the placebo-controlled, double blinded, randomised phase III trial 111-301 in subjects in the age range of 5 to < 18 years. With respect to the demographic and other baseline factors it is concluded that the population available reflects adequately the characteristic of the target population. However, the majority of safety data is derived from the population of children between the age of ≥5 and ≤8 years. Data in younger children below the age of ≤5 years at the time of treatment start (as well as ≥ 15 years) is very limited and restricted to 8 (or 1) patient. This database is too limited to allow a valid conclusion regarding potential differences, even in the absence of signals. The use in patients 2 to 5 years old is listed as missing information in the RMP. Additional data will be available from the ongoing still blinded randomised study **111-206** (final results expected in Q3 2022), which is an imposed condition to the marketing authorisation and from the corresponding extension study **111-208** which is a Category 3 study in the RMP.

A particular strength of vosoritide's clinical development programme is the availability of placebo-controlled data. Although this data allows mainly a comparison to placebo only during the first 52 weeks, longer duration of exposure (≥12 month) was reported for 96 (58.5%) subjects in the pooled population. The median duration of exposure (13.7 months), corresponding to 255.13 person-years of treatment exposure. Most of the safety data derive from the pivotal trial, while the maximum duration of 69.3 months was largely driven by the treatment duration in 111-202/205 studies.

Overall, it is concluded that the exposure is adequate for the population subjects ≥5 year, as data available include also long-term safety outcome. Nevertheless, more robust long-term safety is needed considering the long-term treatment duration (probably up to 13 or 18 years of treatment). Long term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential is listed as missing information in the RMP and additional data will be collected from the ongoing and planned pharmacovigilance activities.

Taking into account the size of the database, rare and unforeseeable safety events can generally not be excluded. This will be followed in the routine pharmacovigilance activities including PSUSA submission.

Safety data is available only from the target population since vosoritide was specifically designed to treat ACH patients.

Adverse events

In the placebo-controlled trial 111-301, the incidence of AEs was similar between the vosoritide (98.3%) and placebo (98.4%), which may allow to conclude with respect to frequency of AEs that the overall toxicity is not significantly increased compared with placebo. The low toxicity of vosoritide seen in animals seems also applicable for the human target population. This assumption is further confirmed by the observation that most of the adverse events were Grade 1 TEAEs (vosoritide: 96.7 % versus placebo: 97.4%) and Grade 3 (severe) TEAEs were less frequent (vosoritide: 5.0% versus placebo: 4.9%) and overall balanced between the vosoritide and placebo arms. The absence of any grade ≥4 AEs and deaths indicate also a rather low toxicity. Only one subject discontinued the study treatment (vosoritide arm) due to Grade 1 anxiety to injections.

85% of the TEAEs observed were injection site reactions (ISR), which could be interpreted also at least as partially related due to the mode of administration and the need for daily injections. Injection site reactions were slightly more frequent in subjects in the vosoritide arm (Vosoritide: 85% / Placebo: 82%). Nevertheless, the event rates as calculated by dividing the total number of events (m) by the total treatment exposure in each treatment group demonstrate that at least some of these TEAEs have to be seen drug related (Vosoritide 126.7 versus Placebo: 34.8). Injection site reaction is listed as ADR with very common frequency in Section 4.8 of the SmPC.

Adverse events reported in the pivotal trial 111-301 with a ≥ 5% difference between the vosoritide group compared to placebo and in ≥ 5 subjects were: injection site reaction (73.3% versus 47.5%), injection site swelling (38.3% versus 9.8%), vomiting (26.7% versus 19.7%), arthralgia (15.0% versus 6.6%), injection site urticaria (13.3% versus 3.3%), blood pressure decreased (11.7% versus 4.9%), diarrhoea (10.0% versus 3.3%), ear pain, and influenza (10.0% versus 4.9% each).

In the larger pooled safety population, which includes 104 additional patients to those investigated in the pivotal trial 111-301, the frequency of the most commonly reported adverse events (AEs) were rather similar: ISR (49.4%), injection site erythema (47.0%), nasopharyngitis (28.7%), injection site swelling (24.4%), cough (20.1%), headache (20.1%), pyrexia (23.2%), and vomiting (22.6%). Most AEs were Grade 1 (mild) in severity. Assessment of the details did result in the identification of any relevant or clinically meaningful difference. In the limited data of subjects received a higher dose of 30 µ/kg, no evidence is seen for a clear dose dependency of any of these events.

In the All Treated population, the most common treatment-related AEs reported in ≥ 10% of subjects were injection site reaction (48.8%), injection site erythema (47.0%), injection site swelling (24.4%), hypotension (11.6%), and injection site urticaria (10.4%). Other treatment related AEs reported in >1 subject, apart from ISR-related events, were blood pressure decreased (4.9%), vomiting (3.0%), dizziness (3%), headache (1.8%), fatigue, pre-syncope, and nausea (1.2% each).

Based on the pharmacodynamic properties of vosoritide, injection site reaction and blood pressure are identified as adverse reactions of vosoritide.

The applicant was requested to discuss whether the increased frequency of arthralgia in the vosoritide group could be a sign of articular/periarticular inflammation. The applicant pointed out that in Study 111-301, there was a greater proportion of subjects with pre-existing conditions (mainly tibial bowing but also pre-existing knee pain) in the vosoritide group (6/9 subjects) compared to the placebo group (1/4 subjects). The condition of tibial bowing itself is likely to promote arthralgia. The applicant emphasised that there were no serious or severe events of arthralgia, and that there was no discontinuation from treatment due to such an event, no procedural intervention was required, and that there was no worsening of events over time. Further, it was stated that there was no meaningful difference in the incidence of arthralgia not only during the dose escalation proportion (only one AE of

arthralgia reported for the lowest dose level of 2.5 µg/kg/day) of the phase 2 study 111-202, but also during the up to 69 months treatment in 111-202/205 (vosoritide: 8/22 [36%], placebo: 3/8 [38%]). Additionally, the applicant mentioned that effects related to exaggerated pharmacology might be possible in paediatric patients, but this would be expected at higher doses. The CHMP agreed that the available data do not suggest exaggerated pharmacology and not to include arthralgia in section 4.8 of the SmPC.

Adverse events of special interest

According the non-clinical and secondary pharmacology data, injection sites reactions (ISR), blood pressure decreases and heart rate changes, hypersensitivity (SMQ narrow terms) and fractures as well as slipped capital femoral epiphysis or avascular necrosis or osteonecrosis were defined as adverse events of special interest probably related to vosoritide.

Although similar number of subjects were reported with **injection sites reactions** in the vosoritide (51 (85.0%) subjects) and placebo arm (50 (82.0%) subjects) groups, the total number of events reported were higher in the vosoritide group (6983 events with an event rate of 120.4 AEs/person-year) compared to placebo (1776 events with an event rate of 29.2 AEs/person-year). ISR is identified as a drug related adverse event, which could be expected for an active injectable peptide product associated with immunisation to some degree over time. However, the grading is reassuring, since only 5 Grade 2 (moderate) events were described in the vosoritide arm in two subjects probably reflecting immunisation (2 events of injection site urticaria, and 1 event of injection site vesicles while further 2 events were summarised as injection site reaction only).

The majority of ISRs resolved in < 24 hours; those lasting ≥ 24 hours in the vosoritide group compared to placebo, were injection site reactions (V:15 versus Plc:6 events) and injection site bruising (V: 15 versus Plc:10 events).

Data submitted regarding the pooled safety population seemed to be overall in line with the findings in the trial 111-301 population, but due to slightly different mode of reporting, the lower incidence of 53 % may be less reliable compared with the data from the pivotal RCT.

In summary, according to the data all ISR events reported during the study were described as transient, non-serious, and in the majority as mild, resolving without medical intervention. This finding seems to be confirmed by the observation that no subjects discontinued from treatment due to ISR-related events.

Consistent with the biological effects of CNP on vascular function (cGMP release) transient decreases in DBP could be expected and were observed in the non-clinical studies. **Blood pressure decreases** were described under the most common ADRs reported after ISR (85%) and vomiting (27%). A decreased blood pressure was observed in 8 (13.3 %/ 11 events) patients treated with vosoritide compared to 3 (4.9%/ 3 events) in the placebo arm of the pivotal trial 111-301. All events were Grade 1 (mild), and no subject discontinued treatment due to an AE of decrease in BP. A numerically slightly higher rate of 28 (17.1%) events is reported in the All Treated Population. However, there were no Grade 3 or 4 events, and none of the events were serious or led to discontinuation of study treatment. With one exception, the events with BPD were asymptomatic and even in the only symptomatic case severity was Grade 1 (post-dose SBP decrease of <20 mmHg/ DBP decrease of <10 mmHg). No patients in the whole safety population needed any specific treatment and the only symptomatic episode observed was short-lasted (< 5 minutes with dizziness and vomiting after sitting up quickly) and self-limiting. It needs to be considered in addition that in orthostatic events other factors as hydration status, anxiousness etc. have to be taken into account as hidden cofactors also and may have contributed to the symptoms. Moreover, a trend to arterial hypertension is reported in ACH

children. The data indicate a mild risk of blood pressure decrease derived from vosoritide in the target population, which resolves spontaneously without treatment needed. Hypotension is listed in Section 4.8 of the SmPC as ADR with frequency very common and precautions for use to reduce the risk of potential blood pressure decrease are included in Sections 4.2 and 4.4 of the SmPC.

The applicant evaluated symptoms that could potentially be associated with blood pressure decrease. **Fatigue** was reported in [6.7%] subjects treated with vosoritide versus none with placebo, **nausea** was reported in 5.0% subjects with vosoritide versus 6.6% subjects with placebo, **presyncope** was reported in 3.3% subjects with vosoritide versus none with placebo, and **dizziness** was reported in 6.7% subjects with vosoritide versus 1.6% subject with placebo. Many of these events in the vosoritide group occurred at home without corresponding BP measurements, and hence due to the lack of BP values at the time of the event, no causality could be associated between these reported AEs with a reduction in BP. The adverse reactions of pre-syncope, dizziness and fatigue are considered clinically relevant and included as ADR in Section 4.8 of the SmPC. Nausea is also included as an ADR as this AE was considered as treatment related AE.

Syncope was added as an ADR based on occurrence of 2 events of syncope in 1 subject (3%) in relation to blood draws during the Phase 2 open-label study 111-202 (N = 35); no events of syncope were reported in study 111-301.

Tachycardia was only reported in two subjects in the pooled safety population. No case was reported from the pivotal trial. In the two cases in the pooled safety population, no interventions were needed and the reasons for the tachycardia remain unknown, in spite of cardiological diagnostic. Non-clinical data indicate no increased risk for arrhythmogenic events.

Since vosoritide is a peptide, immunisation and potential **hypersensitivity adverse events (HAE)** are of special interest with respect to safety. The applicant included adequate investigations of immunisation into the clinical trials, which allow a reliable assessment. In the placebo controlled pivotal trial 111-301 (N=131) the incidence for HAEs was higher in vosoritide group (16 [26.7%] subjects with 81 events) compared to placebo (7 [11.5%] subjects with 13 events). This difference was largely driven by a higher incidence and event rate for injection site urticaria in the vosoritide group. Since only moderate 2 Grade events of injection site urticaria were observed, both in the same subject treated with vosoritide and all other HAEs were Grade 1 (mild), the risk derived from HAEs seems to be moderate and higher compared with that in placebo treated subjects. The CHMP considered reassuring that no Grade 3 or higher events were reported and no subjects experienced events meeting NIAID/FAAN criteria for anaphylaxis. The event rates for HAEs in the pooled safety population with a significantly longer observation period: 44 (26.8%) of All Treated subjects (N=164) is in line with the results of the pivotal trial 111-301. For HAEs with an event rate of 1.54 AEs/person-year is calculated. In conclusion, the risk for the target population due to HAEs can be assessed as mild to moderate, probably also during longer treatment periods as needed.

An increased **risk for bone and joint malformation** probably leading to **osteonecrosis** and **cartilage dysfunction** was observed in healthy animals. Although the relevance of the observed findings in animal for the human ACH target population might be questionable, events like spontaneous or fractures due to inadequate trauma are of special interest. Similarly, events indicating growth associated impairment of bone and cartilage composition, which may lead to avascularnecrosis/osteonecrosis or slipped capital femoral epiphysis are relevant. Overall, two fractures, both events followed an adequate trauma and did not occur spontaneously, are reported in the pooled safety population. Both fractures healed without complications. The events were assessed as not related to vosoritide treatment. No events of avascular necrosis or osteonecrosis or slipped capital femoral epiphysis occurred in any of the treatment groups. The issue concerns mainly the

vulnerable population of children below the age of 5 years .. At the end at least in the population > 5 years of age, there is currently no data-driven evidence that would indicate that the non-clinical findings are relevant for the human ACH target population. Further data will be collected in the post marketing setting from the ongoing trials and the planned PASS as agreed in the RMP.

In general, the imaging data available regarding bone-age and bone health seemed to confirm that the improvements in growth was not associated with premature bone maturation as assessed by the effect of vosoritide on bone age. Similarly, there is currently no evidence of disproportionate skeletal growth, accelerated bone age, abnormal bone morphology or negative changes in bone mineral density or content with vosoritide treatment over time.

No deaths occurred in the clinical trials and **low rate of SAEs** is reported with 10 SAEs in 9 subjects across all Phase 2 and 3 vosoritide studies. Three (3 (5.0%)) subjects in the pivotal RCT 111-301 experienced 4 SAEs in the Vosoritide group compared with 4 (6.6%) subjects, who experienced 5 SAEs in the placebo group. None of these events was assessed as drug-related.

Similar TEAE events and rates were observed also in the updated safety data from the ongoing trial 111-302, particularly in the newly exposed former placebo population from 111-301.

Laboratory parameters as adverse events

With respect to the haematological parameter in the laboratory AEs, slight differences between vosoritide and placebo were noted in favour for placebo. Decreased WBC and decreased neutrophils in a number of patients on vosoritide compared to placebo are reported. However, it is acknowledged that the majority of shifts that occurred were self-limiting, resolved on or before the next scheduled visit and no haematotoxicity was described in the animal studies. Therefore, these findings are considered unlikely to indicate a safety risk of vosoritide.

In the phase III trial, more Grade 1 Alkaline phosphatase increased measurements were reported in the vosoritide group (n=10, 16.7%) compared to placebo (n=4, 6.6%). The applicant argues that this was driven by increase in the bone-specific alkaline phosphatase (BSAP) which is consistent with the expected effect of vosoritide on bone growth due to increased chondrocyte and osteoblast activity. Upon the CHMP's request, the applicant agreed to include alkaline phosphatase increase as adverse reaction in Section 4.8 of the SmPC.

Neither in the pivotal trial 111-301 nor in the pooled safety population clinically meaningful changes in the mean values for the other clinical chemistry parameters over time were identified with respect to vosoritide. According the data no clinically significant changes in any chemistry parameters at any time in the total study population is reported. CNP activity is not specific to bone growth. Both CNP and its target receptor are ubiquitous in the human body and CNP is present in the brain and in seminal plasma. The physiological effects of CNP include also regulations of neuronal development/morphology and function of the hypothalamic-pituitary-adrenal axis. The applicant summarised, as requested by the CHMP, the current knowledge regarding the impact of vosoritide on the hypothalamic-pituitary-adrenal axis; there was no evidence in animals that steroid synthesis or the level of other hormones may be relevantly impacted by vosoritide. This is further supported by the biodistribution studies which demonstrated that vosoritide does not cross the BBB (0,3%) in animals. Similarly, the limited data indicate no delay in puberty in treated subjects compared with those who received placebo. No safety signal was identified from the data available.

Subgroup analyses were not performed in trial 111-301 and only presented for the pooled safety population (All Treated pooled group), which is acceptable to the CHMP. In these restricted analyses differences in a limited population of 164 patients, safety outcome regarding sex, race/ethnicity groups and geographical regions did not to indicate any reliable difference.

Safety data in ACH subjects below the age of 5 years is restricted to 8 patients only. The safety profile in these younger children appears similar to older children, however, no reliable conclusions can be drawn at present. Overall, in the small orphan population the reliability of subgroup analyses may be challenged in general. The use in patients 2 to 5 years old is listed as missing information in the RMP. Additional data will be available from the ongoing trial(s) 111-206/208 in accordance with the agreed RMP.

Immunisation

Since vosoritide is a peptide, immunisation and potential hypersensitivity adverse events (HAE) are of special interest. The effect of **anti-vosoritide antibodies** was evaluated in the context of reported ISRs, HAEs, and safety impact associated with cross-reactive antibodies. Across the study anti-drug antibodies, responses were detected in approximately 34% to 63% of subjects across studies with the incidence being 38% (59/156) in the All Treated population. **Neutralising antibodies (NAb**) were detected in 2% (3/156) of All Treated subjects at a single visit after which they reverted to NAb negative status at the next time point and remained negative for all subsequent study visits. According the information available the presence of neutralising antibodies in the 3 subjects had no negative impact on the AVG observed.

In general, it is agreed that the limited immunogenicity results currently available did not indicate a high risk from immunogenicity-caused complications. Nevertheless, this risk exists and uncertainty remains regarding the overall impact on risk burden associated with vosoritide treatment.

The applicant has presented two in-vitro studies to investigate the potential for **drug-drug interaction**. Both studies did not indicate the potential for induction or inhibition of the cytochromes investigated. The potential for transporter mediated interactions, however, has obviously not been addressed. Since the product is parenterally administered no interactions due to food on PK has to be taken into account.

In addition, vosoritide is described to have **no known potential for drug abuse**. No studies were conducted to investigate the effect of withdrawal or rebound.

Discontinuation or treatment interruption due to adverse events

In the pooled safety population 3 (1.8%) **subjects discontinued treatment due to an AE**. 1 subject treated with 30 µg/kg due to a Wolff-Parkinson syndrome (Grade 1), and 2 subjects treated with 15 µg/kg due to AEs of procedural anxiety (Grade 1) and transaminases increased (Grade 2) each. With respect to the case of increased transaminase, which was extensively investigated, it is acknowledged that an independent paediatric hepatologist presumed after evaluation that "the event is likely to be attributable to mild hepatitis with a possible infectious aetiology including parasitic infections, e.g. *Toxocara*, or community-acquired infections such as parvo B19, adeno or hepatitis E virus". Moreover, the non-clinical trials did not indicate vosoritide-related effects on the liver in monkeys or rats treated with vosoritide daily for up to 44 or 26 weeks, respectively. Insofar, at least the nonclinical findings do not raise any important safety concerns pertaining to hepatotoxicity for the human use. After receiving the applicant's response, the uncertainty regarding this finding seems further reduced.

The proportion of subjects experiencing **AEs and SAEs that led to study drug interruption** was balanced between the vosoritide (10 [16.7%] and 2 [3.3%] subjects, respectively) and placebo (10 [16.4%] and 2 [3.3%] subjects, respectively) groups. Thus, it may be seen as an additional confirmation that vosoritide's safety risk profile is mild and differences observed regarding the types of some adverse events are explained by the pharmacological effects of the product sufficiently.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

There is no data regarding the use of vosoritide during pregnancy. The proposed use of vosoritide is limited to the paediatric population and pregnancy testing was included in the study as well as recommendations for contraception in fertile and sexually active adolescent patients. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, as a precautionary measure, in section 4.6 of the SmPC states that it is preferable to avoid the use of vosoritide during pregnancy.

Voxzogo has a moderate influence on the ability to drive, cycle and use machines. Vosoritide may cause transient decreases in blood pressure that are usually mild but syncope, pre-syncope, dizziness, as well as other signs and symptoms of decreased blood pressure have been reported as adverse reactions. The patient's response to treatment should be considered and if appropriate, advised not to drive, cycle or use machines for at least 60 minutes after injection.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Vosoritide has an acceptable safety profile and treatment is generally well tolerated from the available clinical development safety data. The safety profile in animals is rather similar to that observed in the human population. No signal for additional safety risk in human was identified during the clinical development.

The main adverse reactions identified during the clinical development are related to injection site reactions, blood pressure decrease, vomiting, nausea, fatigue and increased alkaline phosphatase.

However, long-term safety risk, particularly risk for bone and joint malformation probably leading to osteonecrosis and cartilage dysfunction after longer treatment durations cannot fully be assessed at present. The available data did not indicate that the improvements in growth is associated with any detectable premature bone maturation, disproportionate skeletal growth or abnormal bone morphology. Moreover, there was no evidence suggestive of any off-target effects including renal or CNS.

The limited immunogenicity results currently available did not indicate a high risk from immunogenicity-caused complications. Nevertheless, this risk exists and uncertainty regarding potential long-term outcome remains.

The applicant applies for the treatment of ACH children above the age of 2 years. However, currently safety in the population of children with ACH in the age of between 2 to 5 years can be only assessed from 4 sentinel patients. Although exposure in the now presented updated safety report was significantly higher and the preliminary data presented seems to indicate no differences regarding the observed adverse events and safety risks from the pivotal trials 111-206/208, the reliability of conclusion based on this data is limited. In order to overcome this limitation, the ongoing clinical trial 111-206 is proposed as a category 1 study to collect further efficacy and safety data in the population of 2 to 5 years old.

The CHMP considers the following measures necessary to address issues related to safety:

- Long term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential is a missing information in the RMP. Additional data will be collected post-

marketing from the ongoing long-term studies (111-205 / 111-208 / 111-302) and the planned PASS, which are classified as Category 3.

- Use in patients 2 to 5 years is a missing information in the RMP. Additional information will be collected from the ongoing study 111-206 which is imposed as a condition to the marketing authorisation and from 2 additional Category 3 studies (ongoing long-term study 111-208 and planned PASS).

2.7. Risk Management Plan

Safety concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	• Long-term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential • Use in pregnancy • Use in patients 2 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) :	Q2 2023 and subsequently at 2-yearly intervals
			Final CSR (Anticipated)	June 2027
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 2 to 5 years old	Safety Report (Anticipated) :	Q2 2023 and subsequently at 2-yearly intervals
			Final CSR (Anticipated)	June 2037

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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) :	Q2 2023 and subsequently at 2-yearly intervals
			Final CSR (Anticipated)	July 2030
111-603 Vosoritide PASS Planned	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 2 to 5 years old	Protocol Submission and Registration to EU PAS register	Q4 2021
			Safety Report (Anticipated) Final CSR (Anticipated) :	Q2 2023 and subsequently at 2-yearly intervals 2033

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential **(Missing information)**	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Ongoing clinical studies 111-205, 111-208, 111-302, and planned PASS Study 111-603.
Use in pregnancy **(Missing information)**	Routine risk minimisation measures: SmPC Sections: 4.6, 5.3 PL Section: 2 Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy Follow-up Form Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients 2 to 5 years old **(Missing information)**	Routine risk minimisation measures: SmPC Sections: 4.8, 5.1 PL Sections: None Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Ongoing clinical study 111-208 and planned PASS Study 111-603

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that vosoritide has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers vosoritide to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found partly acceptable by the QRD group. In particular, the QRD group agreed to an English only vial label. The Group accepted the justification submitted regarding, mainly, the low patient numbers anticipated within individual Member States and the technical restrictions due to the small size of the containers (2 mL).

In regards to the outer carton, no consensus was reached, considering that the product will be used by caregiver/patient, and bearing in mind that the numbers of patients anticipated per Member State were not low. The Group agreed, that, as a first option, the applicant should explore a multilingual outer carton, with the possibility of revisiting this in the future. If an agreement cannot be reached, it was concluded that the applicant would need to approach Member States individually. It was also agreed that the solvent label would need to be in the national language, in DE at least.

The labelling subject to translation exemption as per the QRD Group decision above will, however, be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.10.3. 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.

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 characterised 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 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.

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

Current treatments for ACH are mainly limited to surgical interventions, including cervico-medullary 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, while supportive care options are available to assist with activities of daily living via the use of adaptive devices, many young patients choose to undergo invasive limb-lengthening procedures with prolonged recovery as an attempt to ameliorate disproportionate short stature.

While as much as 15 to 30 cm gain in standing height can be achieved, limb lengthening remains a controversial, long and arduous process. It is performed rarely in the US and with varied frequency in the EU. 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 and is rarely used by paediatric endocrinologists for this condition. Therefore, a clear unmet medical need for the condition can be stated.

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**) pivotal phase 2 RCT (0-≤5 years). 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 their corresponding extension trials):

a.) 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.

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

Study 111-301 is a completed multicentre, randomised, 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. Randomisation (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 randomised 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 **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.

c.) Pivotal trial(s) for subjects from 0 to 60 months of age:

Study 111-206 is an ongoing 52-week multicentre, phase 2 randomised, 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 or will be enrolled into three age cohorts based on age [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 eldest population. Subjects in the extension trial 111-208 will receive vosoritide until they reach final or near final height. However, this trial was started in June 2018 and is still ongoing. Only 11 sentinel patients could be evaluated regarding efficacy and safety; they were transferred to the **extension trial 208**. Since the trial is still ongoing and blinded, efficacy in children between 2 and 5 years of age is available for 4 sentinel subjects in this population.

3.2. Favourable effects

- In ACH subjects > 5 years of age 52 weeks of treatment with vosoritide 15 µg/kg daily in **study 111-301** resulted in a highly statistically significant improvement in AGV vs placebo (LSM change from baseline 1.57 cm/year, (95% CI 1.22, 1.93, with a two-sided p<0.0001). This represents restoration of a substantial proportion of the estimated 2 cm/year AGV deficit observed between children with ACH and those with average stature in this age range. The positive effect on AGV appears to be consistent in all sub-groups according the available subgroup analyses. **Updated results (cut-off 02. Nov 2020)** from all 117/121 subjects who were continuing in the study until the latest data cut-off had at least an additional 52-weeks of treatment with vosoritide and

demonstrated consistent improvement in AGV observed at 52 weeks (mean AGV 5.67 cm/year) and after 104 weeks (mean AGV 5.64 cm/year).

- In ACH subjects > 5 years of age improvements in AGV resulted also in improvements in height Z-score after one year of treatment. Subjects treated with vosoritide in trial 111-301 showed a highly statistically significant improvement in height Z-score (referenced to average growth of health children) compared with those treated with placebo [LS mean difference of +0.28 SDS (CI 0.17, 0.39, p <0.0001)]. Improvement in height was also observed when compared to ACH specific growth curves.
- The maintenance of positive effect on AGV is also indicated by a continuous improvement in height Z-score, with a change from baseline of +0.24 SDS after 52 weeks of treatment and to +0.45 SDS after 104 weeks of treatment. Improvement in the upper to lower body segment ratio was also observed, with a change from baseline of -0.03 after 52 weeks and -0.09 after 104 weeks of treatment. Furthermore, the treatment effect continued to be maintained beyond 2 years as observed for 14 subjects with 130 weeks on-treatment data with vosoritide.
- Efficacy of vosoritide was also confirmed in subjects that switched from placebo to vosoritide in **study 111-302**. One-year on vosoritide treatment data in these patients showed a similar improvement in growth velocity as those patients originally randomised to vosoritide and treated for one year in **study 111-301**.
- A sustained positive effect on AGV was observed in patients treated up to 5 years with vosoritide leading to a cumulative improvement in standing height of over 9 cm compared to an age- and sex-matched natural history population suggesting that the growth promoting effect of vosoritide is maintained over time.
- The sustained acceleration in linear growth is illustrated by the change in trajectory of growth curves towards the reference height distribution of average stature children.
- The durability of vosoritide effect on skeletal growth is also supported by a sustained increase in CXM, a highly specific marker of endochondral ossification confirming continuing effect of vosoritide on growth plates over time.

3.3. Uncertainties and limitations about favourable effects

- Data on long-term efficacy is limited. However, all 117/121 subjects ≥ 5 years of age who were continuing in the study at the most recent data cut-off had at least an additional 52-weeks of treatment with vosoritide.
- The improvement in linear growth was not associated with an undue increase in bone maturation. This is important since an acceleration of bone maturation would decrease the expected final height gain.
- Although, 24 month data from 4 sentinel subjects aged 2 to <5 years suggest consistent improvement in growth, the placebo-controlled phase III **study 111- 206** (and the extension **study 111-208**) are still ongoing and therefore no results are currently available on the randomised groups. The efficacy in this patient subgroup is further supported by extrapolation of the efficacy demonstrated in patients 5 years and above since the same underlying pathophysiology applies to all age groups and vosoritide acts as a disease modifier the same way across all age groups. In addition, vosoritide pharmacology with bone-specific biomarker response has shown time course and pattern of changes in younger children consistent with changes seen in the older

children treated with vosoritide. However, since uncertainties remain in children 2 to 5 years of age, the ongoing **study 111-206** in this subgroup is important for the collection of additional efficacy data and final results will be submitted post-marketing as a condition to the marketing authorisation.

- Although the dose finding regarding the 15 µg/kg daily dose seems to be adequately justified in children above age of 2 years, it is unclear whether a higher dose of 30 µg (investigated currently in **study 111-206**) would be more adequate in younger children. This will be addressed when final results from the ongoing **study 111-206** which is imposed as a condition to the marketing authorisation are submitted.
- Although, in ACH subjects ≥ 5 years of age the positive effect on AGV as well as Height Z-score appears to be consistent in all sub-groups according to the available subgroup analyses, interpretation of results in small subgroups remains uncertain. However, based on biological/mechanistic considerations, vosoritide is expected to exert favourable effects in all patients with ACH as long as their growth plates are open, although the benefit in young patients with a higher growth potential is likely greater than in older children.
- The limited long-term data do not indicate any deterioration and in fact suggest a favourable impact on upper to lower body segment ratio, since in some patients treated for over 5 years a trend for a small numerical improvement was observed. From the general growth characteristics in ACH, a potentially more pronounced improvement may be expected in children below the age of 5. However, data available are not robust enough to confirm this assumption. Data will be provided on height velocity, standing height, height Z-score changes, and upper to lower body segment ratios from the ongoing **studies 111-205** and **111-302**, which are Category 3 studies in the agreed RMP.
- The impact of vosoritide treatment on QoL evaluation in the pivotal **study 111-301** remains uncertain, since the data available indicate no change in comparison to placebo. Further information on this individually important, but regulatory not decisive information may become available from the ongoing studies post-marketing.

3.4. Unfavourable effects

- The safety profile observed in the vosoritide clinical development programme appears rather benign. As far as currently known, there have been no important risks associated with vosoritide. All SAEs observed during the clinical trial programme were confirmed to be not drug related and no unexpected safety signal were observed across the studies.
- In the placebo-controlled study 111-301, the incidence of AEs was similar between the vosoritide (98.3%) and placebo (98.4%), therefore, with respect to frequency of AEs, the overall toxicity is not significantly increased compared with placebo. The low toxicity of vosoritide seen in animals seems also be applicable for the human target population.
- The overwhelming majority of the events were Grade 1 TEAEs (vosoritide: 96.7 % versus placebo: 97.4%). Grade 3 (severe) TEAEs were less frequent (vosoritide: 5.0% versus placebo: 4.9%) and overall balanced. No grade ≥4 AEs or deaths were observed in the clinical programme.
- Adverse events reported more frequently in the pivotal trial 111-301 with a ≥ 5% difference between the vosoritide group compared to placebo and in ≥ 5 subjects were injection site reaction (73.3% versus 47.5%), injection site swelling (38.3% versus 9.8%), vomiting (26.7% versus 19.7%), arthralgia (15.0% versus 6.6%), injection site urticaria (13.3% versus 3.3%), blood

pressure decreased (11.7% versus 4.9%), diarrhoea (10.0% versus 3.3%), ear pain, and influenza (10.0% versus 4.9% each).

- Pharmacodynamically reasoned adverse events of injection site reaction and blood pressure are considered related to vosoritide.
- The incidence rates of injection site reactions were increased with vosoritide as were the event rates (total number of events (m)/total treatment exposure in each treatment group), which identifies that the majority of these TEAEs are seen as drug related (Vosoritide 126.7 versus Placebo: 34.8). However, the vast majority of injection sites reactions were of mild severity and only 5 were Grade 2 (moderate) events in the vosoritide arm.
- A decreased blood pressure was observed in 8 (13.3%/ 11 events) patients treated with vosoritide compared to 3 (4.9%/ 3 events) in the placebo arm of the pivotal trial 111-301. All events were Grade 1 (mild), and no subject discontinued treatment due to an AE of decrease in BP. A numerically slightly higher rate of 28 (17.1%) events is reported in the All Treated Population. However, there were no Grade 3 or 4 events, and none of the events were serious or led to discontinuation of study treatment or needed of medical intervention even during long term exposure.
- The following symptoms that could potentially be associated with blood pressure decrease occurred at a higher frequency in the vosoritide group than the placebo group. **Fatigue** (6.7% subjects treated with vosoritide versus none with placebo), **nausea** (5.0% subjects with vosoritide versus 6.6% subjects with placebo), **presyncope** (3.3% subjects with vosoritide versus none with placebo), and **dizziness** (6.7% subjects with vosoritide versus 1.6% subject with placebo). However, no causality could be associated between these reported AEs with a reduction in BP, they are therefore considered as adverse reactions to vosoritide.
- Anti-drug antibody responses were detected in approximately 34% to 63% of subjects across studies with the incidence being 38% (59/156) in the All Treated population. NAb were detected in 2% (3/156) of All Treated subjects at a single visit after which they reverted to NAb negative status at the next time point and remained negative for all subsequent study visits. According the information available, the presence of neutralising antibodies in the 3 subjects had no negative impact on the AVG observed.
- Since vosoritide is a peptide and immunisation was frequently observed in the pooled safety population, hypersensitivity adverse events (HAE) are a risk associated with vosoritide. The incidence for HAEs was higher in vosoritide group (16 [26.7%] subjects with 81 events) compared to placebo (7 [11.5%] subjects with 13 events). This difference was largely driven by a higher incidence and event rate for injection site urticaria in the vosoritide group. Since only moderate 2 Grade events of injection site urticaria were observed, both in the same subject treated with vosoritide and all other HAEs were Grade 1 (mild), the risk derived from HAEs, although higher compared with that in placebo treated subjects, appears to be moderate. No Grade 3 or higher events were reported and no subjects experienced events meeting NIAID/FAAN criteria for anaphylaxis also in the currently available updated safety data.

3.5. Uncertainties and limitations about unfavourable effects

- The majority of safety data is derived from the population of children between the age of 5 and 18 years. Data in younger children below the age of 5 years at the time of treatment start (as well as ≥ 15 years) is very limited and restricted to 8 (or 11) patient. No safety signals have been

detected in these patients, but additional data will be collected post-marketing. Additional information in patients 2 to 5 years will be collected from the ongoing study 111-206 which is imposed as a condition to the marketing authorisation and from 2 additional Category 3 studies (ongoing long-term study 111-208 and planned PASS).

- Information is currently missing to address the long-term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential:
    - Although currently no relevant long-term risks with vosoritide were identified from the safety data in the pooled population, it needs to be considered that long-term experience is still limited. A total of 56 subjects have so far been treated for at least 2 years (initially randomised to vosoritide in 111-301), and an additional 61 subjects for 1 year (initially randomised to placebo in **study 111-301**.
    - An increased risk for bone and joint malformation probably leading to osteonecrosis and cartilage dysfunction was observed in non-clinical studies in healthy animals. No event of avascular necrosis/osteonecrosis or slipped capital femoral epiphysis was observed in children until data cut-off. The only bone related events beside arthralgia were two fractures, both following an adequate trauma and not considered related to vosoritide treatment. Although the undue effects of vosoritide observed in healthy animals are probably not fully relevant in the human target population, potential adverse long-term effects of vosoritide on the skeleton remains an uncertainty.
    - Although the limited immunogenicity results currently available as well as the absence of subjects with anaphylaxis do not indicate a high risk from immunogenicity-caused adverse reactions, uncertainty remains.
    - Therefore, additional data will be collected post-marketing from the ongoing long-term studies (111-205 / 111-208 / 111-302) and the planned PASS, which are classified as Category 3.
- There is no data regarding the use of vosoritide during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, as a precautionary measure, the SmPC section 4.6 states that it is preferable to avoid the use of vosoritide during pregnancy.

3.6. Effects Table

Table 60: Effects Table for Voxzogo for the treatment of achondroplasia in patients 2 years of age and older and whose epiphyses are not closed – effects in ACH patients in the age of ≥5 to ≤18 years.

Effect	Short Description	Unit	Treatment Voxzogo 15 µg/kg BW od N=60	Control (Placebo) N=61	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment Voxzogo 15 µg/kg BW od N=60	Control (Placebo) N=61	Uncertainties/ Strength of evidence	References
Annualised growth velocity (AGV at 52 weeks)	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	1.71 cm/year (95% CI: 1.40, 2.01)	0.13 cm/year (95% CI: −0.18, 0.45)	LS mean change from baseline: 1.57 cm/year (95% CI: 1.22, 1.93; with a two-sided p-value of p<0.0001)	CSR 111-301
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	+0.27 SDS (95% CI: 0.18, 0.36)	−0.01 SDS (95% CI: −0.10, 0.09)	Difference in LS mean change from baseline: 0.28 (95% CI 0.17, 0.39) p-value (ANCOVA):<0.0001	CSR 111-301
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	Mean: -0.04	Mean: -0.03	Difference in LS mean change from baseline: -0.01 (95% CI 0.05, 0.02) p-value (ANCOVA):0.5060	CSR 111-301
Change from baseline standing height	Quantify treatment benefit on growth over the long-term period.	cm	Mean: 5.59	Mean 3.93	Difference in LS mean change from baseline: 1.57 95% CI 1.21, 1.93 p-value (ANCOVA) <0.0001	CSR 111-301
Unfavourable Effects						
Subjects with any AE		n (%)	59 (98.3	60 (98.4)		CSR 111-301
Subjects with any treatment-related AE		n (%)	53 (88.3)	51 (83.6)		CSR 111-301

Effect	Short Description	Unit	Treatment Voxzogo 15 µg/kg BW od N=60	Control (Placebo) N=61	Uncertainties/ Strength of evidence	References
Subjects with any SAE		n (%)	3 (5.0)	4 (6.6)		CSR 111-301
Treatment-related SAEs		n (%)	0 (0.0)	0 (0.0)		CSR 111-301
Subjects with any AE of CTCAE grade ≥ 3,		n (%)	3 (5.0)	3 (4.9)	All events were not-related, 9 events all not-related in the pooled safety pop., n=164	CSR 111-301
Injection sites reactions	AEs/person-year	n	120.4	29.2	Mostly erythema, rarely urticaria, more frequent in vosoritide	CSR 111-301
Blood Pressure decrease		n (%)	8 (13.3)	3 (4.9)	Mild and asymptomatic	CSR 111-301
Hyper-sensitivity events		n (%)	16 (26.7)	7 (11.5)	ADAs in about 30 -62%, neutralizing Abs in 2 subjects only	CSS
Avascular necrosis / osteonecrosis		n (%)	0	0 (0.0)	No events also in the pooled target population	CSR 111-301
Slipped capital femoral epiphysis		n (%)	0	0 (0.0)	No events also in the pooled target population	CSR 111-301

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Subjects with ACH have markedly reduced and disproportionate short stature resulting in physical disability and potential complications such as hydrocephalus or spinal cord compression. Considering that the rarely used treatment option of surgical limb lengthening remains a controversial, long and potentially dangerous procedure and has no impact on the other comorbidities resulting from impaired endochondral bone formation in ACH subjects, a high medical need for an alternative treatment can be confirmed. Vosoritide is the first targeted therapy for children with ACH which can, at least partially, correct the consequences of the underlying pathophysiological defect by downregulating the FGFR3 signaling in chondrocytes.

Vosoritide has been shown to be efficacious in ACH children from 5 to <18 years of age. Data from the pivotal placebo-controlled phase 3 **study 111-301/302**, together with the available long-term data in

study 202/205, demonstrate a consistent statistically significant and clinically relevant improvement in longitudinal growth. Results are robust as indicated by a consistent outcome for the key secondary endpoints Height Z-Scores as well as standing height. A least squared (LS) mean difference of 1.57 cm/year in AGV (95% confidence interval [CI] 1.22, 1.93, two-sided p <0.0001) is assessed as an important clinical benefit in the target population since it restores a significant proportion of the estimated 2 cm/year AGV deficit observed between children with ACH and healthy children with normal growth. Moreover, the effect appears to be maintained over time and could result in a substantial cumulative increase in final height, esp. since vosoritide does not appear to accelerate bone maturation. About 75% of the normal growth in the corresponding age could be reached in a best-case scenario.

Such a degree of improvement in height may allow persons with ACH to perform daily activities taken for granted in an average height world, this is considered to be an important benefit.

In addition, a small favourable effect on body proportions was noted, but it is acknowledged that significantly longer treatment periods may be needed to confirm a benefit for patients. Further data will be collected post-marketing to address this issue from the ongoing **studies 111-205** and **111-302**, which are Category 3 studies in the agreed RMP.

Although improvement of daily-life activities are known to impact the quality of life, potentially more obvious in the adolescence than in childhood, the quality of life data from study 111-301 remain inconclusive. The young age of the patients and the rather short placebo-controlled observation period may explain this finding.

Although currently available data suggest that the treatment effect of vosoritide is maintained, longer term data confirming that final height can indeed be meaningfully increased will be available from the ongoing long term studies (**studies 111-205** and **111-302)**, which are Category 3 studies in the agreed RMP.

While efficacy in ACH patients aged 5 years and older has clearly been demonstrated, data for subjects in the age range 2 to <5 years from the pivotal RCTs 111-206/208 is currently very limited. Although, the 130-weeks growth data on 4 sentinel subjects from this study are considered promising, the number of subjects remains small. It is nevertheless fully acknowledged that starting treatment as soon as possible may be important to achieve optimal effects on final height and potentially other complications of ACH, and the applicant further justified the efficacy in patients 2 to 5 years by extrapolation of the efficacy established in children above 5 years of age. The extrapolation is based on the same underlying pathophysiology, vosoritide mechanism of action across all age groups and PD data from the ongoing study 111-206 that have shown a similar increase of CXM, which is related to growth rate, for the younger and the older subgroups. Thus, it is agreed that the scientific argumentation and the provided PD data further support the extrapolation of efficacy from the older to the younger patients. However, since uncertainties remain in children 2 to 5 years of age, the ongoing study 111-206 in this subgroup is important for the collection of additional efficacy data and final results will be submitted post-marketing.

From the safety assessment it is concluded that vosoritide has an acceptable safety profile and treatment is generally well tolerated. There have been no important safety risks identified associated with vosoritide at present. The majority of AEs were Grade 1 (mild) and no unexpected safety findings were observed. No life-threatening or fatal AEs were reported, and no participants discontinued from treatment as a result of an adverse reaction. Insofar, the low toxicity observed in animals seems to be similar to that observed in the human population. No signal for any additional safety risk in human became obvious during the clinical development. Moreover, there was no evidence suggestive of any off-target effects including renal or CNS.

Although the absence of significant toxicities is encouraging, it should be taken into account that the safety database is numerically limited (due to the rarity of the disease) and that assessment of younger ACH children (<5 years of age) is even more limited. However, it is important to note that at the time of update no new safety signal was detected even after significantly longer exposure.

Daily injections were generally well-tolerated in the Phase 2 and 3 studies for up to 5.8 years (69.3 months) as indicated by the absence of any < grade 3 adverse events during the clinical trial. Insofar, injection site reactions were the most common treatment related events, with transient injection site erythema and injection site wheal and flare being the most common reactions observed. Since vosoritide needs to be taken once daily subcutaneous injected this may be a tolerability issue but does not mean an important risk for the target population.

Due to the biological effects of CNP on vascular function, transient decreases in diastolic BP, that were mostly asymptomatic and self-limiting, were observed as the second most frequent adverse event. Since grade ≥2 DBP event were rare and none of the subjects included in the clinical trials needed any specific treatment for this adverse event, this adverse event is not considered as an important and significant safety risk.

At present, there is no signal that the improvements in growth is associated with any detectable premature bone maturation, disproportionate skeletal growth or abnormal bone morphology. However, potential long-term risks, particularly regarding bone and joint malformation that could lead to osteonecrosis and cartilage dysfunction after longer treatment durations is not fully evaluable at present. This seems to be the most important uncertainty regarding safety assessment. Long term safety will be further characterised in the post-marketing setting from the ongoing long-term studies (111-205 / 111-208 / 111-302) and the planned PASS, which are classified as Category 3.

Since vosoritide is a peptide, immunogenicity and potential hypersensitivity adverse events (HAE) are of special interest. The limited immunogenicity results currently available did not indicate a risk from immunogenicity-caused complications, but anti-drug antibodies were detected with an incidence of 38% (59/156) in the pooled (all Treated) population. Neutralising antibodies (NAb) were detected in only 2% (3/156) of the same population, probably transient, and had no negative impact on growth. This is reassuring but, in principle, the risk for anaphylactic reactions exists and uncertainty remains. Immunogenic potential will also be further characterised as part of the long-term studies (111-205 / 111-208 / 111-302) and the planned PASS.

The applicant applies for a label in the treatment of children with ACH above the age of 2 years. Although clinical data in patients < 5 years of age are very limited, the efficacy results are encouraging and the safety profile appears similar to that observed in older children. The efficacy in this patient subgroup is further supported by the established efficacy in patients 5 years and older. Since early treatment intervention is likely necessary to achieve maximum treatment benefit, the inclusion of patients from age 2 years in the indication is agreed to. However, the ongoing pivotal study 111-206 is important for the collection of additional efficacy and safety data and to address the remaining uncertainties. Therefore, provision of final results from study 111-206 is imposed as a condition to the marketing as indicated in the Annex IID of the marketing authorisation.

3.7.2. Balance of benefits and risks

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.

The applicant estimated that, in a best-case scenario, about 75% of the normal growth in the corresponding age could be restored which could lead to a significant improvement in final height and potentially in body proportions and other features and complications of ACH. However, further long-term data will need to be generated post-marketing to verify such benefits.

The safety profile of vosoritide appears rather benign and so far, no serious risks have been identified.

Therefore, the B/R relationship is clearly positive in children ≥ 5 years of age with ACH.

Clinical data in ACH children age 2 to < 5 years are 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 are promising and the safety profile seems similar to the older age group. The efficacy in this patient subgroup is 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 is also acknowledged that starting treatment as soon as possible may be important to achieve optimal effects on final height and potentially other complications of ACH. Nevertheless, results from the ongoing study 111-206 are necessary to address the remaining uncertainties in the youngest patients. Therefore, provision of final results from study 111-206 is imposed as a condition to the marketing authorisation.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Voxzogo is positive in the following indication:

Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Voxzogo is favourable in the following indication:

Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

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 randomised, 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 to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that vosoritide is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

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