Health Technology Briefing
January 2024

Vosoritide for treating achondroplasia in children

Company/Developer	BioMarin Pharmaceutical Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26713	NICE TSID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Vosoritide is in clinical development for the treatment of achondroplasia in children aged 0 to 59 months. Achondroplasia is a rare genetic bone growth disorder and the most common form of disproportionate short stature. Achondroplasia is caused by a change in the structure of a gene called the fibroblast growth factor receptor 3 (*FGFR3)* gene, which causes the body's cartilage cells, called chondrocytes, to continuously send out signals to slow bone growth. Patients with this condition have short stature, curvature of the spine and an enlarged head (macrocephaly). These characteristics may lead to health challenges including reduced breathing for short periods of time, upper airway obstruction, obesity, hearing loss and dental problems.

Vosoritide works by attaching to a receptor called natriuretic peptide receptor type B (NPR-B) on the surface of cells, thereby inhibiting the activity of FGFR3. This blockage helps to stimulate the normal growth of bones, thereby improving the symptoms of the disease. Vosoritide is administered subcutaneously (under the skin). If licensed, vosoritide will offer a therapeutic option for children aged 0 to 59 months with achondroplasia.

Proposed Indication

Treatment of patients with achondroplasia who are aged 0 to 59 months. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.[1]

Technology

Description

Vosoritide (Voxzogo, BMN 111) is an analogue of C-type natriuretic peptide (CNP) which retains the biologic properties of native CNP but has an extended half-life due to its resistance to neutral-endopeptidase digestion. A CNP analogue antagonises the mitogen-activated-protein (MAP) kinase pathway downstream of the fibroblast growth factor receptor 3 (FGFR3) and may also act independently in the growth plate.[2] In achondroplasia, it is a change in the structure of the FGFR3 gene that causes the body's cartilage cells (chondrocytes) to continuously send out signals to slow bone growth and these signals are stronger than the signals that tell bones to grow. As a result, the cells in the cartilage have trouble lining up to form new bone, causing slowed bone growth.[3] Inhibiting the FGFR3 signalling cascade counteracts the effect of constitutive FGFR3 activation on chondrocyte function and promotes endochondral bone growth by stimulating chondrocyte proliferation and differentiation.[4]

Vosoritide is in phase II clinical development for the treatment of achondroplasia patients aged 0 to 59 months2. In phase II clinical trials (NCT03583697, NCT03989947), 15 µg/kg or 30 µg/kg of vosoritide (according to age and weight of the patient) is administered via subcutaneous (SC) injection daily.[1,5]

Key Innovation

Vosoritide is a recombinant CNP analogue that was developed to have a longer half-life than its endogenous form in order to prolong pharmacologic activity. The endogenous form has an estimated half-life of 2.6 min, which is extended in vosoritide due to its resistance to neutral-endopeptidase digestion, allowing for once daily SCadministration.[2] If vosoritide is licensed for the treatment of achondroplasia in children under the age of 2 years old in the United States (US) and European Union (EU), it would benefit more than 1,000 eligible children in US and Europe, and will offer a treatment option for children with achondroplasia who currently have no effective therapies available.[6]

Regulatory & Development Status

Vosoritide currently has Marketing Authorisation in the EU for the treatment of achondroplasia in patients aged 2 years and older whose epiphyses are not closed. The diagnosis of achondroplasia must be confirmed by appropriate genetic testing.[7,8]

Vosoritide is also in phase II/III clinical development for the following indications:[9]

- Turner syndrome
- short stature
- mucopolysaccaridosis (MPS) types IVA and VI

Vosoritide has the following regulatory designation:[10]

- An orphan drug in the EU in January 2013 for achondroplasia.

Patient Group

Disease Area and Clinical Need

Achondroplasia is a rare genetic bone growth disorder and the most common form of disproportionate short stature. Achondroplasia is caused by a mutation in the *FGFR3* gene, which impairs the growth of bone in the cartilage of the growth plate. Whilst the most visible effects are in the arms, legs, and face, nearly all of the bones in the body are affected.[11] Achondroplasia is characterised by distinctive features including disproportionate short stature, curvature of the spine and an enlarged head (macrocephaly). These characteristics may lead to health challenges including: reduced breathing for short periods of time, upper airway obstruction, obesity, hearing loss and dental problems.[11] The condition is autosomal dominant however most cases are not inherited. More than 80% of individuals with achondroplasia have parents of normal stature and are born with achondroplasia as a result of a new *FGFR3* gene change in their family.[12] Patients who have inherited the defective gene from both parents are the most severely affected and normally die around birth or a few months afterwards. In patients with only one defective *FGFR3* gene, achondroplasia causes long-term disability and may result in a shorter life span because of its effects on the heart.[10] Death in the first year of life can occur due to pressure on the spinal cord, caused by abnormalities at the craniocervical junction.[13]

About 1 in 25,000 babies born in the UK have achondroplasia.[14] In England (2022-23), there were 218 finished consultant episodes (FCE) and 204 hospital admissions with a primary diagnosis of achondroplasia (ICD-10 code Q774), resulting in 285 bed days and 97 day cases in England. Of the total FCE, 58 were for children aged 0, and 62 for children aged 1-4 years.[15]

Recommended Treatment Options

There are no National Institute for Health and Care Excellence (NICE) recommended treatments for achondroplasia in children aged 0 to 59 months.

Clinical Trial Information

Trial	**111-206,** NCT03583697; A phase 2 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of BMN 111 in infants and young children with achondroplasia, age 0 to < 60 months. **Phase II** – Completed **Location(s):** UK, USA, Australia and Japan **Study completion date**: January 2022	111-208, NCT03989947: A phase 2 open-label long-term extension study to evaluate the safety and efficacy of BMN 111 in children with achondroplasia. **Phase II -** Active, not recruiting. **Location(s):** UK, USA, Australia and Japan **Primary completion date:** September 2026
Trial Design	Randomised, parallel assignment, quadruple masking	Single group assignment, open label
Population	N=75 (actual), children aged up to 59 months with diagnosis of achondroplasia , confirmed by genetic testing	N=73 (actual), participants aged 15 months and older who must have completed study 111-206

		on investigational treatment (vosoritideor placebo)
Intervention(s)	Subcutaneous injection of 15 µg/kg of vosoritide daily.	Once daily subcutaneous injections of recommended dose of vosoritide based on weight-band dosing.
Comparator(s)	Subcutaneous injection of 15 µg/kg of placebo daily.	None
Outcome(s)	Primary outcome measure: • Evaluate the effect of BMN 111 on change from baseline in length/height Z-scores [Time frame: One year] See trial record for full list of other outcomes	Primary outcome measures: • Evaluate the incidence of Treatment-Emergent Adverse Events [Safety and Tolerability} [Time frame: "Through study completion, an average of 5 years"] • Evaluate change in height/length z-score in children with ACH treated with BMN 111 [Time frame: "Through study completion, an average of 5 years"] See trial record for full list of other outcomes.
Results (efficacy)	In the full analysis population, vosoritide (n=43) compared to placebo (n=32), increased height Z-score by 0.30 SD (95% CI 0. 07, 0.54); increased AGV by 0.92cm/year (95% CI 0.24, 1.59); and did not worsen upper-to-lower body segment ratio which changed by -0. 06 (95% CI -0.15, 0. 03).[16]	-
Results (safety)	All patients reported at least one adverse event. Four serious adverse events occurred with vosoritide and 8 with placebo, none were treatment-related. Two participants discontinued, one on vosoritide with pre-existing respiratory morbidity who had a fatal respiratory arrest and one on placebo who withdrew consent.[16]	-

Estimated Cost

The cost of vosoritide is not yet known.

Relevant Guidance

NICE Guidance

NICE technology appraisal awaiting development. Vosoritide for treating achondroplasia in children and young people under 18 years (GID-TA10700). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified

Other Guidance

- The Sydney Children's Hospital Network. Achondroplasia: Practice Guidelines for Allied Health Professionals: Practice guideline by The Sydney Children's Hospital Network. 2021.[17]
- Kubota T, et al. Clinical Practice Guidelines for Achondroplasia. Clinical pediatric endocrinology: case reports and clinical investigations: official journal of the Japanese Society for Pediatric Endocrinology. 2020.[18]

Additional Information

BioMarin Pharmaceutical Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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