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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Avalglucosidase alfa for late-onset Pompe disease

NIHRIO ID	9947	**NICE ID**	8623
Developer/Company	Sanofi	**UKPS ID**	647265

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Avalglucosidase alfa is in clinical development for the treatment of late-onset Pompe disease. Pompe disease is an inherited, genetic disorder which results in the deficiency of the enzyme 'acid alpha-glucosidase' (GAA). This deficiency leads to progressive accumulation of glycogen, a type of sugar, usually stored in muscle tissues particularly around the heart, skeletal muscle and respiratory muscles. Late-onset Pompe disease develop after one year of age, and is a serious, progressive, debilitating, and ultimately life threatening disease associated with high morbidity. Enzyme replacement therapy with alglucosidase alfa is a recommended treatment approach but the main drawback of the current option is the limited uptake by affected muscles leading to limited clinical benefits in some patients.

Avalglucosidase alfa is a next-generation enzyme replacement therapy that works by providing GAA enzyme activity in patients with Pompe disease. It is a chemically modified version of alglucosidase alfa that is designed for improved delivery to affected muscles with a potential for improving muscle coordination, strength, and respiratory function of patients with Pompe disease. Early studies found that avalglucosidase alfa improved symptoms in both patients who have previously received alglucosidase alfa and those who have not. If licensed, avalglucosidase alfa will offer an additional treatment option for late-onset Pompe disease.

PROPOSED INDICATION

Treatment of late-onset Pompe disease in paediatrics and adults.[1-3, a]

TECHNOLOGY

DESCRIPTION

Avalglucosidase alfa (neoGAA) is a next-generation, glycoengineered recombinant acid α-glucosidase (GAA) replacement therapy with increased bis-M6P levels on the molecule in order to increase receptor-mediated uptake.[4] The replacement enzyme helps to break down glycogen and stops its build up in the lysosomes. The GAA in this medicine is attached to several molecules called 'bismannose-6-phosphate-tetra-mannose glycan'. This is expected to increase the uptake of the enzyme by affected muscles (muscles used for movement), thereby improving muscle coordination, respiratory function, and strength of patients with Pompe disease.[5]

Avalglucosidase alfa is currently in clinical development for the treatment of late-onset Pompe disease in paediatrics and adults. In both phase II and III clinical trial (NCT02782741, COMET; NCT03019406, Mini-COMET), participants received avalglucosidase alfa intravenously every other week in various study designs. There is no maximum duration for study treatment reported on the trial registry.[1,2]

INNOVATION AND/OR ADVANTAGES

Response to GAA replacement is determined by a number of factors, such as the magnitude of muscle GAA uptake achieved on therapy, the severity of damage at treatment initiation and the extent of lysosomal glycogen accumulation.[4]

Alglucosidase alfa enzyme replacement therapy (ERT) using recombinant human GAA (rhGAA), is currently the only approved treatment for Pompe disease. Alglucosidase alfa irrefutably has provided clinical benefits, particularly for increasing survival in infantile-onset Pompe disease patients. The ERT appears to slow disease progression but has not been shown to halt or reverse disease for the majority of patients, and thus, significant unmet medical needs remain. The most apparent limitation is the poor response of skeletal and respiratory muscles to alglucosidase alfa treatment. The effectiveness of alglucosidase alfa is limited primarily due to its limited drug uptake to affected muscles.[6]

Avalglucosidase alfa is, in essence, alglucosidase alfa that was chemically modified to attach synthetic bisphosphorylated oligosaccharides to improve binding to cation-independent mannose 6-phosphate receptor (CI-MPR). The resultant avalglucosidase alfa glyco-conjugate was shown to have significantly higher binding affinity for CI-MPR and better muscle targeting, resulting in greater glycogen reduction in GAA double KO mice as compared to alglucosidase alfa at equivalent dose.[6]

Avalglucosidase alfa was evaluated in human clinical trials and preliminary results after 24 weeks of treatment from a phase 1/2 study showed that previously untreated patients treated with 20 mg/kg avalglucosidase alfa every other week increased their mean distance walked in 6-minute walk tests (6MWT) by 24.3±23.0 m over baseline while ERT switch patients had a decline of −6.2±64.3 m. Avalglucosidase alfa was also shown to improve pulmonary function as measured by upright % predicted forced vital capacity (FVC), maximum expiratory pressure

[a] Information provided by Sanofi on UK PharmaScan.

(MEP) and maximum inspiratory pressure (MIP) in naïve patients and stabilized pulmonary function in ERT-switch patients.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Avalglucosidase alfa does not currently have Marketing Authorisation in the EU/UK for any indication.

Avalglucosidase alfa was granted EU orphan drug designation in March 2014.[5]

PATIENT GROUP

DISEASE BACKGROUND

Pompe disease is an inherited genetic disorder described medically as an 'autosomal recessive disease'.[7] Pompe disease, also known as acid maltase deficiency or glycogen storage disease type II (GSD II), is a rare and often fatal muscle disease caused by mutations in the GAA gene, which encodes the lysosomal hydrolase GAA.[8] 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.[9] Respiratory, skeletal and cardiac muscles are most profoundly affected.[10]

The signs and symptoms of Pompe disease are directly related to the muscles affected. The disease is progressive in nature, and in infants affects proximal, respiratory and cardiac muscles. In children and adults, the respiratory and skeletal muscles are most commonly affected (muscle weakness).[7]

This disease is classified into two main types; infantile-onset or late-onset. The infantile-onset Pompe is the most severe form and manifests within the first months of life with muscle weakness, respiratory impairment, and rapidly progressive hypertrophic cardiomyopathy that is fatal by 1 to 2 years of age if untreated.

Late-onset forms develop after one year of age and are characterised by a gradually progressive proximal muscle weakness (with little or no cardiac involvement) that eventually causes significant morbidity, respiratory failure, and early mortality in children and adults.[9,11]

CLINICAL NEED AND BURDEN OF DISEASE

In 2019 in the EU, Pompe disease was estimated to affect approximately 0.3 in 10,000 people.[12] According to European Orphanet data, in 2018 the reported birth prevalence for glycogen storage disease due to acid maltase deficiency was 0.8 per 100,000 people and 1.75 per 100,000 for the late-onset form.[13]

According to the 2018-19 Hospital Episodes Statistics data for England, collectively there were 354 finished consultant episodes (FCE), 305 admissions which resulted in 116 day cases and 1,604 FCE bed days for glycogen storage disease (ICD-10 code: E74.0).[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Based on the available evidence, clinical experience and discussion, consensus was reached regarding when to start and stop treatment. Treatment should be started in patients who meet **all** of the following criteria:[15]

1. The patient should have a confirmed diagnosis of Pompe disease, as established by enzyme activity testing in leukocytes, fibroblasts or skeletal muscle and/or demonstration of pathogenic mutations in both alleles of the GAA gene. Note. A positive dried-blood-spot screening test should always be followed by one of these tests for confirmation of the diagnosis.
2. The patient should be symptomatic, i.e. should have skeletal muscle weakness or respiratory muscle involvement as observed using clinical assessments.
3. The patient should commit to regular treatment (every other week) and regular monitoring (at least once per year) to evaluate his/her response to treatment.
4. The clinician should commit to regular treatment and monitoring.
5. The patient should have residual skeletal and respiratory muscle function, which is considered functionally relevant and clinically important for the patient to maintain or improve.
6. The patient should not have another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate.

Stopping treatment should be considered for **any one** of the following reasons:[15]

1. The patient suffers from severe infusion-associated reactions that cannot be managed properly.
2. High antibody titers are detected that significantly counteract the effect of ERT. The patient wishes to stop ERT.
3. The patient does not comply with regular infusions or yearly clinical assessments.
4. The patient has another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate.
5. There is no indication that skeletal muscle function and/or respiratory function have stabilized or improved in the first 2 years after start of treatment, as assessed using clinical assessments

If after stopping treatment the disease deteriorates faster than during treatment, restarting ERT can be considered. Continuation of ERT can be considered during pregnancy and lactation.

CURRENT TREATMENT OPTIONS

Alglucosidase alfa (Myozyme) is an enzyme produced by recombinant DNA technology licensed for long-term enzyme replacement therapy in Pompe disease.[16]

Although some studies suggest that ERT is more beneficial if started early in the course of disease, there were also a number of studies assessing the effects of ERT specifically in more severely affected patients. Studies indicate that respiratory function and muscle strength can also improve/stabilize in patients who required ventilation during part of the day or had an FVC in a supine position below 30%, and/or were fully wheelchair dependent or able to walk <40 m.[15]

Based on the evidences available, an effect of ERT should be observed within this period. An improvement or stabilization in motor and/or respiratory function suggests that the treatment

is having an effect and should be continued. If the patient shows a substantial deterioration in both motor and respiratory functions, stopping treatment should be discussed. Therefore, the restarting treatment option could be considered if disease progression appears to be enhanced after ERT has been stopped.[15]

PLACE OF TECHNOLOGY

If licensed, avalglucosidase alfa will offer an additional treatment option for paediatrics and adults with late-onset Pompe disease.

CLINICAL TRIAL INFORMATION

Trial	COMET, NCT02782741, EFC14028, EudraCT 2016-000942-77; aged ≥ 3 years; avalglucosidase alfa vs alglucosidase alfa; phase III
Sponsor	Sanofi
Status	Ongoing
Source of Information	Trial registry;[1] Press release[17]
Location	EU countries (including the UK), Canada, USA, and other countries
Design	Randomised, active-controlled, double-blind and multi-center study
Participants	N=102; treatment-naïve LOPD patients aged 3 years and older; has confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations.
Schedule	Participants were randomised 1:1 to: - Avalglucosidase alfa 20 mg/kg intravenously every 2 weeks. - Alglucosidase alfa 20 mg/kg intravenously every 2 weeks.
Follow-up	From baseline to 49 weeks
Primary Outcomes	Change from baseline in percent predicted forced vital capacity (%FVC) in upright position [Time frame: baseline to 12 months]
Secondary Outcomes	• Change from baseline in six-minute walk test scores [Time frame: baseline to 49 weeks] • Change from baseline in maximal inspiratory pressure in upright position [Time frame: baseline to 49 weeks] • Change from baseline in maximal expiratory pressure in upright position [Time frame: baseline to 49 weeks] • Change from baseline in hand-held dynamometry measurement [Time frame: baseline to 49 weeks] • Change from baseline in Quick Motor Function Test scores [Time frame: baseline to 49 weeks] • Change from baseline in 12- Item Short-form health survey scores [Time frame: baseline to 49 weeks] • Number of participants with adverse events [Time frame: baseline to 49 weeks and up to 6 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date is March 2020.

Trial	Mini-COMET, NCT03019406, ACT14132, EudraCT 2016-003475-21; patients <18 years; avalglucosidase alfa vs alglucosidase alfa; phase II	NEO-EXT, NCT02032524, LTS13769; child, adult, older adult; avalglucosidase alfa, phase II/III, extension
Sponsor	Genzyme, a Sanofi company	Genzyme, a Sanofi Company
Status	Ongoing	Ongoing
Source of Information	Trial registry;[2] Company	Trial registry[3]
Location	EU countries (including the UK), USA, and other countries	EU countries (including the UK) and USA
Design	Randomised, active-controlled, open label study	Single group, open-label
Participants[b]	N=22; IOPD patients, age range 6 months to 17 years; has confirmed GAA enzyme deficiency from any tissue source; has cardiomyopathy at the time of diagnosis; has been receiving a stable dose of alglucosidase alfa regularly for a minimum of 6 months immediately prior to study entry. Patients who have previously been treated with alglucosidase alfa and demonstrated either clinical decline (Stage 1) or sub-optimal clinical response (Stage 2).	N=21; patients with Pompe disease who previously completed a neoGAA study.
Schedule[b]	Participants will be randomised: • Cohort 1 (target n=5) and Cohort 2 (target n=5) will receive avalglucosidase alfa throughout the study. • Cohort 3 (target n=10) randomly selected (1:1) to receive either avalglucosidase alfa or alglucosidase alfa for the first 6 months of the study, and will then all receive avalglucosidase alfa for the rest of the study. • Cohort 1 and 2 will be given 20 mg/kg and 40 mg/kg respectively and the dose for cohort 3 will be 40 mg/kg provided it is well tolerated. Patients will participate in the study for up to 3 years.	Avalglucosidase alfa administered intravenously every 2 weeks.
Follow-up	From baseline to 6 months	Up to 6 years
Primary Outcomes	• Number of participants with adverse events [Time frame: baseline to 6 months]	• Assessment of adverse events (AEs) and treatment-emergent adverse events (TEAEs), including infusion-associated reactions (IARs) and

[b] Information provided by Sanofi.

	• Number of participants with immunogenicity response [Time frame: baseline to 6 months]	deaths [Time frame: screening/baseline until year 6] • Laboratory assessments including hematology, biochemistry and urinalysis [Time frame: monthly, from baseline until year 3 then quarterly until year 6] • Vital signs [Time frame: screening/baseline until year 6]
Secondary Outcomes	• Assessment of pharmacokinetic parameter: maximum concentration (Cmax) [Time frame: baseline to 6 months] • Assessment of pharmacokinetic parameter: area under curve (AUC) [Time frame: baseline to 6 months] • Change from baseline in Gross Motor Function Measure-88 Test [Time frame: baseline to 6 months] • Change from revised Gross Motor Function Classification System score [Time frame: baseline to 6 months] • Change from baseline in Pompe specific Pediatric Evaluation of Disability Inventory (Pompe PEDI) Functional Skills Scale: Mobility Domain Test score (normative standard score) [Time frame: baseline to 6 months] • Change from baseline in Pompe PEDI Functional Skills Scale: Mobility Domain Test score (scaled score) [Time frame: baseline to 6 months] • Change from baseline in Quick Motor Function Test scores [Time frame: baseline to 6 months] • Change from baseline in Left Ventricular Mass Index [Time frame: baseline to 6 months] • Change from baseline in Left Ventricular Mass Index Z score	• Electrocardiogram [Time frame: every 6 months, from baseline until year 6] • Anti-neoGAA antibodies, and neutralizing antibody formation in anti-neoGAA positive patients; anti-alglucosidase alfa IgG antibodies [Time frame: monthly, from baseline up to 6 months, then every 3 months until year 6; every 6 months from baseline until year 6] • Cmax (Maximal concentration of the compound in the blood) [Time frame: at 6 months, then yearly until year 6] • AUC (Area under the curve, relates to the quantity of compound that produces an effect) [Time frame: at 6 months, then yearly until year 6] • t1/2 (half-life, which is the time needed to eliminate half of the compound) [Time frame: at 6 months, then yearly until year 6] • Skeletal muscle glycogen content [Time frame: every 2 years, from baseline until year 6] • Skeletal muscle magnetic resonance images for qualitative and quantitative muscle degenerative assessments [Time frame: every 2 years, from baseline until year 6] • Urinary Hex4 [Time frame: at 6 months, then yearly until year 6] • Plasma analyses of circulating mRNA and micro RNA [Time frame: at 6 months, then yearly until year 6] • Serum analyses of skeletal muscle RNA expression [Time frame: at 6 months, then yearly until year 6]

	[Time frame: baseline to 6 months] • Change from baseline in Eyelid position measurements: Interpalpebral fissure distance (IPFD) [Time frame: baseline to 6 months] • Change from baseline in Eyelid position measurements: Margin reflex distance-1 (MRD-1) [Time frame: baseline to 6 months] • Change from baseline in Eyelid position measurements: Margin pupil distance (MPD) [Time frame: baseline to 6 months] • Change from baseline in Creatine kinase value [Time frame: baseline to 6 months]	
Key Results	-	
Adverse effects (AEs)	-	
Expected reporting date	Data expected to be reported in November 2019.	Estimated primary completion date is December 2021.

ESTIMATED COST

The cost of avalglucosidase 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.
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- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Laboratory Services). E06/S/c.

OTHER GUIDANCE

- Van der Ploeg AT, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. 2017.[15]
- Barba-Romero, et al. Clinical guidelines for late-onset Pompe disease. 2012.[18]
- The American College of Medical Genetics and Genomics (ACMG). Pompe disease diagnosis and management guideline. 2006.[19]

ADDITIONAL INFORMATION

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