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Newcastle University

Health Technology Briefing
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Cipaglucosidase alfa/miglustat for treating children and adolescents with late-onset Pompe disease

Company/Developer	Amicus Therapeutics

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27162	NICE TSID: N/A	UKPS ID: 668801

Licensing and Market Availability Plans

Currently in phase 3 clinical trials.

Summary

Cipaglucosidase alfa with miglustat is in development for the treatment of late onset Pompe disease in children aged 12-17 years. Pompe disease is an inherited, genetic disorder which results in the deficiency of the enzyme 'acid alpha-glucosidase'. This deficiency leads to progressive accumulation of glycogen, a type of sugar, usually stored in muscle tissues particularly around the heart, skeletal muscle and diaphragm. Enzyme replacement therapy is the currently recommended treatment approach but does not reverse the primary abnormality. There are also not many options for treating children.

Cipaglucosidase alfa is a recombinant human acid alfa glucosidase (rhGAA) enzyme that shows significantly improved uptake into muscle cells and translates into optimised glycogen reduction in disease-relevant muscles in non-clinical models. Miglustat is the enzyme stabiliser that enhances the plasma exposure of cipaglucosiade alfa, resulting in improved delivery of active enzyme to key disease-relevant tissues. If licensed, cipaglucosidase alfa with miglustat will offer an additional treatment option for patients with Pompe disease with potentially improved efficacy.

Proposed Indication

Late-onset Pompe disease in children and adolescents aged 12 to 17 years.[1]

Technology

Description

Cipaglucosidase alfa with miglustat (AT-GAA) is a combination therapy that consists of recombinant human acid alpha-glucosidase (rhGAA) enzyme, cipaglucosidase alfa (ATB200), administered with a small molecule pharmacological chaperone, miglustat (AT2221) for the treatment of Pompe disease.[2,3] Cipaglucosidase alfa is designed to effectively enter muscle cells and miglustat stabilises the cipaglucosidase alfa so it maintains its activity over time.[3]

Cipaglucosidase alfa with miglustat is currently in phase 3 clinical development (NCT03911505) for the treatment of late-onset Pompe disease in children and adolescents aged 12 to 17 years. Cipaglucosidase alfa is administered intravenously and miglustat is administered as an oral capsule.[1,4]

Key Innovation

Although the currently recommended treatment option has demonstrated some clinical benefits, there may be limitations in its delivery to skeletal muscles due to sub-optimal levels of mannose 6 phosphate (M6P), a carbohydrate that binds the cation-independent mannose 6 phosphate receptor (CI-MPR) present on the surface of muscle cells to mediate enzyme internalization and delivery to lysosomes where un-degraded glycogen accumulates. Cipaglucosidase alfa has a substantially higher amount of M6P compared with the current treatment option leading to an improved binding to CI-MPR and cellular uptake. Furthermore, in animal models, co-administration of miglustat has proved to further stabilize cipaglucosidase alfa, thereby enhancing the delivery of catalytically active enzyme to muscle cell lysosomes for glycogen reduction.[5]

The clinical outcomes using the current therapy available vary markedly among patients. Beyond this, there is a consensus that the current therapy available does not reverse, but rather attenuates disease progression, and that the unmet medical needs remain.[6]

Regulatory & Development Status

Cipaglucosidase alfa with miglustat does not currently have Marketing Authorisation in the UK for any indication.

Cipaglucosidase alfa with miglustat is currently also in phase II and III clinical development for late-onset Pompe disease in adults and glycogen storage disease type 2 infantile onset (Infantile onset Pompe disease).[7]

Cipaglucosidase alfa with miglustat has received an orphan drug designation in the EU in 2018 for the treatment of Pompe disease.[8]

Patient Group

Disease Area and Clinical Need

Pompe disease is an inherited autosomal recessive disorder.[9] It is also known as acid maltase deficiency or glycogen storage disease type II (GSD II) and is a rare and often fatal muscle disease caused by mutations

in the GAA gene, which encodes the lysosomal hydrolase acid α-glucosidase (GAA).[6] The enzyme deficiency leads to progressive accumulation of glycogen in the lysosomal compartment in multiple tissues, including musculoskeletal, cardiac, respiratory, vascular, gastrointestinal, and nervous systems.[10] Skeletal and cardiac muscles are most profoundly affected.[11] The signs and symptoms of Pompe disease are directly related to the muscles affected. The disease is progressive in nature, and affects proximal, respiratory and cardiac (infants) muscle.[9] Pompe disease has two forms: infantile-onset Pompe disease and late-onset Pompe disease.[12] Late-onset Pompe disease can be diagnosed in children as young as one and has also been known to present much later in life. Some people have been diagnosed in their 60s and 70s. As well as the start of symptoms being very individual they also vary from mild to severe. Although it is progressive, the rate also varies greatly between individuals. Most common symptoms include breathing problems, morning headaches and daytime sleepiness. Muscle weakness, pain and soreness occurs for everyone, especially in those muscles closest to the spine and core. Fatigue and overwhelming tiredness are another common symptoms. Many people first notice problems climbing stairs, or a family member mentions their 'odd' walking style. They may notice frequent falls or stumbles for no apparent reason.[13]

The UK incidence of late-onset Pompe disease is approximately 1 in 40,000 with about 200 people currently diagnosed in the UK.[12,14] In England in 2021-22, there were 408 finished consultancy episodes (FCE) and 383 admissions for glycogen storage disease (ICD-10 code: E74.0), of which late-onset Pompe disease makes up a subset, which resulted in 701 FCE bed days and 201 day cases.[15]

Recommended Treatment Options

National Institute of health and care excellence recommends avalglucosidase alfa for long-term enzyme replacement therapy for the treatment of patients of all ages with Pompe disease, a glycogen storage disorder caused by deficiency of acid alpha-glucosidase.[16]

Clinical Trial Information

Trial	**ZIP Study-OL, NCT03911505,** An Open-label Study of the Safety, Pharmacokinetics, Efficacy, Pharmacodynamics, and Immunogenicity of Cipaglucosidase Alfa/Miglustat in Pediatric Subjects Aged 0 to < 18 Years With Late-onset Pompe Disease **Phase III:** Recruiting **Locations:** Australia, Canada, US, Japan and Taiwan **Primary completion date:** June 2026
Trial Design	Open label, Single group assignment
Population	N=22 (estimated);aged 0 to <18 years diagnosed with late onset pompe disease.
Intervention(s)	Cipaglucosidase alfa intravenous (IV) infusion co-administered with mMiglustat oral capsule
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Incidence of treatment-emergent adverse events (TEAEs) from baseline [Time frame: 52 weeks] For full list of outcomes see the trial record.
Results (efficacy)	-

Results (safety)	-

Estimated Cost

The cost of cipaglucosidase alfa with miglustat is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Avalglucosidase alfa for treating Pompe disease [TA821]. August 2022.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.

Other Guidance

- M Tarnopolsky, H Katzberg, BJ Petrof, S Sirrs, HB Sarnat, K Myers, et al. Pompe Disease: Diagnosis and Management. Evidence-Based Guidelines from a Canadian Expert Panel. 2016.[17]
- MA Barba-Romero, E Barrot, J Bautista-Lorite, E Gutierrez-Rivas, I Illa, LM Jimenez, et al. Clinical guidelines for late-onset Pompe disease. 2012.[18]

Additional Information

The UKPS record created by Amicus Therapeutics is unavailable to view.

References

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