Health Technology Briefing
October 2024

Navepegritide for treating achondroplasia in children and adolescents aged 2 to 15 years old

Company/Developer	Ascendis Pharma UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28386	NICE ID: Not available	UKPS ID: 674981

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Navepegritide is in clinical development for the treatment of achondroplasia. Achondroplasia is a genetic condition that causes impaired bone growth, particularly in the limbs and the spine. It is caused by a change in the fibroblast growth factor receptor 3 (FGFR3) gene which is a regulator of bone growth at cartilage growth plates (the areas from which bones grow in length). Reduction in bone growth causes clinical features associated with achondroplasia including short upper arms, leg bowing and short stature; this can result in long-term complications such as back and leg pain, apnoea (interruption of breathing, especially during sleep), obesity and curved spine. The FGRF3 gene is also expressed in tissues throughout the body, which can cause serious muscular, neurological, and cardiorespiratory complications. Currently there is no treatment for achondroplasia; symptoms can be managed through surgery to correct orthopaedic complications of achondroplasia such as leg bowing.

Navepegritide is given as a subcutaneous (underneath the skin) weekly injection. It inhibits the activity of the FGFR3 gene, which is altered in achondroplasia leading to reduced bone growth in people with the condition. Navepegritide works by providing sustained release of, and continuous exposure to, C-type natriuretic peptide (CNP, a type of protein that promotes bone growth) by protecting CNP from degradation by the immune system, enabling it to work for longer. Consequently, fewer injections are required. If licenced, navepegritide would provide a treatment option for patients with achondroplasia who have few, well tolerated therapies available.

Proposed Indication

For the treatment of children and adolescents with achondroplasia.[1,2]

Technology

Description

Navepegritide (TransCon CNP) is an investigational prodrug of C-type natriuretic peptide (CNP), administered once weekly and designed to provide sustained release and continuous exposure of active CNP for the treatment of paediatric achondroplasia.[3] CNP inhibits the downstream signalling pathway of the fibroblast growth factor receptor 3 (FGFR3) which is constitutively activated in achondroplasia.[4,5] Inhibition of downstream signalling of FGFR3 by CNP restores chondrocyte differentiation and promotes bone growth.[4] In navepegritide, CNP is transiently bound to an inert polyethylene glycol carrier to prolong its half-life via shielding from proteolytic degradation and CNP clearance mechanisms.[4]

Navepegritide is in phase II/III clinical development for patients with achondroplasia.[1,2] In this phase II/III trial ApproaCH (NCT05598320), navepegritide is administered once-weekly via 100 µg/kg subcutaneous injection.[2]

Key Innovation

There are currently no pharmacological treatment options available for achondroplasia. Current therapies for achondroplasia are primarily orthopaedic or surgical interventions aimed at improving complications associated with achondroplasia such as bowed legs or lower spine curvature.[6] Navepegritide targets the underlying mechanisms of achondroplasia.[4] Native CNP has a short half-life, therefore would require continuous administration to provide beneficial therapeutic effects.[5] Navepegritide is a prodrug of CNP, and provides sustained release of CNP supporting continuous exposure with a once-weekly dosing regimen.[4] In the phase II trial ACcomplisH, navepegritide was associated with favourable safety and tolerability, and fewer achondroplasia related adverse events compared to placebo.[4] Additionally, navepegritide dosed at 100 µg/kg/week resulted in significantly higher annualized growth velocity vs placebo at week 52.[4] If licenced, navepegritide will offer a treatment option for patients who have few effective therapies available.

Regulatory & Development Status

Navepegritide does not currently have marketing authorisation in the EU/UK for any indication.

Navepegritide was awarded EMA orphan designation in 2020.[7]

Navepegritide is currently not in clinical development for any other conditions.[8]

Patient Group

Disease Area and Clinical Need

Achondroplasia is a genetic condition affecting the development of bones, caused by a change in the FGFR3 gene which is a regulator of bone growth at cartilage growth plates.[9] Clinical features result from decreased growth of bones that grow through cartilage.[9] Achondroplasia is characterised by an unusually large head (macrocephaly), short upper arms (rhizomelic dwarfism), elbow flexion contractures, trident

hands, leg bowing and short stature (adult height of approximately 4 feet).[9,10] It can result in long-term complications such as back and leg pain, apnoea, obesity, curved spine, bowed legs and hydrocephalus.[10]

Approximately 1 in 25,000 people are born with achondroplasia.[6] Achondroplasia occurs because of a spontaneous change in the FGFR3 gene in approximately 80 percent of patients; in the remaining 20 percent it is inherited from a parent.[9] In England, between 2022-2023 there were 1,364 diagnoses of achondroplasia (ICD10 code Q77.4), resulting in 218 finished consult episodes (FCE) for achondroplasia, resulting in 97 day cases and 285 FCE bed days.[11] If there is no craniocervical junction compression (compression of the brain stem or upper spinal cord by bones in the head and neck), life expectancy is not affected by achondroplasia.[9]

Recommended Treatment Options

There are currently limited treatment options for achondroplasia, with no pharmacological treatment options recommended by NICE.

Intramedullary distraction for upper limb lengthening is recommended by NICE as a surgical treatment option for achondroplasia:[12]

Infants born with achondroplasia often have a curve in the lower spine, which is treated using a brace, some people with achondroplasia also have bowed legs and require surgery to straighten them.[6]

Clinical Trial Information

Trial	NCT05598320; A phase 2b, multicenter, double-blind, randomized, placebo-controlled trial evaluating efficacy and safety of subcutaneous doses of TransCon CNP administered once weekly for 52 weeks in children with achondroplasia followed by an open label extension period. **Phase II/III –** Active, not recruiting **Locations:** 3 EU countries, United States, Australia, Canada and New Zealand **Primary completion date:** August 2024	NCT05929807; A phase 2, multicenter, long-term, open label extension trial evaluating safety, tolerability, and efficacy of subcutaneous doses of TransCon CNP administered once weekly in children and adolescents with achondroplasia **Phase II/III –** Enrolling by invitation **Locations:** 4 EU countries, United States, Australia, and New Zealand **Primary completion date:** January 2039
Trial Design	Randomised, parallel assignment, quadruple blinded	Single group assignment.
Population	N (actual) = 84; children with clinical diagnosis and genetic confirmation of achondroplasia; able to stand without assistance; between 2 to 11 years old at time of screening.	N (estimated) = 140; Participants with achondroplasia who have completed a clinical trial with TransCon CNP; children aged 3 to 15 years old.

Intervention(s)	Once weekly subcutaneous injection of 100 µg/kg TransCon CNP.	TransCon CNP 100 mcg delivered once weekly by subcutaneous injection
Comparator(s)	Once weekly subcutaneous injection of 100 µg/kg placebo for TransCon CNP.	No comparator.
Outcome(s)	Primary outcome: Annualised growth velocity (cm per year) at 52 weeks See trial record for full list of outcomes.	Primary outcomes: - Incidence of treatment emergent events over an average of 10 years - Height Z scores (number of standard deviations) over an average of 10 years See trial record for full list of outcomes.
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

The cost of navepegritide is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Vosoritide for treating achondroplasia in children (TA11528). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Vosoritide for treating achondroplasia in children and young people under 18 years (TA10700). Expected date of issue to be confirmed.
- NICE clinical guideline. Intramedullary distraction for upper limb lengthening. (IPG722). April 2022.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard contract for medical genetics (all ages). E01/S/a.
- NHS England. 2013/14 NHS Standard contract for paediatric surgery: neonates. E02/S/c.

Other Guidance

- Savarirayan R, Ireland P, Irving M, Thompson D, Alves I, et al. International Consensus Statement on the diagnosis, multidisciplinary management, and lifelong care of individuals with achondroplasia. 2022.[13]
- European Achondroplasia Forum. The first European consensus on principles of management for achondroplasia. 2021.[14]
- Kubota T, Adachi M, Kitaoka T, Hasegawa K, Ohata Y, *et al*. Clinical Practice Guidelines for Achondroplasia. 2020.[15]

Additional Information

References

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