

HEALTH TECHNOLOGY BRIEFING MAY 2020

Vosoritide for achondroplasia

NIHRIO ID	9602	NICE ID	9914
Developer/Company	BioMarin International Limited	UKPS ID	Not available

Licensing and market availability plans	Currently in phase III clinical trials.
--	---

SUMMARY

Vosoritide is in clinical development for the treatment of achondroplasia. Achondroplasia represents the most common form of short-limb dwarfism, a condition where the bones in the arms and legs do not form properly and are shorter than normal. Patients with achondroplasia have a short stature, an enlarged head with a prominent forehead, bowed legs, ear problems, respiratory issues, compression of the spinal cord, as well as short fingers, toes, lower legs and upper arms. No pharmacologic therapies have been approved for achondroplasia in the EU.

In patients with achondroplasia, the gene FGFR3 is permanently 'switched on', and this prevents the normal growth of bones, ultimately leading to bones that are shorter than normal. Vosoritide works by attaching to a receptor called natriuretic peptide receptor type B (NPR-B) on the surface of cells, which is thought to 'switch off' the activity of FGFR3. This is expected to stimulate the normal growth of bones, thereby improving the symptoms of the disease. If licenced, vosoritide will offer a therapy option for patients with achondroplasia who currently have no effective treatment available.

PROPOSED INDICATION

Treatment of achondroplasia.¹

TECHNOLOGY

DESCRIPTION

Vosoritide (BMN-111) is an investigational drug derived from a natural human peptide that is a positive regulator of bone growth. Vosoritide employs an analog of C-type natriuretic peptide (CNP) that, through interaction with its cognate receptor natriuretic peptide receptor-B (NPR-B), antagonizes the mitogenactivated-protein (MAP) kinase pathway downstream of the fibroblast growth factor receptor 3 (FGFR3) receptor.^{1,2} FGFR3 is a negative regulator of bone growth that is mutated in achondroplasia.¹ Vosoritide may also act independently in the growth plate.²

Vosoritide is in phase III clinical development for the treatment of achondroplasia. In clinical trials (NCT03197766, NCT03424018) vosoritide is administered via daily subcutaneous injection of 15 micrograms per kilogram ($\mu\text{g}/\text{kg}$).^{3,4}

INNOVATION AND/OR ADVANTAGES

No pharmacologic therapies have been approved for achondroplasia, except for growth hormone which is available only in Japan and the long-term complications are unknown, demonstrating an unmet medical need.⁵

Vosoritide is a recombinant C-type natriuretic peptide 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.^{2,5}

Once-daily subcutaneous administration of vosoritide promotes long-bone growth in juvenile, skeletally normal mice and monkeys and corrects the dwarfism phenotype in mice with achondroplasia.⁵

In phase 2 clinical trials, a sustained increase in the annualized growth velocity was observed at doses of 15.0 and 30.0 $\mu\text{g}/\text{kg}$ of vosoritide for up to 42 months in children with achondroplasia. In the recently completed phase 3 trial the placebo-adjusted change from baseline in growth velocity after one year of treatment with vosoritide, was 1.6 cm per year.^{5,6}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Vosoritide does not currently have Marketing Authorisation in the EU/UK for any indication.

In January 2013, orphan designation was granted by the European Commission to vosoritide for the treatment of achondroplasia.⁷

Vosoritide is in phase II clinical development for dominantly inherited short stature.⁸

PATIENT GROUP

DISEASE BACKGROUND

Achondroplasia is the most common form of human dwarfism and is characterized by failure of normal conversion of cartilage into bone, which results in disproportionate short stature. This condition is caused by a mutation in the FGFR3, a negative regulator of bone growth. Disproportionate growth between endochondral bone and underlying organs leads to a number of orthopedic, neurological, respiratory, ear, nose, and throat (ENT) issues and increased mortality.¹ Adults reach a height of 131±5.6 cm (men) and 124±5.9 cm (women).⁹

The condition is autosomal dominant however most cases are not inherited. More than 80% of children with achondroplasia have parents of average stature and have the condition as the result of a spontaneous gene mutation.^{1,9} 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.⁷

Beyond disproportionate short stature, people with achondroplasia can experience serious health complications, including foramen magnum compression, sleep apnea, bowed legs, mid-face hypoplasia, permanent sway of the lower back, spinal stenosis, recurrent ear infections and obesity. Some of these complications can result in invasive surgeries such as spinal cord decompression and straightening of bowed legs. Some people with achondroplasia also suffer from chronic pain.¹

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of achondroplasia is approximately 4.0 per 100,000 live births and it is estimated to affect more than 250,000 individuals worldwide.^{10,11}

In achondroplasia, there is only a slight decrease in life expectancy compared to the general population, potentially due to cardiovascular disease.⁹ Death in the first year of life can occur due to pressure on the spinal cord, caused by abnormalities at the craniocervical junction.¹²

In 2018-19 there were 229 finished consultant episodes and 215 hospital admissions with a primary diagnosis of achondroplasia (ICD-10 code Q77.4), resulting in 542 bed days and 99 day cases in England.¹³

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Management of achondroplasia is multidisciplinary and anticipatory care is essential. Neonates should have imaging of the brain and cervical spine to assess the foramen magnum and check for hydrocephalus as well as polysomnography to check for central sleep apnea. Abnormalities in either study should warrant a prompt referral to neurosurgical colleagues for evaluation and possible surgical treatment. Regardless of imaging, activities which lead to a risk of injury to the craniocervical junction should be avoided.⁹

Treatment of ear infections and serous otitis media, along with assessment of any hearing problems is needed. Speech therapy can be offered if concerns arise. Treatment of obstructed sleep apnea may include adenotonsillectomy, weight loss, and/or continuous positive airway pressure. Weight gain should be monitored in childhood to avoid later complications. Social and psychological support should be offered. Progressive and symptomatic leg bowing can be

treated surgically. Adult patients may require a lumbar laminectomy to treat spinal stenosis. Some may choose controversial limb lengthening procedures.⁹

CURRENT TREATMENT OPTIONS

There are no NICE recommended medicines for the treatment of achondroplasia.

Anti-inflammatory drugs may be helpful in patients with degenerative joint disease.¹²

PLACE OF TECHNOLOGY

If licensed, vosoritide will offer a therapy option for patients with achondroplasia who currently have no effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03197766 , 2015-003836-11 ; A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children With Achondroplasia Phase III Location: 3 EU countries (inc UK), United States, Australia, Japan and Turkey.	NCT03424018 , 2017-002404-28 ; A Phase 3, Open-Label Long-Term Extension Study to Evaluate the Safety and Efficacy of BMN 111 in Children With Achondroplasia Phase III - Extension Location: EU (inc UK) countries, United States, Australia, Japan and Turkey.
Trial design	Randomised, double blind, placebo-controlled.	Open label, single group assignment.
Population	N = 121, aged 5 to 18 years, ACH confirmed with genetic testing.	N = 119, aged 6 years and older, completed Study 111-301.
Intervention(s)	Subcutaneous injection of 15 µg/kg of vosoritide daily.	Subcutaneous injection of 15 µg/kg of vosoritide daily.
Comparator(s)	Matched placebo.	None.
Outcome(s)	Primary outcome(s): <ul style="list-style-type: none"> Change from baseline in mean Annualized Growth Velocity [Time frame: one year] <p>See trial record for full list of other outcomes.</p>	Primary outcome(s): <ul style="list-style-type: none"> Change from baselines in mean annualized growth velocity [Time frame: through study completion, an average of 1 year] <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	<ul style="list-style-type: none"> The placebo-adjusted change from baseline in growth velocity after one year of treatment with vosoritide, the primary endpoint, was 1.6 cm/yr (p<0.0001).⁶ 	-
Results (safety)	<ul style="list-style-type: none"> Vosoritide was generally well tolerated with no clinically 	-

	significant blood pressure decreases. ⁶	
--	--	--

Trial	NCT02055157 , 2013-004137-32 ; A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children With Achondroplasia Phase II Location: Australia, France, United Kingdom and United States.	NCT02724228 , 2015-004004-30 ; A Phase 2, Open-Label, Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of BMN 111 in Children With Achondroplasia Phase II - Extension Location: Australia, France, United Kingdom and United States.
Trial design	Open label, sequential assignment.	Open label, single group assignment.
Population	N = 35, aged 5 to 14 years, ACH confirmed with genetic testing.	N = 30, aged 5 to 14 years, completed 24 months of BMN 111 treatment in Study 111-202.
Intervention(s)	BMN 111 2.5, 7.5, 15, 30 ug/kg administered daily for 24 months in an open-label sequential dose adjustment fashion.	BMN 111 15 or 30 µg/kg administered daily.
Comparator(s)	None.	None.
Outcome(s)	Primary outcome(s): <ul style="list-style-type: none"> Safety Measures [Time frame: 6 months and approximately 24 months] See trial record for full list of other outcomes.	Primary outcome(s): <ul style="list-style-type: none"> Incidence of Treatment-Emergent Adverse Events [Time Frame: through study completion, every 3 months] See trial record for full list of other outcomes.
Results (efficacy)	<ul style="list-style-type: none"> Over 54 months that children in cohort 3 (N=10) of the study, at a dose of 15 µg/kg/day, achieved a statistically significant (p< 0.005) cumulative additional mean height gain of 9.0 cm compared to children, matched for age and gender, in a new natural history achondroplasia dataset (N=619).¹⁴ 	
Results (safety)	<ul style="list-style-type: none"> Adverse events occurred in 35 of 35 patients (100%), and serious adverse events occurred in 4 of 35 patients (11%). Therapy was discontinued in 6 patients (in 1 because of an adverse event).⁵ 	

Trial	NCT03583697, 2016-003826-18 ; 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 Location(s): Australia, Japan, United Kingdom, United States
Trial design	Randomised, double blind, parallel assignment.
Population	n = 70, children aged up to 59 months, diagnosis of achondroplasia confirmed by genetic testing, at least 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry or at least 3 months of observation prior to treatment.
Intervention(s)	Daily subcutaneous injection of 15 micrograms per kilogram of BMN111.
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcome(s): <ul style="list-style-type: none"> Evaluate the effect of BMN 111 on change from baseline in length/height Z-scores [Time frame: one year] See trial for full list.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of vosoritide is unknown.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- 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. 2020.¹¹
- Health Supervision for Children with Achondroplasia. Guidelines from the American Academy of Pediatrics. 2005.¹⁵

ADDITIONAL INFORMATION

BioMarin International Limited Mirum Pharmaceuticals 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

- 1 Biomarin. *Vosoritide (BMN 111) for Achondroplasia*. 2020. Available from: <https://www.biomarin.com/products/pipeline/bmn-111/> [Accessed 18 Feb 2020].
- 2 Klag KA, Horton WA. Advances in treatment of achondroplasia and osteoarthritis. *Human Molecular Genetics*. 2015;25(R1):R2-R8. Available from: <https://doi.org/10.1093/hmg/ddv419>.
- 3 Clinicaltrials.gov. A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children With Achondroplasia. *Trial ID: NCT03197766*. 2020;Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT03197766>.
- 4 Clinicaltrials.gov. An Extension Study to Evaluate the Efficacy and Safety of BMN 111 in Children With Achondroplasia. *Trial ID: NCT03424018*. 2018;Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT03424018>.
- 5 Savarirayan R, Irving M, Bacino CA, Bostwick B, Charrow J, Cormier-Daire V, et al. C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. *New England Journal of Medicine*. 2019;381(1):25-35. Available from: <https://doi.org/10.1056/NEJMoa1813446>.
- 6 Biomarin. *BioMarin Announces Positive Final Results from Placebo-Controlled Phase 3 Data in Children with Achondroplasia Treated with Vosoritide*. 2019. Available from: <https://investors.biomarin.com/2019-12-16-BioMarin-Announces-Positive-Final-Results-from-Placebo-Controlled-Phase-3-Data-in-Children-with-Achondroplasia-Treated-with-Vosoritide> [Accessed 24 Mar 2020].
- 7 European medicines Agency. *EU/3/12/1094*. 2013. Available from: <https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3121094> [Accessed 13 Mar 2020].
- 8 Clinicaltrials.gov. *BMN-111 | Phase 2, 3*. 2020. Available from: https://clinicaltrials.gov/ct2/results?term=BMN-111&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 13 Mar 2020].
- 9 Orphanet. *Achondroplasia*. 2019. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=15 [Accessed 18 Feb 2020].
- 10 Orphanet. *Prevalence and incidence of rare diseases: bibliographic data*. 2020. Available from: https://www.orpha.net/consor/cgi-bin/Education_Home.php?Lng=EN.
- 11 Kubota T, Adachi M, Kitaoka T, Hasegawa K, Ohata Y, Fujiwara M, 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;29(1):25-42. Available from: <https://doi.org/10.1297/cpe.29.25>.
- 12 Patient.info. *Achondroplasia*. 2014. Available from: <https://patient.info/doctor/achondroplasia> [Accessed 13 Mar 2020].
- 13 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19>
- 14 BioMarin. *BioMarin Announces Cumulative Additional Height Gain of 9.0 cm over 54 months versus Natural History in Children with Achondroplasia Treated with Vosoritide in Phase 2 Study*. 2019. Available from: <https://investors.biomarin.com/2019-11-14-BioMarin-Announces-Cumulative-Additional-Height-Gain-of-9-0-cm-over-54-months-versus-Natural-History-in-Children-with-Achondroplasia-Treated-with-Vosoritide-in-Phase-2-Study> [Accessed 24 Mar 2020].
- 15 Trotter TL, Hall JG. Health Supervision for Children With Achondroplasia. *Pediatrics*. 2005;116(3):771. Available from: <https://doi.org/10.1542/peds.2005-1440>.