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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Tralesinidase alfa for mucopolysaccharidosis type IIIB (Sanfilippo syndrome type B)

NIHRIO ID	12741	**NICE ID**	9633
Developer/Company	Allievex Corporation	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trial

SUMMARY

Tralesinidase alfa is in clinical development for the treatment of patients with mucopolysaccharidosis type IIIB (MPS IIIB) also known as Sanfilippo syndrome type B. MPS IIIB is a rare and progressive genetic disorder caused by the deficiency of one of the enzymes needed to break down complex sugar molecules called mucopolysaccharides. Clinically, patients have behavioural problems, intellectual deterioration, sleep disorders, hearing impairment, facial dysmorphism, organomegaly, bowel disturbances, mild skeletal changes, and shortened life span. The clinical severity ranges from mild to severe.

Tralesinidase alfa is an investigational enzyme replacement therapy (ERT) designed to replace the faulty enzyme with a healthy one in patients with MPS IIIB. Tralesinidase alfa is delivered directly to the fluid surrounding the brain (cerebrospinal fluid). If licensed, tralesinidase alfa will offer new therapy option for patients with MPS IIIB who currently have no treatment options.

PROPOSED INDICATION

Treatment of children and adults with mucopolysaccharidosis type IIIB (MPS IIIB, Sanfilippo syndrome type B).[1,2]

TECHNOLOGY

DESCRIPTION

Tralesinidase alfa (BMN 250) is an investigational enzyme replacement therapy (ERT) using a novel fusion of recombinant human alpha-N-acetyglucosaminidase (NAGLU) with a peptide derived from insulin-like growth factor 2 (IGF2) for the treatment of MPS IIIB or Sanfilippo syndrome. Designed to restore NAGLU activity in the brain, tralesinidase alfa is delivered directly to the fluid surrounding the brain (cerebrospinal fluid) by an intracerebroventricular infusion (ICV).[3]

Tralesinidase alfa is currently in phase II clinical development for the treatment of children with MPS IIIB. In the phase II clinical trial (NCT03784287), participants will receive tralesinidase alfa, 300 mg administered weekly by ICV infusion that will continue for up to 288 weeks.[2, a]

INNOVATION AND/OR ADVANTAGES

For most lysosomal storage diseases (LSDs), there is no cure. Gene therapy is an attractive tool for treatment of LSDs caused by deficiencies in secretable lysosomal enzymes, in which neither full restoration of normal enzymatic activity nor transduction of all cells of the affected organ is necessary. However, some LSDs, such as MPSIII diseases or Sanfilippo syndrome, represent a difficult challenge because patients suffer severe neurodegeneration with mild somatic alterations. The disease's main target is the central nervous system (CNS) and enzymes do not efficiently cross the blood–brain barrier even if present at very high concentration in circulation. No specific treatment has been approved for MPSIII.[4]

Due to the inability of intravenous ERT to permeate the blood-brain barrier sufficiently to prevent neurologic disease progression, intravenous ERT has not been investigated in MPSIII as intensively as it has for other lysosomal storage diseases. Other methods of ERT administration, such as intrathecal injections, are effective in delivering ERT to normalize substrate storage in the CNS of MPSIII animal models.[5]

Tralesinidase alfa is an ERT administered by ICV infusion designed to overcome these challenges by delivering the ERT directly to the brain.[1,2,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tralesinidase alfa does not currently have Marketing Authorization in the EU for any indication.

Tralesinidase alfa was granted EU orphan drug designation for MPS IIIB (Sanfilippo syndrome type B) in January 2015.[7]

Sponsorship of the development program was transferred from BioMarin to Allievex Corporation on October 23, 2019. The Sponsorship transfer has been filed with the Competent Authorities. Validation was received January 3, 2020.[a]

[a] Information provided by Allievex Corporation

PATIENT GROUP

DISEASE BACKGROUND

MPS IIIB is a genetic disorder that makes the body unable to break down large sugar molecules called glycosaminoglycans (GAGs, formerly called mucopolysaccharides). Specifically, people with this condition are unable to break down a GAG called heparan sulfate. Affected individuals can have severe neurological symptoms, including progressive dementia, aggressive behaviour, hyperactivity, seizures, deafness, loss of vision, and an inability to sleep for more than a few hours at a time. MPS IIIB is caused by alterations (mutations) in the NAGLU gene. This gene provides the instructions for producing an enzyme called N-alpha-acetylglucosaminidase, which is needed to completely break down heparan sulfate. MPS IIIB is inherited in an autosomal recessive manner. There is no specific treatment for this condition. Most people with MPS IIIB live into their teenage years, and some live longer.[8]

There are four main types of MPS III, whereby type B occurs when a person is missing or does not produce enough alpha-N- acetylglucosaminidase.[9] Patients with MPS IIIB usually appear normal at birth, but developmental delay is usually evident by age 2-5 years. Mental and motor development reach a peak by 3-6 years of age after which behavioural disturbances and intellectual decline usually occur. However, behavioural problems such as hyperactivity and irritability may become obvious earlier. Death can occur from before the age of 10 until the third or fourth decades of life, with the average being around 15 to 20 years of age.[10]

CLINICAL NEED AND BURDEN OF DISEASE

Sanfilippo syndrome type B is a rare disease and according to the report performed by the Orphanet Report Series in January 2019, the prevalence estimated in Europe for Sanfilippo syndrome type B was 0.2 per 100,000 people.[11]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of MPS III is symptomatic and supportive. It is important for children with MPS III to be managed by a multidisciplinary team of specialists to give these children the best quality of life. At different stages this could include a combination of the following: a neurologist, developmental paediatrician, metabolic/genetics specialist, orthopaedics, gastroenterologist, ophthalmologist, cardiologist, endocrinologist, allied health (e.g. physiotherapy, occupational therapy, behavioural therapists) and an ENT (ear, nose and throat) specialist.[10]

CURRENT TREATMENT OPTIONS

There are currently no approved treatments for MPS III. Current MPS III research is focusing on gene therapy, chaperone therapy, intracerebroventricular and intrathecal enzyme therapy.[12]

PLACE OF TECHNOLOGY

If licensed, tralesinidase alfa will offer new therapy option for patients with MPS IIIB (Sanfilippo syndrome type B).

CLINICAL TRIAL INFORMATION

Trial	NCT02754076, 250-201, EudraCT 2015-001985-25; A phase 1/2 open-label dose-escalation study to evaluate the safety, tolerability, pharmacokinetics and efficacy of intracerebroventricular BMN 250 in patients with mucopolysaccharidosis type IIIB (MPS IIIB, Sanfilippo syndrome type B) **Phase I/II** - ongoing **Location(s):** EU (including the UK), US, and other countries	NCT03784287, BMN 250-202, EudraCT 2017-003083-13; A multicenter, multinational, extension study to evaluate the long term safety and efficacy of intracerebroventricular BMN 250 in patients with mucopolysaccharidosis type IIIB (MPS IIIB, Sanfilippo syndrome type B) **Phase II** - ongoing **Location(s):** EU (including the UK), US, and other countries
Trial design	Single group assignment, open-label	Single group assignment, open-label
Population	n=33 (estimated); age range 1 to 10 years; individuals eligible to participate in part 1 of this study must meet all of the following criteria: has deficient NAGLU enzyme activity at screening; is ≥ 1 and < 11 years of age; has presented with signs/symptoms consistent with MPS IIIB; for individuals who have not presented with signs/symptoms of disease (eg, siblings of known patients), the determination of eligibility will be at the discretion of the BioMarin medical monitor in conjunction with the site investigator. Individuals eligible to participate in part 2 had to have participated in and met protocol requirements for transitioning from Study 250-901 or participated in Part 1 of Study 250-201.	n=33; age up to 18 years; have completed 48 weeks in part 2 of study 250-201 and enter 250-202 within 8 weeks of study completion.
Intervention(s)	In part 1, patients will receive up to 3 escalating doses of tralesinidase alfa (30, 100 and 300 mg) via ICV infusion every week until the maximum tolerated tested dose (MTTD) is established. In part 2, patients will receive weekly doses of tralesinidase alfa via ICV infusion that will continue for 48 weeks at the MTTD established in part 1.	All subjects will receive tralesinidase alfa at the MTTD established in 250-201, 300mg administered weekly by ICV infusion that will continue for up to 240 weeks.
Comparator(s)	-	-
Outcome(s)	• Safety Evaluation of weekly infusions of tralesinidase alfa (Part	• Evaluate the Long-term safety and tolerability of tralesinidase

	1 and part 2) - Number of participants with abnormal clinical laboratory values and/or adverse events that are related to treatment. [Time frame: entire study period, up to 48 weeks] • Development Quotient (DQ) as efficacy variable with analysis of rate of change of DQ score on treatment vs. rate of change of DQ score prior to treatment. [Time frame: Assessed at study end, up to 48 weeks. collected at: part 1 - baseline; part 2 - weeks 12, 24, 36, and 48] See trial record for full list of other outcomes	alfa administered in up to 33 subjects with MPS IIIB by assessing the number of participants with abnormal clinical laboratory values and/or Adverse Events related to the treatment [Time frame: entire study period, up to 240 weeks] • Evaluating the impact of long-term tralesinidase alfa treatment on cognitive function in up to 33 patients with MPS IIIB as assessed by developmental quotient (DQ) [Time frame: entire study period, up to 240 weeks] See trial record for full list of other outcomes
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

The cost of tralesinidase alfa is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance was identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

NHS England. 2013/14 NHS Standard contract for lysosomal storage disorders service (children). E06/S(HSS)/c.

OTHER GUIDANCE

No relevant guidance was identified.

ADDITIONAL INFORMATION

Allievex Corporation 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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