Health Technology Briefing
October 2024

UX111 for treating mucopolysaccharidosis type IIIA

Company/Developer	Ultragenyx Pharmaceutical Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28580	NICE ID: Not available	UKPS ID: 673473

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

UX111 is in clinical development for the treatment of mucopolysaccharidosis type IIIA (MPS IIIA). MPS, also known as Sanfilippo syndrome, is a rare genetic condition that causes fatal brain damage and is a type of childhood dementia. MPS III is caused by the lack of an enzyme that normally breaks down and recycles a large, complex sugar molecule called heparan sulphate. This heparan sulphate accumulates and causes damage to the cells of the body, particularly the brain and spinal cord. MPS IIIA is a subtype of MPS III which is caused by a change in a gene. Developmental delay is usually evident in children with MPS IIIA by age 2-5 years. Mental and motor development peak by 3-6 years of age, after which intellectual decline usually occurs. Death can occur from before the age of 10 or not until the third of fourth decades of life, with the average being around 15 to 20 years of age. There is currently no approved treatment for MPS IIIA. Therefore, there is a high unmet need for treatment options for MPS IIIA.

UX111 is a gene therapy which delivers a functional copy of the SGSH gene to cells of the central nervous system and peripheral organs. The therapy is designed to address the underlying enzyme deficiency that results in progressive cell damage and neurodevelopmental and physical decline. UX111 is administered as a one-time infusion into a vein. If licenced, UX111 will be the first approved treatment option for patients with MPS IIIA.

Proposed Indication

Treatment of mucopolysaccharidosis IIIA (MPS IIIA).[1]

Technology

Description

UX111 (ABO-102, scAAV9.U1a.hSGSH) is a novel gene therapy. UX111 is dosed in a one-time intravenous infusion (IV) using a self-complementary AAV9 vector to deliver a functional copy of the SGSH gene to cells of the central nervous system and peripheral organs. The therapy is designed to address the underlying sulfamidase enzyme deficiency responsible for abnormal accumulation of glycosaminoglycans in the brain and throughout the body that results in progressive cell damage and neurodevelopmental and physical decline.[2,3]

UX111 is in clinical development for the treatment of MPS IIIA. In the phase I/II/III clinical trial (Transpher A, NCT02716246), UX111 is administered intravenously (IV).[1]

Key Innovation

Data has demonstrated that treatment with UX111 AAV gene therapy resulted in rapid and sustained decreased levels of heparan sulfate (HS) in cerebrospinal fluid (CSF) in patients with MPS IIIA, and that sustained reduction in CSF HS exposure over time was correlated with improved long-term cognitive development.[4] There are currently no approved treatments for MPS III.[5] Therefore, if licenced, UX111 will become the first treatment option for MPS IIIA patients.

UX111 may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[6] Gene therapies such as UX111 are only given once, therefore have the benefit of reducing the treatment burden, and also have the potential to be curative.

Regulatory & Development Status

UX111 does not currently have marketing authorisation in the EU/UK for any indication.

UX111 has the following regulatory designations/awards:

- An orphan drug in the EU in 2016 for the treatment of patients MPS IIIA[7]
- A PRIME status for MPS IIIA by the EMA in December 2019[8]
- A Fast Track by the US FDA for MPS IIIA in October 2016[9]
- A Regenerative Medicine Advanced Therapy for the treatment of MPS IIIA in April 2018[10]
- A Rare Paediatric Disease by the US FDA[11]

Patient Group

Disease Area and Clinical Need

MPS III, also known as Sanfilippo syndrome, is a rare genetic condition that causes fatal brain damage and is a type of childhood dementia. MPS III is caused by the lack of an enzyme that normally breaks down and recycles a large, complex sugar molecule, HS. This HS accumulates and causes damage to the cells of the

body, particularly in the CNS (brain and spinal cord). There are four subtypes of MPS III: A, B, C, and D. Each type is caused by a change (variant or mutation) in a different gene.[12] MPS IIIA is caused by variants in the N-sulphoglucosamine sulphohydrolase gene.[13] Children with MPS III usually appear healthy at birth, but developmental delay is usually evident by age 2-5 years.[12] Children generally achieve ambulation but have significantly impaired fined motor skills as well as delay in speech.[13] This is followed by a period of developmental plateau in milestone acquisition with an increase in behavioural and sleep difficulties. In the next phase of the disease, children begin to demonstrate regression in language, motor, and cognition and some may develop epilepsy.[12,14] Eventually, neurodegeneration leads to dysphagia, immobility, and unresponsiveness.[13] Death can occur from before the age of 10 years or not until the third of fourth decades of life, with the average being around 15 to 20 years of age.[12]

The combined estimated prevalence of MPS III (types A, B, C and D) is between 1:50,000 and 1:250,000 depending on the population studied. Type A is the most common globally.[12] The annual incidence of MPS III in the UK is 0.84 to 1.77 per 100,000 live births, with 71% being diagnosed as MPS IIIA.[15] Therefore, the annual incidence of MPS IIIA in the UK can be estimated as 0.60 to 1.26 per 100,000 live births. In England (2022-23), there were 288 finished consultant episodes (FCEs) and 286 admissions for other MPS (ICD-10 code E76.2) (i.e., not MPS type I or type II), which resulted in 249 day cases and 63 FCE bed days.[16]

Recommended Treatment Options

There is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) specifically for MPS IIIA.

In the absence of a disease-modifying treatment for MPS III, the primary goal of management is to optimise the quality of life for patients and their families.[17]

Clinical Trial Information

Trial	**Transpher A; NCT02716246;** Phase I/II/III Gene Transfer Clinical Trial of scAAV9.U1a.hSGSH for Mucopolysaccharidosis (MPS) IIIA **Phase II/III –** Active, not recruiting **Location(s):** Spain, USA, and Australia **Primary completion date (estimated):** January 2025
Trial Design	Non-randomised, single group assignment, open label
Population	N=28; diagnosis of MPS IIIA; aged from birth to 2 years or children older than 2 years with a minimum cognitive development quotient of 60 years or above
Intervention(s)	**Arm 1:** UX111 0.5 X 10^13 vg/kg IV **Arm 2:** UX111 1 X 10^13 vg/kg IV **Arm 3:** UX111 3 X 10^13 vg/kg IV
Comparator(s)	-
Outcome(s)	Primary outcome: change from baseline in cognitive domain Bayley Scales of Infant and Toddler Development raw scores – third edition (BSID-III) [Time frame: baseline, up to month 24] See trial record for full list of other outcomes.

Results (efficacy)	Treatment with UX111 (3x1013 vg/kg) resulted in rapid and reduction (< 50%) in toxic CSF HS exposure, and that sustained reduction in CSF HS exposure over time was correlated with improved long-term cognitive development, with cognitive function measured using Bayley-III (BSITD-IIID cognitive raw scores) and an estimated yearly rate of change (EYC) calculated. At the time of the data cut-off, the individual EYC in cognitive raw scores showed a positive rate of change indicating either stability or gains from baseline in 16 of the 17 patients during the expected window of plateau into decline.[4] Treatment with UX111 also led to reductions in CSF gangliosides (GM2 and GM3), and stabilised total cortical volume on brain MRI to within normal limits.[18]
Results (safety)	UX-111 for the treatment of pediatric patients with MPS IIIA had a manageable safety profile.[18] The most frequently reported treatment-related adverse events to date were elevations in liver enzymes and the majority of these events were mild (grade 1) or moderate (grade 2) in severity. The only treatment-related adverse event ≥ grade 3 reported to date was one event of increased alanine aminotransferase that resolved, which is a known effect of AAV gene therapy.[4]

Trial	NCT04360265; A Long-term Follow-up Study of Patients With MPS IIIA From Gene Therapy Clinical Trials Involving the Administration of ABO-102 (scAAV9.U1a.hSGSH) **Phase III –** Enrolling by invitation **Location(s):** One EU country, USA and Australia **Primary completion date (estimated):** June 2027
Trial Design	Non-randomised, parallel assignment, open label
Population	N=33; completed a prior clinical trial involving the administration of UX111. After 24 months, patients from the phase 1/2/3 Transpher A study are transferred to a long-term follow-up study where they will be monitored for a minimum of 3 additional years to determine the long-term safety and efficacy of UX111.
Intervention(s)	-
Comparator(s)	-
Outcome(s)	Primary outcome: adverse events [Time frame: up to year 5] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT04088734; A Phase I/II Open Label, Single-dose, Gene Transfer Study of scAAV9.U1a.hSGSH (ABO-102) in Patients With Middle and Advanced Phases of MPS IIIA Disease **Phase I/II –** Terminated **Location(s):** Spain, USA, and Australia

	Study completion date: March 2022
Trial Design	Single group assignment, open label
Population	N=5; diagnosis of MPS IIIA; cognitive development quotient lower than 60; ambulatory; age range of 2 years up to 18 years.
Intervention(s)	UX111 3x10^13 vg/kg IV
Comparator(s)	-
Outcome(s)	Primary outcomes: • Incidence, type and severity of related treatment-emergent adverse events by time frame [Time frame: from the first dose of study drug to <30 days postdose, day 30, 60, 90, 180 and month 12] • Incidence, type and severity of serious adverse events by time frame [Time frame: from signing of informed consent through day 60, 90, 180 and up to day 454 (> 12 months)] • Change from baseline in multiples of normal liver and spleen volumes after treatment [Time frame: baseline, day 30, 180, month 12] • Change from baseline in cerebrospinal fluid heparan sulphate levels after treatment [Time frame: baseline, day 30, day 180, month 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of UX111 was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Lysosomal Storage Disorders Service (Children). E06/S(HSS)/c.

Other Guidance

- Muschol N, Giugliani R, Jones SA, Muenzer J, Smith NJC, Whitley CB, et al. Sanfilippo syndrome: consensus guidelines for clinical care. 2022.[17]

Additional Information

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