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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

ATB200/AT2221 for Late onset Pompe disease in adults and adolescents >12 years – first line

NIHRIO ID	3774	**NICE ID**	9927
Developer/Company	Amicus Therapeutics Europe Ltd	**UKPS ID**	646177

Licensing and market availability plans	Currently in phase I/II clinical trial

SUMMARY

ATB200 co-administered with AT2221 is in development for the treatment of Pompe disease. 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 a recommended treatment approach.

ATB200 (cipaglucosidase alfa) is a recombinant human acid alfa glucosidase (rhGAA) enzyme that shows significantly improved uptake into muscle cells compared with algucosidase alfa at similar doses and translates into optimised glycogen reduction in disease-relevant muscles in non-clinical models. AT2221 (miglustat) is the pharmacological chaperone that stabilises and enhances the plasma exposure of ATB200, resulting in improved delivery of active enzyme to key disease-relevant tissues. If licensed, ATB200/AT2221 will offer an additional treatment option for patients with Pompe disease with potentially improved efficacy.

PROPOSED INDICATION

Adults and adolescents aged >12 years diagnosed with late-onset Pompe disease – first line.[a,1]

TECHNOLOGY

DESCRIPTION

ATB200/AT2221 is a co-administration 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]

Use of ATB200/AT2221 through co-administration is being developed with the primary objective of improving patient outcomes based on valid therapeutic principles. Specifically,

1) ATB200 is the main active substance that has been engineered to provide improved targeting of enzyme activity required for reduction of lysosomal glycogen in affected tissues; and
2) AT2221 is a pharmacological chaperone that protects ATB200 from denaturation in systemic circulation and serves as a PK enhancer to improve the delivery of active ATB200 to lysosomes. Administration of AT2221 every 2 weeks, the proposed regimen for combination use with ATB200, would have no direct effect on Pompe disease.[a]

In the currently ongoing phase I/II (NCT02675465), ATB200/AT2221 is administered at different doses in four different stages. Details of the ascending dosing regimen are described in the clinical trial table section of this briefing.[1,3,4]

INNOVATION AND/OR ADVANTAGES

Although alglucosidase alfa 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. ATB200 has a substantially higher amount of M6P compared with alglucosidase alfa leading to an improved binding to CI-MPR and cellular uptake. Furthermore, in animal models, co-administration of AT2221 has proved to further stabilize ATB200 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]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Neither ATB200 nor AT2221 currently have Marketing Authorisations in the EU/UK.

ATB200/AT2221 is currently in phase III clinical development for the treatment of late-onset Pompe disease (LOPD).[7]

[a] Information provided by Amicus Therapeutics

Orphan designations have been granted by the European Commission for both ATB200 (EMA/OD/0000004425)[8] and AT2221 (EMA/OD/0000004241)[9] in the treatment of glycogen storage disease type II (Pompe disease).

In February 2019, the U.S. Food and Drug Administration (FDA) granted Amicus a Breakthrough Therapy Designation to ATB200/AT2221 for the treatment of late onset Pompe disease.[10]

In November 2019 ATB200/AT2221 was granted a PIM by the MHRA Ref PIM 2019/0009.[b]

In September 2017, ATB200/AT2221was granted US orphan drug status for the treatment of Pompe disease.[11]

The active substance in AT2221, miglustat, is currently licenced in the EU/UK as a monotherapy for the treatment of adults with mild to moderate type 1 Gaucher disease (only in treatment of patients for whom enzyme replacement therapy is unsuitable) and for the treatment of progressive neurological manifestations in adult and paediatric patients with Neimann-Pick type C disease.[12] This is however at a substantially different dose and with a different mechanism of action to that intended in the treatment of Pompe disease. [b]

PATIENT GROUP

DISEASE BACKGROUND

Pompe disease is an inherited genetic disorder described medically as an 'autosomal recessive disease'.[13] 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 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.[14] Skeletal and cardiac muscles are most profoundly affected.[15]

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. In adults, the skeletal muscle is most commonly affected (muscle weakness).[13] This disease can be further classified as infantile onset or late-onset being the infantile-onset 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. Late-onset forms develop after one year of age and are characterized 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.[16]

CLINICAL NEED AND BURDEN OF DISEASE

In 2019 in the EU, Pompe disease was estimated to affect approximately 0.3 in 10,000 people.[17] 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.[18]

[b] Information provided by Amicus Therapeutics

The population size that may benefit from this treatment has not been ascertained from the sources available but the company currently estimate this to be around 100-120 patients treated in a small number of designated specialist centres (5) in England. [c]

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).[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Although the underlying basis of Pompe disease is progressive muscular degeneration, the disease can affect different organs and systems.[20] Patient care and management of this multisystemic disorder are often coordinated by a neuromuscular physician, neurologist or metabolic disease specialist. Healthcare providers that have expertise in such disciplines as respiratory medicine, cardiology, bone health, nutrition, speech and language, occupational therapy, physical therapy, social work, psychology, community work, and palliative care physicians form an integral part of a multidisciplinary team of healthcare.[21]

For the management of Pompe disease the following are recommended approaches: the use of enzyme replacement therapy, treatment of cardiac failure and respiratory failure, diet therapy, physiotherapy and occupational therapy, genetic counselling.[22]

CURRENT TREATMENT OPTIONS

Alglucosidase alfa is an enzyme produced by recombinant DNA technology licensed for long-term enzyme replacement therapy in Pompe disease.[23]

PLACE OF TECHNOLOGY

If licensed, ATB200/AT2221 will offer an additional treatment option for patients with late onset Pompe disease.

CLINICAL TRIAL INFORMATION

Trial	**PROPEL,** NCT03729362, ATB200-03; A Phase 3 Double-blind Randomized Study to Assess the Efficacy and Safety of Intravenous ATB200 Co-administered With Oral AT2221 in Adult Subjects With Late Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo **Phase III** - ongoing **Location(s):** EU countries (not include the UK), US and other countries
Trial design	Double-blind, randomized controlled study
Population	N=110 (planned); aged ≥18 years; weighing ≥ 40 kg at screening ; diagnosed with Pompe disease; who has either received enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme/Lumizyme) or ERT-naïve subjects
Intervention(s)	The study will consist of a screening period up to 30 days, a 12-month treatment period, and a 30-day safety follow-up period.

[c] Information provided by Amicus Therapeutics

	Infusion visits will be scheduled every 2 weeks for administration of study drug trough end of study. Each subjects will be randomly assigned to either: - ATB200 20 mg/kg IV + AT2221 260 or 195 mg PO (based on weight) Duration of the study: The duration of treatment is 52 weeks.
Comparator(s)	Alglucosidase alfa 20 mg/kg IV + Placebo PO
Outcomes	To assess the efficacy of ATB200/AT2221 co-administration on ambulatory function, as measured by the 6-Minute Walk Test (6MWT), compared with alglucosidase alfa/placebo.
Results (efficacy)	-
Results (safety)	-

Trial	NCT02675465, ATB200-02; An Open-Label, Fixed-Sequence, Ascending-Dose, First-in-Human Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Intravenous Infusions of ATB200 Co-Administered With Oral AT2221 in Adult Subjects With Pompe Disease **Phase I/II -** ongoing **Location(s):** EU countries (including the UK), US and other countries
Trial design	Single arm, open-label study
Population[d]	N=32 (planned); aged between 18 and 65 years; diagnosed with Pompe disease; who has either received enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme/Lumizyme) or ERT-naïve subjects
Intervention(s)[d]	This phase 1/2 study was designed to include 4 cohorts of LOPD subjects: Cohort 1, ambulatory ERT-experienced (2-6 yrs on prior ERT); Cohort 2, nonambulatory ERT-experienced (> 2 yrs on prior ERT); Cohort 3, ERT-naïve ambulatory; and Cohort 4, ambulatory ERT experienced (≥ 7 years). The study is also designed to evaluate ATB200 and AT2221 co-administration with ATB200 in 4 stages: Stage 1, ATB200 alone at doses of 5, 10, 20 mg/kg IV (Cohort 1); Stage 2, 3 doses of ATB200 20 mg/kg IV + AT2221 PO at low dose of 130 mg 2 weeks apart, followed by 3 doses of ATB200 20 mg/kg IV + AT2221 PO at high dose of 260 mg 2 weeks apart (Cohort 1); Stage 3, ATB200 20 mg/kg IV + 260 mg AT2221 PO administered every 2 weeks apart (all cohorts); and Stage 4, an open-label extension of Stage 3 (all cohorts). Duration of the study: Stage 1: 6 weeks; Stage 2: 12 weeks; Stage 3: 24 months; Stage 4: see next section below.
Comparator	-
Outcome(s)[d]	• To evaluate the safety and tolerability of single-ascending doses of intravenously (IV) infused ATB200. • To evaluate the safety and tolerability of single-ascending doses of IV infused ATB200 as a fixed dose, co-administered with ascending oral doses of AT2221.

[d] Information provided by Amicus Therapeutics

	• To characterize the pharmacokinetics (PK) of single-ascending doses of IV infused ATB200. • To characterize the single- and multiple-dose PK of IV infused 20 mg/kg ATB200 when co-administered with oral 130 mg or 260 mg AT2221. • To characterize the PK of single- and multiple-oral doses of 130 mg or 260 mg AT2221 when co-administered with IV infused ATB200.
Results (efficacy)[e]	Interim analysis #7 (data cut off of 30 December 2018) Results from Study ATB200-02 (Cohort 1, ERT-experienced ambulatory LOPD subjects) indicates marked improvements in clinically significant functional endpoints, most notably the 6MWD [mean increase of 24 metres at month 6, 42 metres at month 12, and 54 metres at month 24], in ERT-experienced subjects who have switched to ATB200/AT2221 after being treated for an average of approximately 5 years with the existing standard of care, alglucosidase alfa. Forced vital capacity, the primary measure of pulmonary function, was generally stable in ERT-experienced ambulatory patients. Other pulmonary tests included maximal inspiratory pressure (MIP), a measure of inhalation and maximal expiratory pressure (MEP), a measure of exhalation. MIP was stable and MEP increased in ERT-experienced ambulatory patients. Muscle strength data are available from the ERT-experienced, nonambulatory patients (Cohort 2) who had been treated with alglucosidase alfa for an average of approximately 9 years prior to switching to ATB200/AT2221. These results show an improvement in muscle strength in several muscle groups in both quantitative (dynamometry) and qualitative manual muscle testing (MMT). All 5 ERT-naïve patients showed increases in 6MWD at all time points out to month 24. The ERT-naïve patients (n=5) showed mean increases of 42 metres at month 6 , 63 meters at month 12 , and 55 metres at month 21. Forced vital capacity improved progressively till 21 months in ERT-naïve patients. Other pulmonary tests included maximal inspiratory pressure (MIP), a measure of inhalation, and maximal expiratory pressure (MEP), a measure of exhalation. MIP and MEP increased in ERT-naïve patients. Muscle strength improved in all patients. Improvements were seen in fatigue as measured by the fatigue severity scale.
Results (safety)[e]	Safety and tolerability data from the use of ATB200/AT2221 in Study ATB200-02 are available for 25 subjects and a total of greater than 1,110 infusions (data cut off of 30 December 2018). Adverse events have been generally mild to moderate and transient. There were two treatment discontinuations: one in Cohort 1 due to an infusion-associated reaction [IAR] leading to chest pain (non-cardiac) and one in Cohort 2 due to an IAR leading to pharyngeal oedema, pruritic rash and urticaria. No deaths have been reported. Nine serious adverse events (SAEs) were reported in 5 subjects [severity: 2 severe, 5 moderate, 2 mild (with 3 events in 1 patient)]. These were lymphadenopathy, diffuse large B-cell lymphoma, vaso-vagal syncope, and pneumonia, lower respiratory tract infection, pharyngeal oedema, pruritic rash, urticarial, abdominal pain. All SAEs were considered probably related to treatment. Out of greater than 1,110 infusions, there were 15 events of infusion-associated reactions [IARs] in 7 subjects. These IARs are generally mild to moderate in nature, and are manageable with reduction or temporary stopping of infusion flow, pre-medication with corticosteroids,

[e] Information provided by Amicus Therapeutics

	antihistamines and paracetamol. No life-threatening or fatal infusion associated reactions have been observed in clinical studies so far. Three IARs occurred in 3 ambulatory ERT-experienced subjects (Cohort 1). These were fatigue, headache and pain in the chest in each subject. Four IARs occurred in 2 no ambulatory ERT-experienced subjects (Cohort 2) with 1 subject reporting pharyngeal oedema, pruritic rash and urticarial leading to treatment discontinuation and 1 subject reporting skin discoloration (this subject had a similar IAR with previous therapy). Five AEs in 3 events of IARs occurred in an ERT-naïve subject (Cohort 3) who had hand pruritus, erythema, burning sensation, hyperhidrosis and chest discomfort. IARs were controlled with pre-medications in this subject. One IAR occurred in 1 ambulatory ERT-experienced subjects (Cohort 4) who reported headache. To date, no important risks have been identified that would preclude the use of ATB200 co-administered with AT2221.

ESTIMATED COST

The cost of ATB200/AT2221 is not known yet.

Should ATB200/AT2221 be licenced it would replace a proportion of patients who would currently be eligible for treatment with alglucosidase alfa. Therefore it is not expected to have a significant impact on the total budget for treating Pompe.[f]

Miglustat is already marketed in the UK for the treatment of mild to moderate type I Gaucher's disease for whom enzyme replacement therapy is unsuitable (under expert supervision) and the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease; a pack of 84 x 100 mg capsule costs £3,934.17.[24]

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 (adults). E06/S(HSS)/c Appendix 1.
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[f] Information provided by Amicus Therapeutics

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ADDITIONAL INFORMATION

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.