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Newcastle University

Health Technology Briefing
April 2023

Pariglasgene brecaparvovec for treating glycogen storage disease type 1a

Company/Developer	Ultragenyx Pharmaceutical Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26631	NICE TSID: 11865	UKPS ID: 666081

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Pariglasgene brecaparvovec is in development for the treatment of patients with glycogen storage disease type 1a (GSD1a). GSD1a is an inherited disorder caused by the lack of an enzyme (type of protein) called glucose-6-phosphatase (G6Pase) which aids in the breakdown of glycogen (a complex sugar stored in the body) to glucose (a simple sugar). This lack of efficient glycogen breakdown results in low blood sugar, and a build-up of glycogen in the liver, kidneys, and gut which can result in long-term complications such as liver and kidney disease and muscle weakness. Current treatment options for patients with GSD1a are limited and involve placing patients on strict uncooked cornstarch diets and the avoidance of fasting to prevent hypoglycaemia (low blood sugar). Current treatment does not correct the underlying cause of the disease, and patients remain at risk of serious long-term complications.

Pariglasgene brecaparvovec is a medicine that consists of a virus that has been modified to contain a gene that produces normal G6Pase. When given to patients via intravenous infusion, the virus is expected to carry this gene into liver cells. This would enable the liver cells to produce G6Pase so that glycogen can be broken down into glucose. The virus used in this medicine (adeno-associated virus) does not cause disease in humans. If licenced, pariglasgene brecaparvovec may provide a new treatment option for patients with GSD1a and would be the first approved to correct the underlying cause of the disease.

Proposed Indication

Treatment of glycogen storage disease type Ia (GSD1a) in adults and children aged 8 years and above patients.[1]

Technology

Description

Pariglasgene brecaparvovec (DTX401) is an investigational adeno-associated virus Serotype-8 gene therapy designed to deliver stable expression and activity of glucose-6-phosphatase (G6Pase) using a single intravenous (IV) infusion.[2] The IV infusion of pariglasgene brecaparvovec to GSD1a patients is expected to provide G6Pase activity resulting in the efficient release of glucose from glycogen stores in the liver, thereby reducing the risk of hypoglycaemia during periods of fasting and the long-term complications associated with GSD1a.[1-3]

Pariglasgene brecaparvovec is currently in phase III development (NCT05139316) for the treatment of patients with GSD1a, who are unable to maintain normal glucose levels.[1,2]

Key Innovation

There is an unmet need in patients with GSD1a, as the current treatment options for GSD1a do not correct the underlying cause of the disease and patients remain at risk of serious long-term complications such as hepatocellular adenomas, hepatocellular carcinoma, renal disease, and osteoporosis.[4] If licenced, pariglasgene brecaparvovec, as a new medicinal product, may provide a safe and more effective way of treating GSD1a and addressing the unmet needs of GSD1a patients. In phase I/II trials for pariglasgene brecaparvovec, there was no report of dose-limiting toxicity and serious related treatment-emergent adverse events in any of the participants within the trial.[5]

Pariglasgene brecaparvovec was classified as an advanced therapy medicinal product (ATMP), more specifically as a Gene Therapy Medicinal Product by the European Medicines Agency (EMA) in July 2016.[6] The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[7]

Regulatory & Development Status

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

Pariglasgene brecaparvovec has been awarded the following regulatory designations:[2,3,8,9]

- Orphan drug designation in the EU in 2016 for the treatment of glycogen storage disease type Ia.
- PRIME status for the treatment of GSD1a by EMA in September 2022.
- Fast Track designation by the U.S. Food and Drug Administration (FDA) in July 2018.
- Regenerative Medicine Advanced Therapy designation by the U.S. FDA.
- Orphan drug designation by the UK MHRA
- Orphan drug designation by the U.S. FDA

Patient Group

Disease Area and Clinical Need

Glycogen storage diseases (GSD) are a collection of inherited metabolic disorders caused by pathogenic variants in the genes that encode proteins involved in glycogen synthesis (glycogenesis), glycogen breakdown into glucose (glycogenolysis), and/or glucose synthesis from non-sugar sources (gluconeogenesis).[4] GSD type 1 (GSD1) is a type of GSD that results from deficient G6Pase activity and is differentiated into four subtypes namely: GSD1a, GSD1b, GSD1c, and GSD1d.[10] GSD1a accounts for 80% of GSD1 cases, and is caused by an autosomal recessive inheritance of defective G6Pase enzyme.[4] The G6Pase enzyme helps in the breakdown of glycogen into glucose.[3] Autosomal recessive inheritance is a term that describes a condition where a child inherits two copies of defective genes from both parents.[11] The symptoms of GSD1a include enlarged liver and kidneys, poor growth, intellectual impairment, abnormally low muscle tone, seizure, frequent infections, and ulcers in the mouth and gut.[3,12]

The incidence of GSD1 is around 1 in 100,000 in the UK, with about 300 people diagnosed with GSD1.[13] In England (2021-22), there were 408 finished consultant episodes (FCEs) and 383 admissions GSD (ICD-10 code E74.0), of which GSD1a makes up a large subset of the population.[14] This resulted in 201 day cases and 701 FCE bed days.[15]

Recommended Treatment Options

There are no National Institute for Health and Care Excellence (NICE) recommended treatments for GSD1a.[16] Current strategies for the management of patients with GSD1a centres on a high degree of personalised medically prescribed dietary treatment that involves oral glucose replacement therapy in the form of uncooked cornstarch, in addition to regular meals and snacks to manage blood glucose levels.[4] Additionally, Xanthine oxidase inhibitor (allopurinol) has also been recommended for the pharmacological treatment of GSD1a.[17]

Clinical Trial Information

Trial	NCT05139316, EudraCT 2020-004184-12; A Study of Adeno-Associated Virus Serotype 8-Mediated Gene Transfer of Glucose-6-Phosphatase in Patients With Glycogen Storage Disease Type 1a (GSD1a) **Phase III** – Active, not recruiting **Location(s):** Five EU countries, US, Canada and Brazil **Study completion date:** April 2024
Trial Design	Randomised, double-blinded, quadruple masked, crossover assignment, placebo-controlled.
Population	N=50; patients with documented GSD1a confirmed by molecular testing or enzymatic activity on liver biopsy, aged 8 years and above.
Intervention(s)	Single peripheral IV infusion of pariglasgene brecaparvovec solution (Nonreplicating, recombinant, adeno-associated virus serotype 8), followed by single peripheral IV infusion of placebo (normal saline infusion) at 48 weeks.
Comparator(s)	Single peripheral IV infusion of placebo, followed by single peripheral IV infusion of pariglasgene brecaparvovec solution.

Outcome(s)	Primary outcome measures: - Percent Change from Baseline to Week 48 in Daily Cornstarch Intake [Time frame: Baseline, Week 48] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT03517085, EudraCT 2016-003023-30; Safety and Dose-Finding Study of DTX401 (AAV8G6PC) in Adults With Glycogen Storage Disease Type 1a (GSD1a) **Phase I/II** – Completed **Location(s):** Two EU countries, US and Canada **Study completion date:** November 2021
Trial Design	Open-label, non-randomised, non-masked, parallel assignment.
Population	N= 12; patients with documented GSD1a confirmed by molecular testing, aged 18 years and above.
Intervention(s)	Pariglasgene brecaparvovec (IV infusion)
Comparator(s)	-
Outcome(s)	Primary outcome measures: - Number of Participants with Adverse Events (AEs), Treatment-Emergent AEs (TEAEs), Serious TEAEs, Discontinuations Due to TEAEs, and Dose-Limiting Toxicities (DLTs) [Time frame: AEs Prior to Dosing: From signing the informed consent form (ICF) to first dose of study drug. TEAEs: From first dose of study drug through the End of Study (EOS)/Early Withdrawal visit (up to Week 52) plus 30 days]. See trial record for a full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Trial	NCT03970278, EudraCT 2018-004473-27; Long-Term Follow-up to Evaluate the Safety and Efficacy of Adeno Associated Virus (AAV) Serotype 8 (AAV8)-Mediated Gene Transfer of Glucose-6-Phosphatase (G6Pase) in Adults With Glycogen Storage Disease Type 1a (GSD1a) **Status:** Active, not recruiting **Location(s):** Two EU countries, US and Canada **Primary completion date:** December 2025

Trial Design	Non-interventional, observational, prospective cohort, non-probability sampling.
Population	N= 12; patients of ages 18 years and above with GSD1a, who received Pariglasgene brecaparvovec in a previous study 401GSD1A01.
Intervention(s)	-
Comparator(s)	-
Outcome(s)	Primary outcome measures: - Number of Participants with Adverse Events (AEs), Serious AEs and Discontinuations Due to AEs [Time frame: Up to 260 weeks following Pariglasgene brecaparvovec administration]. See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of Pariglasgene brecaparvovec is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- The American College of Medical Genetics and Genomics. Diagnosis and management of glycogen storage disease type I: a practice guideline. 2014.[18]
- Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GPA. Guidelines for management of glycogen storage disease type I—European study on glycogen storage disease type I (ESGSD I). 2002.[17]

Additional Information

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