15 December 2022
EMA/CHMP/794395/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pombiliti

International non-proprietary name: cipaglucosidase alfa

Procedure No. EMEA/H/C/005703/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

4-MU-α-Glc	4-methylumbelliferyl-α-D-glucopyranoside
6MWD	6-minute walk distance
6MWT	6-Minute walk test
ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AT2221	INN: miglustat; *N*-butyl-deoxynojirimycin; iminosugar that is used as an enzyme stabiliser to ATB200 (a recombinant human acid α-glucosidase)
ATB200	INN: cipaglucosidase alfa; recombinant human acid α-glucosidase (rhGAA) enzyme with optimised carbohydrate structures, including mannose 6-phosphate (M6P), to enhance uptake and delivery of active ATB200 to lysosomes
AUC	Area under the plasma drug concentration-time curve
AUCtmax-24h	Time of maximum concentration at the end of infusion to 24 hours post-start of infusion
BDS	Bulk drug substance
bis-M6P	Bis-phosphorylated mannose 6-phosphate
BSE	Bovine spongiform encephalopathy
CHG	Change from baseline
CHMP	Committee for Evaluation of Human Medicinal Products
CHO	Chinese hamster ovary
CI	Confidence interval
CI-MPR	Cation-independent mannose 6-phosphate receptor
CK	Creatine kinase
C_{max}	maximum observed plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
CSR	Clinical study report
CRADA	Cross-reactive alglucosidase alfa ADA
CTD	Common technical document
DART	Developmental and reproductive toxicology
DLP	Data lock point
DPH	Diphenhydramine
ECG	Electrocardiogram

EFD	Embryo-fetal developmental
EM	Exposure margin
EMA	European Medicines Agency
EOPC	End of production cell
ERA	Environmental risk assessment
ERT	Enzyme replacement therapy
ERT-experienced	refers to subjects previously treated with alglucosidase alfa for at least 2 years prior to enrolment
ERT-naïve	refers to subjects who have not been previously treated with alglucosidase alfa, or have received no more than 1 dose of ERT more than 6 months before the Baseline Visit (Australia only)
EU	European Union
FEED	Fertility and early embryonic development to implantation
FVC	Forced vital capacity
GAA	Human acid α-glucosidase, may be specified as either GAA enzyme activity or GAA protein
GAA	Gene that encodes human acid α-glucosidase
Gaa	Gene that encodes acid α-glucosidase (non-human)
GAA activity	Active enzyme activity measured using 4-MU-α-Glc as substrate; represents both endogenous GAA and exogenous rhGAA
GCP	Good clinical practices
GLP	Good laboratory practices
GMP	Good manufacturing practices
GSD	Glycogen storage disease
GSGC	Gait, climbing Sstairs, Gowers' maneuver, and rising from a chair test; a clinical outcome assessment scoring system to assess motor function in Pompe disease
HCP	Host cell protein
Hex4	Hexose tetrasaccharide; commonly designated as Glc4, representing a biochemical entity (Glc-a-1-6 Glc-a1-4 Glc-a-1-4Glc) determined in urine or plasma as a marker of active glycogen metabolism
IAR	Infusion associated reaction
IBD	International birth date
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
IgE	Imunoglobulin E
IgG	Imunoglobulin G
IOPD	infantile-onset Pompe disease
IPC	In-process control
IPT	In-process test
ITT	Intent-to-treat
ITT-OBS	Intent-to-treat–observed

IV	intravenous(ly)
JP	Japanese Pharmacopoeia
Kd	Equilibrium dissociation constant
KO	Knock-out
LAMP1	Lysosome-associated membrane protein 1
LC-MS	Liquid chromatography coupled with mass spectroscopy detection
LC-MS/MS	liquid chromatography tandem mass spectroscopy
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOPD	Late-onset Pompe disease
LS	Least aquares carried forward
M6P	Mannose-6-phosphate
MAA	Marketing authorisation application
MCB	Master cell bank
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
mITT	Modified intent-to-treat
MMRM	Mixed-effect model for repeated measures
MMT	Manual muscle testing
MRHD	Maximum recommended human dose.
MRI	Magnetic resonance imaging
MSD	Meso scale discovery
Myozyme	Commercially available rhGAA; also referred to as alglucosidase alfa
N/A	Not applicable
NA	Not analysed
NAb	Neutralising antibody
NAS	New active substance
NLT	Not less than
NMT	Not more than
NORs	Normal operating ranges
PARs	Proven acceptable ranges
PBS	Phosphate-buffered saline
PD	Pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
PIC	Powder in capsule
PIP	Paediatric investigation plan

PK	Pharmacokinetic(s)
PL	Package leaflet
PND	Postnatal day
popPK	Population pharmacokinetics
PP	Per protocol
PP	Process parameter
PPQ	Process performance qualification
PRO	Patient-reported outcome
PROMIS	Patient-reported outcomes measurement information system
PT	Preferred term
QMT	Quantitative muscle testing
QOD	Every other day
QoL	Quality of life
QOW	Every other week
QTcF	QT interval corrected using Fridericia's formula
QTPP	Quality target product profile
rhGAA	Recombinant human acid α-glucosidase
rhGAA	Human recombinant acid A-glucosidase
RMP	Risk management plan
SAE	serious adverse event
SAP	Statistical analysis plan
SD	Sprague-Dawley
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System organ class
SVC	Slow vital capacity
t½α	Alpha phase elimination half-life or distribution elimination half-life
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TK	Toxicokinetics
t_{max}	Time to reach the maximum observed concentration
TSE	Transmissible spongiform encephalopathies
TUG	Timed up and go
ULN	Upper limit of normal
UPLC	Ultra-performance liquid chromatography

US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
vs	Versus
WCB	Working cell bank
y	Years

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amicus Therapeutics Europe Limited submitted on 5 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Pombiliti, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2020.

Pombiliti, was designated as an orphan medicinal product EU/3/18/2000 on 21 March 2018 in the following condition: Pompe disease.

The applicant initially applied for the following indication:

Pombiliti is indicated in co-administration with miglustat for the long-term treatment of adults aged 18 years and older with a confirmed diagnosis of Pompe disease (acid α-glucosidase [GAA] deficiency).

The final indication is as follows:

Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0204/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0204/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance cipaglucosidase alfa contained in the above medicinal product to be considered as a new active substance as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

During the procedure, following the CHMP request, the applicant submitted data to support a claim for the active substance cipaglucosidase alfa contained in the above medicinal product to be considered as a new active substance in comparison to alglucosidase alfa previously authorised in the European Union as Myozyme, as the applicant claimed that cipaglucosidase alfa differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

Based on the review of the data, it is considered that the active substance cipaglucosidase alfa contained in the medicinal product Pombiliti is not qualified as a new active substance.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 November 2014	EMEA/H/SA/2904/1/2014/SME/III	*Dr Norbert Benda and Dr Caroline Auriche*
29 May 2019	EMEA/H/SA/2904/3/2019/PA/I	*Dr Karl-Heinz Huemer and Dr Hans Ovelgönne*
12 November 2020	EMEA/H/SA/2904/5/2020/PA/II	*Dr Hans Ovelgönne and Prof Brigitte Schwarzer-Daum*

Protocol Assistance was only requested for the combination cipaglucosidase alfa and miglustat. The applicant received Scientific advice from the CHMP on the development of the indication from the

CHMP on 20 November 2014 (EMEA/H/SA/2904/1/2014/SME/III), 29 May 2019 (EMEA/H/SA/2904/3/2019/PA/I), and 12 November 2020 (EMEA/H/SA/2904/5/2020/PA/II). The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

Quality:

- Overall PPQ plan including the proposed number of validation batches for the ATB200 drug substance.
- Process control strategy.
- Plan to demonstrate the in-process intermediate microbial hold duration.
- Viral clearance validation study plan for MAA.
- Analytical strategy for the control and release of ATB200 drug substance, including specifications.
- Total stability package and shelf life.
- Principal molecular structural features of recombinant human acid alpha-glucosidase and if molecular structures are non-similar to another product.

Non-clinical:

- Acceptability of the nonclinical toxicology programme to support clinical trials and MAA.
- Timing of the developmental and reproductive toxicology (DART) studies with the combination.
- Mitigation of infusion-associated reactions prior to administration in the toxicology programme.
- Acceptability of the principle of a 3-month co-administration bridging toxicity study and of the pharmacokinetic and immunogenicity measurements in the non-clinical toxicology studies to support clinical trials and MAA.

Clinical:

- Acceptability of the design of the proposed first in human co-administration study.
- Non-similarity of the intended therapeutic indication vs that of another product.
- Non-similarity of the therapeutic indications based on combination therapy.
- Totality of evidence planned to support non-similarity of cipaglucosidase alfa (ATB200) versus another product.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	5 November 2021
The procedure started on	25 November 2021

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 February 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	01 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 March 2022
The following GCP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
— A GCP inspection at two clinical investigator sites and the sponsor site in the United States of America between 28 February 2022 – 18 March 2022. The outcome of the inspection carried out was issued on 28 April 2022.	28 April 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 July 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 August 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 September
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 October 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	11 November 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	1 December 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	15 December 2022

a marketing authorisation to Pombiliti on	
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	15 December 2022

2. Scientific discussion

2.1. Problem statement

Cipaglucosidase alfa (also referred to as ATB200, recombinant human acid α-glucosidase [rhGAA]) is a novel next-generation product being developed for co-administration with miglustat (also referred to as *N*-butyl-deoxynojirimycin [AT2221]) for the treatment of adult patients with Pompe disease.

2.1.1. Disease or condition

The applicant initially applied for the following indication: Pombiliti is indicated in co-administration with miglustat for the long-term treatment of adults aged 18 years and older with a confirmed diagnosis of Pompe disease (acid α-glucosidase [GAA] deficiency).

2.1.2. Epidemiology

Pompe disease (also known as acid maltase deficiency or glycogen storage disease [GSD] type II) is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alpha-glucosidase (GAA), an enzyme that degrades glycogen.

The estimated global incidence of Pompe disease is 1:40,000, with variations in incidence reported between different ethnic groups (Martiniuk, 1998, Am J Med Genet; Ausems, 1999, Eur J Hum Genet; Poorthuis, 1999, Hum Genet; Hirschhorn, 2001, The Metabolic and Molecular Bases of Inherited Disease). All presentations of Pompe disease are caused by the same underlying deficiency of lysosomal GAA. However, there is significant heterogeneity in the clinical presentation of Pompe disease, and the disease manifests as a broad clinical spectrum with a continuum of clinical signs and symptoms (Chen, 2000, Mol Med Today; Hirschhorn, 2001, The Metabolic and Molecular Bases of Inherited Disease; van den Hout, 2003, Pediatrics; Kishnani, 2004, J Pediatr).

Pompe disease has been classified into different phenotypes based on age at onset of symptoms, the extent of organ involvement, and the rate of progression to death. These phenotypes range from a rapidly progressive infantile-onset form of the disease (IOPD, incidence 1:100,000) to a more slowly progressing late-onset form (LOPD) with symptom onset any time after infancy through adulthood; there is considerable variability and overlap between these two extremes.

The majority of patients with Pompe disease are classified with late-onset Pompe disease (LOPD).

2.1.3. Biologic features, aetiology and pathogenesis

Pompe disease is caused by the deficiency of lysosomal acid alpha-glucosidase (GAA). Defects in both alleles of the gene for GAA, located on chromosome 17q25, result in reduced or absent enzyme activity. The deficiency in lysosomal GAA in Pompe disease results in the accumulation of glycogen to a variable extent in all muscles of patients with the disorder, leading to impaired contractile function. It is hypothesised that rupture of enlarged lysosomes leads to spill-over of lysosomal enzymes into the muscle cell cytoplasm, leading to the eventual destruction of the muscle cell with fibrosis and fatty

replacement as a consequence and progressive dysfunction of portions of muscle or even entire muscles. Imaging techniques such as total body MRI have shown that even Pompe disease patients who do not appear to have clinical evidence of skeletal muscle involvement may have evidence of fatty replacement of parts of their muscles on MRI. T2 imaging can reveal large amounts of fatty infiltration with or without (+/-) fibrosis on MRI of their lower limbs, yet patients appear to be walking quite normally due to adaptive compensatory mechanisms.

All presentations of Pompe disease are caused by the same underlying deficiency of lysosomal GAA. Currently, over 500 mutations of GAA, including missense, nonsense, splicing defect, and frameshift mutations, have been found. However, there is significant heterogeneity in the clinical presentation of Pompe disease, and the disease manifests as a broad clinical spectrum with a continuum of clinical signs and symptoms, depending on the amount of residual enzyme activity (Chen, 2000, Mol Med Today; Hirschhorn, 2001, The Metabolic and Molecular Bases of Inherited Disease; van den Hout, 2003, Pediatrics; Kishnani, 2004, J Pediatr).

2.1.4. Clinical presentation, diagnosis and prognosis

After infancy the majority of patients with Pompe disease present with late-onset Pompe disease (LOPD), which takes a more variable course than infantile-onset Pompe disease (Byrne et al., 2011; van der Ploeg et al., 2008). Longer disease duration of between 10-15 years, as well as FVC ≤80% predicted, are risk factors for more rapidly progressive disease (van der Beek, 2012, Orphanet J Rare Dis), and more than half of LOPD patients will eventually require ventilation after 10-15 years of symptomatic disease progression. Initial symptoms of LOPD typically include muscle weakness with a limb-girdle distribution, which often manifests as difficulties in climbing stairs, walking, running, and rising from a chair or lying position. Shortness of breath and respiratory dysfunction due to the involvement of respiratory muscles, fatigue, exercise intolerance, and muscle pain are also common and may present at any time in the illness (Müller-Felber et al., 2007; Schüller et al., 2012; van der Beek et al., 2009, 2012; Wokke et al., 2008). Over time, progressive loss of muscle strength reduces mobility and interferes with the ability to independently complete activities of daily living, including toileting and dressing, resulting in decreased quality of life (Hagemans et al., 2004, 2005; Müller-Felber et al., 2007). Many LOPD patients ultimately end up confined to a wheelchair and require ventilation, and LOPD is also associated with increased mortality relative to the general population (Güngör et al., 2011). Although Pompe disease manifestations vary between individuals, studies in LOPD patients (Ausems et al., 1999) have confirmed that respiratory failure precedes death in nearly all subjects. The most common cause of death in patients with Pompe disease, regardless of the age of disease onset and/or the severity of skeletal muscle weakness, is respiratory failure (Hirschhorn et al., 2001; Güngor et al., 2011; Winkel et al., 2005).

2.1.5. Management

Currently, the only treatment option for Pompe disease patients and standard-of-care is long-term enzyme replacement therapy (ERT) with alglucosidase alfa, globally approved for the treatment of all subsets of Pompe disease under the tradenames of Myozyme and Lumizyme. Enzyme replacement therapy substitutes a deficient enzyme by intravenous infusion of the recombinant human enzyme at regular intervals. The enzyme is taken up into the cells via the mannose-6-phosphate receptor and transported to the lysosome.

Approval of alglucosidase alfa was based on early clinical trials demonstrating its ability to reduce cardiac hypertrophy and prolong invasive ventilator-free survival in infants with infantile-onset Pompe disease (IOPD studies ALGLU01602 and ALGLU01702) and to stabilise respiratory function and improve walking distance in children and adults with LOPD (study ALGLU02704).

Studies in LOPD patients suggest that some patients on alglucosidase alfa continue to exhibit some decline in respiratory function, albeit at a slower pace than prior to treatment. Responses to treatment in LOPD patients vary between individuals, and there might be room for improvement.

2.2. About the product

The rationale for ERT in lysosomal storage disorders in general, and Pompe disease in particular, is that lysosomes are accessible to exogenous or extracellular proteins. The feasibility of using ERT in Pompe disease has been supported by studies in cultured skeletal muscle cells and fibroblasts and in animal models of Pompe disease and efficacy was established in clinical trials with alglucosidase alfa.

Cipaglucosidase alfa (ATB200, rhGAA) is developed as a next-generation ERT for Pompe disease. Cipaglucosidase alfa contains higher amounts of mannose 6-phosphate (M6P), which is the natural motif for identifying and transporting soluble lysosomal enzymes to lysosomes, as compared to alglucosidase alfa. Importantly, cipaglucosidase alfa contains bis-phosphorylated high mannose oligosaccharide structures, which are known to have the highest affinity of all known carbohydrates for the cation-independent mannose 6-phosphate receptor (CI-MPR). This specialised glycosylation leads to substantially better binding to the CI-MPR (Tong and Kornfeld, 1989) on cell surfaces, which mediates the internalisation and delivery of exogenous rhGAA to lysosomes, particularly at low enzyme concentrations in muscles post-dosing.

Like all lysosomal enzymes, cipaglucosidase alfa is unstable at neutral pH and denatured and inactivated in the bloodstream following intravenous (IV) infusion.

Cipaglucosidase alfa is developed for co-administration with miglustat. The clinical effectiveness and safety of the monotherapy of cipaglucosidase alfa have not been studied.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment, as the product was not considered to be of major public health interest: Like alglucosidase alfa, cipaglucosidase alfa is an enzyme replacement therapy. It does not exert a novel mechanism of action. Having additional therapeutic options for LOPD patients is valuable, but this is not considered sufficient to argue an unmet medical need and accelerated access.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 105 mg of cipaglucosidase alfa (ATB200) as active substance.

Other ingredients are: sodium citrate dihydrate (E331), citric acid monohydrate (E330), mannitol (E421), polysorbate 80 (E433).

The product is available in a 20 mL neutral borosilicate clear type I glass vial sealed with a 20 mm chlorobutyl rubber stopper and with aluminium over seal with dark grey plastic button.

2.4.2. Active substance

2.4.2.1. General information

The active substance (INN: cipaglucosidase alfa) is a human recombinant acid α-glucosidase (rhGAA), derived from recombinant Chinese hamster ovary (CHO) cell culture. The structure contains 896 amino acids and includes 7 N-glycosylation sites and 5 disulphide bridges. The glycoprotein molecule has a molecular mass of approximately 110 kDa.

The mechanism of action of cipaglucosidase alfa involves binding to the cation-independent mannose 6-phosphate receptor (CI-MPR), the primary cell surface receptor that mediates the internalisation and delivery of exogenous enzyme replacement therapies (ERTs) to lysosomes. Receptor binding occurs through the specialised carbohydrate mannose-6-phosphate (M6P), particularly bis-M6P, which contains 2 M6P residues on the same N-glycan and has been shown to have a very high affinity for the CI-MPR. Upon internalisation and delivery to the lysosomes, cipaglucosidase alfa degrades glycogen to glucose, and therefore reduces glycogen substrate levels.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturing and testing of the active substance is performed by WuXi Biologics Co., Ltd., Wuxi, Jiangsu China. The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with Good Manufacturing Practice (GMP).

Description of manufacturing process and process controls

The main steps of the active substance manufacturing process are: fermentation, recovery and purification.

The manufacturing process is well described and an acceptable batch definition has been provided. For each step operation, ranges are given and in-process controls are in place. Use conditions for chromatography columns, their sanitisation, equilibration, loading, capacities, washing, elution and monitoring have been described.

Cipaglucosidase alfa BDS is stored in pre-sterilised containers. All product contact materials meet the requirements of the current compendial requirements.

Control of materials

Sufficient information on cell substrates and raw materials used in the active substance manufacturing process has been submitted. Compendial materials are controlled in accordance with applicable pharmacopoeias, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. Sufficient information on the materials used in the manufacturing process has been provided.

Information on the development and control of the cell substrate has been presented and is considered adequate.

The development of the producing cell line and stepwise selection of clones has been described. Sufficient information of the parental cell line, the master cell bank (MCB) and working cell bank (WCB) manufacture and the strategy to maintain cell bank supply has been provided. Genetic stability has been demonstrated for cells at and beyond the limit of cell age, as suggested by stability data of the WCB presented on EOPCs in section 3.2.A.2 section.

Control of critical steps and intermediates

An extensive list of normal operating ranges (NORs) and proven acceptable ranges (PARs), together with in-process controls, indicate tight control of the upstream and downstream production process steps of the active substance. Overall, the proposed settings for process parameter (PP) normal operating ranges and in-process controls/in-process tests (IPCs/IPTs) ranges are supported by the process characterisation/design studies and process performance qualification (PPQ) runs. The applicant has adequately justified the control strategy applied for cipaglucosidase alfa and defined the critical process steps and their controls. Actions taken if limits are exceeded are specified.

The stability of process intermediates during their proposed holding time is generally well supported by studies on their physico-chemical properties and by the times applied in PPQ studies.

Process validation

The active substance process validation strategy was been adequately described in the dossier. The control strategy as detailed in the dossier (operating ranges, criticality assignments of controls) has been further clarified upon request and the criticality of quality attributes adequately explained.Three PPQ runs have been successfully performed. For the PPQ batches, two production lines have been used. Sufficient information on IPC and intermediate test data as well as on removal of process-related impurities in the PPQ study has been provided.

In conclusion, the cipaglucosidase alfa active substance manufacturing process has been adequately validated. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled, demonstrating that the purification process consistently produces cipaglucosidase alfa active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

A tabulated overview is presented on quality attributes, their testing, criticality assignment and their control strategy. Sufficient information on the establishment of the control strategy and the criticality assignments has been supplied to support the suitability of the control strategy.

Engineering runs were performed at small scales, one of which was used to manufacture clinical supplies for Phase 1/2 studies. The active substance manufacturing process was scaled up to enable adequate clinical supply for Phase 3 clinical studies and future commercial demand. The changes applied during scaled-up are presented and motivated.

A comprehensive comparability report of clinical and commercial scale batches has been provided consisting of three sections: characterisation, release analysis results and stability. The comparability analysis sufficiently supports the comparability of cipaglucosidase alfa batches from these process scales.

Characterisation

The structure and physicochemical properties of multiple cipaglucosidase alfa active substance batches from both clinical and commercial scales were characterised by a battery of analytical methods.

The results are in line with the proposed primary, secondary, and tertiary structure. The information presented initially had significant flaws with respect to characterisation of the cipaglucosidase alfa structure, its purity and biological activity and the appropriate Module 3 section has, in response to the Major Objection and related other concerns raised during the assessment, been supplemented considerably. The entire sequence of the molecule is covered by sequencing, the glycan structures have been analytically confirmed, and the determination of glycan site occupancy and the reporting of mass spectrometry results have been clarified. The consistency of glycosylation during clinical development and routine manufacture is supported.

The bioactivity of cipaglucosidase alfa in human fibroblasts is determined indirectly by measuring the enzymatic activity of internalised active substance following cell lysis. Additional studies were performed for the characterisation of bioactivity, including its kinetics and binding aspects, and the relevancy of the bioassay was further justified.

In addition, adequate characterisation of product-related impurities has been presented, and therefore, the controls strategy for such impurities can be endorsed. The applicant has analysed post-translational modifications. Analysis of post-translational modifications occurring during stress conditions and as present in regularly produced cipaglucosidase alfa batches has also been performed and locations and levels of oxidation and deamidation under stressed conditions were investigated.

Clearance and control of process-related impurities have been sufficiently discussed.

In conclusion, the cipaglucosidase alfa active substance has been adequately characterised in terms of its structure, purity and biological activity and the analytical results are consistent with the proposed structure and considered appropriate for this type of molecule.

2.4.2.3. Specification

The active substance specification have been defined in accordance with ICH Q6B and includes general compendial tests and specific tests for identity, protein concentration, purity, potency, impurities, and safety tests.

Results from the statistical analysis of both release and stability data were used to support the justification of the proposed specifications. A number of specification limits were initially considered too wide and were further justified or tightened by the applicant

In summary, the proposed tests panel and acceptance criteria for batch release testing are considered adequate.

Analytical methods

Sufficiently detailed descriptions of analytical procedures have been provided. For non-compendial methods, the system suitability acceptance criteria and test sample acceptance criteria have been described. The test method validation parameters chosen are in line with ICH guidance and, in general, the approach chosen is rational and sufficiently detailed validation reports have been provided.

Batch analysis

Batch analysis data are provided for both small scale and commercial scale engineering, non-clinical, clinical/PPQ batches. All batches met specifications at the time of manufacture using the analytical procedure in-effect at the time. The results confirm consistency of the manufacturing process.

Reference materials

The applicant has adequately described the reference standards (RS) used. The primary and working RS have been appropriately characterised with analytical methods. The analysis has included the release testing methods and additional characterisation. Both primary and working reference standards are considered representative of the production process and clinical performance, and meet the release specifications of the product.

2.4.2.4. Stability

A 36-months shelf-life for the cipaglucosidase alfa active substance is claimed when stored at -80°C ± 10°C.

The stability studies and conditions have been conducted according to ICH guidelines. Relevant parameters were selected to study the stability profile of the active substance.

The claimed shelf-life for the cipaglucosidase alfa active substance when stored at -80°C ± 10°C is based on the data obtained from long-term, accelerated and stressed conditions. The representativeness of the required storage containers for the commercial process has been justified. Samples have been investigated for the release parameters and no significant changes have been observed.

A forced degradation study in which the active substance had been subjected to various stress conditions has been performed to explore the decomposition routes. The results of the photostability study (conducted in accordance with ICH Q1B), suggest that the active substance is unstable when exposed to light and therefore should be protected from strong light.

Based on presented stability data, the proposed shelf life of 36 months for the cipaglucosidase alfa stored at -80°C ± 10°C in the proposed container is considered acceptable.

A post-approval stability protocol and stability commitment have been given.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and Pharmaceutical Development

Cipaglucosidase alfa (ATB200) finished product is a sterile, white to slightly yellowish lyophilised powder in vial. The finished product contains the following excipients: sodium citrate dihydrate, citric acid monohydrate, mannitol and polysorbate 80. Each vial containing 105 mg of active substance is reconstituted with 7.2 mL sterile water for injection and diluted with 0.9 mg/mL (0.9%) sterile saline solution prior to intravenous infusion. The reconstituted volume appears as a clear to opalescent, colourless to a yellowish solution.

All excipients in the finished product are introduced during the active substance manufacture, except for nitrogen which is introduced at the end of the lyophilisation process. The water for injection, also introduced during the active substance manufacture, is removed during the lyophilisation process of the finished product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. No novel excipients or no excipients of human or animal origin are used in the finished product formulation. There is no overfill/overage in the cipaglucosidase alfa finished product.

The primary packaging is a 20 mL clear Type I glass vial with a fluoro-resin coated rubber stopper and aluminium seal with a plastic flip-off cap. The clear glass tubing vial meets Ph. Eur. 3.2.1 specifications for Type I borosilicate glass. The rubber stopper meets the requirements for Type I closures specified in Ph. Eur. General Chapter 3.2.9. In addition to meeting the requirements laid out in Ph. Eur., the container closure system has been risk assessed for its potential to be a source of organic and inorganic leachables into the finished product and the overall conclusion is that the risk of leachables in the lyophilised powder dosage forms from the container closure system is low.

In summary, the choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The pharmaceutical development approach was based on the following elements: definition of a Quality Target Product Profile (QTPP), identification of potential critical quality attributes (CQAs) of the finished product, selection of the appropriate manufacturing process, determination of the CQAs of the active substance, selection of the excipients and the container closure system and the definition of the quality control strategy.

Through the lifecycle of the finished product manufacturing process, the overall process flow has remained consistent from the clinical to commercial process, except for some key optimisations. The changes brought throughout process development were adequately presented and did not raise concerns. The differences between early finished product formulations and the later commercial formulation were assessed and are considered adequately justified. Formulation development aimed to develop a stable liquid formulation to support lyophilisation. The goal of this study was to select a suitable formulation. The formulations evaluated in this study have been designed using acceptable

excipients commonly used in parenteral products. The results of these studies have been analysed, and physical and chemical stability of the formulations were assessed.

Overall, the applicant has sufficiently addressed the physicochemical properties of the finished product during pharmaceutical development and has clearly shown how understanding of these properties was translated into the final manufacturing process.

2.4.3.2. Manufacture of the product and process controls

The cipaglucosidase alfa finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP at qualified vendors. A process flow diagram for the manufacture of cipaglucosidase alfa finished product is provided in the dossier, with detailed descriptions of the manufacturing steps. A batch formula has been provided for the intended commercial batch size range for cipaglucosidase alfa finished product, expressed as active substance volume entering the process.

The finished product is released in the EEA by Manufacturing Packaging Farmaca (MPF) B.V., Neptunus 12, Heerenveen, 8448CN, Netherlands.

The active substance is pre-formulated and no actual formulation steps take place during finished product manufacture. The finished product manufacturing process is standard and consists of active substance transfer and thaw, pooling and mixing, sterile filtration, filling into the vial, lyophilisation, and capping. There are no reprocessing steps in the finished product manufacturing process.

Adequate justification has been provided regarding the applied in-process controls and selection of certain process parameters and material attributes as critical, providing reassurance that all critical steps and intermediates are sufficiently controlled. Adequate information regarding sterilisation of (empty) vials and stoppers has been provided.

Overall, the manufacturing process and the equipment used are considered adequately described.

Three consecutive commercial-scale batches have been produced and investigated for PPQ, which is in line with EMA's Guideline on process validation for finished products. Batch numbers and genealogy are provided, and analytical results at the release of the PPQ batches are listed in the batch analyses.

During the execution of the three consecutive PPQ batches, active substance thawing, pooling, and mixing steps were investigated with enhanced sampling performed after the mixing step of the active substance pool. Sterile filtration and hold times were evaluated. Handling of materials, use of media fills and environmental monitoring for microbial contaminations were sufficiently addressed.

The submitted data demonstrate that the process is generally well controlled, with little variation in the reported results, which were all within defined limits.

A simulated transportation study was conducted to replicate the actual movement of the finished product required to complete the manufacturing, labelling/packaging, and distribution process steps for global supply chain. The longest transport time in the supply chain is not expected to exceed 84 hours which is well within the qualified durations.

In conclusion, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification, analytical procedures, batch analysis

The release specification includes: general tests, safety characteristics, protein concentration, identity, purity and product-related impurities, and potency.

In line with the request raised for the active substance, acceptance criteria for cipaglucosidase alfa finished product was also tightened during the assessment for several quality attributes. Moreover, as requested during the assessment, the applicant extended the identity testing to further assure unequivocal identification.

Overall, the parameters included in the finished product specification are found adequate to control the quality of the cipaglucosidase alfa finished product.

No new product-related impurities are found in the finished product. As there are no new excipients added during the manufacture of the cipaglucosidase alfa finished product, the impurities present or potentially present in the finished product are considered the same as those identified and controlled in the active substance.

Elemental impurities were evaluated according to ICH Q3D. A detailed description of this risk assessment is included. It is concluded that the overall risk of a potential release of elemental impurities into the cipaglucosidase alfa finished product is low and no specific control is considered necessary. This conclusion is agreed.

In response to a major objection raised during the assessment, a risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

Analytical methods used for testing of the finished product are either identical to the ones used for testing of the active substance or concern compendial methods, except for some product specific tests for which acceptable descriptions of the methods are provided.

Batch analysis

Data on batches of 105 mg/vial cipaglucosidase alfa manufactured at the declared finished product manufacturer are provided. Genealogy and use have been indicated. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The reference standard used for the active substance is also used for testing the finished product. See active substance section on reference materials.

2.4.3.4. Stability of the product

The finished product shelf-life claimed by the applicant is 36 months at the recommended storage conditions of 5°C ± 3°C and protected from light using light-resistant packaging.

The stability studies were performed on primary and supportive batches stored at 5°C ± 3°C (long-term storage condition) and 25°C ± 2°C/60 ± 5% relative humidity (accelerated storage condition) in accordance with the ICH guidelines. A set of specifications as per standard ICH Q6B guideline were employed for the finished product.

Data provided for 36 months at recommended storage conditions of 5°C ± 3°C are confirmed to meet specifications and show minimal degradation. Based on the data from the photostability studies (conducted in accordance with ICH Q1B), it is agreed that the product should be stored protected from light. Reconstitution and in-use instructions in the SmPC are consistent with the reported stability findings of the in-use studies.

Data presented at accelerated conditions showed slight variation for some of the tested parameters, but the results were within specifications. All PPQ lots had similar degradation profiles to the demo, engineering, and clinical batches at accelerated conditions.

Based on available stability data, the shelf-life of Pombiliti finished product of 36 months and storage conditions as stated in the SmPC (*Store in a refrigerator (2°C - 8°C)*. *Keep the vial in the outer carton in order to protect from light*) are acceptable. For the reconstituted product, the chemical, physical, and microbiological in-use stability has been demonstrated for 24 hours at 2°C - 8°C. For the diluted product after reconstitution, the chemical, physical, and microbiological in-use stability has been demonstrated between 0.5 mg/mL and 4 mg/mL for 24 hours at 2°C to 8°C, followed by 6 hours at room temperature (up to 25°C) to allow for infusion.

A post-approval stability protocol and stability commitment have been given. The ongoing stability programme will be followed up by the annual incorporation of at least one additional commercial-scale batch as stated in a stability commitment.

2.4.3.5. Adventitious agents

A certification from the manufacturer that all materials, equipment and facilities used for the manufacture of the active substance do not contain or have no contact with any materials or additives directly derived from animals or humans which may have Transmissible Spongiform Encephalopathies/Bovine Spongiform Encephalopathy (TSE/BSE) infection risk and certificates for the medium used have been provided. Except for the cell substrate, the raw materials used in the manufacturing process of cipaglucosidase alfa are free of animal-derived components. The cell banks used are subjected to a panel of virus tests. The process is further evaluated by virus testing of representative unprocessed bulk and end-of-production cell testing. As harvesting is done continuously, the applicant has clarified the timepoint of harvest-testing during routine production and also included such information in the appropriate sections of the CTD.

The active substance purification process was evaluated for its ability to remove/inactivate viruses by spiking studies. Therefore, it can be concluded that the virus validation is adequate.

2.4.3.6. GMO

Not applicable.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure, two major objections were raised, concerning (1) insufficient characterisation data to support the proposed structure for the active substance and (2) missing risk evaluation for the presence of nitrosamine impurities in the product. The Major Objections, as well as all the other concerns, have been satisfactorily resolved.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for investigation which pertain to the testing for Host cell proteins (HCPs).

2.5. Non-clinical aspects

2.5.1. Introduction

Cipaglucosidase alfa (ATB200, recombinant human acid α-glucosidase (rhGAA) is a new biological entity developed as a next-generation ERT for Pompe disease. Cipaglucosidase alfa has the same mechanism of action as alglucosidase alfa but differs structurally based on its post-translational N-linked oligosaccharide structures. Specifically, cipaglucosidase alfa contains higher amounts of mannose 6-phosphate (M6P), the natural motif for identifying and transporting soluble lysosomal enzymes to lysosomes compared to alglucosidase alfa. Importantly, cipaglucosidase alfa contains bis-phosphorylated high mannose (bis-M6P) oligosaccharide structures that are known to have the highest affinity of all known carbohydrates for the cation-independent mannose 6-phosphate receptor (CI-MPR). Cipaglucosidase alfa, like all rhGAA lysosomal enzymes, is unstable at neutral pH and can be denatured and inactivated in the bloodstream following intravenous infusion.

2.5.2. Pharmacology

Cipaglucosidase alfa was evaluated in a series of non-clinical pharmacology, pharmacokinetic, and toxicology studies. These studies were conducted to evaluate the nonclinical safety and characterise efficacy in the *in vivo* animal models. Evaluation of cipaglucosidase alfa was performed with and without the co-administration of the enzyme stabiliser miglustat; alglucosidase alfa alone was added as a reference for efficacy evaluation. Since the clinical route of administration is intravenous (IV) infusion, all non-clinical studies also administered cipaglucosidase alfa via the IV route.

2.5.2.1. Primary pharmacodynamic studies

Comparative *in vitro* binding studies with cipaglucosidase alfa or alglucosidase alfa to cation-independent mannose 6-phosphate receptor (CI-MPR) showed that while alglucosidase alfa bound 27% of CI-MPR, cipaglucosidase alfa bound 95% and with high affinity to CI-MPR.

In vitro studies evaluating binding kinetics were conducted by the applicant. Cipaglucosidase alfa binds with sub-nanomolar (Kd=0.9nM) affinity to its target, CI-MPR, at physiological pH. Under acidic conditions encountered in the endosome, cipaglucosidase alfa dissociates from CI-MPR. A Kd could therefore not be determined. The binding of miglustat to cipaglucosidase alfa was tested at neutral pH in PBS, plasma or whole human blood and in acidic pH buffer with varying miglustat concentrations by rapid equilibrium dialysis. Miglustat bound cipaglucosidase alfa in diluted plasma with an estimated Kd of 10.51 ± 2.25 µM and in diluted whole blood at approximately 15.05 ± 7.05 µM. Similar results were obtained in PBS. Miglustat binding increased stability of cipaglucosidase alfa and reduce irreversible enzyme inactivation in blood as demonstrated in a thermostability study. This complex is then likely taken up by cells where miglustat dissociates from cipaglucosidase alfa.

In rat muscle cells (L6 myoblasts) and Pompe patient P545L skin fibroblasts, cipaglucosidase alfa internalised effectively with an uptake constant of 15nM and 5nM, respectively. Consequently, the maximum internalised acid αglucosidase (GAA) activity was also increased when rat and human cells were incubated with cipaglucosidase alfa 787 nmol/mg/hr and 383 nmol/mg/hr, respectively. GAA activity was also lower when rat and human cells were incubated with alglucosidase alfa. This suggests that the higher M6P content of cipaglucosidase alfa improves cellular uptake and thus potentially also improves efficacy over alglucosidase alfa.

In denaturation experiments, cipaglucosidase alfa was more stable in acidic pH than at physiological pH, which could be dose-dependently stabilised by co-incubation with miglustat providing evidence of the added benefit of miglustat co-administration. In whole blood, cipaglucosidase alfa retained its activity for longer by coincubation with increasing concentrations of miglustat up to 170µM.

To evaluate the performance of cipaglucosidase alfa in an *in vivo* setting, cipaglucosidase alfa was administered to GAA knockout mice after incubating the formulation at room temperature for 4 hours alone or with miglustat. Cipaglucosidase alfa exposure was moderately increased (67µmol/ml/hr.hr vs. 74µmol/ml/hr.hr, respectively). The co-administration of cipaglucosidase alfa and miglustat showed a trend toward increased glycogen reduction but was not statistically significant compared to cipaglucosidase alfa alone, although compared to vehicle there was a statistically significant trend of further glycogen reduction over administration of cipaglucosidase alfa alone.

Co-administration of miglustat improved efficacy of 20 mg/kg cipaglucosidase alfa but not 10 mg/kg. Compared to alglucosidase alfa alone, combined administration resulted in 2.8- and 2.3-fold greater glycogen reduction in the quadriceps and triceps, respectively. Increasing the dose of miglustat did not

improve GAA activity, which was considered suggestive of inhibition of cipaglucosidase alfa efficacy through unknown mechanisms. Anti-drug antibody titers were comparable in all test-article groups, which does not suggest a lower immunogenic profile for either cipaglucosidase alfa or the combination compared to alglucosidase alfa. Investigations of dose refinement showed that in GAA knockout mice, lower doses of cipaglucosidase alfa resulted in significantly greater glycogen reduction compared to alglucosidase alfa, indicating improved potency and efficacy of cipaglucosidase alfa.

In a pivotal proof of concept study, the effect of GAA activity after 4 or 6 repeated biweekly (every other week) administrations of alglucosidase alfa (20 mg/kg) or cipaglucosidase alfa (10 or 20 mg/kg) with or without coadministration of miglustat (20 or 30 mg/kg) was evaluated in GAA knockout mice. Cipaglucosidase alfa dose-dependently reduced glycogen levels in muscle, which was significantly greater (up to 1.8x in skeletal muscle) compared to alglucosidase alfa and did so at comparatively lower exposures. However, GAA activity was overall not significantly improved compared to alglucosidase alfa at any dose or combination. Furthermore, these differences more or less plateaued after 4-weeks, after which the efficacy of alglucosidase alfa approached but did not meet that of cipaglucosidase alfa. This was particularly noted in heart tissue. Extended administration did not further improve glycogen turnover. Thus, while proof of concept has been demonstrated that coadministration of miglustat and cipaglucosidase alfa may result in better clearance of glycogen, its superiority over alglucosidase alfa has only been demonstrated on a biochemical level.

Further histopathological and functional evaluations have been performed with cipaglucosidase alfa. Histological evaluation showed that administration with cipaglucosidase alfa (20 mg/kg) also reduced upregulation of lysosome-associated membrane protein 1 (LAMP1), which is associated with lysosome proliferation and impaired muscle physiology. This reduction was independent of the target tissue being slow- or fast-twitch fibres, whereas alglucosidase alfa did not modulate LAMP1 in fast-twitch fibres. Decreases in LAMP1 were further attenuated after co-administration of miglustat. Muscles responsive to cipaglucosidase alfa and miglustat administration included quadriceps and diaphragm, two key skeletal muscles that are composed predominantly of type II fibres. Finally, the co-administration of cipaglucosidase alfa and miglustat also significantly reduced autophagy markers LC3A II and p62, suggesting autophagy can be reversed in Pompe disease. A study evaluating lysosome proliferation and autophagy in the quadriceps of GAA KO mice showed a reduction of LAMP and LC3 after co-administration of cipaglucosidase alfa and miglustat. Clearance of autophagic build-up and restoration of muscle architecture was noted in the white gastrocnemius, further suggesting a reversal of muscle damage in Pompe disease.

Long-term administration (12 biweekly administrations) using alglucosidase alfa alone, cipaglucosidase alfa or its co-administration with miglustat in GAA knockout mice animals showed increased GAA activity and glycogen turnover, decreased lysosomal proliferation and autophagy and improved muscle repair mechanisms for the co-administration of cipaglucosidase alfa and miglustat. Cipaglucosidase alfa alone or its co-administration with miglustat was statistically significantly better in lowering glycogen in tissue compared to alglucosidase alfa alone. Co-administration of cipaglucosidase alfa and miglustat increased GAA activity, but this did not necessarily lead to improved biochemical parameters compared to administration of cipaglucosidase alfa alone. Furthermore, the improved biochemical profile in these animals did not lead to statistically significant changes compared to alglucosidase alone in a wire hang study. However, performance in the cipaglucosidase alfa and cipaglucosidase alfa/miglustat treatment groups tended to maintain latency vs vehicle-treated animals. Similarly, there was no difference in improvement in grip strength with cipaglucosidase alfa compared to alglucosidase alfa test group animals whereas for the cipaglucosidase alfa/miglustat treatment group, statistically significant improvement over alglucosidase alfa was noted. While cipaglucosidase alfa/miglustat treatment has

demonstrably improved GAA activity and histopathological modulation of the Pompe phenotype, its functional effect over administration of alglucosidase alfa appears to be modest.

2.5.2.2. Secondary pharmacodynamic studies

Given the high specificity of cipaglucosidase alfa for CI-MPR, no additional (secondary) pharmacology is expected beyond the intended target pharmacology. Therefore, further studies are not necessary.

2.5.2.3. Safety pharmacology programme

Safety pharmacology was implemented part of the GLP 26-week toxicity studies in rats and monkeys, respectively and the 13-week toxicity study in monkeys. Cipaglucosidase alfa alone or co-administered with miglustat did not pose an acute risk to CNS, respiratory or cardiovascular systems.

2.5.2.4. Pharmacodynamic drug interactions

To prevent hypersensitivity reactions to cipaglucosidase alfa, diphenhydramine was used in most repeat-dose studies. Diphenhydramine did not affect glycogen reduction *in vivo*, although in one study, there was a slightly lower trend of glycogen reduction in some tissues. Co-administration with an immune suppressant (methotrexate, 5mg/kg) did not improve the management of hypersensitivity reactions.

No further pharmacodynamic drug interactions investigations have been conducted. This was considered acceptable since cipaglucosidase alfa is a protein and is expected to be metabolically degraded through peptide hydrolysis, thus unlikely to be candidate for cytochrome P450 mediated drug-drug interactions.

2.5.3. Pharmacokinetics

In order to characterise the pharmacokinetic (PK) of cipaglucosidase alfa in the claimed indication, the following studies were conducted: single-dose PK studies in *Gaa* KO mice, SD rats, and Cynomolgus monkey, where cipaglucosidase alfa was dosed separately or co-administered with miglustat. In addition, toxicokinetic data were collected in the scope of the repeat-dose toxicity studies conducted in the rat and monkey.

Methods to measure rhGAA enzyme activity in rat, cynomolgus monkey and rabbit plasma were validated under GLP compliance to quantify cipaglucosidase alfa enzyme levels in plasma and determine TK parameters using the synthetic substrate 4-methylumbelliferyl-α-glucopyranoside (4-MU-α-Glc).

As a complementary approach, liquid chromatography tandem mass spectroscopy (LC-MS/MS) methods were also validated in compliance with GLP to quantify cipaglucosidase alfa in Sprague-Dawley (SD) rat, Cynomolgus monkey and rabbit plasma samples during GLP toxicity studies, with LLOQ values of 0.5 µg/mL for all three species.

Bridging Meso Scale Discovery (MSD) assays were implemented and validated in compliance with GLP for the detection of anti-cipaglucosidase alfa antibodies (anti-drug antibodies, ADA) in rat and monkey plasma as part of the cipaglucosidase alfa immunotoxicity assessment.

The absence of method validation of GAA activity assay in *Gaa* KO mice plasma was justified during the procedure.

In *Gaa* KO mice receiving a 30 minutes IV infusion of 5, 10 and 20 mg/kg cipaglucosidase alfa, dose-dependent increases in C_{max} and AUC values were observed, while $t_{1/2}$ remained similar over the dose range tested (range ~0.6-0.8 h). Alglucosidase alfa dosed at 20 mg/kg revealed a longer $t_{1/2}$ (~1.3 h), indicating slower clearance from plasma compared to cipaglucosidase alfa. Co-administration of miglustat at 10 mg/kg together with 20 mg/kg cipaglucosidase alfa showed similar PK parameters.

In *Gaa* KO mice receiving an IV bolus of 5, 10, and 20 mg/kg cipaglucosidase alfa showed similar results to the IV infusion described above: dose-dependent increases in Cmax and AUC were observed. Again, cipaglucosidase alfa at 20 mg/kg exhibited faster plasma clearance ($t_{1/2}$ ~0.8 h) as compared to alglucosidase alfa 20 mg/kg ($t_{1/2}$ ~1.4 h), resulting in an approximate 50% lower plasma exposure (AUC) value.

In SD rats receiving an IV bolus of 5, 10 and 20 mg/kg cipaglucosidase alfa, dose-dependent increases in C_{max} and AUC were observed. Miglustat 10 mg/kg co-administered with cipaglucosidase alfa 20 mg/kg trended towards a slight increase in cipaglucosidase alfa half-life (~0.9 h compared to ~0.8 h in cipaglucosidase alfa alone) and an increase in C_{max} and AUC.

Comparison of two engineering batches of cipaglucosidase alfa (EB1 and EB2) showed similar $t_{1/2}$ to research-grade material (although AUC and C_{max} appear to be different but are not discussed in the study report), as shown by comparison of 10 mg/kg IV bolus infusions in *Gaa* KO mice which resulted in similar $t_{1/2}$ for both doses (range ~0.5-0.6 h). Subsequently, the PK parameters of EB2 were determined by IV dosing *Gaa* KO mice with 5, 10, 20 and 100 mg/kg of cipaglucosidase alfa, either in the presence or absence of orally pre-dosed miglustat 10 or 30 mg/kg. The distribution-phase half-life of cipaglucosidase alfa increased modestly with increasing dose (~0.6 h at 5 mg/kg dose to ~0.7 h at 20 mg/kg). The 100 mg/kg dose exhibited a considerably increased elimination half-life (~1.1 h) compared to the lower doses. Both 10 and 30 mg/kg miglustat co-administration exhibited similar effects on cipaglucosidase alfa PK values, with co-administration being more pronounced at 5 mg/kg (~47% increase in half-life) and 10 mg/kg (37% increase in half-life) compared to 20 mg/kg cipaglucosidase alfa (~21% increase in half-life). However, when comparing the AUC0-5hr values, the increases in exposure were smaller, indicating only a slight increase in exposure: ≤21% for the 5 mg/kg dose, ≤26% for the 10 mg/kg dose and ≤10% for the 20 mg/kg dose.

The effect of miglustat on cipaglucosidase alfa PK parameters was assessed in the cynomolgus monkey as well. In this study, AUC_t and distribution-phase half-life were 3230 hr*µg/mL and ~1.3 hr, respectively. The addition of 175 mg miglustat resulted in an AUC_t of 6130 hr*µg/mL and a distribution-phase half-life of ~3.1 hr for cipaglucosidase alfa.

In support of clinical testing, large-scale batches of cipaglucosidase alfa were produced. These batches were subsequently compared to the previous clinical scale batches by performing IV dosing studies using both *Gaa* KO mice and SD rats. Results demonstrated that the various batches of cipaglucosidase alfa before and after scale-up exhibited similar $t_{1/2}$ following IV bolus injection at 10 mg/kg in *Gaa* KO mice. Similarly, these batches displayed a similar PK profile in SD rats: the distribution-phase half-life of the various batches of cipaglucosidase alfa was similar (ranging from ~0.5 h to ~0.6 h) no significant differences in either AUC or C_{max} were detected across the various batches.

Cipaglucosidase alfa co-administered with miglustat in *Gaa* KO mice was also studied using a dosing condition that mimics the clinical administration scenario. The cipaglucosidase alfa enzyme solution was incubated for 4 hours at room temperature to mimic the human clinical settings of continuous

infusion in Pompe disease patients. Mice received an IV bolus injection of cipaglucosidase alfa at 20 mg/kg alone or with miglustat 10 mg/kg co-administration. The results demonstrated that under these conditions, miglustat co-administration improved cipaglucosidase alfa PK (reduced clearance and increased half-life) in plasma by ~10% based on AUC values, particularly during the distribution phase.

Tissue uptake was assessed by measuring GAA enzyme activity in quadriceps, triceps and heart muscle (relevant disease target tissues) in Gaa KO mice, following cipaglucosidase alfa 20 mg/kg IV infusion with and without miglustat 10 mg/kg oral co-administration. Cipaglucosidase alfa alone exhibited dose-dependent increases in GAA enzyme activity 24 hours post IV infusion in quadriceps, triceps, and heart muscle. At 20 mg/kg, cipaglucosidase alfa exhibited levels of enzyme activity in tissues similar to alglucosidase alfa. Co-administration of 10 mg/kg miglustat with 20 mg/kg cipaglucosidase alfa demonstrated a trend of increased GAA activity in skeletal muscle (quadriceps and triceps), but not in the heart.

No dedicated studies on the metabolism, excretion, pharmacokinetic drug interactions of cipaglucosidase alfa were conducted in animals. This is considered acceptable by the CHMP.

2.5.4. Toxicology

The toxicology programme was designed to determine the safety profile of cipaglucosidase alfa in a series of toxicology studies in the rat, rabbit, and monkey. Completed studies include repeat-dose toxicology studies of 13 weeks/3 months (monkey) and 26 weeks/6 months (rat and monkey) in duration. Developmental and reproductive toxicology studies included fertility (rat), embryo-fetal toxicity (rat and rabbit), and pre- and post-natal developmental toxicity (rat) studies. Local tolerance was evaluated in the repeat-dose toxicity studies.

2.5.4.1. Single dose toxicity

No adverse effects were noted at single doses up to 200 mg/kg, resulting in an AUC0-24h of 9360 and 11400 ng.h/mL for female rats and cynomolgus monkey, respectively. However, for both studies, no dedicated negative controls groups were included. In the rat, a comparison to historical controls was performed. The omission of a control group is not considered adequate in general. However, as this concerns a non-pivotal non-GLP single-dose study, it is considered sufficient within this situation. In cynomolgus monkey, treatment data were compared to pre-dose data in the same animals.

2.5.4.2. Repeat dose toxicity

Cipaglucosidase alfa was tested in the rat and cynomolgus monkey in 6-month repeat-dose toxicity studies with I.V. dosing every other week. In rats, diphenhydramine (DPH) hydrochloride was administered I.P. before treatment to prevent potential anaphylactic and/or hypersensitivity response to the human protein. Only limited findings were observed in the rat, consisting of decreased serum glucose and increases in WBC, lymphocytes, basophils and serum calcium concentration (the latter in males only). The effects were minimal and transient, and no related histopathological changes were observed. Therefore, these findings are considered non-adverse. The exposure margin (EM) based on two selected peptide fragments at the highest dose tested in the rat was 18 (male) and 11 (female) fold exposure in humans at 20 mg/kg in the phase III study.

No adverse findings were observed in the 6-month cynomolgus monkey repeat-dose toxicity study up to an exposure margin of 19 (male) and 14 (female) fold exposure at MRHD.

In addition, ADAs were observed in all cipaglucosidase alfa treated rat and cynomolgus monkey groups, with most of the animals testing positive for NAbs. However, no ADA-related adverse events were noted.

In a three-month repeat-dose toxicity study in cynomolgus monkey, the co-administration of cipaglucosidase alfa and miglustat was investigated up to 100/175 mg/kg, respectively. No adverse effects were noted by combination exposure to cipaglucosidase alfa and miglustat. At the highest doses of cipaglucosidase alfa/ miglustat tested, the exposure margin for two selected peptide fragments was 11 (male) and 8 (female) and the exposure margin for miglustat was 9 (male) and 11 (female) fold, both compared to exposure in human at MRHD.

2.5.4.3. Genotoxicity

Cipaglucosidase alfa (recombinant glycoprotein) is not expected to exhibit mutagenic potential. No genotoxicity studies were performed. This is considered acceptable by the CHMP.

2.5.4.4. Carcinogenicity

Cipaglucosidase alfa (recombinant glycoprotein), is not expected to be carcinogenic. No carcinogenicity studies were performed. This is considered acceptable by the CHMP.

2.5.4.5. Reproductive and developmental toxicity

All reproductive toxicology exposure margins were calculated by correcting the exposure obtained in the animal studies (with dosing every other day and AUC values reported of 0-48 hours) for the dosing regimen in the human situation (dosing every other week and AUC values reported of 0-336 hours). Consequently, 7-fold lower exposure margins will be obtained in case of comparing exposure during the first 24 hours after dosing, during which the majority of the exposure takes place, based on the very short half-life of cipaglucosidase alfa in rats, rabbits and humans.

In a FEED study in rats, cipaglucosidase alfa did not have an adverse effect on female or male fertility up to an exposure margin of 183- and 263-fold exposure at MRHD, respectively.

In treated female rats, preimplantation loss was significantly increased following treatment with either 60 mg/kg miglustat alone (21.6%) or 60 mg/kg miglustat in combination with 400 mg/kg cipaglucosidase alfa (21.4%) compared to the control group (9.6%).

Cipaglucosidase alfa was found to be negative for embryo-foetal developmental toxicity in rat and rabbit up to an exposure margin of 129 and 55-fold exposure at MRHD, respectively. In addition, miglustat and cipaglucosidase alfa + miglustat were tested in both the rat and rabbit. The addition of miglustat did not change the outcome in rat EFD (miglustat exposure margin of 29-fold). However, in the rabbit EFD toxicity study, a significant increase in cardiovascular malformations was observed in the cipaglucosidase alfa + miglustat treatment groups, including increases in the atretic pulmonary trunk (4 of litters/6 foetuses), ventricular septum defect (5 litters/7 foetuses), dilated aortic arch (5 litters / 13 foetuses), malpositioned atrium (litter 1 / foetuses 2), dextrocardia (litter 2 / foetuses 2) three-chambered heart (litter 2/ foetuses 3) and large ventricles (l litter 2/ foetal 3). The exposure level at which these miglustat-induced effects were observed was 22-fold exposure at MRHD. In the

pre- and postnatal developmental toxicity study, no adverse findings on F0 and F1 were observed with QOD cipaglucosidase alfa treatment alone, up to 129-fold exposure at MRHD.

The co-administration of cipaglucosidase alfa and miglustat increased maternal mortality, as was observed in the rat reproductive toxicity studies, together with a small non-significant increase in total litter loss (n=3, DHP control n=1). Other postnatal pup survival values were also not significantly altered and were within the historical control range. In addition, based on the elevation in maternal mortality, decreased maternal activity, and slightly increased incidence of pups with no milk in the stomach at necropsy, the slight increase in total litter loss in the combination group can be considered due to maternal neglect of the pups. In the cipaglucosidase alfa/miglustat treatment group, a decrease in pup weight was observed on PND 14 and PND 21, which correlated with the signs of maternal neglect and no milk present in the stomach of pups.

2.5.4.6. Toxicokinetic data

The main toxicokinetics (TK) studies were performed in the rat and monkey.

In SD rats dosed every other week with 0, 30, 70 or 200 mg/kg cipaglucosidase alfa, concentrations were approximately 1 to 2 times higher in males compared to females. The overall effect of dose level and repeat dosing on cipaglucosidase alfa TK were consistent between the sexes. Slightly longer distribution-phase half-life values (range = 0.98 to 2.1 h) and slightly shorter elimination-phase half-life values (range = 6.33 to 10.1 h) were observed after the day 85 and day 169 doses compared to day 1. Little to no accumulation was observed with repeated administration once every other week (accumulation ratios in males and females combined, based on C_{max} and $AUC_{0\text{-}t}$, ranged from 1.1 to 2.2). The incidence of neutralising antibodies ranged from 90% to 100% in the 30 mg/kg dose group, 80% to 100% in the 70 mg/kg dose group, and 45% to 75% in the 200 mg/kg dose group. There was no trend of titers increasing with increasing cipaglucosidase alfa dose. However, the reasonably consistent exposure observed in the TK animals on days 85 and 169 as compared to day 1 suggests that ADA did not substantially alter cipaglucosidase alfa TK during the course of this study, indicating a comparable tissue uptake of the enzyme despite the presence of ADAs/NAbs. The exposure multiples based on AUC data were 11-18 for female and male rats, respectively, indicating sufficient exposure.

In cynomolgus monkeys dosed every other week up to 13 weeks with 0, 50 (with or without 25 mg/kg miglustat) and 100 mg/kg (with or without 175 mg/kg miglustat) cipaglucosidase alfa, exposure increased with dose between 50 and 100 mg/kg dose levels and was similar for males and females. The mean day 1 initial distribution-phase half-life (males and females combined), based on the first three-time points past t_{max}, ranged from 1.28 to 3.07 hours. The mean day 1 elimination-phase half-life ranged from 1.70 to 11.1 hours. A similar range of values was observed after the day 85 dose. Little to no accumulation was observed. The addition of 175 mg/kg miglustat to the 100 mg/kg cipaglucosidase alfa dose resulted in decreased cipaglucosidase alfa clearance and increased (approximately 2-fold) plasma exposure, relative to 100 mg/kg cipaglucosidase alfa monotherapy. All animals were positive for ADAs on days 85 and 99 (100% incidence). There was no obvious trend of increasing cipaglucosidase alfa ADA titers with increasing doses. The number of animals positive for neutralising antibodies at day 99 ranged from 3 of 8 animals for the 100 mg/kg cipaglucosidase alfa monotherapy group, 4 of 8 animals in the 100 mg/kg cipaglucosidase alfa with 175 mg/kg miglustat group to 5 of 8 animals in the 50 mg/kg cipaglucosidase alfa in combination with 25 mg/kg miglustat. There was no obvious effect of ADAs on cipaglucosidase alfa exposure or other TK parameters, indicating a comparable tissue uptake of the enzyme despite the presence of ADAs/NAbs. The

exposure multiples based on AUC data were 5-6 for female and male monkeys in the cipaglucosidase alfa monotherapy group, indicating sufficient exposure.

In cynomolgus monkeys dosed every other week up to 26 weeks with 0, 30, 60 and 200 mg/kg cipaglucosidase alfa, cipaglucosidase alfa exposure increased with dose between the 30, 60, and 200 mg/kg dose levels and was similar or slightly higher in males when compared to females. The mean day 1 distribution-phase half-life (males and females combined), based on the first 3 time points past t_{max}, increased slightly with increasing dose and ranged from 0.709 to 2.59 hours. In general, the mean day 1 elimination-phase half-life was longer than the mean distribution-phase half-life. The mean elimination-phase half-life values generated using total cipaglucosidase alfa protein ranged from 1.78 to 2.85 hours. Little to no accumulation was observed with repeated administration once every other week. While all animals were positive for ADA titers and most were positive for the presence of NAbs between days 85 and 211, there was no obvious effect of ADAs or NAbs on cipaglucosidase alfa exposure or other TK parameters, indicating a comparable tissue uptake of the enzyme despite the presence of ADAs/NAbs. There was no obvious trend of titers increasing with increasing dose levels. The exposure multiples based on AUC data were 14-19 for female and male monkeys, respectively, indicating sufficient exposure.

Several reproductive toxicology studies (FEED, EFD) were performed using rat and rabbit. In general, the exposure multiples for these studies were >50-fold, indicating sufficient exposure for these studies.

2.5.4.7. Local tolerance

No adverse findings on local tolerance were observed in the repeat-dose toxicity studies.

2.5.4.8. Other toxicity studies

Cipaglucosidase alfa did not induce haemolysis *in vitro* in human blood nor flocculation *in vitro* in human plasma and serum up to a concentration of 2.8-fold exposure in the FIH trial and 3.3-fold exposure reported in PopPK analysis.

2.5.5. Ecotoxicity/environmental risk assessment

According to "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2), no ERA studies have been submitted. This is acceptable since cipaglucosidase alfa, is an enzyme consisting of naturally occurring amino acids linked to a glycan molecule.

2.5.6. Discussion on non-clinical aspects

Together with binding kinetics data evaluating the affinity of cipaglucosidase alfa to the CI-MPR receptor and the affinity of miglustat to cipaglucosidase alfa, the submitted pharmacology data sufficiently demonstrate the mode of action and proof of concept of cipaglucosidase alfa and miglustat co- administration.

Despite the absence of a rationale for the choice of miglustat as co-administration with cipaglucosidase alfa, its binding appears to increase stability of cipaglucosidase alfa and reduce irreversible enzyme inactivation in blood as demonstrated in a thermostability study. The complex cipaglucosidase

alfa/miglustat is thought to be likely taken up by the cells where miglustat dissociates from cipaglucosidase alfa. The high concentration of glycogen accumulated in lysosomes of Pompe patients is expected to outcompete miglustat binding for cipaglucosidase alfa, leaving cipaglucosidase alfa fully available for glycogen hydrolysis.

The studies suggested that administration of cipaglucosidase alfa results in a dose-dependent increase in GAA activity in disease-relevant tissues (including quadriceps, triceps, gastrocnemius, and heart), leading to increased glycogen turnover, which was generally further improved with miglustat. Further long-term studies also showed improved histopathological muscle repair in animals when cipaglucosidase alfa/miglustat are co-administered.

Despite this, long-term administration of cipaglucosidase alfa/miglustat did not necessarily improve biochemical parameters compared to administration of cipaglucosidase alfa alone. In addition, whilst cipaglucosidase alfa/miglustat treatment has demonstrated improved GAA activity and histopathological modulation of the Pompe phenotype, its functional effect over administration of alglucosidase alfa appeared to be modest. With inconsistent effect on glycogen turnover in all investigated muscle types and the lack of improved physiological outcome measures, an efficacy claim of superiority over alglucosidase alfa cannot be justified from a non-clinical perspective.

In general, the effect of co-administration of miglustat with cipaglucosidase alfa resulted in only modest increases in cipaglucosidase alfa exposure in mice and rats, whereas the effect was more pronounced in the monkey. Co-administration of 10 mg/kg miglustat with 20 mg/kg cipaglucosidase alfa demonstrated a trend of increased GAA activity in skeletal muscle (quadriceps and triceps), but not in the heart.

In monkeys, miglustat increased cipaglucosidase alfa plasma exposure approximately by ~2-fold compared to cipaglucosidase alfa alone. During the procedure, the applicant sufficiently justified that this finding would unlikely impact on the safety profile in clinical setting.

Both rat and monkey showed distribution-phase half-life values ranging from ~2-4 hours. The elimination-phase half-life values were higher for both species, ranging from 6-8 hours for the rat, and 3-7 hours for the monkey, although the higher values observed are probably caused by the presence of measurable concentrations after 168 hours in a few animals. As expected, little to no accumulation was observed for both species. Presence of miglustat showed different effects in rat and monkey. Whereas there was no or only a small increase in half-life of cipaglucosidase alfa in rats, monkeys did show an increase in half-life in the presence of miglustat by ~50-100%, as observed for distribution-phase half-life. However, a small or no effect on cipaglucosidase alfa half-life in *Gaa* KO mice was reported in the presence of miglustat, leading to similar or slightly higher exposures for miglustat co-administration groups. Altogether, the comparative data across species did not reveal any particular concerns for the CHMP.

Overall, cipaglucosidase alfa was well tolerated by rats and monkeys in pharmacology and repeat dose toxicity studies employing doses of up to 20 mg/kg and 200 mg/kg, respectively. These findings are expected given the nature of the product (enzyme replacement therapy) and valid with sufficient exposure multiples for toxicokinetic studies. In line with ICH S6(R1), relevant endpoints of safety pharmacology studies were incorporated in the repeat dose toxicity studies and did not reveal any concerns. In line with ICHS6(R1) guidelines, no carcinogenicity and genotoxicity studies were performed.

A FEED study in rats revealed no effects on male fertility. However, an increased incidence of preimplantation loss was observed in female rats treated with cipaglucosidase alfa/miglustat. As this

only occurred in the miglustat (co)-treated groups, this adverse effect is considered related to miglustat treatment. In the cipaglucosidase alfa + miglustat treatment group, miglustat exposure was 33 (M), and 30 (F) fold exposure at MRHD. Based on these results indicating a potential risk for decreased fertility and/or pregnancy loss in women taking miglustat prior to and during pregnancy, the following information is included in section 4.6 of the SmPC *"Animal studies with miglustat alone as well as with cipaglucosidase alfa and miglustat have shown reproductive toxicity, see section 5.3. Pombiliti in combination with miglustat therapy is not recommended during pregnancy and in women of childbearing potential not using contraception."*

Cipaglucosidase alfa was found to be negative for EFD toxicity in rat and rabbit up to an exposure margin of 129- and 55-fold exposure at MRHD, respectively. However, in the rabbit EFD toxicity study, a significant increase in cardiovascular malformations was observed in the cipaglucosidase alfa + miglustat treatment groups. Such findings were not observed in the cipaglucosidase alfa groups nor in the groups treated with 60 mg/kg miglustat alone. Based on the reported occurrence of cardiovascular malformations and variations in rabbits following exposure during organogenesis to the co-administration of cipaglucosidase alfa and miglustat, the following statement is included in section 5.3 of the SmPC: *"The combination of cipaglucosidase alfa with miglustat resulted in increased cardiovascular malformations (aortic pulmonary trunk, ventricular septum defect, and dilated aortic arch) in rabbits".*

In the pre-and postnatal developmental toxicity study, no adverse findings on F0 and F1 were observed with QOD cipaglucosidase alfa treatment alone, up to 129-fold exposure at MRHD.

In rats, the co-administration of cipaglucosidase alfa and miglustat (EM 29-fold) increased maternal mortality, and a small non-significant increase in total litter loss was observed. Together with these findings, decreased maternal activity, and slightly increased incidence of pups with no milk in the stomach at necropsy were reported indicating that the slight increase in total litter loss in the combination group could be considered due to maternal neglect of the pups. In particular, in the cipaglucosidase alfa/miglustat treatment group, a decrease in pup weight was observed on PND 14 and PND 21 and correlated with the signs of maternal neglect and no milk present in the stomach of pups.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, cipaglucosidase alfa is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of cipaglucosidase alfa have been adequately documented and meet the requirements to support this application.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the

Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study Number	Study Design and Phase	Study Objective(s)	Subjects (N, Mean Age [Range], and Number of Sites)	Treatment (Dosage, Form, Dose, and Route)
Phase 1 study in healthy subjects				
AT2221-01 (completed)	Randomised, open-label, 3-way crossover Phase 1	Relative bioavailability	N = 18 (10 M/8 F) 38.8 (19 to 60) y 1 site	- Single dose of one 65-mg Phase 1/2 (PIC) miglustat capsule swallowed whole - Single dose of one 65-mg Phase 3 miglustat capsule swallowed whole - Single dose of one 65-mg Phase 3 miglustat capsule reconstituted in water
Studies in adult subjects with LOPD (≥ 18 y)				
ATB200-02 (ongoing)	First-in-human, open-label, fixed-sequence, ascending-dose Phase 1/2	Stage 1: safety, tolerability, and PK (completed) Stage 2: safety, tolerability, PK, and PD (completed) Stage 3 (ongoing; 2 y) and Stage 4 (ongoing): long-term safety, tolerability, efficacy, PK, PD, and immunogenicity	N = 29 46.0 (18 to 66) y 17 sites	- Stage 1: single-ascending dose of 5, 10, and 20 mg/kg cipaglucosidase alfa IV - Stage 2: 3 doses of 20 mg/kg cipaglucosidase alfa IV + 130 mg miglustat oral capsules QOW, followed by 3 doses of 20 mg/kg cipaglucosidase alfa IV + 260 mg miglustat oral capsules QOW - Stages 3 and 4: 20 mg/kg cipaglucosidase alfa IV + 260 mg miglustat oral capsules QOW
ABT200-03 (completed)	Multicentre, double-blind, randomised, active-controlled Phase 3	Efficacy and safety <u>Primary endpoint:</u> Change from Baseline to Week 52 in the 6MWD measured in meters, which is the distance walked in the 6MWT	N = 123 46.8 (19 to 74) y 62 sites	- 20 mg/kg cipaglucosidase alfa IV + 195/260 mg miglustat oral capsules QOW[a] - 20 mg/kg alglucosidase alfa IV + placebo oral capsules QOW
ABT200-07 (ongoing)	Open-label extension to Study ATB200-03 Phase 3	Safety and efficacy	N = 115[b] 47.9 (22 to 75) y[c]	20 mg/kg cipaglucosidase alfa IV + 195/260 mg miglustat oral capsules QOW[a]

Study Number	Study Design and Phase	Study Objective(s)	Subjects (N, Mean Age [Range], and Number of Sites)	Treatment (Dosage, Form, Dose, and Route)
Phase 1 study in healthy subjects				
AT2221-01 (completed)	Randomised, open-label, 3-way crossover Phase 1	Relative bioavailability	N = 18 (10 M/8 F) 38.8 (19 to 60) y 1 site	- Single dose of one 65-mg Phase 1/2 (PIC) miglustat capsule swallowed whole - Single dose of one 65-mg Phase 3 miglustat capsule swallowed whole - Single dose of one 65-mg Phase 3 miglustat capsule reconstituted in water
Studies in adult subjects with LOPD (≥ 18 y)				
ATB200-02 (ongoing)	First-in-human, open-label, fixed-sequence, ascending-dose Phase 1/2	Stage 1: safety, tolerability, and PK (completed) Stage 2: safety, tolerability, PK, and PD (completed) Stage 3 (ongoing; 2 y) and Stage 4 (ongoing): long-term safety, tolerability, efficacy, PK, PD, and immunogenicity	N = 29 46.0 (18 to 66) y 17 sites	- Stage 1: single-ascending dose of 5, 10, and 20 mg/kg cipaglucosidase alfa IV - Stage 2: 3 doses of 20 mg/kg cipaglucosidase alfa IV + 130 mg miglustat oral capsules QOW, followed by 3 doses of 20 mg/kg cipaglucosidase alfa IV + 260 mg miglustat oral capsules QOW - Stages 3 and 4: 20 mg/kg cipaglucosidase alfa IV + 260 mg miglustat oral capsules QOW
ABT200-03 (completed)	Multicentre, double-blind, randomised, active-controlled Phase 3	Efficacy and safety Primary endpoint: Change from Baseline to Week 52 in the 6MWD measured in meters, which is the distance walked in the 6MWT	N = 123 46.8 (19 to 74) y 62 sites	- 20 mg/kg cipaglucosidase alfa IV + 195/260 mg miglustat oral capsules QOW[a] - 20 mg/kg alglucosidase alfa IV + placebo oral capsules QOW
			61 sites	

Abbreviations: 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; F = female; IV = intravenous(ly); LOPD = late-onset Pompe disease; M = male; N = number of subjects; PD = pharmacodynamic(s); PIC = powder in capsule; PK = pharmacokinetic(s); QOW = every other week; y = years

[a] In Studies ATB200-03 and ATB200-07, miglustat dosing is adjusted to 195 mg in subjects ≥ 40 kg to < 50 kg.

[b] Safety population.

[c] Efficacy population.

2.6.2. Clinical pharmacology

Pharmacokinetic data of cipaglucosidase alfa (and miglustat) in adult Pompe disease patients were obtained from the 3 clinical studies (ATB200-02, ATB200-03 and AT2221-01). A PopPK analysis was conducted using available alglucosidase alfa, cipaglucosidase alfa and miglustat plasma concentration data pooled from studies ATB200-02 and ATB200-03 to characterise the pharmacokinetics and to evaluate the effects of intrinsic and extrinsic factors on pharmacokinetics.

For the quantification of GAA activity in plasma samples and the establishment of the specific activity, a validated enzymatic activity method was applied using fluorescent molecule 4-methylumbelliferone (4MU) reaction product.

For the analysis of total anti-cipaglucosidase alfa antibodies in plasma, immunogenicity was monitored using validated ADA assays and followed a tiered bioanalysis approach of screening, confirmation, and titration. Immunogenicity was assessed using a validated electrochemiluminescent assay to screen samples for ADAs.

Anti-drug antibody-positive samples identified with the ADA assay were further evaluated for the presence of NAbs, which decreases drug activity and signal. The methods were validated and showed acceptable performance.

Additional blood samples were collected for the evaluation of cipaglucosidase alfa immunoglobulin E (IgE). IgE antibodies against cipaglucosidase alfa were quantified using a validated fluoroenzyme immunoassay.

Glucose tetrasaccharide (Hex4) in the urinary was analysed by a validated UPLC method with MS detection.

For the analysis of miglustat in plasma and urine, validated LC-MS/MS methods were applied.

2.6.2.1. Pharmacokinetics

Absorption

As cipaglucosidase alfa is administered intravenously, the absolute bioavailability is 100%. After intravenous administration, Cmax values generally occurred at the end of infusion (4h), and after that plasma concentrations declined in a biphasic decline manner. Exposure increased proportionally over the 5 – 20 mg/kg dose range after administration of cipaglucosidase alfa alone.

Plasma total GAA protein exposure increased in a linear, but more than dose-proportional manner over the 5, 10 and 20 mg/kg dose range. In principle, dose proportionality is not an issue, as cipaglucosidase alfa is dosed at 1 dose level, i.e., 20 mg/kg.

After repeated doses of 20 mg/kg cipaglucosidase alfa + 260 mg miglustat, Cmax and AUC were comparable across different PK visits, indicating no time dependency.

Cipaglucosidase alfa pharmacokinetics shows a low to moderate between-subject variability of about 15 – 25% for Cmax and AUC.

Distribution

Cipaglucosidase alfa is not expected to bind to plasma proteins. The mean volume of distribution of cipaglucosidase alfa ranged from 2.0 to 4.7 L. The distribution half-life was increased by 48% following usage of both cipaglucosidase alfa and miglustat. Correspondingly, plasma clearance decreased by 27%, suggesting accelerated uptake into tissues relative to cipaglucosidase alfa without miglustat.

Following the administration of a single dose of miglustat 260 mg in combination with cipaglucosidase alfa 20 mg/kg in fasting adults with Pompe disease in a phase 1/2 trial, total GAA protein partial AUCtmax-24h (time of maximum concentration at the end of infusion to 24 hours post-start of infusion) increased by 44% relative to cipaglucosidase alfa 20 mg/kg alone, indicating binding and stabilisation by miglustat during the distribution phase of elimination. AUCinf and Cmax increased by 28 and 6%.

Cipaglucosidase alfa does not cross the blood-brain barrier.

Elimination

Cipaglucosidase alfa is rather rapidly eliminated from plasma. At the 20 mg/kg dose, the mean clearance was about 1.3 l/h. Concomitant treatment with 260 mg miglustat decreased the clearance to 1.0 l/h, which was confirmed by popPK analysis, i.e. 0.9 l/h. The distribution elimination half-life was about 2 hours.

For elimination, the t½α (alpha phase elimination half-life or distribution elimination half-life) was estimated. Per request, the applicant provided the elimination half-lives, i.e. ranging from 1.6 to 2.6 h.

Dose proportionality and time dependencies

Plasma total GAA protein exposure increased in a linear, but more than dose proportional manner over the 5, 10 and 20 mg/kg dose range.

No unexpected accumulation is observed after once every 2 weeks dosing. After repeated doses of 20 mg/kg cipaglucosidase alfa + 260 mg miglustat, Cmax and AUC were comparable across different PK visits, indicating no time dependency.

Special populations

No studies have been carried out in subjects with renal or hepatic impaired function.

Population PK analysis of gender, race/ethnicity (Asian vs White), and age (range of 27 – 66 years) as a covariate across clinical studies indicate that there is no significant effect on plasma total GAA protein exposure following cipaglucosidase alfa and miglustat co-administration. Body weight appeared to be a covariate for cipaglucosidase alfa clearance. An increase in body weight increases AUC and Cmax. However, over range (51 – 104 kg), the mean ratio at the weight cut-offs (51 and 104 kg) compared to a non-Asian, ERT-naive, 70 kg, 50-year-old male receiving cipaglucosidase alfa monotherapy (used as a reference) was within 80 – 125% range and considered not clinically relevant.

Pharmacokinetic interaction studies

No interaction studies have been performed. Because it is a recombinant human protein, cipaglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions

By pooling different immunosuppressives used in the studies, no effect was observed on plasma total GAA protein exposures.

Pharmacokinetics using human biomaterials

See above.

2.6.2.2. Pharmacodynamics

Mechanism of action

Cipaglucosidase alfa (rhGAA) is developed as an ERT for Pompe disease. Cipaglucosidase alfa has the same mechanism of action as the naturally occurring enzyme but differs structurally based on its posttranslational N-linked oligosaccharide structures.

Cipaglucosidase alfa is intended to replace the absent or impaired endogenous enzyme. Cipaglucosidase alfa is stabilised by miglustat minimising the loss of enzyme activity in the blood during infusion of this hydrolytic glycogen-specific enzyme enriched with bis-M6P N-glycans for high affinity cation-independent mannose-6-phosphate receptor (CI-MPR) binding. After binding, it is internalised in the lysosome where it undergoes proteolytic cleavage and N-glycan trimming which are both required to yield the most mature and active form of the GAA enzyme. Cipaglucosidase alfa then exerts enzymatic activity in cleaving glycogen and reducing intramuscular glycogen and ameliorating tissue damage.

In study ATB200-02, 11 ERT experienced patients were treated with a single dose of 5, 10 or 20 mg cipaglucosidase alfa alone. No pharmacodynamic endpoints were measured, precluding an assessment of the pharmacodynamic effects of cipaglucosidase alfa alone.

Primary and Secondary pharmacology

In studies ATB200-02 and ATB200-03, creatine kinase (CK) and urine glucose tetrasaccharide (Hex4) levels tended to decrease upon treatment with cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo in ERT-naïve patients with Pompe disease. Observed decreases in CK levels tended to be more consistent for cipaglucosidase alfa/miglustat as compared to alglucosidase alfa/placebo.

In the ERT-naïve LOPD study patients, both CK and Hex4 levels tended to decrease upon cipaglucosidase alfa in combination with miglustat (CK -171.3 U/l, Hex4 -2.5 mmol/mol creatinine) and also upon alglucosidase alfa in combination with placebo (CK -23.1 U/l, Hex4 -1.6 mmol/mol creatinine).

In the ERT-experienced LOPD study patients, both CK levels and Hex4 levels tended to decrease upon treatment with cipaglucosidase alfa combined with miglustat (change from baseline at week 52: CK -118.0 U/l, Hex4 -1.7 mmol/mol creatinine), whereas both CK levels and Hex4 levels tended to increase upon treatment with alglucosidase alfa and placebo (change from baseline at week 52: CK +79.6 U/l, Hex4 +1.9 mmol/mol creatinine).

Overall, observed decreases in CK and Hex4 levels tended to be larger for cipaglucosidase alfa/miglustat as compared to those of alglucosidase alfa/placebo in ERT-naïve and also in ERT-experienced study patients with Pompe disease.

No results considering secondary pharmacologic parameters were submitted. This was considered acceptable by the CHMP.

2.6.3. Discussion on clinical pharmacology

The pharmacokinetic profile of cipaglucosidase alfa has been sufficiently characterised. No unexpected accumulation is observed after once every 2 weeks of dosing.

The recommended adult dose of cipaglucosidase alfa is 20 mg/kg, given every 2 weeks. Miglustat should be administered about 1 h before the start of the 4h infusion of cipaglucosidase alfa.

The dosing rationale for cipaglucosidase alfa/miglustat was based upon *in vitro* stability data and non-clinical data. *In vitro* studies demonstrated that the interaction of miglustat with cipaglucosidase alfa in the neutral pH environment of whole blood increases its protein stability and prevents denaturation, resulting in the preservation of cipaglucosidase alfa activity. Non-clinical data suggested a higher cipaglucosidase alfa exposure and uptake at the 20 mg/kg dose with concomitant administration of miglustat. The data indicated an improved cipaglucosidase alfa uptake and glycogen reduction. An optimum was observed at the 10 mg/kg miglustat dose, which would correspond with about 270 mg in adults. The dose of 260 mg miglustat would result in an optimal time of stabilisation of cipaglucosidase alfa in plasma and uptake and glycogen reduction.

Considering the long-term exposure in study ATB200-02 (e.g. after the third dose) the increase in cipaglucosidase alfa exposure due to the addition of miglustat appeared small (about 29%) and thus there is a lack of clear pharmacokinetic rationale for the addition of miglustat. Although the PK data indicated an improved cipaglucosidase alfa uptake and glycogen reduction, differences may be considered not pronounced. The clinical relevance of the co-administration cipaglucosidase alfa/miglustat is thus further discussed based on the efficacy data. See 2.6.6.

Nevertheless, as cipaglucosidase alfa is enriched on sugars, it is to be expected that the intra-cellular and intra-lysosomal uptake is enhanced. The contribution of miglustat to the pharmacodynamic effects of cipaglucosidase alfa appeared to be achieved through bindings and stabilisation of cipaglucosidase alfa in the circulation during infusion. Non-clinical data demonstrated the benefits of miglustat, where it increases the cipaglucosidase alfa area under the curve (AUC), leads to incremental glycogen reduction, and improvements in autophagy and muscle strength. PK data from clinical study ATB200-02 confirmed that adding miglustat increases cipaglucosidase alfa AUC in Pompe patients to levels comparable to those observed in non-clinical studies associated with improvements in disease pathology. Furthermore, these miglustat-mediated increases in cipaglucosidase alfa plasma AUC have been shown to be maintained long-term. This is important as cipaglucosidase alfa is inherently unstable at every infusion for as long as patients are on therapy. Miglustat should be administered under fasting conditions 1h before the start of infusion of cipaglucosidase alfa, as the miglustat tmax is about 2-3 hours and as such high plasma miglustat concentrations were obtained during and after infusion. Administration of miglustat 1 h before the start of infusion of 20 mg/kg cipaglucosidase alfa dose resulted in increased exposure of total GAA protein compared to the administration of cipaglucosidase alfa alone. In fasting adult patients, at the 260 mg miglustat dose level, exposure (AUCtmax-24h) increased 44%, relative to cipaglucosidase alfa 20 mg/kg alone. In addition, plasma levels were significantly increased at 12h and 24h after the start of infusion.

The disposition of cipaglucosidase alfa is not expected to be impacted by hepatic or renal impairment. Based on pharmacokinetics of cipaglucosidase alfa used in co-administration with miglustat, a dose adjustment is not recommended.

In the clinical studies, cipaglucosidase alfa drug substances using a clinical and commercial scale were applied. PopPK on drug exposures, and PD response with 12-month change from baseline in urine hexose tetrasaccharide, did not indicate significant differences between the 2 batches.

The used pharmacodynamic endpoints Hex4 and CK are considered acceptable. These parameters were also used in the studies for alglucosidase alfa, as well as in other publications. Available results from these biomarkers are supportive of the pharmacodynamic effects of cipaglucosidase alfa in combination with miglustat in both ERT-experienced and ERT-naïve patients with Pompe disease.

2.6.4. Conclusions on clinical pharmacology

Overall, the pharmacological profile of cipaglucosidase alfa in human studies has been adequately documented and meet the requirements to support this application.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No dose-response studies were submitted with cipaglucosidase alfa alone or miglustat alone. The dose-response study ATB002-02 evaluated the dose response of cipaglucosidase alfa in combination with miglustat.

Study ATB002-02 is an ongoing Phase 1/2, open-label, fixed-sequence first-in-human study to evaluate the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of intravenous cipaglucosidase alfa alone and when co-administered with oral miglustat in ambulatory (cohorts 1, 3, and 4) and non-ambulatory (cohort 2) adult LOPD patients. Study data until the data cut-off of 15 June 2020 are presented.

The study is conducted in 4 cohorts and 4 stages (see Figure 1).

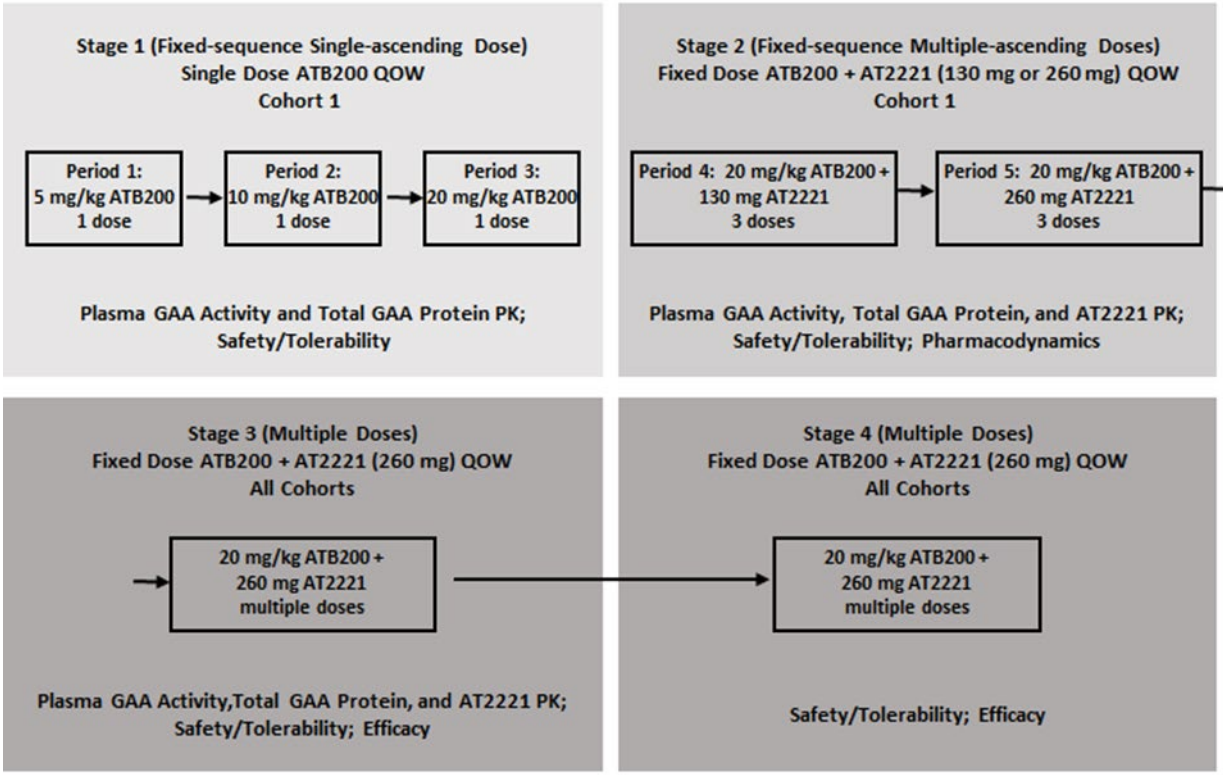


Figure 1 Study design of study ATB002-02

Note: ATB200 = cipaglucosidase alfa; AT2221 = miglustat; Stage 1 evaluates 3 single dose administrations in LOPD patients (cohort 1); stage 2 analyses 2 separate dosages of miglustat combined with 20 mg/kg cipaglucosidase alfa with 3 subsequent administrations for each dosage combination (cohort 1); stage 3 and 4 analyses the effects of 20 mg/kg cipaglucosidase alfa in combination with 260 mg miglustat during 12 months of treatment in various groups of LOPD patients (cohorts 2, 3, and 4).

In all study stages, cipaglucosidase alfa was administered every 2 weeks as an approximate 4-hour intravenous infusion (±15 minutes) at a constant infusion rate. In study stages 2, 3, and 4, miglustat 65 mg oral capsules were administered 1 hour before the intravenous infusion of cipaglucosidase alfa. Study patients fasted for at least 2 hours before and 2 hours after administration of miglustat.

The limited dose-finding part (stage 1 and 2 in cohort 1) consisted of 11 patients treated with a single escalating dose of 5, 10, 20 mg/kg cipaglucosidase alfa in stage 1 and in stage 2 thrice a regimen of two doses of miglustat (130 or 260 mg) combined with 20 mg/kg cipaglucosidase alfa. As each dose of cipaglucosidase alfa monotherapy has only been administered once, no conclusion can be drawn as to the most appropriate dosage and regimen; furthermore, no data on the efficacy of cipaglucosidase alfa alone are available.

Patient-reported outcomes were only evaluated in study stages 3 and 4 of study ATB200-02. However, due to the non-randomised, open-label nature of study ATB200-02, and the limited number of study patients (n= 29), no definitive conclusions can be made with respect to the patient-reported outcomes for this treatment combination, nor with respect to a potential dose-response relationship for these endpoints and thus these data are not presented in this report.

ERT experienced population

For cohorts 1, 2 and 4, 65% of patients were male, with a mean (SD) age ranging from 40.8 (17.0) to 49.4 (9.5) years. The mean (SD) number of years since the diagnosis of Pompe disease was 8.1 (5.5) for Cohort 1, 9.3 (6.2) for Cohort 2, and 10.2 (2.4) for Cohort 4. The mean (SD) duration of ERT treatment ranged from 4.7 (1.4) to 10.1 (4.8) years.

At baseline, the mean (SD) 6-minute walking distance was 393.5 meters (119.7) for all ERT-experienced ambulatory patients (cohorts 1 and 4). Mean (SD) changes from baseline to month 12 were +33.5 meters (49.6) for ERT-experienced ambulatory patients. The sitting forced vital capacity tended to decrease (-1.3%; 95%CI -4, 2), but the supine forced vital capacity tended to increase (+2.7%; 95%CI -2, 7).

ERT-naïve population

For cohort 3, 83% of patients were female, with a mean (SD) age of 49.3 (15.1) years. The mean (SD) number of years since the diagnosis of Pompe disease was 5.2 (4.7).

At baseline, the mean (SD) 6-minute walking distance was 396.0 (75.2) meters for all ERT-naïve ambulatory patients (cohort 3). Mean (95%CI) changes from baseline to month 12 were +57.0 (26, 9) meter for ERT-naive ambulatory patients. Following 12 months of treatment, the sitting (mean improvement 4.5%, 95%CI -4, 13) and supine (mean improvement 1.8%; 95%CI -6, 10) forced vital capacity tended to improve compared to baseline upon co-administration of 20 mg/kg intravenously infused cipaglucosidase alfa and 260 mg miglustat in ERT-naïve patients.

2.6.5.2. Main study

ATB200-03

The study design is represented in Figure 2.

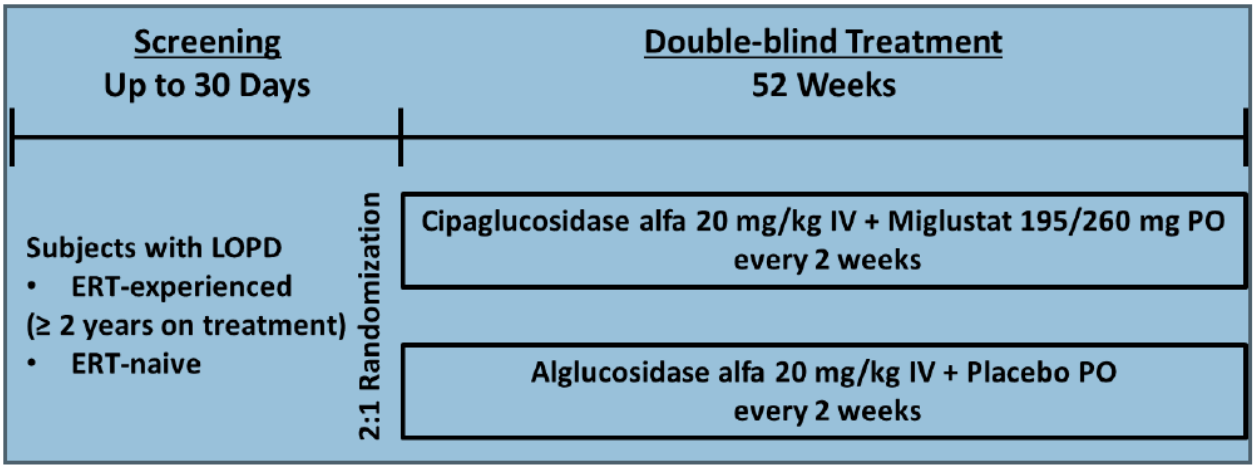


Figure 2 Study design

This was a double-blind, randomised, multicentre, superiority study of cipaglucosidase alfa/miglustat in adult subjects with LOPD who had received ERT with alglucosidase alfa (ERT-experienced) or who had never received ERT (ERT-naïve) compared with alglucosidase alfa/placebo.

Study ATB200-03 is the pivotal Phase 3 study in the clinical programme.

Methods

- **Study Participants**

Main inclusion criteria

Male and female subjects were ≥ 18 years old and weighed ≥ 40 kg at screening; diagnosis of LOPD based on documentation of one of the following: deficiency of GAA enzyme, GAA genotyping; a sitting FVC ≥ 30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III) at screening; subject performed two 6MWTs at screening that were valid, as determined by the clinical evaluator, and that met all of the following criteria: both screening values of 6MWD were ≥ 75 m, both screening values of 6MWD were ≤ 90% of the predicted value for healthy adults and the lower value of 6MWD was within 20% of the higher value of 6MWD.

Main exclusion criteria

Use of invasive or non-invasive ventilation support for > 6 hours per day while awake; hypersensitivity to any of the excipients in cipaglucosidase alfa, alglucosidase alfa, or miglustat.

- **Treatments**

The study drugs used in this study were co-administration of cipaglucosidase alfa with miglustat (intervention) or co-administration of alglucosidase alfa with placebo (control). The doses of cipaglucosidase alfa and alglucosidase alfa were 20 mg per kilogram of body weight. Cipaglucosidase alfa or alglucosidase alfa was administered every 2 weeks as a 4-hour iv infusion. The dose of miglustat was 195 mg (3 × 65 mg oral capsules) for subjects weighing ≥ 40 kg to < 50 kg and 260 mg (4 × 65 mg oral capsules) for subjects weighing ≥ 50 kg.

- **Objectives**

Primary objective

To assess the efficacy of cipaglucosidase alfa/miglustat co-administration on ambulatory function, as measured by the 6-minute walk test (6MWT), compared with alglucosidase alfa/placebo.

Secondary objectives

To assess the effects of cipaglucosidase alfa/miglustat co-administration compared with alglucosidase alfa/placebo on: pulmonary function, as measured by sitting FVC (% predicted); muscle strength; health-related patient-reported outcomes (PROs); motor function; overall clinical impression as assessed by both physician and subject; safety, tolerability, and immunogenicity; biomarkers of muscle injury and disease substrate; population PK of cipaglucosidase alfa and alglucosidase alfa in ERT-experienced subjects using plasma total GAA protein level by signature peptide assay and plasma miglustat concentration; PK of cipaglucosidase alfa, alglucosidase alfa, and miglustat in ERT-naïve subjects using non-compartmental analysis; exposure-response relationship for cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo co-administration.

- **Outcomes/endpoints**

Primary endpoint

The change in 6MWD (the distance walked in the 6MWT, in meters) from baseline to week 52. The test was performed at screenings 1 and 2 and at weeks 12, 26, 38, and 52.

Key secondary endpoints

Changes in: % predicted sitting FVC from baseline to week 52; manual muscle test (MMT) lower extremity score from baseline to week 52; 6MWD from baseline to week 26; Patient-reported Outcomes Measurement Information System (PROMIS)-Physical Function total score from baseline to week 52; GSGC and PROMIS-Fatigue total scores from baseline to week 52.

Other secondary endpoints

Changes in: % predicted 6MWD from baseline to week 52; variables related to motor function from baseline to week 52; variables related to muscle strength from baseline to week 52; variables from PRO measures from baseline to week 52; measures of pulmonary function from baseline to week 52.

Proportion of subjects with improvement in both 6MWD and % predicted FVC

Actual values of the subject's functional status (improving, stable, or declining) at week 52, as measured by the Subject Global Impression of Change (SGIC) and by the Physician's Global Impression of Change (PGIC).

- **Sample size**

To achieve 90% power with a two-sided alpha level of 0.05, a total of 99 evaluable subjects (2:1 ratio) are needed to show superiority based on the t-test with an assumed standard deviation of 7.43%. Approximately 30 ERT-naïve LOPD subjects were planned to be enrolled.

- **Randomisation and Blinding (masking)**

Subjects were randomised with a 2:1 ratio to cipaglucosidase alfa with miglustat (intervention) or co-administration of alglucosidase alfa with placebo (control). A centralised block randomisation procedure was used, stratified by baseline 6MWD (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters) and ERT status (ERT-experienced versus ERT-naïve). The study was planned to be double-blind. A matching placebo for miglustat was to be used with alglucosidase alfa, and black or dark covering over cipaglucosidase alfa and alglucosidase alfa reconstituted solution were used during infusion.

- **Statistical methods**

Analysis populations

The safety population includes all subjects who received at least one dose of study drug.

The intent-to-treat (ITT) population included all randomised subjects who received at least one dose of study drug.

The ITT-OBS population includes all subjects from the ITT population, where in the efficacy analyses all available, observed data without imputation for missing post-baseline data will be used.

The ITT-LOCF population includes all subjects from the ITT population, where in the efficacy analyses missing data will be replaced with the last available value from post-baseline results.

The per-protocol population (PP) includes all subjects from the ITT population who have both baseline and at least one post-baseline assessment and who do not have pre-specified protocol deviations. The per-protocol population 1 (PP1) will be used for the supportive analyses of the 6WMD, while per-protocol population 2 (PP2) will be used for supportive analyses of the % predicted FVC. The PP population will be analysed according to the actual treatment received.

Primary efficacy analysis

The primary endpoint is the change from baseline to week 52 in 6MWD. The 6MWT is to be performed twice at the Week 52/ET visit, and the average of the 2 test values will be used.
The difference in change from baseline to week 52 in 6MWD between intervention and control was analysed using a MMRM model based on the ITT-OBS population. The model included the fixed factors treatment, time (visit number), treatment-by-time interaction, ERT status, and gender, and the covariates baseline 6MWD, baseline age, baseline weight, and baseline height. In this analysis model, the applicant remapped the results of delayed visits to planned visits (see missing values), which could lead to bias in the estimated treatment difference. As requested by the CHMP, the applicant performed a new analysis using the MMRM model based on the ITT-OBS population excluding the outlying subject without imputation at week 52 and based on the actual time point of the assessments during the procedure, since this analysis was considered the most adequate and reliable method to evaluate efficacy. The new MMRM model included the fixed, categorical effects of treatment, enzyme replacement therapy (ERT) status, and gender, as well as the fixed, continuous covariates of time of assessment (days), baseline 6MWD, baseline age, baseline weight, and baseline height, and the treatment-by-time interaction. A random intercept of subject was also included in the model.

Secondary efficacy analyses

For the key and secondary endpoints, the new analysis using the MMRM model based on the ITT-OBS population without the outlying subject and based on the actual time points of assessment was also performed as requested by the CHMP during the procedure.

Multiplicity

To control the overall alpha level, hierarchical testing was planned with an ordering of the secondary endpoints to be tested sequentially after the primary efficacy endpoint was tested statistically significant.

Missing values

Due to COVID-19, not all planned visits could be performed within the time windows, resulting in delayed visits outside the planned visit windows. The applicant remapped the results of the delayed visits to the planned study visits, and these were used in the original primary and other analyses.

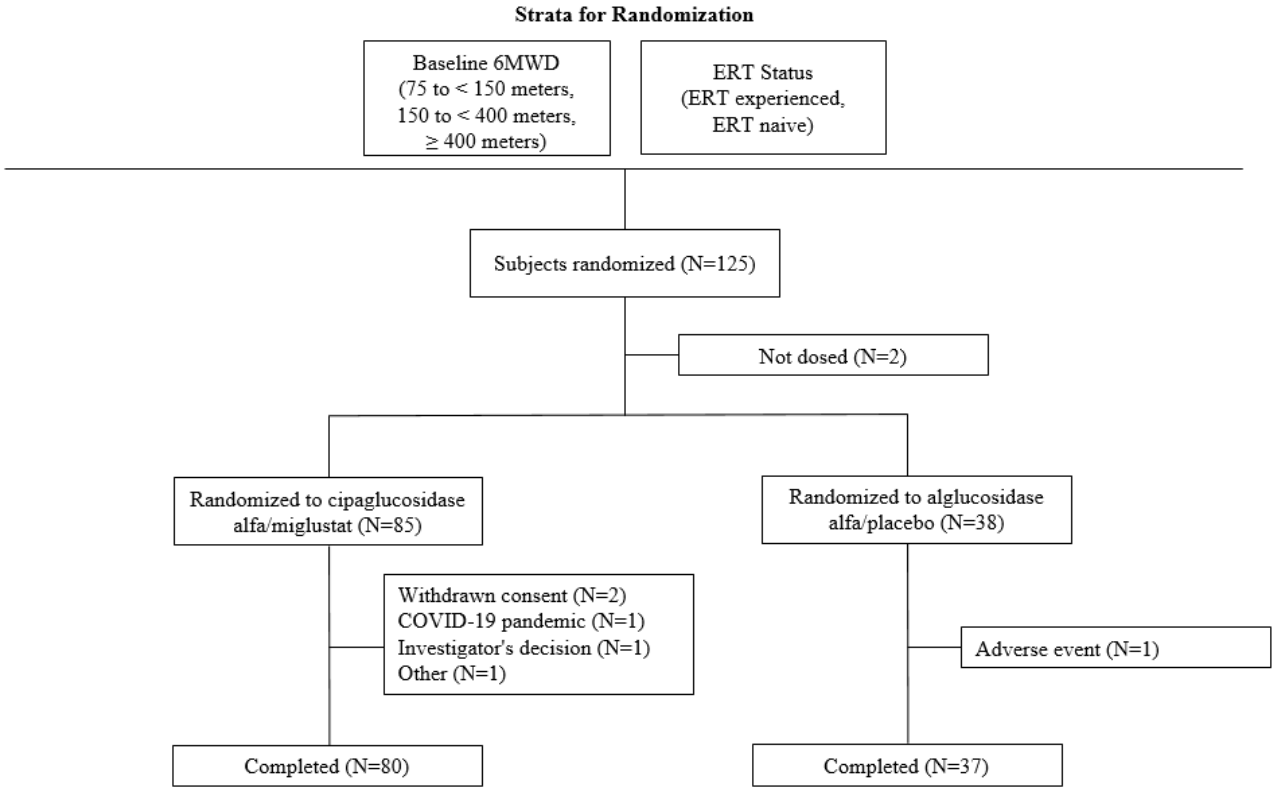
Delayed visits and make-up assessments that go beyond the stated visit windows were remapped to the planned study visit. Suppose a subject had a COVID-19 related situation leading to a delay in the week 26 assessment such that the delayed visit / make-up assessment for week 26 occurs on Day 261 (which is 36 days outside of the planned visit window for week 26, and it’s inside the week 38 visit window), followed by the week 38 assessment on day 300 (which is right within the week 38 visit window). Here, the delayed assessment occurring on day 261 was remapped to the week 26 visit (which was the intended visit). If week 52 is delayed the delayed visit assessments will still be used for analyses. The make-up assessments at week 52 was used as the week 52 results in the original analyses. The requested analyses were not based on remapping visits but used the actual time points of the assessments without imputations.

For efficacy analyses that did not use the MMRM model, the applicant used the last observation carried forward (LOCF) method in case of missing values. These analyses are considered supportive. The LOCF method replaces missing values with values measured at least 12 weeks earlier. As LOPD is expected to deteriorate over time in case of no treatment and the 6MWD is not expected to be a monotone increasing function during the study, the LOCF method is considered a non-conservative approach for dealing with missing values and could lead to overly optimistic results for both treatment groups and

therefore can lead to bias in estimating a treatment effect for a deteriorated illness in time. Therefore, the LOCF method is not considered appropriate, and the analyses using the LOCF method can only be considered as supportive analyses.

Results

- **Participant flow**



- **Recruitment**

Date first subject enrolled: 03 December 2018
Date last subject completed: 15 December 2020

- **Conduct of the study**

In the cipaglucosidase alfa/miglustat group versus alglucosidase alfa/placebo group, 67 (79%) and 28 (74%) subjects, respectively, had a major protocol deviation mostly in the categories of study procedures (49% vs. 47%), investigational product (41% vs. 37%), and informed consent (22% vs. 32%). In total 9 subjects (8 vs. 1) and 16 subjects (11 vs. 5) had a major deviation that was considered to have an impact on the analysis of 6MWD and FVC, respectively, and were excluded from the PP analyses. The reasons were discontinuation (5 vs. 1), using a walking device (4 vs. 0), missing week 52 FVC (8 vs. 3) and non-interpretable FVC at week 52 (0 vs. 1). As most major protocol deviations did not lead to exclusion from the PP population, neither of the protocol deviations (including 2 unblinding events) impacted the integrity of the primary or the key secondary assessments in the study.

In total, 66 (54%) subjects had protocol deviations due to the COVID-19 pandemic (47 (55.3%) subjects in the cipaglucosidase alfa/miglustat group and 19 (50%) subjects in the alglucosidase alfa/placebo group). Examination of the clinical data, for one subject revealed after database lock that the subject had previously been using an anabolic steroid (ostarine) and had deliberately underperformed his screening assessments in order to gain entry into the study. This subject was treatment naïve and randomised to the alglucosidase alfa/placebo arm.

- **Baseline data**

Demographics and baseline characteristics are represented in Table 1.

Table 1 Demographics and baseline characteristics (ITT population)

	Cipaglucosidase alfa/miglustat (N = 85)	Alglucosidase alfa/placebo (N = 38)	Total (N = 123)
Age at informed consent date (years)			
n	85	38	123
Mean (SD)	47.6 (13.2)	45.1 (13.3)	46.8 (13.3)
Gender, n (%)			
Male	36 (42.4)	20 (52.6)	56 (45.5)
Female	49 (57.6)	18 (47.4)	67 (54.5)
Race group[a]			
Asian	3 (3.5)	1 (2.6)	4 (3.3)
Japanese	2 (2.4)	4 (10.5)	6 (4.9)
American Indian or Alaska Native	0	1 (2.6)	1 (0.8)
Black or African American	0	1 (2.6)	1 (0.8)
Native Hawaiian or other Pacific Islander	1 (1.2)	0	1 (0.8)
Caucasian	74 (87.1)	30 (78.9)	104 (84.6)
Other	5 (5.9)	1 (2.6)	6 (4.9)
ERT status, n (%)			
ERT-naïve	20 (23.5)	8 (21.1)	28 (22.8)
ERT-experienced	65 (76.5)	30 (78.9)	95 (77.2)
ERT duration (years)			
n	65	30	95
Mean (SD)	7.5 (3.4)	7.1 (3.6)	7.4 (3.5)
Age at diagnosis (years)			

n	85	38	123
Mean (SD)	39.9 (13.8)	36.9 (15.3)	38.9 (14.3)
Age at first ERT dose (years)			
n	65	30	95
Mean (SD)	40.8 (12.7)	38.7 (15.1)	40.2 (13.5)

Most subjects (95 (77.2%)) were ERT experienced, with a mean (SD) ERT treatment duration of 7.4 (3.5) years. Subjects received prior ERT for an average of 7.5 years in the cipaglucosidase alfa/miglustat group and 7.1 years in the alglucosidase alfa/placebo group.

Baseline 6MWD mean (SD) was 357.9 (111.8) meters and 350.1 (119.8) meters, respectively, for subjects in the cipaglucosidase alfa/miglustat group and alglucosidase alfa/placebo group.

Baseline values for sitting % predicted FVC were 70.7 (19.6) in the cipaglucosidase alfa/miglustat group and 70.0 (21.3) in the alglucosidase alfa/placebo group.

ERT-experienced subjects

Demographics and baseline characteristics for subjects with previous ERT experience were similar to those described for the overall ITT population, with lower mean 6MWD results at baseline 346.9 meters for the cipaglucosidase alfa/miglustat group and 334.6 meters for the alglucosidase alfa/placebo group). Mean baseline results for % predicted FVC are comparable between the treatment groups (67.7).

ERT-naïve subjects

For the 28 ERT-naïve subjects in this study, mean baseline results for 6MWD (397.8 meters) and % predicted FVC (80.0%) were higher in ERT-naïve subjects compared with ERT-experienced subjects.

At baseline, mean 6MWD results were approximately 15 meters lower in the cipaglucosidase alfa/miglustat group (393.6 m) compared with the alglucosidase alfa/placebo group (408.3 m). There were more females in the cipaglucosidase alfa/miglustat group (57.6%) versus the alglucosidase alfa/placebo group (47.4%)

- **Numbers analysed**

The analysis populations in this study are summarised in Table 2. All randomised subjects were included in both the efficacy (ITT) and safety populations, with the exception of 2 subjects in the alglucosidase alfa/placebo group who were excluded from the ITT and safety populations because they did not receive study treatment.

Table 2 Analysis populations

	Cipaglucosidase alfa/miglustat	**Alglucosidase alfa/placebo**	**Total**
All Randomised Population	85	40	125
ITT Population, n (%)a	85 (100.0)	38 (95.0)	123 (98.4)
ITT-OBS, n (%)a	85 (100.0)	38 (95.0)	123 (98.4)
ITT-LOCF, n (%)a	85 (100.0)	38 (95.0)	123 (98.4)

Safety Population, n (%)b	85 (100.0)	38 (100.0)	123 (100.0)
PP Population 1, n (%)b	77 (90.6)	37 (97.4)	114 (92.7)
PP Population 2, n (%)b	74 (87.1)	33 (86.8)	107 (87.0)
Completers, n (%)b	73 (85.9)	33 (86.8)	106 (86.2)
PK Population, n (%)b	85 (100.0)	38 (100.0)	123 (100.0)

Abbreviations: 6MWD= 6-minute walk distance; FVC = forced vital capacity; ITT = Intent-to-Treat; ITT-LOCF = Intent-to-Treat-Last Observation Carried Forward; ITT-OBS = Intent-to-Treat–Observed; mITT = Modified Intent-to-Treat; OBS = observed; PK = pharmacokinetic; PP = Per-protocol; PP Population 1 = the population used for the per-protocol (sensitivity) analysis of 6MWD; PP Population 2 = the population used for the per-protocol (sensitivity) analysis of % predicted FVC
Note: See Section 9.7.2 for the description of each analysis population.
a Percentages were based on the number of subjects in each treatment group for the All Randomised Population.
b Percentages were based on the number of subjects in each treatment group for the ITT Population, which consisted of all randomised subjects who received at least 1 dose of study drug.

- **Outcomes and estimation**

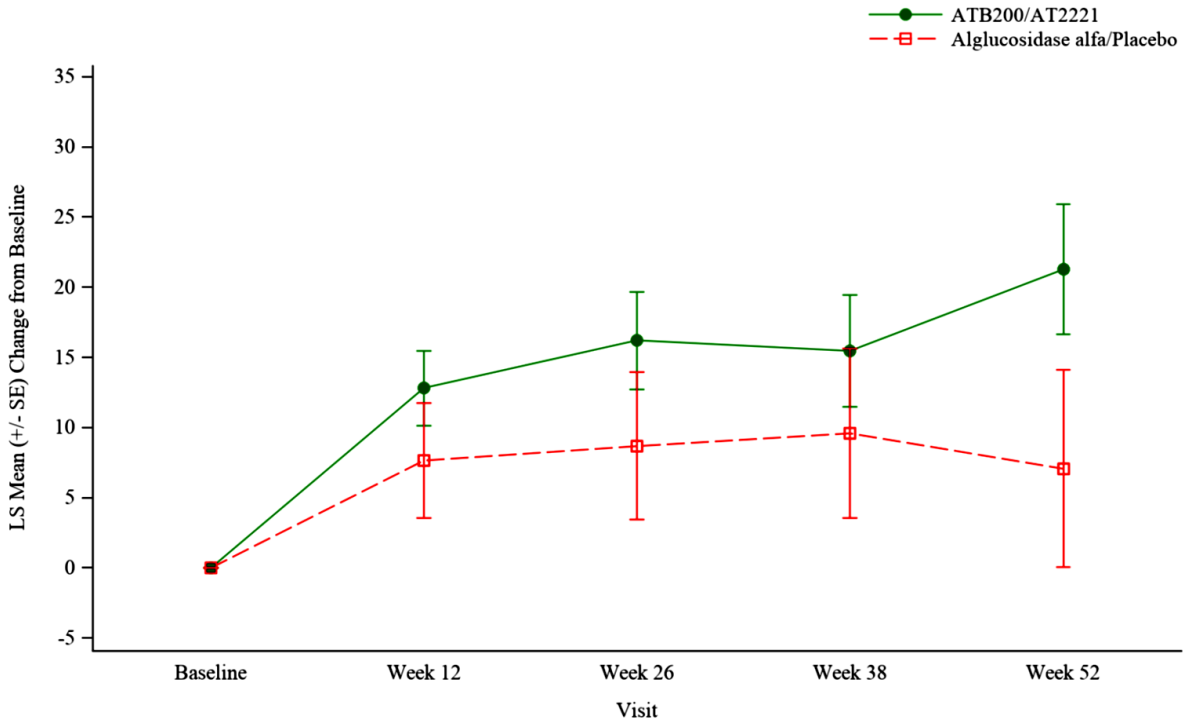
For all analyses, one outlying subject was excluded. Examination of the clinical data revealed that one subject, an ERT-naïve subject in the control arm, had previously been using an anabolic steroid and had deliberately underperformed its screening assessments to gain entry into the study. The study screening Visits showed a 6MWD average of 320 meters and a percent predicted FVC of 83.5%, decreases of 265 meters and 10% from his preceding walk and pulmonary function testing 4 months earlier. At week 52 the subject walked 675 meters, an increase of 355 meters.

Primary endpoint: Change in 6MWD from baseline to week 52 – study ATB200-03

In study ATB200-03, the primary endpoint was analysed with the originally MMRM model based on the ITT-OBS population with remapped visits, excluding the outlying subject. Baseline 6MWD mean (SD) was slightly higher for subjects in the cipaglucosidase alfa/miglustat than for subjects in the alglucosidase alfa group 357.9 (111.8) meters and 350.1 (119.8) meters, respectively. The mean (95%CI) change in 6MWD (meters) from baseline to week 52 showed an estimated mean improvement of 21.3 (12.1, 30.5) meters for the cipaglucosidase alfa/miglustat group compared to 7.1 (-6.9, 21.1) meters for the alglucosidase alfa/placebo group (Figure 3). The estimated mean treatment difference (95%CI) excluding the outlying subject is 14.2 (-2.6, 31.0) meters with two-sided p-value of 0.097, which has to be put in the context of the difference observed at baseline.

This means that the study failed to show the superiority of cipaglucosidase alfa/miglustat based on the 6MWT. From a formal statistical point of view, no further confirmatory conclusions are possible.

Figure 3 Line chart for LS mean (SE) of change in 6MWD (meters) from baseline to week 52 (ITT-OBS Population) – study ATB200-03



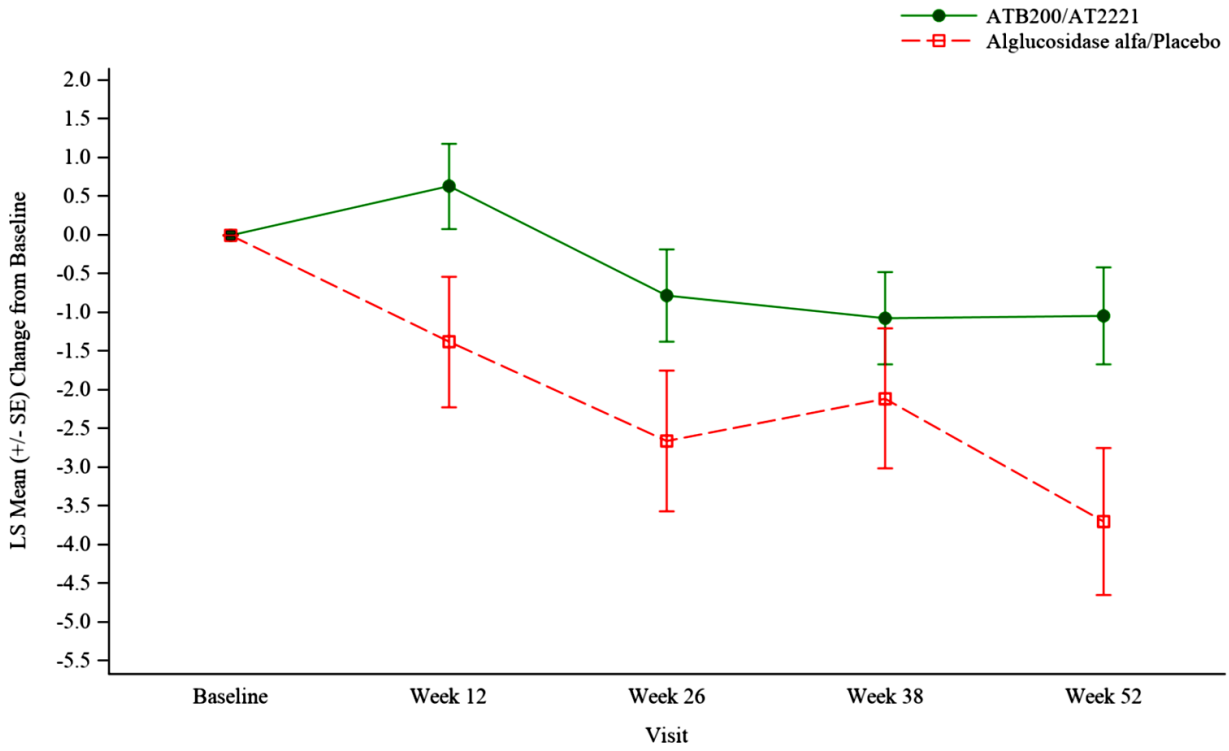
Abbreviations: 6MWD = 6-minute walk distance; AT2221 = miglustat; ATB200 = cipaglucosidase alfa; ITT-OBS = Intent-to-Treat Population that includes all available, observed data without any missing data imputation at Week 52; LS = least squares; MMRM = mixed-effect model repeated measures; SE = standard error; Note: LS mean and SE were obtained from the MMRM.

Using the MMRM model as requested by the CHMP, based on the actual time point of assessments (ITT-OBS Population) and excluding the outlying subject, the estimated mean change in the cipaglucosidase alfa/miglustat group was 20.0 (95% CI 13.1, 26.9) and in the alglucosidase alfa/placebo group 8.3 (95% CI -2.2, 18.8). The estimated mean treatment difference (using this method) is 11.7 (95% CI -1.0, 24.4) with a two-sided p-value of 0.07, indicating that statistical superiority was not demonstrated.

Key secondary endpoints

The first key secondary endpoint was the change in sitting % predicted FVC from baseline to week 52, analysed using the originally MMRM analysis with remapped visits; subjects treated with cipaglucosidase alfa/miglustat showed a -1.0% estimated decline compared with a -4.0% estimated decline in subjects treated with alglucosidase after 52 weeks. The estimated mean difference (95% CI) between the treatments after 52 weeks was 3.0% (0.6%, 5.5%). Figure 4 displays a line plot of the summary statistics by visit.

Figure 4 Line chart for LS mean (SE) of change in sitting % predicted FVC over time (ITT-LOCF population), study ATB200-03



Abbreviations: AT2221 = miglustat; ATB200 = cipaglucosidase alfa; ANCOVA = analysis of covariance; ERT = enzyme replacement therapy; FVC = forced vital capacity; ITT = Intent-to-Treat; LOCF = last observation carried forward; LS = least squares; SE = standard error
Note: LS mean and SE were obtained from the ANCOVA model.

Using the MMRM model as requested by the CHMP, including the actual time point of assessments (ITT-OBS Population) and excluding the outlying subject, the estimated mean change in the cipaglucosidase alfa/miglustat group was -1.4 (95% CI -2.5, -0.3) and in the alglucosidase alfa/placebo group -3.7 (95% CI -5.4, -2.0). The estimated mean treatment difference (using this method) is 2.3 (95% CI 0.2, 4.4).

Table3 summarises results for 5 secondary endpoints for the overall ITT-OBS population based on the MMRM model as requested by CHMP using the actual time point of assessments excluding the outlying subject.

Table 3 Summary of results on 5 secondary endpoints based on MMRM model, actual time point of assessments, (ITT-OBS population excluding outlying subject)– study ATB200-03

Level Endpoint	Cipaglucosidase Alfa/Miglustat LS Mean (95% CI)	Alglucosidase Alfa/Placebo LS Mean (95% CI)	LS Mean Treatment Difference[a]	95% CI of Difference[b]
CHG to Week 52 in sitting % predicted FVC	-1.4 (-2.5, -0.3)	-3.7 (-5.4, -2.0)	2.3	(0.2, 4.4)

Level Endpoint	Cipaglucosidase Alfa/Miglustat LS Mean (95% CI)	Alglucosidase Alfa/Placebo LS Mean (95% CI)	LS Mean Treatment Difference[a]	95% CI of Difference[b]
CHG to Week 52 in MMT lower extremity score	1.7 (1.1, 2.4)	0.7 (-0.4, 1.7)	1.1	(-0.1, 2.3)
CHG to Week 52 in PROMIS-Physical Function total score[c]	2.2 (0.5, 3.9)	-0.3 (-2.9, 2.3)	2.5	(-0.6, 5.7)
CHG to Week 52 in PROMIS-Fatigue total score[c]	-2.0 (-3.2, -0.9)	-1.7 (-3.4, 0.0)	-0.3	(-2.4, 1.8)
CHG to Week 52 in GSGC total score	-0.7 (-1.2, -0.2)	0.8 (0.0, 1.5)	-1.5	(-2.4, -0.6)

CHG = change from baseline; CI = confidence interval; FVC = forced vital capacity; GSGC = Gait, Stairs, Gowers' maneuver, and Chair test; ITT-OBS = Intent-to-Treat Population that includes all available, observed data without any missing data imputation at Week 52; LS = least squares; MMT = manual muscle testing; PROMIS = Patient-reported Outcomes Measurement Information System;
Cipaglucosidase alfa/miglustat – alglucosidase alfa/placebo.
[b] The total score was calculated by summing scores (1 to 5) across all items.

- **Ancillary analyses**

Sensitivity analyses were performed on changes in 6MWD from baseline to week 52 (primary endpoint) and sitting predicted %FVC from baseline to week 52 (key secondary endpoint). Further analyses were requested by the CHMP in- and excluding the outlying subject. The primary efficacy analysis was also performed by ERT status (see Table4 and Table5).

Sensitivity analyses for primary endpoint: change in 6MWD from baseline to week 52

Including outlying subject:

In the MMRM analysis (including the outlying subject) based on the ITT-OBS population using actual time point of assessments, at week 52, the cipaglucosidase alfa/miglustat group had an LS mean improvement in 6MWD of 20.2 m from baseline compared to an LS mean improvement of 17.7 m for the alglucosidase alfa/placebo group. The LS mean treatment difference (95% CI) was 2.6 m (-12.1, 17.2).

Excluding outlying subject:

During the procedure and as requested by the CHMP, sensitivity analyses with the actual time point of assessments were performed with a modified MMRM model for the ITT-OBS population: including country as a random effect; using the 'Control group imputation' and using the pattern mixture multiple imputations, the estimated mean treatment difference for the change in 6MWD from baseline to week 52 varied from +10.8 to +12.3 meters with the lower margin of the 95% CI varying from -1.4 to -0.7 meters. The results of the sensitivity analyses for the primary endpoint showed comparable efficacy results with the primary analysis. The modified MMRM model based on actual time points (excluding the outlying subject) was also used in the analysis based on the PP1 population. The estimated mean treatment difference (95% CI) for the change in 6MWD from baseline to week 52 was 11.4 (-1.1, 24.0).

Sensitivity analyses for the key secondary endpoint: change in sitting predicted %FVC from baseline to week 52

Excluding outlying subject:

Based on the requested MMRM model with actual time points on the ITT-OBS population, sensitivity analyses were performed, including country as a random effect, the 'Control group imputation' and the pattern mixture multiple imputations the estimated mean treatment difference varied from +1.8 to +2.3 % with the lower margin of the 95% CI varying from 0.0 to +0.2%. These sensitivity analyses on the key secondary endpoint also showed comparable efficacy results with the primary analysis. The modified MMRM model (excluding the outlying subject) based on actual time points was also used in the analysis based on the PP1 population. The estimated mean treatment difference (95% CI) was 2.0 (-0.1, 4.1).

ERT-experienced population (n=95)

The mean (SD) 6MWD at baseline was 346.9 meters (110.2) for the cipaglucosidase alfa/miglustat group and 334.6 meters (114.0) for the alglucosidase alfa/placebo group. At week 52, using observed values, the mean 6MWD was 359.8 meters for the cipaglucosidase alfa/miglustat group, with an estimated improvement of 15.9 meters (95%CI 8.3, 23.4) from baseline compared to the estimated mean of 335.7 meters with an estimated improvement of 1.0 meters (95%CI -10.2, 12.1) for the alglucosidase alfa/placebo group. The MMRM model based on the ITT-OBS population with the actual time point of assessments resulted in an estimated mean treatment difference (95%CI) of 14.9 meters (1.2, 28.6) meters.

The mean (SD) % predicted FVC at baseline was 67.9% (19.1) for the cipaglucosidase alfa/miglustat group and 67.5% (21.0) for the alglucosidase alfa/placebo group. At week 52, using observed values and the MMRM model with the actual time point of assessments, the estimated mean (SD) % predicted FVC was 67.4% (20.0) for the cipaglucosidase alfa/miglustat group, with an improvement of -0.2% (95% CI -1.5, 1.1) from baseline compared to the estimated mean % predicted FVC of 60.6% (19.6) and a mean change of -3.8% (95% CI -5.7, -1.9) for the alglucosidase alfa/placebo group. The MMRM model based on the ITT-OBS population with the actual time point of assessments resulted in an estimated mean treatment difference (95% CI) of 3.6% (1.3, 5.9).

Table 4 Summary of remaining endpoints for the ERT-experienced population with actual time point of assessments

Category	Endpoint	Endpoint hierarchy	Overall subjects		Treatment difference
			Cipaglucosidase alfa/miglustat	Alglucosidase alfa/placebo	
			Change week 52 LS Mean (95% CI)	Change week 52 LS Mean (95% CI)	LS Mean (95% CI)
Motor function	GSGC	Key secondary	-0.7 (-1.3, -0.1)	0.5 (-0.4, 1.4)	-1.2 (-2.2, -0.1)
	% Predicted 6MWD	Secondary	3.1 (2.0, 4.3)	0.4 (-1.3, 2.1)	2.7 (0.6, 4.8)
	10m walk (time in sec)	Secondary	-0.8 (-2.1, 0.6)	2.3 (0.3, 4.3)	-3.0 (-5.5, -0.6)
	4 stair climb (in sec)	Secondary	-9.1 (-11.1, -7.0)	-5.7 (-8.8, -2.6)	-3.4 (-7.2, 0.5)
	Gowers (time in sec)	Secondary	-0.1 (-1.7, 1.4)	-2.2 (-4.8, 0.3)	2.1 (-0.9, 5.1)
	Chair test (time in sec)	Secondary	-5.8 (-7.1, -4.6)	-4.8 (-6.8, -2.9)	-1.0 (-3.4, 1.4)
	TUG (time in sec)	Secondary	-0.3 (-2.0, 1.4)	0.1 (-2.5, 2.7)	-0.4 (-3.5, 2.8)
Pulmonary function	FVC (Supine, % predicted)	Secondary	0.2 (-1.2, 1.6)	-2.8 (-4.9, -0.7)	3.0 (0.5, 5.5)
	SVC (Sitting, % predicted)	Secondary	-2.3 (-4.4, -0.2)	-6.0 (-9.2, -2.8)	3.7 (-0.1, 7.5)
	MIP (% predicted)	Secondary	1.8 (-2.1, 5.8)	-1.3 (-6.9, 4.4)	3.1 (-3.8, 10.1)
	MEP (% predicted)	Secondary	-1.4 (-4.9, 2.1)	-3.4 (-8.5, 1.7)	2.1 (-4.2, 8.3)
Muscle strength	Lower MMT	Key secondary	1.8 (1.0, 2.6)	0.9 (-0.3, 2.1)	0.9 (-0.6, 2.3)
	Upper MMT	Secondary	1.9 (1.2, 2.6)	0.4 (-0.7, 1.4)	1.5 (0.3, 2.8)
	Overall MMT	Secondary	3.6 (2.3, 4.9)	1.0 (-0.9, 2.9)	2.6 (0.3, 4.9)
	QMT total	Secondary	7.0 (-3.8, 17.7)	1.9 (-13.8, 17.7)	5.0 (-14.4, 24.4)
QOL	PROMIS-Physical	Key secondary	2.0 (-0.0, 4.0)	-1.6 (-4.5, 1.4)	3.5 (-0.1, 7.1)
	PROMIS-Fatigue	Key secondary	-1.9 (-3.2, -0.6)	-0.7 (-2.6, 1.2)	-1.2 (-3.5, 1.1)
Biomarker	CK	Secondary	-115.0 (-153.9, -76.1)	56.1 (-1.3, 113.6)	-171.1 (-241.3, -100.9)
	HEX4	Secondary	-2.0 (-2.6, -1.4)	2.3 (1.4, 3.1)	-4.3 (-5.3, -3.2)

Abbreviations: 6MWD = 6-minute walk distance; ; CI = confidence interval; CK = creatine kinase; ERT = enzyme replacement therapy; FVC = forced vital capacity; GSGC = Gait, Stairs, Gowers' maneuver, and Chair; Hex4 = hexose tetrasaccharide; LS = least squares carried forward; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; MMT = manual muscle testing; PROMIS = Patient-reported Outcomes Measurement Information System; QMT = Quantitative Muscle Testing; QoL = quality of life; SVC = slow vital capacity; TUG = Timed Up and Go .

Note: Green shading indicates treatment group favoured.

ERT-naïve population (n=27)

The mean (SD) 6MWD at baseline was 394 meters (112) for the cipaglucosidase alfa/miglustat group and 421 meters (136) for the alglucosidase alfa/placebo group. At week 52 using observed values excluding the outlying subject, the mean 6MWD was 427 meters for the cipaglucosidase alfa/miglustat group, with an estimated improvement of 28.5 meters (95%CI 12.4, 44.7) from baseline compared to the mean 6MWD of 459 meters and an estimated improvement of 52.7 meters (95%CI 23.2, 82.3) for the alglucosidase alfa/placebo group. The MMRM analysis based on the ITT-OBS population with the actual time point of assessments without the outlying subject, showed an estimated mean treatment difference (95% CI) of -24.2 (-60.0, 11.7).

The mean (SD) sitting % predicted FVC at baseline was 80.2% (18.7) for the cipaglucosidase alfa/miglustat group and 79.1% (22.6) for the alglucosidase alfa/placebo group. At Week 52 using observed values excluding the outlying subject, the mean (SD) sitting % predicted FVC was 76.8% (19.5) for the cipaglucosidase alfa/miglustat group, with an estimated mean change (95% CI) of -5.2% (-7.5, -2.9) from baseline compared to the mean (SD) % predicted FVC of 72.7% (23.4) and estimated mean change (95%CI) of -2.4 (-6.7, 1.8) for the alglucosidase alfa/placebo group. MMRM analysis based on the ITT-OBS population with actual time points excluding the outlying subject resulted in an estimated mean difference (95% CI) of -2.8% (-7.8, 2.3).

Table 5 Summary of remaining endpoints for the ERT-naïve population excluding the outlying based on MMRM model with actual time point of assessments

Category	Endpoint	Endpoint hierarchy	Overall subjects		Treatment difference
			Cipaglucosidase alfa/miglustat	Alglucosidase alfa/placebo	
			Change week 52 LS Mean (95% CI)	Change week 52 LS Mean (95% CI)	LS Mean (95% CI)
Motor function	GSGC	Key secondary	-0.6 (-1.6, 0.4)	1.3 (-0.4, 3.1)	-1.9 (-4.1, 0.2)
	% Predicted 6MWD	Secondary	5.9 (3.3, 8.5)	9.6 (4.9, 14.4)	-3.7 (-9.5, 2.1)
	10m walk (time in sec)	Secondary	-6.8 (-30.9, 17.3)	1.48 (-40.0, 43.0)	-8.3 (-58.3, 41.8)
	4 stair climb (in sec)	Secondary	-0.1 (-0.5, 0.2)	-0.7 (-1.3, -0.1)	0.5 (-0.2, 1.3)
	Gowers (time in sec)	Secondary	-0.1 (-1.9, 1.7)	-1.3 (-4.3, 1.7)	1.2 (-2.5, 4.9)
	Chair test (time in sec)	Secondary	-0.2 (-0.6, 0.3)	-1.2 (-1.9, -0.4)	1.0 (0.1, 1.9)
	TUG (time in sec)	Secondary	-0.4 (-1.3, 0.6)	-1.0 (-2.6, 0.5)	0.7 (-1.3, 2.6)
Pulmonary function	FVC (Supine, % predicted)	Secondary	-2.3 (-5.2, 0.5)	-4.3 (-9.8, 1.1)	2.0 (-4.4, 8.4)
	SVC (Sitting, % predicted)	Secondary	-3.2 (-6.7, 0.3)	-1.9 (-8.3, 4.5)	-1.3 (-9.0, 6.5)
	MIP (% predicted)	Secondary	5.2 (-2.6, 13.0)	-2.5 (-17.0, 12.0)	7.7 (-9.8, 25.2)
	MEP (% predicted)	Secondary	12.9 (4.7, 21.0)	5.5 (-10.1, 21.1)	7.4 (-11.8, 26.6)
Muscle strength	Lower MMT	Key secondary	1.4 (0.4, 2.5)	-0.0 (-1.9, 1.9)	1.5 (-0.8, 3.7)
	Upper MMT	Secondary	0.7 (-0.2, 1.5)	1.9 (0.3, 3.4)	-1.2 (-3.1, 0.7)
	Overall MMT	Secondary	2.1 (0.5, 3.7)	1.9 (-0.9, 4.8)	0.2 (-3.3, 3.6)
	QMT total	Secondary	17.8 (-4.2, 39.9)	32.7 (-6.7, 72.0)	-14.8 (-62.8, 33.2)
QOL	PROMIS-Physical	Key secondary	2.6 (-1.0, 6.3)	5.8 (-0.9, 12.4)	-3.1 (-11.2, 4.9)
	PROMIS-Fatigue	Key secondary	-3.0 (-5.7, -0.2)	-4.9 (-9.9, 0.0)	2.0 (-4.1, 8.0)
Biomarker	CK	Secondary	-210.7 (-270.6, -150.9)	-19.4 (-124.5, 85.7)	-191.3 (-317.7, -65.0)
	HEX4	Secondary	-2.8 (-3.4, -2.3)	-1.4 (-2.3, -0.4)	-1.5 (-2.6, -0.3)

Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; CK = creatine kinase; ERT = enzyme replacement therapy; FVC = forced vital capacity; GSGC = Gait, Stairs, Gowers' maneuver, and Chair; Hex4 = hexose tetrasaccharide; LS = least squares carried forward; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; MMT = manual muscle testing; PROMIS = Patient-reported Outcomes Measurement Information System; QMT = Quantitative Muscle Testing; QoL = quality of life; SVC = slow vital capacity; TUG = Timed Up and Go.
Note: Green shading indicates treatment group favoured.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6 Summary of efficacy for trial ATB200-03

Title: A Phase 3 double-blind randomised study to assess the efficacy and safety of intravenous cipaglucosidase alfa co-administered with oral miglustat in adult patients with late-onset Pompe disease compared with alglucosidase alfa/placebo		
Study identifier	ATB200-03	
Design	This was a double-blind, randomised, multicentre, international study of cipaglucosidase alfa/miglustat in adult subjects with late-onset Pompe disease who had received ERT with alglucosidase alfa (i.e. ERT-experienced) or who had never received ERT (i.e. ERT-naïve) compared with alglucosidase alfa/placebo.	
	Duration of main phase:	52 weeks
	Duration of Run-in phase:	Not applicable, there was a 30 day screening period
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	
Treatments groups	cipaglucosidase alfa / miglustat	Cipaglucosidase alfa 20 mg/kg. every 2 weeks as a 4-hour intravenous infusion. Miglustat was 195 mg (3 × 65mg oral capsules) for subjects weighing ≥ 40 to < 50 kg and 260 mg (4 × 65mg oral capsules) for subjects weighing ≥ 50 kg. Miglustat was given orally 1 hour prior to each cipaglucosidase alfa infusion. Study follow up was 52 weeks N = 85
	alglucosidase alfa/placebo	Alglucosidase alfa 20 mg/kg every 2 weeks as a 4-hour intravenous infusion. Placebo (3 oral capsules for subjects ≥ 40 to < 50 kg and 4 oral capsules for subjects ≥ 50 kg) was given orally 1 hour prior to each alglucosidase alfa infusion. Study follow up was 52 weeks N = 37

Endpoints and definitions (secondary endpoints hierarchically tested)	Primary endpoint	Change in 6MWT	Change in 6-minute walk test distance walked from baseline to week 52 in meter
	Key secondary endpoint	Change in Sitting %FVC	Change in FVC% predicted in the sitting position from baseline to week 52.
	Key Secondary endpoint	Change in MMT lower extremity	Change in the manual muscle test (MMT) lower extremity score from baseline to week 52
	Key Secondary endpoint	Change in PROMIS physical function	Change in the Patient-reported Outcomes Measurement Information System (PROMIS)-Physical Function total score from baseline to week 52
	Key Secondary endpoint	Change in PROMIS fatigue	Change in the PROMIS-Fatigue total score from baseline to week 52
	Key Secondary endpoint	Change in GSGC	Change in the PROMIS-Fatigue total score from baseline to week 52
Database lock	20JAN2021		

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description for primary efficacy endpoint	The primary efficacy endpoint (change in 6MWD from baseline to Week 52) was analysed using an MMRM model (including treatment, time, treatment-by-time interaction, ERT status, gender, random subject intercept and the covariates baseline 6MWD, baseline age, baseline weight, and baseline height) to compare treatment and control based on the ITT-OBS Population with remapped visits and excluding the outlying subject.		
Analysis population and time point description for key secondary and secondary efficacy endpoints	The key secondary and secondary efficacy endpoints (change from baseline to Week 52) was analysed using an MMRM model (including treatment, time, treatment-by-time interaction, ERT status, gender and the covariates baseline response, baseline age, baseline weight, and baseline height) to compare between treatment and control on the ITT-OBS Population with remapped visits and excluding the outlying subject.		
Descriptive statistics and estimate variability	Treatment group	cipaglucosidase alfa / miglustat	alglucosidase alfa / placebo
	Number of subjects*	81	36

	Change in 6MWT (m) (Mean (95%CI))	21.3 (12.1, 30.5)	7.10 (-6.9, 21.1)
	Change in sitting %FVC Mean (95%CI)	-1.0 (-2.3, 0.3)	-4.0 (-6.0, -2.0)
	Change in MMT lower extremity (Mean (95%CI))	1.6 (0.8, 2.4)	0.9 (-0.4, 2.1)
	Change in PROMIS physical function (Mean (95%CI))	2.1 (0.3, 3.9)	0.1 (-2.7, 2.9)
	Change in PROMIS fatigue (Mean (95%CI))	-2.1 (-3.3, -0.9)	-1.8 (-3.5, 0.04)
	Change in GSGC (Mean (95%CI))	-0.6 (-1.2, 0.04)	0.9 (-0.1, 1.8)
Effect estimate per comparison	6MWT, Primary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	14.2
		95%CI	-2.6, 31.0
		P-value	0.097
	sitting % predicted FVC, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	3.0%
		95%CI	0.6, 5.5%
		P-value	Not applicable
	MMT lower extremity, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	0.7
		95%CI	-0.7, 2.2
		P-value	Not applicable
	PROMIS physical function, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	2.0
		95%CI	-1.4, 5.3

		P-value	Not applicable
	PROMIS fatigue, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	-0.4
		95%CI	-2.5, 1.8
		P-value	Not applicable
	GSGC, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	-1.4
		95%CI	-2.6, -0.3
		P-value	Not applicable

Analysis description	**Other, additional efficacy analyses, not pre-specified**		
Analysis population and time point description for primary efficacy endpoint	The primary efficacy endpoint (change in 6MWD from baseline to Week 52) was analysed using an MMRM model (including treatment, time, treatment-by-time interaction, ERT status, gender, random subject intercept and the covariates baseline 6MWD, baseline age, baseline weight, and baseline height) to compare treatment and control based on the ITT-OBS Population using actual time point of assessments and excluding the outlying subject.		
Analysis population and time point description for key secondary and secondary efficacy endpoints	The key secondary and secondary efficacy endpoints (change from baseline to Week 52) were analysed using the same MMRM as used for the primary endpoint analysis to compare treatment and control on the ITT-OBS Population using actual time point of assessments visits and excluding the outlying subject.		
Descriptive statistics and estimate variability	Treatment group	cipaglucosidase alfa / miglustat	alglucosidase alfa / placebo
	Number of subjects*	85	37
	Change in 6MWT (m) (Mean (95%CI))	20.0 (13.1, 26.9)	8.3 (-2.2, 18.8)
	Change in sitting %FVC Mean (95%CI)	-1.4 (-2.5, -0.3)	-3.7 (-5.4, -2.0)
	Change in MMT lower extremity (Mean (95%CI))	1.7 (1.1, 2.4)	0.7 (-0.4, 1.7)

	Change in PROMIS physical function (Mean (95%CI))	2.2 (0.5, 3.9)	-0.3 (-2.9, 2.3)
	Change in PROMIS fatigue (Mean (95%CI))	-2.0 (-3.2, -0.9)	-1.7 (-3.4, 0.0)
	Change in GSGC (Mean (95%CI))	-0.7 (-1.2, -0.2)	0.8 (0.0, 1.5)

Effect estimate per comparison	6MWT, Primary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	11.7
		95%CI	-1.0, 24.4
		P-value	0.07
	sitting % predicted FVC, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	2.3%
		95%CI	0.2, 4.4%
		P-value	NA
	MMT lower extremity, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	1.1
		95%CI	-0.1, 2.3
		P-value	Not applicable
	PROMIS physical function, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	2.5
		95%CI	-0.6, 5.7
		P-value	Not applicable
	PROMIS fatigue, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	-0.3
		95%CI	-2.4, 1.8
		P-value	Not applicable

	GSGC, key secondary endpoint	Comparison groups	cipaglucosidase alfa / miglustat alglucosidase alfa / placebo
		treatment difference	-1.5
		95%CI	-2.4, -0.6
		P-value	Not applicable
Notes	The study failed to demonstrate superiority, therefore all p-values beyond the primary analysis are not presented. Subgroup analyses indicate that for the ERT-experienced population comparable or even better results are reported for cipaglucosidase alfa/miglustat as compared to alglucosidase alfa/placebo treatment. For the small group of treatment naïve LOPD patients, however, results of cipaglucosidase alfa/miglustat compared to alglucosidase alfa/placebo treatment appeared to be worse.		

*The number of subjects used in an analysis depends on the number of subjects with non-missing values for the analysis.

2.6.5.3. Clinical studies in special populations

No studies have been specifically conducted in special populations (elderly, patients with renal/hepatic impairment). Studies in the paediatric population are not available yet. Based on the available efficacy and PK analyses, the claimed indication (adult LOPD), this is considered acceptable by the CHMP.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Data from Studies ATB200-02, ATB200-03, and ATB200-07 (Pool 2) were pooled for analysis of the long-term efficacy of cipaglucosidase alfa/miglustat. A total of 142 (97.9%) subjects were treated with cipaglucosidase alfa/miglustat, and 38 (95.0%) subjects were treated with alglucosidase alfa/placebo in Pool 2 (including the outlying subject). One (0.7%) subject in the cipaglucosidase alfa/miglustat group and 37 (97.4%) subjects in the alglucosidase alfa/placebo group completed the assigned treatment period, and 8 (4.4%) discontinued due to various reasons, with adverse event (4 subjects) and withdrawal of consent by subject (2 subjects) as the most common.

Age at diagnosis was similar across treatment groups, with the median age being 40 years (range: 1 to 66 years). Most ERT-experienced subjects in both the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo groups had ≥ 5 years previous treatment with alglucosidase alfa (73 (67.6%) subjects and 19 (63.3%) subjects, respectively).

Long term results from pool 2 demonstrate continued improvements on motor (6MWD) and respiratory (sitting % predicted FVC) functions.

The mean (SD) improvement in 6MWD for the cipaglucosidase alfa/miglustat group was 18.2 (42.6) meters at ≤ 15 months (n = 142), 27.5 (51.9) meters at > 15 to ≤ 24 months (n = 59), and 25.2 (72.9) meters at > 24 months (n = 17). The improvements in 6MWD were maintained beyond 24 months, with the outlying subject included or excluded.

The mean (SD) change from baseline in FVC for the cipaglucosidase alfa/miglustat group was -0.4 (6.3) at ≤ 15 months (n = 134), -0.7 (8.3) at > 15 to ≤ 24 months (n = 53), and 1.7 (6.4) at > 24 months (n = 16). These improvements in FVC were maintained beyond 24 months, with the outlying subject included or excluded.

No long-term data for the alglucosidase alfa/placebo group are available, as all subjects switched to cipaglucosidase alfa/miglustat in study ATB200-07.

2.6.5.6. Supportive study(ies)

Study ATB200-007 is an ongoing Phase 3 open-label extension study to assess the long-term safety and efficacy of intravenous cipaglucosidase alfa co-administered with oral miglustat in adult subjects with late-onset Pompe disease.

The primary objective is to assess the long-term safety and tolerability of cipaglucosidase alfa/miglustat (ATB200/AT2221) co-administration.

As of 3 August 2021 (data lock point), data from this study included nearly all enrolled patients with at least an additional 6 months of exposure to cipaglucosidase alfa after the end of the ATB200-03 study, and 33 patients (approximately 30% of patients) with an additional 12 months of exposure to cipaglucosidase alfa. Efficacy analyses in the presented interim clinical study report focused on week 26 results (total of approximately 18 months of treatment for patients in the ATB200-03 cipaglucosidase alfa/miglustat group continuing on cipaglucosidase alfa/miglustat in the ATB200-07 study). The safety analysis includes all available data through the data lock point.

A total of 118 study patients (90 ERT-experienced and 28 ERT-naïve patients) received cipaglucosidase alfa/miglustat and were analysed as 2 treatment subgroups: ATB200-03 cipaglucosidase alfa/miglustat group (N = 81) and ATB200-03 alglucosidase alfa/placebo group (N = 37).

Demographic characteristics, including baseline 6MWD and sitting % predicted FVC as well as MMT and GSGC score, were generally similar between both groups. A majority (66.7%) of patients in both treatment groups had >5 years of prior treatment with ERT (68.9% of subjects in the ATB200-03 cipaglucosidase alfa/miglustat group and 62.1% of patients in the ATB200-03 alglucosidase alfa/placebo group). Treatment compliance was high with an overall mean of 99.4% (99.1% of subjects in the ATB200-03 cipaglucosidase alfa/miglustat group and 100% of subjects in the ATB200-03 alglucosidase alfa/placebo group).

In the overall FAS Population (ERT-experienced and ERT-naïve subjects), the main efficacy endpoints of 6MWD and sitting % predicted FVC showed relative stability over time through week 26 in both cipaglucosidase alfa/miglustat group and alglucosidase alfa/placebo group.

The other main efficacy endpoints of MMT lower extremity, PROMIS-Physical Function, PROMIS-Fatigue, and GSGC scores also showed that patients from both the ATB200-03 cipaglucosidase alfa/miglustat group and the ATB200-03 alglucosidase alfa/placebo group remained stable over time through week 26 with minimal between-group differences.

In the ERT-experienced subgroup, patients remained relatively stable over time through week 26 on 6MWD and sitting % predicted FVC. Overall, ERT-experienced patients had a mean (SD) change of -0.2 meters (30.19) from baseline in 6MWD, and a mean (SD) change of 1.1 (6.33) from baseline in sitting % predicted FVC. Results for MMT lower extremity scores in both groups showed relative stability through week 26 with a minimal visit-to-visit variability. In addition, results for the PROMIS-Physical Function scale and PROMIS-Fatigue scores were similar between patients in the 2 groups. Similarly, GSGC showed stability over time through week 26 (overall mean [SD] change of -0.1 [2.52]).

In the ERT-naïve subgroup, patients in the cipaglucosidase alfa/miglustat group remained relatively stable over time through week 26 on 6MWD and sitting % predicted FVC while patients in the alglucosidase alfa/placebo group demonstrated an increase in both values. Overall, ERT-naïve patients had a mean (SD) change of 5.3 meters (26.99) from baseline in 6MWD and a mean (SD) change of -0.4 (4.54) from baseline in sitting % predicted FVC. Patients in the ATB200-03 alglucosidase alfa/placebo group experienced slight improvements in 6MWD and sitting % predicted FVC at week 12 following initiation with cipaglucosidase alfa/miglustat that continued through week 26, with a mean (SD) change from baseline of 21.7 meters (32.65) in 6MWD and 0.6 (1.52) in sitting % predicted FVC at week 26.

Results for MMT lower extremity scores in both ERT experienced and naïve subgroups showed relative stability through week 26 with minimal visit-to-visit variability. Results for the PROMIS-Physical Function scale and PROMIS-Fatigue scores were similar between patients in the 2 groups. Mean (SD) change from baseline for ERT-naïve patients was -0.0 (7.15) for the PROMIS-Physical Function score and -0.3 (6.80) for the PROMIS-Fatigue score at week 26. Results for GSGC scores were similar, with the GSGC scores showing stability over time through week 26 (overall mean [SD] change of 0.1 [2.45]).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal evidence comes from one double-blind, randomised, multicentre, superiority study of cipaglucosidase alfa/miglustat in adult subjects with LOPD who had received ERT with alglucosidase alfa (i.e. ERT-experienced) or who had never received ERT (i.e. ERT-naïve) compared with alglucosidase alfa/placebo.

The inclusion criteria limit the population to LOPD in adults.

The comparator (alglucosidase alfa) is acceptable as this was the only authorised treatment for adult LOPD patients at the time the clinical study was conducted.

The 6MWT and the FVC are currently considered the best possible endpoints for the assessment of the relevance of the treatment. The 6MWT and the FVC are commonly used as primary or key secondary endpoints in other studies in which adult LOPD patients are evaluated. The use of MMT, PROMIS and GSGC endpoint further strengthens the conclusions based on the 2 key endpoints. The remaining endpoints are considered explorative.

Dose selection for the pivotal Phase 3 study ATB200-03 was based on pharmacokinetics, pharmacodynamics/biomarker, efficacy, and safety data from the ongoing study ATB200-02 investigating the co-administration of cipaglucosidase alfa and miglustat only. The regimen used in the alglucosidase alfa group is in line with the dosing advice in the SmPC. However, the present application does not allow for assessment of the clinical efficacy of cipaglucosidase alfa alone, since the pharmacodynamic and clinical effects of cipaglucosidase alfa alone have not been studied.

In total, 66 (54%) subjects had protocol deviations due to the COVID-19 pandemic (47 (55.3%) subjects in the cipaglucosidase alfa/miglustat group and 19 (50%) subjects in the alglucosidase alfa/placebo group). These protocol deviations could have led to possible bias in estimating the treatment effect: remapping delayed visits due to COVID-19.

According to the applicant, the normality assumption for the MMRM analysis (pre-defined in the SAP) is significantly violated (Shapiro-Wilk test <0.0001) and the applicant considered that the results of the non-parametric ANCOVA were more appropriate for interpretation. However, the CHMP did not agree for the following reasons:

- An analysis with an MMRM model including pre-planned visits and based on the ITT-OBS population was pre-defined in the SAP as the primary efficacy analysis.

- Visual inspection of the residuals from both the original and the requested MMRM analyses did not suggest violation of the normality assumption.

- Due to COVID-19, not all planned visits were performed within the time windows (at least 6 weeks below or above the planned time point) and resulted in delayed visits outside the planned visit windows. The applicant remapped the assessment results of the delayed visits to the earlier planned study visits; however, as a consequence, this remapping may have led to an overestimation of the effect. In general, an MMRM analysis using the actual time points of the assessments is expected to result in a more reliable estimate of the treatment difference compared to an MMRM analysis based on pre-planned fixed visit numbers, especially when the assessments were not performed at the pre-planned visits. There are 17 subjects (13 vs. 4) with a delayed visit of at least 28 days (4 weeks) after the target day, 8 of these 17 subjects (8 vs. 0) had a delay of at least 42 days (6 weeks) after the target day and at least there are two delays (2 vs. 0) with a delay of at least 28 days before the target day. Therefore, using an analysis model based on actual time points is expected to lead to a more precise and reliable estimation of the treatment difference and is considered a more reliable analysis model.

- The non-parametric ANCOVA analysis as proposed by the applicant, used the LOCF method for handling missing data (not the conservative method for 6MWD) and was performed based on remapping of visit time points (not the actual time points were used), which both could introduce bias in the estimated efficacy treatment difference.

Therefore, the requested analyses based on the MMRM model (ITT-OBS) using the actual time points of the assessments without imputation of missing values, excluding the outlying subject, is considered the most adequate and reliable method for the evaluation of efficacy.

Although the study design is acceptable from a clinical point of view, it should be noted that the study failed to demonstrate superiority for the primary endpoint. This means no further hierarchical testing should be done. As the conduct of the study is without major flaws and carried out in accordance with the protocol, the results observed in the comparator arm should show its usual level of efficacy, and results of the primary PP and ITT analysis are in concordance, the results might be used for further clinical assessment.

Efficacy data and additional analyses

Overall population

A total of 123 subjects were randomised and dosed (95 ERT-experienced and 28 ERT-naïve). Most subjects (77.2%, N=95) were ERT experienced, with a mean (SD) ERT treatment duration of 7.4 (3.5) years.

Baseline demographics were representative of an adult population of LOPD patients and were generally similar between the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo treatment arms. Baseline 6MWD and FVC, as well as MMT and GSGC scores, were generally similar between the treatment groups and within the ranges expected for adult patients with LOPD.

One subject, an ERT-naïve patient randomised to the alglucosidase alfa/placebo treatment and who underperformed at baseline and showed outlying residuals in the analysis, was considered to be very influential on the estimation of the treatment difference. The observed results during the treatment period are clinically implausible provided the patient met the in- and exclusion criteria. The CHMP considered reasonable to exclude this subject from all efficacy analyses.

After randomisation, 85 patients were included in the cipaglucosidase alfa/miglustat arm and 38 in the alglucosidase alfa/placebo arm. Two subjects in the alglucosidase alfa/placebo group were excluded from the ITT and safety populations because they did not receive study treatment.

Using the originally presented MMRM analysis for the primary endpoint (6MWD) based on remapped visits and excluding the outlying subject as proposed by the applicant, the estimated mean treatment difference (95%CI) excluding the outlying subject was +14.2 m (-2.6, 31.0) with a two-sided p-value of 0.097.

The CHMP requested efficacy analysis on the primary endpoint (change in 6MWD from baseline to week 52) using MMRM method (excluding the outlying subject) based on the ITT-OBS population, and the actual time point of assessments resulted in an estimated mean change of 20.0 m (95% CI 13.1, 26.9) for the cipaglucosidase alfa/miglustat group and an estimated mean change of 8.3m (95% CI -2.2, 18.8) for the alglucosidase alfa/placebo group. The estimated mean treatment difference is 11.7 meters with 95% CI (-1.0, 24.4) and a 2-sided non-significant p-value of 0.07. It should be noted that the effect observed after cipaglucosidase alfa/miglustat treatment should be considered clinically relevant (MCID is about 21 m) in this mainly ERT experienced (78%) population. Sensitivity analyses showed comparable results. In addition, since the exclusion of the outlying subjects was not predefined in the SAP, comparison of the efficacy analyses with and without the outlying subject was conducted. The results of these efficacy analyses showed in both cases no clinically relevant estimated treatment difference (11.7 meters, 95%CI (-1.0, 24.4) against 2.6 meters with 95%CI (-12.1, 17.2)), The results with and without the outlying subject were not considered clinically relevant different in this worst-case scenario. Overall, the results of these analyses showed the clinical relevance and thus efficacy of the co-administration in the adult LOPD population.

According to the planned hierarchical testing strategy, all other (key secondary and secondary) endpoints will be considered explorative.

Using the MMRM model, the actual time point of assessments (ITT-OBS Population) and excluding the outlying subject, patients treated with cipaglucosidase alfa/miglustat showed an estimated change of -1.4 (95% CI -2.5, -0.3) in sitting FVC compared with an estimated change of -3.7 (95% CI -5.4, -2.0) in patients treated with alglucosidase alfa after 52 weeks. The estimated treatment difference was 2.3 (95% CI 0.2, 4.4). Sensitivity analyses showed comparable results. The change in the cipaglucosidase alfa/miglustat arm may indicate a stabilisation of disease as it cannot be considered a clinically relevant decline, whereas the difference in the alglucosidase alfa arm indicated some clinically relevant deterioration after 52 weeks of treatment.

For the remaining key secondary endpoints (MMT, PROMIS-Physical Function, PROMIS-fatigue and GSGC) results reported are more or less in line with the results of the 6MWT and the sitting %FVC and further support the conclusion that the effects obtained with cipaglucosidase alfa/miglustat appeared to be reasonably robust and consistent, of clinical relevance.

The contribution of miglustat itself to the clinical effects of the co- administration of miglustat and cipaglucosidase alfa in human LOPD patients is unknown since cipaglucosidase alfa on its own has not been evaluated in human LOPD patients. Despite a lack of clear pharmacokinetic rationale for the addition of miglustat, the clinical relevance of the co-administration cipaglucosidase alfa/miglustat has been established based on the efficacy data. An approximate 7% to 30% increases in AUC upon the addition of miglustat in rodent models were associated with a 50% increase in grip strength-wire hang in conducted non-clinical studies which further support the additive value of miglustat to the clinical effects of cipaglucosidase alfa in human adult LOPD patients.

ERT experienced population

The primary endpoint (change in 6MWD from baseline to week 52) resulted in an estimated treatment difference of 14.9 m (95% CI 1.2, 28.6). A MCID for treatment experienced LOPD patients cannot be retrieved from literature. However, in this treatment-experienced population, some deterioration is to be expected after more than 7 years of treatment. Therefore, an observed improvement in this population should be considered clinically beneficial.

The key secondary endpoint (change in sitting % predicted FVC from baseline to week 52) resulted in an estimated mean difference of -0.2 (95% CI -1.5, 1.1) in the cipaglucosidase alfa/miglustat group and of -3.8 (95% CI -5.7, -1.9) in the alglucosidase alfa/placebo group. The clinical difference reported for the cipaglucosidase/miglustat indicates a stabilisation of the disease.

The results from the remaining key secondary endpoints (MMT, PROMIS-Physical Function, PROMIS-fatigue and GSGC) were more or less in line with the results of the primary and key secondary endpoints and support the efficacy of the co-administration of cipaglucosidase alfa/miglustat in this population.

ERT naïve population

For the primary endpoint (change in 6MWD from baseline to week 52), there was an estimated mean improvement of 28.5 m (95% CI 12.4, 44.7) in the 20 ERT-naïve subjects who received cipaglucosidase alfa/miglustat. In the alglucosidase alfa/placebo control group (n = 7; excluding the outlying subject), the mean improvement was 52.7 m (95% CI 23.2, 82.3).

The improvement in the cipaglucosidase alfa/miglustat group is in line with the expected treatment benefit when compared to the published literature on ERT treatment in these treatment naïve patients (A. van der Ploeg, 2010).

The key secondary endpoint (change in sitting % predicted FVC from baseline to week 52) resulted in an estimated mean difference of -5.2 (95% CI -7.5, -2.9) in the cipaglucosidase alfa/miglustat group and of –2.4 (95% CI -6.7, 1.8) in the alglucosidase alfa/placebo group. The estimated mean treatment difference (95% CI) was -2.8 (-7.8, 2.3).

While the 6MWD indicated a clinically relevant effect and the sitting % FVC suggested a deterioration, the underlying data did not clearly imply a treatment benefit in ERT-naïve population. Nevertheless, extrapolation of the data from the ERT-experienced (generally more severe and difficult to treat patients) to ERT-naïve population in LOPD is considered justified, primarily since there is no biologically plausible argumentation that the expected benefit would be less in ERT-naïve LOPD population. Further, the number of patients in this sub-group is very limited and a random drift of the results cannot be excluded. In line with this, treatment with cipaglucosidase alfa/miglustat led to greater improvement (i.e., reductions) in Hex4 and CK, biomarkers of glycogen reduction and muscle damage, respectively, versus alglucosidase alfa in both ERT-experienced and ERT-naïve LOPD populations.

The results from the remaining key secondary endpoints (MMT, PROMIS-Physical Function, PROMIS-fatigue and GSGC) were more or less in line with the results of the primary and key secondary endpoints and did not add to the above discussion on the efficacy in ERT naive population.

Regarding long term data, nearly all enrolled subjects with at least an additional 6 months of exposure to cipaglucosidase alfa after the end of the ATB200-03 study, and 33 subjects (approximately 30% of subjects) with no less than an additional 12 months of exposure to cipaglucosidase alfa have been included in the ongoing study ATB200-07. As of 3 August 2021, results for all main efficacy endpoints did not indicate clinically relevant differences in both the ATB200-03 cipaglucosidase alfa/miglustat group continuing on cipaglucosidase alfa/miglustat and the ATB200-03 alglucosidase alfa/placebo group switching to cipaglucosidase alfa/miglustat, with patients in both groups showing relative stability over time through week 26 in 6MWD, sitting % predicted forced vital capacity (FVC), manual muscle test (MMT) lower extremity, Patient-reported Outcomes Measurement Information System (PROMIS)-Physical Function, PROMIS-Fatigue, and Gait, Stairs, Gowers' maneuver, and Chair (GSGC) scores.

Further data will be available once the ongoing studies (ATB200-02, ATB200-07) are completed and the CHMP considered acceptable to submit them as post-authorisation commitment.

Proposed indication

The initially claimed indication was "Pombiliti is indicated in co-administration with miglustat for the long-term treatment of adults aged 18 years and older with a confirmed diagnosis of Pompe disease (acid α-glucosidase [GAA] deficiency)." As per CHMP recommendation during the procedure, the applicant revised the wording to reflect the proposed treatment in adult LOPD population as follows:

"Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)."

2.6.7. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy of the co-administration of cipaglucosidase alfa and miglustat was demonstrated in adult patients with late-onset Pompe disease (acid α-glucosidase deficiency) in the proposed dosing regimen.

2.6.8. Clinical safety

No clinical studies were submitted evaluating the safety of cipaglucosidase alfa alone or miglustat alone. The safety data are derived from the co-administration of cipaglucosidase alfa and miglustat. In case an adverse event is probably due to one of the components these AE will be presented separately.

The clinical development programme in Pompe disease included 4 clinical studies: study AT2221-01, a bioavailability study of miglustat in healthy volunteers, and studies ATB200-02, ATB200-03, and ATB200-07, which are studies of cipaglucosidase alfa/miglustat in adult patients (≥ 18 years) with late-onset Pompe disease (LOPD). Studies ATB200-02 and ATB200-07 are ongoing.

Study AT2221-01 was completed in 2018; study ATB200-03 was completed and had a database lock of 20 January 2021. Study ATB200-02 is ongoing; it had an interim data cut-off of 19 June 2020 and an

addendum data cut-off of 13 November 2020. Study ATB200-07 is ongoing and had a data cut-off date of 02 February 2021. As of these safety data cut-off dates, 151 patients have been exposed to co-administered cipaglucosidase alfa/miglustat at the proposed dose. The total mean (standard deviation [SD]) duration of exposure was 17.2 (12.82) months, and the maximum duration of exposure was 52.2 months.

To enable an overall evaluation of safety, the safety data were pooled based on the safety population, defined as all patients who took at least one dose of study drug. Safety analyses focus on patients treated with the intended regimen of 20 mg/kg cipaglucosidase alfa intravenous infusion co-administered with 195/260 mg miglustat oral capsules once every other week.

Pooled safety data

Safety data from the Phase 1/2 and Phase 3 studies were pooled, where appropriate, to enable an overall evaluation of safety.

- **Safety pool 1** (controlled study ATB200-03): all treated patients in study ATB200-03 (N = 123) including the outlying subject from efficacy analyses

- **Safety pool 2** (All studies ATB200-02/03/07): all cipaglucosidase alfa/miglustat-treated adult patients with LOPD (3 studies; N = 151) at the intended regimen.

In the clinical studies, cipaglucosidase alfa was co-administered with miglustat. In case adverse events were reported, it was subsequentially analysed whether respective adverse events were due to combined cipaglucosidase alfa/miglustat treatment,cipaglucosidase alfa only, or miglustat only. Below, the general exposure and safety data of the co-administration of cipaglucosidase alfa and miglustat treatment are presented first. Adverse drug reactions that were considered related to cipaglucosidase alfa or miglustat only are addressed in separate sections.

2.6.8.1. Patient exposure

In safety pool 1, the overall mean [SD] exposure duration was 11.8 [1.5] months. The mean exposure of patients who were treated with cipaglucosidase alfa/miglustat (11.8 months) and those who were treated with alglucosidase alfa/placebo (12.0 months) was comparable.

Table 7 Study drug exposure overall – Safety pool 1 (controlled study ATB200-03) - safety population

	Cipaglucosidase alfa/miglustat (N = 85)	Alglucosidase alfa/ placebo (N = 38)
Duration of treatment (months)[a]		
n	85	38
Mean (SD)	11.8 (1.8)	12.0 (0.7)
Duration of treatment (Months),[a] n (%)		
≤ 3	1 (1.2)	0
> 3 to ≤ 6	1 (1.2)	0
> 6 to ≤ 9	2 (2.4)	1 (2.6)
> 9 to ≤ 12	19 (22.4)	4 (10.5)
> 12	62 (72.9)	33 (86.8)

Abbreviations: CSR =clinical study report; max=maximum; min = minimum; N = total number of patients; n = number of patients in category indicated; Q1=first quartile; Q3=third quartile; SD=standard deviation
Note: Percentages were based on the number of patients in each treatment group for the Safety Population.
[a] Duration of treatment (months)=(date of last dose - date of first dose + 1) / 30.4.

In safety pool 2, data are presented in Table8.

Table 8 Study drug exposure overall – Safety pool 2 (all studies ATB200-02/03/07) - safety population

	Cipaglucosidase alfa/miglustat N = 151
Duration of treatment (months)[a]	
n	151
Mean (SD)	17.3 (12.8)
Duration of treatment (months), n (%)	
≥ 6	121 (80.1)
≥ 12	108 (71.5)
≥ 18	53 (35.1)
≥ 24	22 (14.6)

Abbreviations: max=maximum; min = minimum; N = total number of patients; n = number of patients in category indicated; Q1=first quartile; Q3=third quartile; SD=standard deviation
Note: For patients who took cipaglucosidase alfa/miglustat in Study ATB200-03 and then continued in Study ATB200-07, duration of treatment is calculated as the sum of durations in each study.
[a] Duration of treatment (months) = (Date of Last Dose - Date of First Dose + 1) / 30.4.

2.6.8.2. Adverse events

In general, the occurrence of adverse events tended to be higher in safety pool 2 at a longer treatment exposure time (mean 17.3 vs. 11.8 months). Since observed patterns in the occurrence of adverse events in both safety pools 1 and 2 were overall comparable, only the occurrence of adverse events in safety pool 1 is presented below.

Table 9 Overall summary of treatment-emergent adverse events – Safety pool 1 - Safety population

	Cipaglucosidase alfa/miglustat (N = 85)			Alglucosidase alfa/placebo (N = 38)		
	Cipaglucosidase alfa n (%)	Miglustat n (%)	Total n (%)	Alglucosidase alfa n (%)	Placebo n (%)	Total n (%)
Patients who had any TEAE	NA	NA	81 (95.3)	NA	NA	37 (97.4)
Patients who had any TEAE leading to study drug discontinuation	NA	NA	2 (2.4)	NA	NA	1 (2.6)
Patients who had any treatment-related TEAE	24 (28.2)	18 (21.2)	26 (30.6)	10 (26.3)	11 (28.9)	14 (36.8)
Patients who had any TESAE	NA	NA	8 (9.4)	NA	NA	1 (2.6)
Patients who had any TESAE leading to study drug discontinuation	NA	NA	1 (1.2)	NA	NA	1 (2.6)
Patients who had any treatment-related TESAE	1 (1.2)	0	1 (1.2)	0	0	0
Patients who had any TEAE leading to death	NA	NA	0	NA	NA	0

Abbreviations: CSR = clinical study report; N = total number of patients; n = number of patients in category indicated; NA = not analysed; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event
Note: A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.
Note: A treatment-related TEAE was defined as TEAE with the corresponding relationship to study drug marked as definite, probable, or possible. For the total column under each treatment, the patient was counted only once under the category according to the worst relationship for any component of the treatment. If relationship was missing, it was classified as related.
Note: Percentages were based on the number of patients in each treatment group for the Safety Population.

Table 10 summarises the most common treatment-emergent adverse events (in ≥ 10% of patients in either treatment group) by preferred term for safety pool 1.

Table 10 Incidence of treatment-emergent adverse events in ≥ 10% of patients by preferred term - Pool 1 (controlled study ATB200-03) - Safety population

Preferred Term - n (%)	Cipaglucosidase alfa/miglustat (N = 85)	Alglucosidase alfa/placebo (N = 38)
Patients with any TEAE	81 (95.3)	37 (97.4)
Fall	25 (29.4)	15 (39.5)
Headache	20 (23.5)	9 (23.7)
Nasopharyngitis	19 (22.4)	3 (7.9)
Myalgia	14 (16.5)	5 (13.2)
Diarrhoea	11 (12.9)	4 (10.5)
Nausea	10 (11.8)	8 (21.1)

Arthralgia	13 (15.3)	5 (13.2)
Back pain	9 (10.6)	7 (18.4)
Urinary tract infection	12 (14.1)	2 (5.3)
Fatigue	8 (9.4)	5 (13.2)
Pain in extremity	11 (12.9)	2 (5.3)
Musculoskeletal pain	10 (11.8)	2 (5.3)
Oropharyngeal pain	10 (11.8)	2 (5.3)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in category indicated; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event. Note: A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug. Note: A patient who experienced the same TEAE multiple times was counted once for the corresponding SOC and PT.

In safety pool 1, the system organ classes of treatment-emergent adverse events were generally similar between the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo groups. The most frequently reported system organ classes (> 30% of patients in either treatment group) were infections and infestations, musculoskeletal and connective tissue disorders, injury, poisoning, and procedural complications, general disorders and administration site conditions, nervous system disorders, gastrointestinal disorders, and respiratory, thoracic, and mediastinal disorders.

Infections and infestations were reported in 49 (57.6%) patients in the cipaglucosidase alfa/miglustat group and 21 (55.3%) patients in the alglucosidase alfa/placebo group. For the most frequently reported preferred terms (> 10% in either treatment group), nasopharyngitis and urinary tract infection occurred more frequently in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group (19 [22.4%] and 3 [7.9%] patients, respectively, and 12 [14.1%] and 2 [5.3%)] patients, respectively), while upper respiratory tract infection occurred less frequently in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group (3 [3.5%] and 6 [15.8%] patients, respectively).

Musculoskeletal and connective tissue disorders were reported in 45 (52.9%) patients in the cipaglucosidase alfa/miglustat group and 18 (47.4%) patients in the alglucosidase alfa/placebo group. For the most frequently reported preferred terms (> 10% in either treatment group), myalgia and arthralgia occurred at similar frequencies in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo groups (14 [16.5%] and 5 [13.2%], respectively, and 13 [15.3%] and 5 [13.2%] patients, respectively). Pain in extremity and musculoskeletal pain occurred more frequently in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group (11 [12.9%] and 2 [5.3%] patients, respectively; and 10 [11.8%] and 2 [5.3%] patients, respectively).

Injury, poisoning and procedural complications were reported in 36 (42.4%) patients in the cipaglucosidase alfa/miglustat group and 18 (47.4%) patients in the alglucosidase alfa/placebo group. Fall was the most frequently reported preferred term (> 10% in either treatment group) and occurred less frequently in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group (25 [29.4%] and 15 [39.5%] patients, respectively).

General disorders and administration site conditions were reported in 31 (36.5%) patients in the cipaglucosidase alfa/miglustat group and 14 (36.8%) patients in the alglucosidase alfa/placebo group. Fatigue was the most frequently reported preferred term (> 10% in either treatment group) and occurred at

comparable frequencies in the cipaglucosidase alfa/miglustat group and the alglucosidase alfa/placebo group (8 [9.4%] and 5 [13.2%] patients, respectively).

Nervous system disorders were reported in 33 (38.8%) patients in the cipaglucosidase alfa/miglustat group and 15 (39.5%) patients in the alglucosidase alfa/placebo group. Headache was the most frequently reported preferred term (> 10% in either treatment group) and occurred at similar frequencies in the cipaglucosidase alfa/miglustat group and the alglucosidase alfa/placebo group (20 [23.5%] and 9 [23.7%] patients, respectively).

Gastrointestinal disorders were reported in 28 (32.9%) patients in the cipaglucosidase alfa/miglustat group and 17 (44.7%) patients in the alglucosidase alfa/placebo group. For the most frequently reported preferred terms (> 10% in either treatment group), diarrhoea occurred at similar frequencies in the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo groups (11 [12.9%]) and 4 [10.5%], respectively), and nausea occurred less frequently in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group (10 [11.8%] and 8 [21.1%] patients, respectively).

Respiratory, thoracic and mediastinal disorders were reported in 29 (34.1%) patients in the cipaglucosidase alfa/miglustat group and 10 (26.3%) patients in the alglucosidase alfa/placebo group. Oropharyngeal pain was the most frequently reported preferred term (> 10% in either treatment group) and occurred more frequently in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group (10 [11.8%] and 2 [5.3%] patients, respectively).

Severe Adverse Events

Eight (9.4%) patients in the cipaglucosidase alfa/miglustat group and 2 (5.3%) patients in the alglucosidase alfa/placebo group had a severe treatment-emergent adverse event (Table 111).

In patients who received cipaglucosidase alfa/miglustat, 13 severe treatment-emergent adverse events were reported, each in a single patient. In patients who received alglucosidase alfa/placebo, 3 severe treatment-emergent adverse events were reported, each in a single patient.

One case of (accidental) overdose was reported in a patient receiving a 260 mg dose of miglustat/placebo and a dose of both cipaglucosidase alfa and alglucosidase alfa due to human error on the part of the healthcare professional. There were no complications resulting from the extra doses.

Table 11 Incidence of severe treatment-emergent adverse events by system organ class and preferred term- Safety pool 1 (controlled study ATB200-03) - Safety population

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N = 85)	Alglucosidase alfa/placebo (N = 38)
Patients with any severe TEAE	8 (9.4)	2 (5.3)
Gastrointestinal disorders	1 (1.2)	0
Abdominal pain	1 (1.2)	0
Enteritis	1 (1.2)	0
Vomiting	1 (1.2)	0
General disorders and administration site conditions	1 (1.2)	0

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N = 85)	Alglucosidase alfa/placebo (N = 38)
Chills	1 (1.2)	0
Immune system disorders	1 (1.2)	0
Anaphylactoid reaction	1 (1.2)	0
Infections and infestations	0	1 (2.6)
Diverticulitis	0	1 (2.6)
Injury, poisoning and procedural complications	2 (2.4)	0
Accidental overdose	1 (1.2)	0
Fall	1 (1.2)	0
Investigations	1 (1.2)	0
Heart rate irregular	1 (1.2)	0
Nervous system disorders	0	1 (2.6)
Cerebrovascular accident	0	1 (2.6)
Renal and urinary disorders	0	1 (2.6)
Glycosuria	0	1 (2.6)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	0
Dyspnoea	1 (1.2)	0
Skin and subcutaneous tissue disorders	1 (1.2)	0
Pruritus	1 (1.2)	0
Urticaria	1 (1.2)	0
Vascular disorders	2 (2.4)	0
Aortic aneurysm	1 (1.2)	0
Flushing	1 (1.2)	0

Abbreviations: CSR = clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in category indicated; PT = preferred term; SOC = system organ class; TEAE=treatment-emergent adverse event
Note: A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.
Note: If a patient experienced more than 1 TEAE with different severity categories within the same SOC/PT, the patient was counted only once under the worst severity. If severity was missing, it was classified as "severe."
Note: SOCs and PTs were coded with MedDRA Version 23.0.
Note: Percentages were based on the number of patients in each treatment group for the Safety Population.

Adverse events of special interest

The following adverse events of special interest were selected based on known safety profile of other already authorised ERTs in Pompe disease and miglustat already authorised in different indications than Pompe disease. Since observed patterns in the occurrence of adverse events in both safety pools 1 and 2 were overall comparable, further details on the occurrence of adverse events is mainly presented for safety pool 1.

Gastrointestinal disorders (relevant to both cipaglucosidase alfa and miglustat)

In safety pool 1 (controlled study ATB200-03), 28 (32.9%) cipaglucosidase alfa/miglustat-treated patients experienced gastrointestinal disorders treatment-emergent adverse events compared to 17 (44.7%) in alglucosidase alfa/placebo-treated patients.

Gastrointestinal disorder treatment-emergent adverse events occurring with a higher frequency in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group (more than 2% difference) included abdominal pain lower (2.4% versus 0.0%, respectively), diarrhoea (12.9% versus 10.5%, respectively), mouth ulceration (2.4% versus 0.0%, respectively), and vomiting (5.9% versus 2.6%, respectively). The proportion of cipaglucosidase alfa/miglustat-treated patients who experienced gastrointestinal disorders treatment-emergent adverse events tended to be lower for ERT-experienced patients compared to ERT-naïve patients (20/65 [30.8%] and 8/20 [40.0%], respectively).

Cardiac events (relevant to both cipaglucosidase alfa and miglustat)

In study ATB200-02, there were no significant changes in the corrected QT interval using Fridericia's formula (QTcF) or other ECG parameters on ECGs collected immediately following the end of cipaglucosidase alfa infusion up to a dosage of 20 mg/kg through up to 24 months of treatment. No patients had QTcF > 450 msec or QTcF increase from baseline > 60 msec, and 2 patients had QTcF increases from baseline between 30 to 40 msec.

In study ATB200-03, no patients have had substantial increases in heart rate, PR, or QRS duration. No patients had QTcF change from baseline > 60 msec. Eleven patients had QTcF change from baseline > 30 to 60 msec (the largest QTcF change from baseline was 40 msec). One patient randomised to alglucosidase alfa developed new atrial fibrillation at week 52. No patients developed new right bundle branch block, new left bundle branch block, new myocardial infarction, or new ST segment depression. One patient randomised to cipaglucosidase alfa/miglustat developed new T wave inversion in leads I and aVL at week 52.

All incidents of QTc prolongation or changes in other ECG parameters were determined to be cardiac-disease related. The clinical trials showed no evidence of cipaglucosidase alfa/miglustat-related QTc prolongation or changes in other ECG parameters.

Anaphylactic reaction (relevant for cipaglucosidase alfa)

Table12 summarises the anaphylaxis treatment-emergent adverse events.

Table 12 Overall summary of adverse events of interest: anaphylaxis in safety pool 1 and 2 – Safety population

SMQ PT	Pool 1 (Controlled Study ATB200-03)				Pool 2 (All Studies ATB200-02/03/07)		
	AA/ Placebo	Cipaglucosidase alfa/miglustat			Cipaglucosidase alfa/miglustat		
	All (N = 38)	All (N = 85)	ERT-exp (N = 65)	ERT-naïve (N = 20)	All (N = 151)	ERT-exp (N = 117)	ERT-naïve (N = 34)
Anaphylactic reaction[a, n (%)]	11 (28.9)	17 (20.0)	13 (20.0)	4 (20.0)	44 (29.1)	33 (28.2)	11 (32.3)
Dyspnoea	1 (2.6)	6 (7.1)	5 (7.7)	1 (5.0)	12 (7.9)	10 (8.5)	2 (5.9)
Cough	0	4 (4.7)	3 (4.6)	1 (5.0)	12 (7.9)	8 (6.8)	4 (11.8)
Urticaria	0	1 (1.2)	1 (1.5)	0	6 (4.0)	6 (5.1)	0
Pruritus	3 (7.9)	2 (2.4)	2 (3.1)	0	5 (3.3)	3 (2.6)	2 (5.9)
Asthma	1 (2.6)	1 (1.2)	1 (1.5)	0	3 (2.0)	3 (2.6)	0
Chest discomfort	0	1 (1.2)	1 (1.5)	0	3 (2.0)	2 (1.7)	1 (2.9)
Flushing	0	2 (2.4)	1 (1.5)	1 (5.0)	3 (2.0)	2 (1.7)	1 (2.9)
Hypotension	0	0	0	0	2 (1.3)	1 (0.9)	1 (2.9)
Rash	3 (7.9)	2 (2.4)	2 (3.1)	0	8 (5.3)	5 (4.3)	3 (8.8)
Rash erythematous	1 (2.6)	1 (1.2)	1 (1.5)	0	2 (1.3)	1 (0.9)	1 (2.9)
Anaphylactoid reaction	0	1 (1.2)	1 (1.5)	0	1 (0.7)	1 (0.9)	0
Angioedema	0	0	0	0	1 (0.7)	1 (0.9)	0
Cyanosis	0	0	0	0	1 (0.7)	1 (0.9)	0
Hyperventilation	0	0	0	0	1 (0.7)	0	1 (2.9)
Lip swelling	0	0	0	0	1 (0.7)	0	1 (2.9)
Ocular hyperaemia	0	0	0	0	1 (0.7)	1 (0.9)	0
Oedema	0	0	0	0	1 (0.7)	1 (0.9)	0
Periorbital oedema	0	0	0	0	1 (0.7)	1 (0.9)	0
Pharyngeal oedema	0	0	0	0	1 (0.7)	1 (0.9)	0
Pharyngeal swelling	1 (2.6)	0	0	0	0	0	0
Rash pruritic	0	0	0	0	1 (0.7)	0	1 (2.9)
Sneezing	1 (2.6)	1 (1.2)	0	1 (5.0)	1 (0.7)	0	1 (2.9)
Swelling	0	0	0	0	1 (0.7)	0	1 (2.9)
Swollen tongue	0	0	0	0	1 (0.7)	1 (0.9)	0

SMQ PT	Pool 1 (Controlled Study ATB200-03)				Pool 2 (All Studies ATB200-02/03/07)		
	AA/ Placebo	Cipaglucosidase alfa/miglustat			Cipaglucosidase alfa/miglustat		
	All (N = 38)	All (N = 85)	ERT-exp (N = 65)	ERT-naïve (N = 20)	All (N = 151)	ERT-exp (N = 117)	ERT-naïve (N = 34)
Tachypnoea	0	0	0	0	1 (0.7)	1 (0.9)	0
Throat tightness	1 (2.6)	0	0	0	0	0	0
Wheezing	0	0	0	0	1 (0.7)	1 (0.9)	0

Abbreviations: AA = alglucosidase alfa; AE = adverse event; ERT = enzyme replacement therapy; exp = experienced; N = total number of patients; n = number of patients in category indicated; PT = preferred term; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event
Note: TEAE was defined as any event that started or changed in the intensity on or after the first dose of study drug.
Note: Study drug was defined as the intended regimen of cipaglucosidase alfa IV + miglustat oral capsules
Note: TEAEs that occur more than 30 days from the last dose of study drug were not counted.
a TEAEs with PT in anaphylactic reaction SMQ (narrow and broad terms).

In safety pool 1, Seventeen (20.0%) cipaglucosidase alfa/miglustat-treated patients experienced anaphylaxis treatment-emergent adverse event(s) compared to 11 (28.9%) alglucosidase alfa/placebo-treated patients. Among the cipaglucosidase alfa/miglustat-treated patients, the most frequent anaphylaxis treatment-emergent adverse events by preferred term (i.e. occurring in ≥ 2.0% of patients) were dyspnoea (6/85 [7.1%]), cough (4/85 [4.7%]), flushing (2/85 [2.4%]), pruritus (2/85 [2.4%]), and rash (2/85 [2.4%]). Among the alglucosidase alfa/placebo-treated patients, the most frequent anaphylaxis treatment-emergent adverse events by preferred term (i.e. occurring in ≥ 2.0% of patients) were pruritus (3/38 [7.9%]), rash (3/38 [7.9%]), asthma (1/38 [2.6%]), dyspnoea (1/38 [2.6%]), pharyngeal swelling (1/38 [2.6%]), rash erythematous (1/38 [2.6%]), sneezing (1/38 [2.6%]), and throat tightness (1/38 [2.6%]). The proportion of cipaglucosidase alfa/miglustat-treated patients who experienced anaphylaxis treatment-emergent adverse events was similar among ERT-experienced and ERT-naïve patients (13/65 [20.0%] and 4/20 [20.0%], respectively).

Most of the anaphylactic reaction treatment-emergent adverse events in safety pool 1 were non-serious and did not lead to discontinuation of study drug.

One cipaglucosidase alfa/miglustat-treated patient experienced a serious anaphylactic reaction treatment-emergent adverse event that led to discontinuation of study drug. This patient experienced a serious anaphylactic reaction (verbatim preferred term anaphylactoid reaction) characterised by generalised pruritus, urticaria, difficulty in breathing, dizziness, bradycardia, and hypotension that resolved after stopping infusion and appropriate management. The patient was ERT experienced, and no premedication was given with the prior ERT; the patient did not experience infusion-associated hypersensitivity reactions with previous ERT treatment.

One other cipaglucosidase alfa/miglustat-treated patient was discontinued due to a non-serious anaphylactic reaction treatment-emergent adverse event. This patient was discontinued from the study (investigator decision) following several reported non-serious infusion-associated reactions, including urticaria and pruritus. The patient was ERT experienced, and no pre-medications had been given with the prior ERT. The patient had experienced past infusion-associated reactions with prior ERT.

No other anaphylactic reaction treatment-emergent adverse events in study ATB200-03 were serious, and no other anaphylactic reaction treatment-emergent adverse events led to discontinuation of study drug.

In addition to safety pool 1, three other cipaglucosidase alfa/miglustat-treated patients from safety pool 2 experienced serious anaphylactic reaction treatment-emergent adverse events, all of which resolved. Two of the patients were discontinued from the studies. The third patient (study ATB200-02) experienced chills, cough, dyspnoea, flushing, urticaria, and wheezing that were successfully managed and the patient was able to continue in the study.

Among the ERT-naïve cipaglucosidase alfa/miglustat-treated patients in safety pool 2 (N = 34), most of the patients experienced anaphylaxis and hypersensitivity treatment-emergent adverse events within the first 8 months of treatment. Six of 34 (17.6%) patients experienced anaphylaxis treatment-emergent adverse events within > 0 to 4 months, and 5/30 (16.7%) patients experienced anaphylaxis treatment-emergent adverse events within > 4 to 8 months. Two of 28 (7.1%) patients experienced anaphylaxis treatment-emergent adverse events within > 8 to 12 months after starting treatment, 3/26 (11.5%) patients experienced anaphylaxis treatment-emergent adverse events within > 12 to 16 months, 2/13 (15.4%) patients experienced anaphylaxis treatment-emergent adverse events within > 16 to 20 months, 2/7 (28.6%) patients experienced anaphylaxis treatment-emergent adverse events within > 20 to 24 months, and 1/6 (16.7%) patient experienced anaphylaxis treatment-emergent adverse events within > 24 months after starting treatment.

Infusion-associated reactions (relevant to cipaglucosidase alfa)

Table13 summarises the infusion-associated reactions, as determined by investigators (based on the temporality and nature of the event relative to infusion onset).

Table 13 Summary of adverse events of interest: infusion-associated reactions in safety pool 1 and 2 – Safety population

	Pool 1 (Controlled Study ATB200-03)				Pool 2 (All Studies ATB200-02/03/07)		
	Alglucosidase alfa/placebo	Cipaglucosidase alfa/miglustat			Cipaglucosidase alfa/miglustat		
	All (N = 38)	All (N = 85)	ERT-exp (N = 65)	ERT-naïve (N = 20)	All (N = 151)	ERT-exp (N = 117)	ERT-naïve (N = 34)
IAR[a], n (%)	10 (26.3)	21 (24.7)	16 (24.6)	5 (25.0)	43 (28.5)	34 (28.8)	9 (27.3)

Abbreviations: AE = adverse event; ERT = enzyme replacement therapy; exp = experienced; IAR = infusion-associated reaction; N = total number of patients; n = number of patients in category indicated; PT = preferred term; TEAE = treatment-emergent adverse event
a TEAEs identified by investigator to represent an IAR, regardless of PT.

Among the cipaglucosidase alfa/miglustat-treated patients, the most frequent infusion-associated reactions by preferred term (i.e. occurring in ≥ 2.0% of patients in either treatment group) were dizziness (4/85 [4.7%]), abdominal distension (3/85 [3.5%]), and headache (3/85 [3.5%]), and the following preferred terms occurring in 2 patients (2.4%) each: chills, diarrhoeal, dysgeusia, dyspnoea, flushing, pruritus, pyrexia, and rash. Among the alglucosidase alfa/placebo-treated patients, the most frequent infusion-associated reactions by preferred term (i.e. occurring in ≥ 2.0% of patients) were dizziness (2/38 [5.3%]),

fatigue (2/38 [5.3%]), headache (2/38 [5.3%]), and nausea (2/38 [5.3%]), and the following preferred terms occurring in 1 patient (2.6%) each: abdominal pain upper, abdominal pain, asthenia, dyspepsia, feeling hot, infusion site erythema, migraine, migraine with aura, myalgia, pain, pruritus, rash papular, pyrexia, restlessness, and throat tightness. The proportion of cipaglucosidase alfa/miglustat-treated patients who experienced infusion-associated reactions was similar for ERT-experienced patients versus ERT-naïve patients (16/65 [24.6%] versus 5/20 [25.0%], respectively).

Most of the reported infusion-associated reactions (7/8) in study ATB200-03 were non-serious. One cipaglucosidase alfa/miglustat-treated patient (1/85 [1.2%]) experienced a serious infusion-associated reaction, compared to no alglucosidase alfa/placebo-treated patients (0/38 [0.0%]). This serious infusion-associated reaction (anaphylactoid reaction) was characterised by generalised pruritus, urticaria, difficulty in breathing, dizziness, bradycardia, and hypotension and resolved after stopping the infusion and appropriate management. This patient was discontinued from the study as a result of this infusion-associated reaction.

In addition to safety pool 1, five cipaglucosidase alfa/miglustat-treated patients from safety pool 2 experienced serious infusion-associated reaction(s): one patient with pharyngeal oedema and urticaria (study ATB200-02), one patient with pyrexia (study ATB200-02), one patient with chills, cough, dyspnoea, flushing, urticaria, and wheezing (study ATB200-02), one patient with presyncope (study ATB200-02), one patient with hypotension and urticaria (study ATB200-07). Most infusion-associated reactions were medically managed such that the patients were able to continue on cipaglucosidase alfa. Only 4 cipaglucosidase alfa/miglustat-treated patients experienced infusion-associated reactions during or after cipaglucosidase alfa infusions that led to study drug discontinuation. These are the same 4 patients who were discontinued due to anaphylactic reaction treatment-emergent adverse events described above.

Immune-mediated reactions (relevant to cipaglucosidase alfa)

Potential immune-mediated reactions were identified from the clinical trial database, based on company-selected terms suggestive of a type III immune-mediated reaction, for safety pool 1 and 2. The following preferred terms were applied: arthritis, cutaneous vasculitis, erythema multiforme, erythema nodosum, glomerulonephritis, haemolytic anaemia, nephritis, nephrotic syndrome, proteinuria, purpura, skin lesion, skin necrosis, type III immune complex mediated reaction, and vasculitis.

In safety pool 1, few potential immune-mediated reactions were identified. Among cipaglucosidase alfa/miglustat-treated patients, 1 (1.2%) patient experienced a treatment-emergent adverse event of arthritis (within >4 to 8 months after starting cipaglucosidase alfa). Among alglucosidase alfa/placebo-treated patients, 1 (2.6%) patient experienced proteinuria, and 2 (5.3%) patients experienced skin lesion.

Hypersensitivity reactions (relevant to cipaglucosidase alfa)

Table 14 summarises the anaphylaxis and hypersensitivity treatment-emergent adverse events and ERT experience, based on the anaphylactic reaction standardised MedDRA query (SMQ)(narrow and broad terms) and hypersensitivity SMQ (narrow and broad terms).

Table 14 Summary of adverse events of interest: anaphylaxis and hypersensitivity in safety pools 1 and 2

	Pool 1 (Controlled Study ATB200-03)				Pool 2 (All Studies ATB200-02/03/07)		
	Alglucosidase alfa/placebo	Cipaglucosidase alfa/miglustat			Cipaglucosidase alfa/miglustat		
SMQ	All (N = 38)	All (N = 85)	ERT-exp (N = 65)	ERT-naïve (N = 20)	All (N = 151)	ERT-exp (N = 117)	ERT-naïve (N = 34)
Anaphylactic reaction[a]	11 (28.9%)	17 (20.0%)	13 (20.0%)	4 (20.0%)	44 (29.1%)	33 (28.2%)	11 (32.4%)
Hypersensitivity[b]	14 (36.8%)	15 (17.6%)	10 (15.4%)	5 (25.0%)	33 (21.9%)	23 (19.7%)	10 (29.4%)

Abbreviations: ERT = enzyme replacement therapy; exp = experienced; N = total number of patients; n = number of patients in category indicated; PT = preferred term; SMQ = standardised MedDRA query
a TEAEs with PT in anaphylactic reaction SMQ (narrow and broad terms).
b TEAEs with PT in the hypersensitivity SMQ (narrow and broad terms).

In safety pool 1, 15 (17.6%) cipaglucosidase alfa/miglustat-treated patients experienced hypersensitivity treatment-emergent adverse events compared to 14 (36.8%) of alglucosidase alfa/placebo-treated patients. Among the cipaglucosidase alfa/miglustat-treated patients, the most frequent hypersensitivity treatment-emergent adverse events by preferred term (i.e. occurring in ≥ 2.0% of patients) were conjunctivitis (2/85 [2.4%]), flushing (2/85 [2.4%]), mouth ulceration (2/85 [2.4%]), pruritus (2/85 [2.4%]), and rash (2/85 [2.4%]).

Among the alglucosidase alfa/placebo-treated patients, the most frequent hypersensitivity treatment-emergent adverse events by preferred term (i.e. occurring in ≥ 2.0% of patients) were pruritus (3/38 [7.9%]), rash (3/38 [7.9%]), application site eczema (1/38 [2.6%]), application site rash (1/38 [2.6%]), asthma (1/38 [2.6%]), dermatitis (1/38, [2.6%]), dermatitis allergic (1/38, [2.6%]), dermatitis contact (1/38 [2.6%]), eosinophil count increased (1/38 [2.6%]), infusion site rash (1/38 [2.6%]), pharyngeal swelling (1/38 [2.6%]), rash erythematous (1/38 [2.6%]), sneezing (1/38 [2.6%]), and throat tightness (1/38 [2.6%]).

Among the ERT-naïve cipaglucosidase alfa/miglustat-treated patients in safety pool 2, most of the patients experienced anaphylaxis and hypersensitivity treatment-emergent adverse events within the first 8 months of treatment. Four of 34 (11.8%) patients experienced hypersensitivity treatment-emergent adverse events within > 0 to 4 months, and 4/30 (13.3%) patients experienced hypersensitivity treatment-emergent adverse events within > 4 to 8 months. Two of 28 (7.1%) patients experienced hypersensitivity treatment-emergent adverse events within > 8 to 12 months, 2/26 (7.7%) patients experienced hypersensitivity treatment-emergent adverse events within > 12 to 16 months, 2/13 (15.4%) patients experienced hypersensitivity treatment-emergent adverse events within > 16 to 20 months, 1/7 (14.3%) patient experienced hypersensitivity treatment-emergent adverse events within > 20 to 24 months, and 2/6 (33.3%) patients experienced hypersensitivity treatment-emergent adverse events within > 24 months after starting treatment.

Tremor (may be relevant to miglustat)

In safety pool 1, 2 (2.4%) cipaglucosidase alfa/miglustat-treated patients experienced tremor treatment-emergent adverse event(s) compared to 0 (0.0%) alglucosidase alfa/placebo-treated patients. The tremor treatment-emergent adverse events occurred within the first 4 months of treatment.

Peripheral neuropathy (may be relevant to miglustat)

Peripheral neuropathy treatment-emergent adverse events were not identified in the clinical trial database.

Treatment-related adverse events

The reported adverse drug reactions were attributed to cipaglucosidase alfa, miglustat, or both cipaglucosidase alfa and miglustat. The primary assessment with respect to adverse drug reactions was made by the study investigator. Potential adverse drug reactions that were identified by the investigator were subsequentially reviewed by the applicant. Some treatment-emergent adverse events that were assessed as treatment-related by the investigator were refuted as adverse drug reactions upon in-depth review by the applicant (based upon lack of biological plausibility, confounding medical history, or improbable drug event-causal relationship).

In safety pool 1, the incidence of drug-related treatment-emergent adverse events tended to be lower in the cipaglucosidase alfa/miglustat as compared to the alglucosidase alfa/placebo group (26 [30.6%] and 14 [36.8%] patients, respectively). See Table15.

In the cipaglucosidase alfa/miglustat group, the most frequently reported drug-related treatment-emergent adverse events (i.e. considered related to cipaglucosidase alfa or miglustat) were in the system organ class of nervous system disorders (14 [16.5%] patients), and the most frequently reported drug-related treatment-emergent adverse event was headache (6 [7.1%] patients).

In the alglucosidase alfa/placebo group, the most frequently reported drug-related treatment-emergent adverse events (i.e. considered related to alglucosidase alfa or placebo) were in the system organ class of gastrointestinal disorders (8 [21.1%] patients), and the most frequently reported drug-related treatment-emergent adverse event was nausea (5 [13.2%] patients).

Table 15 Incidence of study drug-related treatment-emergent adverse events by system organ class and preferred term (based on pooled designation) – Safety pool 1 (controlled study ATB200-03) - Safety population

	Cipaglucosidase alfa/miglustat (N = 85)			Alglucosidase alfa/placebo (N = 38)		
SOC PT – n (%)	Cipaglucosidase alfa	Miglustat	Total	Alglucosidase alfa	Placebo	Total
Patients with any related TEAE	24 (28.2)	18 (21.2)	26 (30.6)	10 (26.3)	11 (28.9)	14 (36.8)
Eye disorders	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Blepharospasm	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Gastrointestinal disorders	7 (8.2)	11 (12.9)	11 (12.9)	3 (7.9)	8 (21.1)	8 (21.1)
Abdominal discomfort	0	1 (1.2)	1 (1.2)	0	0	0

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N = 85)			Alglucosidase alfa/placebo (N = 38)		
	Cipaglucosidase alfa	Miglustat	Total	Alglucosidase alfa	Placebo	Total
Abdominal distension	3 (3.5)	3 (3.5)	3 (3.5)	0	2 (5.3)	2 (5.3)
Abdominal pain	0	0	0	1 (2.6)	3 (7.9)	3 (7.9)
Abdominal pain lower	0	1 (1.2)	1 (1.2)	0	0	0
Abdominal pain upper	1 (1.2)	1 (1.2)	1 (1.2)	1 (2.6)	2 (5.3)	2 (5.3)
Constipation	0	1 (1.2)	1 (1.2)	0	1 (2.6)	1 (2.6)
Diarrhoea	2 (2.4)	5 (5.9)	5 (5.9)	0	2 (5.3)	2 (5.3)
Dyspepsia	0	0	0	1 (2.6)	1 (2.6)	1 (2.6)
Flatulence	1 (1.2)	1 (1.2)	1 (1.2)	0	2 (5.3)	2 (5.3)
Irritable bowel syndrome	0	0	0	0	1 (2.6)	1 (2.6)
Nausea	0	2 (2.4)	2 (2.4)	2 (5.3)	5 (13.2)	5 (13.2)
Oesophageal spasm	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Rectal haemorrhage	0	1 (1.2)	1 (1.2)	0	0	0
General disorders and administration site conditions	8 (9.4)	2 (2.4)	8 (9.4)	5 (13.2)	3 (7.9)	5 (13.2)
Asthenia	0	0	0	1 (2.6)	1 (2.6)	1 (2.6)
Chest discomfort	1 (1.2)	0	1 (1.2)	0	0	0
Chills	2 (2.4)	0	2 (2.4)	0	0	0
Facial pain	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Feeling hot	0	0	0	1 (2.6)	0	1 (2.6)
Fatigue	1 (1.2)	0	1 (1.2)	4 (10.5)	3 (7.9)	4 (10.5)
Infusion site erythema	0	0	0	1 (2.6)	0	1 (2.6)
Infusion site swelling	1 (1.2)	0	1 (1.2)	0	0	0
Malaise	1 (1.2)	0	1 (1.2)	0	0	0
Pain	1 (1.2)	0	1 (1.2)	1 (2.6)	1 (2.6)	1 (2.6)
Pyrexia	3 (3.5)	1 (1.2)	3 (3.5)	1 (2.6)	0	1 (2.6)
Immune system disorders	1 (1.2)	0	1 (1.2)	0	0	0
Anaphylactoid reaction	1 (1.2)	0	1 (1.2)	0	0	0
Injury, poisoning and procedural complications	1 (1.2)	0	1 (1.2)	0	0	0
Skin abrasion	1 (1.2)	0	1 (1.2)	0	0	0
Investigations	2 (2.4)	1 (1.2)	2 (2.4)	0	0	0
Blood urea increased	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Body temperature fluctuation	1 (1.2)	0	1 (1.2)	0	0	0
Lymphocyte count decreased	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N = 85)			Alglucosidase alfa/placebo (N = 38)		
	Cipaglucosidase alfa	Miglustat	Total	Alglucosidase alfa	Placebo	Total
Musculoskeletal and connective tissue disorders	3 (3.5)	4 (4.7)	4 (4.7)	2 (5.3)	1 (2.6)	2 (5.3)
Muscle spasms	1 (1.2)	2 (2.4)	2 (2.4)	0	0	0
Muscular weakness	1 (1.2)	1 (1.2)	1 (1.2)	1 (2.6)	0	1 (2.6)
Musculoskeletal stiffness	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Myalgia	1 (1.2)	1 (1.2)	1 (1.2)	1 (2.6)	1 (2.6)	1 (2.6)
Nervous system disorders	14 (16.5)	7 (8.2)	14 (16.5)	6 (15.8)	2 (5.3)	6 (15.8)
Balance disorder	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Cognitive disorder	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Dizziness	4 (4.7)	0	4 (4.7)	2 (5.3)	0	2 (5.3)
Dysgeusia	2 (2.4)	2 (2.4)	2 (2.4)	0	0	0
Headache	6 (7.1)	2 (2.4)	6 (7.1)	2 (5.3)	1 (2.6)	2 (5.3)
Hypoaesthesia	0	0	0	1 (2.6)	1 (2.6)	1 (2.6)
Migraine	1 (1.2)	1 (1.2)	1 (1.2)	1 (2.6)	1 (2.6)	1 (2.6)
Migraine with aura	1 (1.2)	1 (1.2)	1 (1.2)	1 (2.6)	0	1 (2.6)
Paraesthesia	1 (1.2)	0	1 (1.2)	0	0	0
Somnolence	1 (1.2)	0	1 (1.2)	0	0	0
Tremor	1 (1.2)	1 (1.2)	1 (1.2)	0	0	0
Psychiatric disorders	1 (1.2)	0	1 (1.2)	1 (2.6)	0	1 (2.6)
Nightmare	1 (1.2)	0	1 (1.2)	0	0	0
Restlessness	0	0	0	1 (2.6)	0	1 (2.6)
Respiratory, thoracic and mediastinal disorders	3 (3.5)	1 (1.2)	3 (3.5)	1 (2.6)	0	1 (2.6)
Dyspnoea	3 (3.5)	1 (1.2)	3 (3.5)	0	0	0
Throat tightness	0	0	0	1 (2.6)	0	1 (2.6)
Skin and subcutaneous tissue disorders	5 (5.9)	0	5 (5.9)	2 (5.3)	1 (2.6)	2 (5.3)
Mechanical urticaria	1 (1.2)	0	1 (1.2)	0	0	0
Pruritus	2 (2.4)	0	2 (2.4)	2 (5.3)	1 (2.6)	2 (5.3)
Rash	2 (2.4)	0	2 (2.4)	0	0	0
Rash erythematous	1 (1.2)	0	1 (1.2)	0	0	0
Urticaria	1 (1.2)	0	1 (1.2)	0	0	0
Vascular disorders	3 (3.5)	0	3 (3.5)	0	0	0
Flushing	2 (2.4)	0	2 (2.4)	0	0	0
Hypertension	1 (1.2)	0	1 (1.2)	0	0	0

Abbreviations: CSR = clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in category indicated; PT = preferred term; SOC = system organ class; TEAE=treatment-emergent adverse event

Note: A TEAE was defined as any event that started or changed in intensity on or after the first dose of study drug.

Note: "Related" included definite, probable, and possibly related; "not related" included unlikely and unrelated.

Note: If a patient experienced more than 1 TEAE with different relationship categories within the same SOC/PT, only the worst case (related TEAE) was reported.

Note: The pooled designation (in the total column) was considered "related" if the 2 categories of the individual relationships were discordant (i.e. "related" to one and "not related" to the other); the pooled designation (in the total column) was concordant with the individual categories if the 2 categories of the individual relationships are concordant (i.e. "related" to both, or "not related" to both).

Note: If relationship was missing, it was classified as "related."

Note: SOCs and PTs were coded with MedDRA Version 23.0.
Note: Percentages were based on the number of patients in each treatment group for the Safety Population.

2.6.8.3. Serious adverse event/deaths/other significant events

In safety pool 1, 9 (7.3%) patients had at least 1 treatment-emergent serious adverse event: 8 (9.4%) patients in the cipaglucosidase alfa/miglustat group and 1 (2.6%) patient in the alglucosidase alfa/placebo group (Table16).

In the cipaglucosidase alfa/miglustat group, the system organ class of gastrointestinal disorders had the largest number of patients with treatment-emergent serious adverse events (abdominal pain, enteritis, and vomiting in 1 patient each). In the cipaglucosidase alfa/miglustat group, no treatment-emergent serious adverse event was experienced by more than one patient. The single treatment-emergent serious adverse event in the alglucosidase alfa/placebo group was a cerebrovascular accident.

The treatment-emergent serious adverse event of anaphylactoid reaction was the only treatment-emergent serious adverse event in the cipaglucosidase alfa/miglustat group considered to be treatment-related. This treatment-emergent serious adverse event also led to study treatment discontinuation.

No study drug-related treatment-emergent serious adverse event was reported in the alglucosidase alfa/placebo group.

Table 16 Incidence of treatment-emergent serious adverse events by system organ class and preferred term – Safety pool 1 (controlled study ATB200-03) - Safety population

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N=85)	Alglucosidase alfa/placebo (N=38)
Patients with any serious TEAE	8 (9.4)	1 (2.6)
Cardiac disorders	1 (1.2)	0
Bradycardia	1 (1.2)	0
Gastrointestinal disorders	1 (1.2)	0
Abdominal pain	1 (1.2)	0
Enteritis	1 (1.2)	0
Vomiting	1 (1.2)	0
Immune system disorders	1 (1.2)	0
Anaphylactoid reaction	1 (1.2)	0
Infections and infestations	1 (1.2)	0
Viral myositis	1 (1.2)	0
Injury, poisoning and procedural complications	2 (2.4)	0
Contusion	1 (1.2)	0
Ilium fracture	1 (1.2)	0
Skin laceration	1 (1.2)	0
Nervous system disorders	0	1 (2.6)
Cerebrovascular accident	0	1 (2.6)
Surgical and medical procedures	1 (1.2)	0
Removal of internal fixation	1 (1.2)	0
Vascular disorders	1 (1.2)	0
Aortic aneurysm	1 (1.2)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in category indicated; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event
Note: A patient experiencing the same TEAE multiple times was counted once for the corresponding SOC/preferred term.
Note: SOCs and PTs were coded with MedDRA Version 23.0.
Note: Percentages were based on the number of patients in each treatment group for the Safety Population.

Deaths

In safety pool 1 and 2 no treatment-emergent adverse events were observed that led to death.

2.6.8.4. Laboratory findings

Haematology

In safety pool 1, the proportion of patients meeting predefined limits of change criteria was low and similar between the treatment groups. No meaningful trends were observed for haemoglobin, platelets, leukocytes and eosinophils/leukocytes parameters in the clinical studies.

Clinical chemistry evaluations

In safety pool 1, transient changes were noted with a low proportion of patients for all predefined criteria except for changes in absolute creatine kinase (CK) values in the category 2× upper limit of normal (ULN) range or ≥ 2× baseline visit (54.1% of patients in the cipaglucosidase alfa/miglustat group and 78.9% of patients in the alglucosidase alfa/placebo group). Of note, CK levels above the ULN are expected in the LOPD population, as increased elevated CK can be indicative of muscle injury.

No patient met Hy's Law criteria (ALT or aspartate aminotransferase [AST] > 3 × ULN + total bilirubin > 2 × ULN + alkaline phosphatase ≤ 2 × ULN) as no patient met ALT or AST > 3 × ULN + total bilirubin > 2 × ULN.

Urinalysis

No meaningful trends in mean changes were observed for urinalysis variables over time in the clinical studies.

Vital signs

No meaningful changes in vital signs were observed over time in the safety pool 1. Transient changes were noted with a low proportion of patients for all predefined criteria except for changes in body weight in the category of > 5% increase from baseline (24 [28.2%] patients in the cipaglucosidase alfa/miglustat group and 7 [18.4%] patients in the alglucosidase alfa/placebo group).

Electrocardiograms

In safety pool 1, few patients in either treatment group experienced a change in QT interval corrected using Fridericia's formula (QTcF) > 30 msec, and no patient experienced a change > 60 msec. No patient in the cipaglucosidase alfa/miglustat group had an absolute QTcF > 480 msec; 1 patient in the alglucosidase alfa/placebo group had an absolute QTcF > 500 msec.

2.6.8.5. In vitro biomarker test for patient selection for safety

No data have been submitted regarding *in vitro* biomarker test for patient selection for safety. It is noted that the diagnosis of Pompe disease in the pivotal study ATB200-03 was either based on deficiency of the GAA enzyme, or GAA genotyping.

2.6.8.6. Safety in special populations

No formal studies were conducted in special populations.

The disposition of cipaglucosidase alfa is not expected to be impacted by hepatic or renal impairment.

Severe treatment-emergent adverse events tend to occur more frequently upon cipaglucosidase alfa/miglustat than alglucosidase alfa/placebo treatment in female (10.2% versus 0%, respectively) but not in male patients with Pompe disease (8.3% and 10%, respectively) in pool 1. Based on review of these

severe treatment-emergent adverse event cases reported in female subjects and the severe treatment-emergent adverse events reported in male subjects treated with cipaglucosidase alfa/miglustat, there are no safety concerns suggestive of a gender effect. The difference in female subjects was considered a chance finding due to the low number of patients and events (5 cases in females and 3 cases in males).

One ERT-naïve patient with Pompe disease became pregnant during study treatment with cipaglucosidase/miglustat. Study treatment was discontinued, and an elective abortion was conducted. The patient completed study participation.

In safety pool 1, there were no meaningful differences between ERT-experienced and ERT-naïve patients with respect to the incidence of treatment-emergent adverse events, discontinuations due to treatment-emergent adverse events, drug-related treatment-emergent adverse events, treatment-emergent serious adverse events, infusion-associated treatment-emergent adverse events, laboratory values, vital signs, and ECGs. Nevertheless, a lower proportion of ERT-experienced patients in the cipaglucosidase alfa/miglustat group were reported to meet predefined criteria for changes in body weight in the category of > 5% increase from baseline compared to the alglucosidase alfa/placebo group (23.1% versus 45.0%, respectively). The percentage of patients with treatment-emergent serious adverse events also appeared to be higher in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group for both ERT-experienced and ERT-naïve patients (ERT-experienced: 9.2% versus 3.3%, respectively; ERT-naïve: 10.0% versus 0%, respectively).

In safety pool 1, there were no meaningful differences across regions with respect to the incidence of treatment-emergent adverse events, treatment-emergent serious adverse events, discontinuation due to treatment-emergent adverse events, most laboratory values, most vital signs, and ECGs. The following differences were observed for drug-related treatment-emergent adverse events, treatment-emergent adverse events associated with infusion, CK values, and body weight:

The incidence of drug-related treatment-emergent adverse events tended to be lower for the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo in North/South America (26.9% versus 46.7%, respectively) but was similar between the treatment groups in Europe (30.2% and 25.0%, respectively) and Asia Pacific (37.5% and 36.4%, respectively).

The incidence of treatment-emergent adverse events associated with infusion tended to be lower in the cipaglucosidase alfa/miglustat group compared to the alglucosidase alfa/placebo group in North/South America (26.9% versus 40.0%, respectively), but it was similar between the cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo groups for Europe (18.6% and 16.7%, respectively) and Asia Pacific (37.5% and 18.2%, respectively).

A difference between treatment groups in proportion of patients with body weight > 5% increase from baseline tended to be observed in North America, where 30.8% of patients in the cipaglucosidase alfa/miglustat group had a body weight > 5% increase from baseline compared to 6.7% in the alglucosidase alfa/placebo group.

2.6.8.7. Immunological events

The effect of immunogenicity on safety was assessed using data from studies ATB200-02 and ATB200-03.

Across studies ATB200-02 and ATB200-03, the anti-drug antibody prevalence (defined as the proportion of all individuals having drug-reactive total antibodies, including pre-existing antibodies at any point in time) was 92.1% (140/152) in all patients (100% of the 152 patients were evaluable); the anti-drug antibody

prevalence was 93.9% (107/114) for patients treated with cipaglucosidase alfa and 86.8% (33/38) for patients treated with alglucosidase alfa across both studies.

Across both studies, the anti-drug antibody incidence (defined as the proportion of the study population found to have seroconverted or boosted their pre-existing anti-drug antibody during the study period, sum of both treatment-induced and treatment-boosted anti-drug antibody-positive patients as a proportion of the evaluable patient population) was 65.8% (75/114) for patients treated with cipaglucosidase alfa and 34.2% (13/38) for patients treated with alglucosidase alfa.

No obvious differences in overall, and stratified (by study, ERT history, *GAA* genotype, gender, or age) anti-rhGAA antibody incidence, titre, and neutralising antibodies (NAbs) were observed.

Overall, there was no clear trend in infusion-associated reaction occurrence with the incidence of anti-rhGAA immunoglobulin E (IgE) or total anti-rhGAA antibodies.

In study ATB200-07, all 11 patients (7 patients randomly assigned to cipaglucosidase alfa/miglustat and 4 patients randomly assigned to alglucosidase alfa/placebo treatment in Study ATB200-03 that were ERT-naïve when they entered Study ATB200-03) continued to show positive specific anti-drug antibodies and titers up to 6 (n = 3), 12 (n = 6), or 26 weeks (n = 2) in this ongoing long-term extension study. All 11 patients were positive specific for antibodies cross-reactive to alglucosidase alfa at some (n = 1) or all time points (n = 3) in the study. The majority of cipaglucosidase alfa/miglustat-treated patients were positive for at least 1 of 3 types of NAbs after treatment. No infusion-associated reactions were observed at any of the study visits for any of these 11 patients in study ATB200-07. These results are consistent with the overall antibody results for ERT-experienced patients in studies ATB200-02 and ATB200-03.

As already mentioned, potential immune-mediated reactions were identified from the clinical trial database, based on selected terms suggestive of a type III immune-mediated reaction.

Approximately half of patients with cipaglucosidase alfa anti-rhGAA anti-drug antibodies were found to be positive for cross-reactive alglucosidase alfa ADA (CRADA), and vice versa.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been conducted using co-administered cipaglucosidase alfa/miglustat, which is considered acceptable by the CHMP.

2.6.8.9. Discontinuation due to adverse events

Five patients discontinued from the studies due to adverse events: 2 in study ATB200-02, 2 in study ATB200-03 (pool 1), and 1 in study ATB200-07 only. In addition, one patient discontinued from study ATB200-03 due to an adverse event and subsequently enrolled in study ATB200-07.

In safety pool 1, 3 patients in the cipaglucosidase alfa/ miglustat group and 1 patient in the alglucosidase alfa/placebo group discontinued due to an adverse event as follows: COVID-19–related pneumonia (not drug related), infusion-associated reaction/anaphylactic event (probably drug related) and infusion associated reaction/chills (drug related). In the alglucosidase alfa group, the adverse event leading to discontinuation was a stroke unrelated to study drug.

The patient who discontinued due to adverse events in study ATB200-07, switched from alglucosidase alfa/placebo in study ATB200-03 to cipaglucosidase alfa/miglustat in study ATB200-07 and had 2 treatment-

emergent serious adverse events (angioedema (reported verbatim as "giant urticaire"; clinical safety database reconciliation outstanding: recoding to "urticaria" ongoing) and hypotension), which led to study drug interruption on day 1 of the study ATB200-07.

2.6.8.10. Post marketing experience

There is no postmarketing experience available since cipaglucosidase alfa is not approved in any country at the present time.

2.6.9. Discussion on clinical safety

Since cipaglucosidase alfa and miglustat were administered in combination in conducted clinical studies, it is not possible to determine the contribution of each active component to the overall safety profile.

One hundred and fifty-one (151) patients were treated with 20 mg/kg cipaglucosidase alfa in combination with 260 mg miglustat once every two weeks. In the controlled study ATB200-03 (pool 1), 62 patients were exposed to cipaglucosidase alfa/miglustat for more than one year. In pooled studies ATB200-02/03/07 (pool 2), the exposure to cipaglucosidase alfa/miglustat was at least one year in 108 patients, and at least 2 years in 22 patients at the data lock-point (DLP).

The number of patients treated with the co-administration of cipaglucosidase alfa and miglustat at the recommended dosing regimen (n=151) is limited for a safety database and is expected since Pompe disease is rare (incidence about 1/40,000).[1] Further data will be available once the ongoing studies (ATB200-02, ATB200-07) are completed, and these are part of the additional pharmacovigilance activities to characterise the long-term use beyond 2 years. In addition, the applicant agreed to put in place a prospective observational registry of patients with Pompe disease to collect long term data in real world evidence setting (see 2.7).

The safety profile of miglustat in the authorised indications type 1 Gaucher disease and Niemann-Pick type C disease is well-known. The Cmax after administration of a single dose of 260 mg miglustat (3,000 ng/ml) is numerically lower compared to administration of a single dose of miglustat approved in type 1 Gaucher disease and Niemann-Pick type C disease. In addition, the approved miglustat dosing (100 mg or 200 three times daily based on the authorised indications) is higher than the miglustat dosing that is proposed for Pompe disease (260 mg once every 2 weeks) in the present application. The total miglustat exposure per 2 weeks for proposed Pompe disease indication (260 mg) is 3.1-6.2% of that for currently authorised miglustat indications. Due to the lower Cmax and AUC of miglustat for the intended use in co-administration with cipaglucosidase alfa in Pompe disease as compared to the miglustat currently approved in other indications, the safety profile of miglustat at recommended dosing for the intended use in co-administration with cipaglucosidase alfa in Pompe disease is expected to be more favourable than the miglustat dosing for the other (approved) indications.

In conducted clinical studies, the Cmax of a cipaglucosidase alfa dosage of 20 mg/kg was 325 µg/ml. Upon administration of cipaglucosidase alfa in combination with miglustat the Cmax ranged from 323-345 µg/ml. Considering the addition of miglustat to cipaglucosidase alfa had no or limited impact on the Cmax of

[1] Majed Dasouki, Omar Jawdat, Osama Almadhoun, Mamatha Pasnoor, April L. McVey, Ahmad Abuzinadah, Laura Herbelin, Richard J. Barohn, Mazen M. Dimachkie. Neurol Clin. 2014 Aug; 32(3): 751–ix.

cipaglucosidase alfa, the safety profile of miglustat in combination with cipaglucosidase alfa is not expected to be much different compared to that of cipaglucosidase alfa alone.

In general, the occurrence of treatment-emergent adverse events (TEAEs) tended to be higher at a longer treatment exposure time (mean 17.3 vs. 11.8 months). For example, the occurrence of severe treatment-emergent adverse events (9.4 vs. 13.2%), treatment-related adverse events (30.6 vs. 41.1%), anaphylactic reactions (20.0 vs. 29.1%), infusion-associated reactions (24.7 vs. 28.5%), and hypersensitivity reactions (17.6 vs. 21.9%) upon cipaglucosidase alfa/miglustat treatment tended to be lower in safety pool 1 as compared to safety pool 2 respectively.

However, the pattern of observed treatment-emergent adverse events from the analysed safety populations (pools 1 and 2) was comparable and the data from the pivotal study ATB200-03 (pool 1) is consequently used to characterise the safety profile of the co-administration of cipaglucosidase alfa and miglustat.

The most common TEAEs in the cipaglucosidase alfa/miglustat group were fall (29.4%), headache (23.5%), nasopharyngitis (22.4%), and myalgia (16.5%).

The occurrence of severe TEAEs tended to be about twice as high in the cipaglucosidase alfa/miglustat group (9.4%) compared to the alglucosidase alfa/placebo group (5.3%). Each severe treatment-emergent adverse event was observed in a single patient. One severe treatment-emergent adverse event in the cipaglucosidase alfa/miglustat group (anaphylactoid reaction) was considered to be treatment-related, compared to none in the alglucosidase alfa/placebo group. Nevertheless, since almost all severe treatment-emergent adverse events were considered unrelated to study drug, the observed trend for an increased occurrence of severe treatment-emergent adverse events upon treatment with cipaglucosidase alfa/miglustat as compared to alglucosidase alfa/placebo has limited impact on the overall safety profile of cipaglucosidase alfa/miglustat.

Furthermore, the incidence of treatment-related adverse events tended to be lower in the cipaglucosidase alfa/miglustat as compared to the alglucosidase alfa/placebo group (30.6 and 36.8% patients, respectively). The most frequently reported drug-related treatment-emergent adverse event upon cipaglucosidase alfa/miglustat included headache (7.1%), diarrhoea (5.9%), and dizziness (4.7%).

The occurrence of anaphylactic reactions (20.0 vs. 28.9%), infusion-associated reactions (24.7 vs. 26.3%), and hypersensitivity reactions (17.6 vs. 36.8%) tended to occur less frequently upon cipaglucosidase alfa/miglustat compared to alglucosidase alfa/placebo treatment. This is considered an advantage of cipaglucosidase alfa infusion in combination with miglustat relative to alglucosidase alfa infusion, considering the proposal for use of cipaglucosidase alfa as home-based infusions. During the pivotal study patients received cipaglucosidase alfa or alglucosidase alfa by infusion, both at home and at the clinical site; therefore, home infusion is considered acceptable and the SmPC and RMP contain detailed recommendations for this setting.

The occurrence of anaphylactic reactions (both 20%), and infusion-associated reactions (24.6 vs. 25.0%) were observed at similar frequencies in respectively ERT-experienced and ERT-naïve patients. However, hypersensitivity reactions tended to occur less frequently among ERT-experienced compared to ERT-naïve patients (15.4 vs. 25.0% respectively). This difference may be explained by the fact that hypersensitivity reactions in Pompe disease develop with time (Toh et al. 2020). In addition, this finding may also be related to Pompe disease patients who have experienced hypersensitivity to ERT may be less likely to participate in a clinical study on a new ERT-based therapy for Pompe disease.

One case of (accidental) overdose was reported in a patient receiving a 260 mg dose of miglustat/placebo and a dose of both cipaglucosidase alfa and alglucosidase alfa due to human error on the part of the healthcare professional. There were no complications resulting from the extra doses.

The occurrence of gastro-intestinal treatment-emergent adverse events which may be due to both cipaglucosidase alfa and miglustat tended to be lower upon cipaglucosidase alfa/miglustat treatment (32.9%) compared to alglucosidase alfa/placebo treatment (44.7%). Tremor, a known adverse drug reaction of miglustat tended to be observed more frequently upon cipaglucosidase alfa/miglustat (2.4%) compared to alglucosidase alfa/placebo treatment (0%). Tremor has been included in the list of adverse drug reactions.

No death was reported in all the safety population sets.

In general, predefined significant changes in haematology and clinical chemistry evaluations, and urinalysis tended to occur at lower or comparable rates for cipaglucosidase alfa/miglustat as compared to alglucosidase alfa/placebo treatment.

No patients have had substantial increases in heart rate, PR, or QRS duration. All incidents of QTc prolongation or changes in other ECG parameters were considered cardiac disease related. With respect to other vital signs, systolic and diastolic blood pressure between cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo groups were comparable. However, abnormal changes in weight appeared to be reported more frequently among patients who were treated with cipaglucosidase alfa/miglustat as compared to those who were treated with alglucosidase alfa/placebo, especially in female patients. Upon further analysis, no clinically relevant confounders were identified that could explain the opposing weight change trend observed in alglucosidase alfa/placebo-treated female patients. Given the similar trend in the mean and median increase in baseline weight observed across both male and female cipaglucosidase alfa/miglustat-treated patients and in alglucosidase alfa/placebo-treated male patients, the difference in weight change between cipaglucosidase alfa/miglustat and alglucosidase alfa/placebo groups (especially in females) is likely a chance finding and attributable to the small sample sizes in the gender subgroups.

In general, there were no remarkable differences with respect to gender, age, ERT status or regions with respect to the incidence of TEAEs, laboratory or ECG test results. However, severe TEAEs were reported more frequently upon cipaglucosidase alfa/miglustat than alglucosidase alfa/placebo treatment in female (10.2% versus 0%, respectively) but not in male patients with (8.3% and 10%, respectively). Based on review of these severe TEAEs reported in female subjects and in male subjects treated with cipaglucosidase alfa/miglustat, there are no safety concerns suggestive of a gender effect. The difference in female subjects is considered a chance finding due to the low number of patients and events (5 cases in females and 3 cases in males).

Safety was not evaluated with regard to race due to the low numbers of patients in the non-Caucasian categories, each accounting for <5% of the safety population in safety pool 2.

No signal emerged from the review of TEAE in elderly patients treated with cipaglucosidase alfa/miglustat. However, no definitive conclusions can be drawn on the safety of cipaglucosidase alfa/miglustat in patients aged ≥ 65 years due to the relatively low number of patients in this demographic group (n = 11) and the lack of patients aged ≥ 75 years.

The proportions of patients who had any treatment-related TEAEs were reported upon treatment with cipaglucosidase alfa/miglustat treatment appeared to be lower for ERT-experienced compared to ERT-naïve patients in safety pool 1 (29.2 vs. 35.0%), and also in safety pool 2 (40.2 vs. 44.1%). Analysis of safety profiles in both pools (i.e., treatment naïve and experienced) did not show a significant difference in the nature, seriousness, and distribution of treatment-related treatment-emergent adverse events experienced by subjects. The observed differences between the incidence rate of treatment-related TEAEs in ERT-naïve versus ERT-experienced patients were mostly attributed to non-serious treatment-related treatment-

emergent adverse events, which are listed adverse drug reactions for other ERT products and are proposed adverse drug reactions for the cipaglucosidase alfa/miglustat use in combination.

One pregnancy in an ERT-naïve patient with Pompe disease was reported during study treatment with cipaglucosidase/miglustat. Study treatment was discontinued, and an elective abortion was conducted. The patient completed study participation. Based on animal studies, cipaglucosidase alfa in combination with miglustat therapy is not recommended during pregnancy. More information on special populations of interest such as pregnant or lactating women treated with cipaglucosidase alfa and miglustat co-administration are planned to be collected as part of additional pharmacovigilance activities. In particular, the applicant agreed to put in place a prospective observational registry of patients with Pompe disease to collect long term data in real world evidence setting (see 2.7).

The anti-drug antibody prevalence tended to be higher for patients who were treated with cipaglucosidase alfa (93.9%) compared to those who were treated with alglucosidase alfa (86.8%) in studies ATB200-02 and ATB200-03. A similar trend was observed with respect to the anti-drug antibody incidence during the first year of treatment (65.8 vs. 34.2%). However, there was no clear trend in infusion-associated reaction occurrence with the incidence of anti-rhGAA immunoglobulin E (IgE) or total anti-rhGAA antibodies. Hence, there is thus so far no evidence that respective antibodies affect the overall safety profile of cipaglucosidase alfa/miglustat treatment to a clinically relevant extent. Since a class effect and biological plausibility with cipaglucosidase alfa cannot be ruled out, this safety concern has been reflected among important potential risks within the proposed RMP for cipaglucosidase alfa and will be monitored through the additional pharmacovigilance activities in place (see 2.7). In addition, a general warning on immune complex related reaction for ERTs has been included in the SmPC to monitor for clinical signs and symptoms of systemic immune complex-related reactions while receiving cipaglucosidase alfa with miglustat. If immune complex-related reactions occur, discontinuation of the administration of cipaglucosidase alfa should be considered and appropriate medical treatment should be initiated. The risks and benefits of re-administering cipaglucosidase alfa following an immune complex-related reaction should be reconsidered for each individual patient.

Approximately half of patients with cipaglucosidase alfa anti-rhGAA anti-drug antibodies were found to be positive for cross-reactive alglucosidase alfa ADA (CRADA), and vice versa. These results indicate that most CRADA positive patients treated with the co-administration of cipaglucosidase alfa and miglustat did not have hypersensitivity, anaphylaxis, or infusion-associated reactions (20 to 32% of CRADA-positive subjects experienced such events). Proportions of CRADA-positive patients were similar between patients with and without hypersensitivity, anaphylaxis, or infusion-associated reactions, indicating no clear association between these immune reactions and CRADA. Immunomodulation/desensitisation protocols are often used in IOPD patients. Such protocols were not used in ATB200-03 study setting, considering the adult LOPD population included. Therefore, there was no influence of any immunomodulation/ desensitisation protocols on the occurrence of anaphylactic reactions, infusion-associated reactions, and hypersensitivity reactions in each treatment group that could be shown in the ATB200-03 study setting.

Since no correlation between the infusion-associated hypersensitivity reactions experienced with cipaglucosidase alfa and anti-drug antibodies (ADA) was observed, no additional and specific immunosurveillance programme is considered necessary at this timepoint.

Due to the nature of the product, it is not expected that drug abuse, withdrawal and rebound are likely to occur, no information is available on these aspects for the co-administration of cipaglucosidase alfa and miglustat and this is considered acceptable by the CHMP. However, these substances may have minor influence on the ability to drive and to use machines due to the potential for experiencing dizziness and this has been reflected appropriately in the SmPC.

2.6.10. Conclusions on the clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC. Appropriate measures including additional pharmacovigilance activities and risk minimisation activities (see 2.7) have been put in place to ensure safe and effective use of the product in the recommended indication.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies
Important potential risks	Immune complex related reaction Medication error in home infusion setting
Missing information	Use in pregnant and lactating women Long-term use (> 24 months)

Abbreviations: IgE = immunoglobulin E; IgG = immunoglobulin G.

2.7.2. Pharmacovigilance plan

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
ATB200-02 – A Phase 1/2 open-label, fixed-sequence, ascending-dose, first-in-human study to assess the safety, tolerability, PK, pharmacodynamics, and efficacy of IV infusions of cipaglucosidase alfa co-administered with oral miglustat in adult subjects with Pompe disease Ongoing	Objectives from the open-label extension portions of the study (i.e. Stage 3 and Stage 4) include evaluations of long-term efficacy, safety, and tolerability of cipaglucosidase alfa/miglustat in all subjects from Stage 3.	• IARs including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies; • Immune complex related reaction; • Medication error in home infusion setting; • Long-term use (> 24 months).	Final report (planned)	2025 [a]

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
ATB200-07 – A Phase 3, open-label extension study to assess the long-term safety and efficacy of IV cipaglucosidase alfa co-administered with oral miglustat in adult subjects with late-onset Pompe disease Ongoing	The primary objective is to assess the long-term safety and tolerability of cipaglucosidase alfa/miglustat. Secondary objectives include assessments of long-term efficacy (as measured by various parameters), long-term effect on biomarkers of muscle injury and disease substrate, and immunogenicity.	• IARs including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies; • Immune complex related reaction; • Medication error in home infusion setting; • Long-term use (> 24 months).	Final report (planned)	2026 [b]
Prospective observational registry – A prospective observational registry of patients with Pompe disease Planned	The goal of the registry is to assess long-term safety and effectiveness of Pompe disease treatments in patients with LOPD and IOPD. Eligible patients include those who are currently receiving a medical therapy for Pompe disease (regardless of dose/dosing frequency) and those who are not currently receiving any medical therapy for Pompe disease. The objectives are to evaluate long-term safety of Pompe disease treatments through collection of AEs and SAEs occurring in patients with Pompe disease, including IARs, hypersensitivity reactions (including anaphylaxis), immune complex related reactions, and pregnancy exposures; to evaluate long-term real-world effectiveness of Pompe disease treatments through collection of functional outcomes assessments; to evaluate long-term real-world impact of Pompe disease treatments on QOL using patient reported outcome measures	• IARs including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies; • Immune complex related reaction; • Medication error in home infusion setting; • Use in pregnant and lactating women; • Long-term use (> 24 months).	Final report (planned)	Q1 2035

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

Abbreviations: AE = adverse event; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; IOPD = infantile-onset Pompe disease; IV = intravenous; LOPD = late-onset Pompe disease; PK = pharmacokinetics; Q = Quarter; QOL = quality of life; SAE = serious adverse event.

[a] The Stage 4 treatment period of this study will continue as an open-label extension until regulatory approval or marketing authorisation and/or commercialisation in the participating subject's country, or study termination by the sponsor.

[b] This study will continue until regulatory approval or marketing authorisation and/or commercialisation in the participating subject's country, or study termination by the sponsor.

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, and 4.8; • PL Sections 2 and 4; • As stated in the SmPC (Section 4.3) and PL (Section 2), treatment is contraindicated in patients with history of life-threatening IARs (e.g. anaphylaxis and severe cutaneous reactions) to the active substance or any of the excipients when rechallenge was unsuccessful; • As stated in the SmPC (Section 4.2), premedication used for patients that have switched from another ERT to Pombiliti in combination with miglustat should be continued when starting Pombiliti; • As stated in the PL (Section 2), patients are instructed to tell their doctor if they notice any signs of IARs or allergic events and such signs are listed in Section 4; • Recommendations for managing IARs including hypersensitivity and anaphylactic reactions are provided in the SmPC, including rate reduction or stoppage of infusion, guidance on resumption or re-initiating, recommendations regarding corrective treatment and premedications, and cardiopulmonary resuscitation equipment. Other routine risk minimisation measures beyond the Product Information: • Prescription only. Additional risk minimisation measures: • Home infusion guide; • Patient/caregiver's guide including an infusion diary.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry.

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Immune complex related reaction	Routine risk minimisation measures: • As stated in the SmPC (Section 4.4), patients should be monitored for clinical signs and symptoms of systemic immune complex related reactions; • Recommendations for managing immune complex related reactions are provided in the SmPC (Section 4.4), including discontinuation of Pombiliti in combination with miglustat and appropriate medical treatment. Other routine risk minimisation measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry.
Medication error in home infusion setting	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, and 6.6; • PL Section 3; • As stated in the SmPC (Section 4.2), treatment should be supervised by healthcare professionals experienced in the management of Pompe disease; • As stated in the SmPC (Section 4.2), home infusions may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months, and recommendations regarding a decision to move to home infusions are described in the SmPC (Section 4.2); • As stated in the SmPC (Section 4.4), for patients who experience anaphylaxis or severe allergic reactions in the home setting, if they continue on treatment, their next infusions must occur in a clinical setting equipped to deal with such medical emergencies; • The SmPC (Section 6.6) contains detailed instruction regarding preparation of the medicinal product (including calculating the dose, activities before reconstitution, reconstituting the lyophilised cake/powder, dilution and preparation of the infusion bag, and preparing for administration); • Recommendations for managing IARs including hypersensitivity and anaphylactic reactions are provided in the SmPC. Other routine risk minimisation measures beyond the Product Information: • Prescription only. Additional risk minimisation measures: • Home infusion guide; • Patient/caregiver's guide including an infusion diary.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry.

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Missing information: Use in pregnant and lactating women	Routine risk minimisation measures: • SmPC Sections 4.6 and 5.3; • PL Section 2; • Recommendations regarding use in pregnant women and use in breastfeeding women are provided in the SmPC (Section 4.6) and PL (Section 2); • As stated in the SmPC (Section 4.6) and PL (Section 2), female patients of childbearing potential are advised to maintain reliable contraceptive methods prior, during, and for 4 weeks after stopping Pombiliti in combination with miglustat; • As stated in the PL (Section 2), Pombiliti should not be used during pregnancy, and patients are instructed to tell their doctor if they are pregnant, may be pregnant, or are planning to become pregnant; • As stated in the PL (Section 2), Pombiliti in combination with miglustat should not be used in breastfeeding women, and patients are instructed to tell their doctor if they are breastfeeding. Other routine risk minimisation measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Prospective observational registry.
Missing information: Long-term use (> 24 months)	Routine risk minimisation measures: • None Other routine risk minimisation measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • ATB200-02; • ATB200-07; • Prospective observational registry.

Abbreviations: IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; PL = package leaflet; SmPC = Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with an international birth date (IBD). The new EURD list entry will therefore use the European Birth Date (EBD) to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons: Pombiliti is administered under the supervision of a healthcare professional, in the clinical or home setting, and on the grounds of space limitations.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Pombiliti (cipaglucosidase alfa) is included in the additional monitoring list as the additional monitoring list as it is a biological product, which will be authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pombiliti (cipaglucosidase alfa) is intended for long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alpha-glucosidase (GAA). Defects in both alleles of the gene for GAA, located on chromosome 17q25, result in reduced or absent enzyme activity, leading to progressive intralysosomal accumulation of undegraded glycogen. The resulting damage to affected cells produces a range of symptoms that characterise Pompe disease, including metabolic myopathy leading to neuromuscular dysfunction.

Currently, over 500 mutations of GAA, have been found. Clinical presentation of Pompe disease is heterogeneous in timing, severity, and ranges of symptoms observed and is dependent on the residual enzyme activity. The disease is classified into different phenotypes based on age at the onset of symptoms, the extent of organ involvement, and the rate of progression to death. The phenotypes range from a rapidly progressive infantile-onset form (IOPD) characterised by virtually complete absence (less than 1%) of acid alpha-glucosidase (GAA)-activity to a more slowly progressive late-onset form (LOPD). This application considers adult patients with LOPD only. No information on IOPD patients who are currently treated with alglucosidase alfa was submitted.

The majority of patients with Pompe disease present after infancy with late-onset Pompe disease (LOPD), which takes a more variable course. In untreated patients, undegraded glycogen accumulates in the diaphragm and respiratory muscles, and respiratory function declines over time, leading to dependence on external ventilation and, ultimately, to respiratory failure, the most common cause of death regardless of the age of disease onset. Glycogen also accumulates in skeletal muscles, and motor function declines over time, leading to problems with activities of daily living, reduced mobility, and eventually dependence on a wheelchair. Quality of life is usually severely affected by the burden of the disease.

The aim of new treatments is to serve as an alternative for the already registered alglucosidase alfa, or to further slowdown deterioration observed in adult LOPD patients treated with alglucosidase alfa.

3.1.2. Available therapies and unmet medical need

The development and approval of ERT have profoundly changed the natural course of the disease, considerably extending productivity and quality of life for patients with LOPD. However, it is recognised that the progressive decline in muscle function in patients with Pompe disease is not completely abrogated with alglucosidase alfa ERT.

Studies in LOPD patients suggest that some patients on alglucosidase alfa continue to exhibit some decline in respiratory function, albeit at a slower pace than prior to treatment. After the start of ERT the patients described a transitory effect, more stabilisation of symptoms than a recovery. Those who could increase the dose reported a more tangible effect after the dose increase. Some had no effect and could not try a higher

dose. Thus, responses to treatment in LOPD patients vary, and there might be room for improvement, but overall, there is not a huge unmet medical need in this population.

Cipaglucosidase alfa (ATB200, rhGAA) is developed as a next-generation ERT for Pompe disease. Cipaglucosidase alfa contains higher amounts of mannose 6-phosphate (M6P), which is the natural motif for identifying and transporting soluble lysosomal enzymes to lysosomes, as compared to alglucosidase alfa. Importantly, cipaglucosidase alfa contains bis-phosphorylated high mannose oligosaccharide structures, which are known to have the highest affinity of all known carbohydrates for the cation-independent mannose 6 phosphate receptor (CI-MPR). This specialised glycosylation leads to better binding to the CI-MPR (Tong and Kornfeld, 1989) on cell surfaces, which mediates the internalisation and delivery of exogenous rhGAA to lysosomes, particularly at low enzyme concentrations in muscles post-dosing. Like all lysosomal enzymes, cipaglucosidase alfa is unstable at neutral pH and denatured and inactivated in the bloodstream following intravenous (IV) infusion.

Miglustat (AT2221, N-butyl-deoxynojirimycin) is a small-molecule enzyme stabiliser that binds to and prevents the inactivation of the cipaglucosidase alfa enzyme in the blood. Based on the knowledge of the metabolic pathway leading to the accumulation of glycogen miglustat cannot be considered a substrate reduction therapy (SRT), miglustat alone has no specific effects on the burden of diseases in the group of glycogen storage diseases (for example McArdle, von Gierke and Pompe disease).

3.1.3. Main clinical studies

The pivotal evidence comes from one double-blind, randomised, multicentre, superiority study (ATB200-03) including 123 adult subjects with LOPD in which the clinical effects of cipaglucosidase alfa/miglustat (N= 85) were compared with those of alglucosidase alfa/placebo (n=38). Most patients had received prior enzyme replacement therapy (ERT) (cipaglucosidase alfa/miglustat: 65 of 85 patients, alglucosidase alfa/placebo: 30 of 38 patients). Patients were treated with cipaglucosidase alfa 20 mg/kg combined with miglustat 195/260mg eow or alglucosidase alfa 20mg/kg every other week. Besides the well-known endpoints for Pompe disease (6-minute walking test (6MWT) and forced vital capacity (FVC)), motor function, respiratory function, muscle strength and quality of life were measured. The treatment duration in study ATB200-03 was 52 weeks.

No children were included in the study. No patients with IOPD were studied.

Results from study ATB200-02, an ongoing Phase 1/2, open-label, fixed-sequence first-in-human study, are considered supportive. This also applies to the ongoing open-label extension study ATB200-07 in which patients are followed up for more than 24 months.

3.2. Favourable effects

Using the originally presented MMRM analysis for the primary endpoint (6MWD) based on remapped visits and excluding the outlying subject as presented by the applicant, the estimated mean treatment difference (95%CI) excluding the outlying subject is +14.2 m (-2.6, 31.0) with a two-sided p-value of 0.097, favouring the cipaglucosidase alfa/miglustat arm.

After 52 weeks of treatment with cipaglucosidase alfa/miglustat in the ITT-OBS population using the most adequate and reliable MMRM method based on the actual time point of assessments and excluding the outlying subject, the least square (LS) mean change from baseline for the 6MWD (primary endpoint) in the

cipaglucosidase alfa/miglustat group was 20.0 m (95% CI 13.1, 26.9) (primary endpoint) versus 8.3 m (95% CI -2.2, 18.8) in the alglucosidase alfa/placebo group. The estimated mean treatment difference is 11.7 m (95% CI -1.0, 24.4) with a two-sided p-value of 0.07. The LS mean change from baseline for the sitting predicted %FVC showed a change of -1.4% (95% CI -2.5, -0.3) (key secondary endpoint) versus -3.7% (95% CI -5.4, -2.0) in the alglucosidase alfa/placebo group. The estimated mean difference (95% CI) between the treatments after 52 weeks was 3.0% (0.6%, 5.5%).

For the remaining key secondary endpoints (MMT, PROMIS-Physical Function, PROMIS-fatigue and GSGC), results reported are more or less in line with the results of the 6MWT and the sitting %FVC and further support the conclusion that the effects obtained with cipaglucosidase alfa/miglustat appeared to be reasonably robust and consistent.

In the ERT-experienced study population (n=95), using the same model, the LS mean improvement observed in the 6MWD during the first year of treatment was +15.8m (95% CI 8.3, 23.4) for the cipaglucosidase alfa/miglustat group and +0.9m (95% CI -10.2, 12.1) for the alglucosidase alfa/placebo group. The LS mean treatment difference was 14.9 m (95% CI 1.2, 28.6) in favour of the cipaglucosidase alfa/miglustat-treated patients. Analysing the sitting predicted %FVC the LS mean difference at week 52 as compared to baseline was -0.2 (95% CI -1.5, 1.1) in the cipaglucosidase alfa/miglustat group and -3.8 (95% CI -5.7, -1.9) in the alglucosidase alfa/placebo group. The estimated LS mean treatment difference (95% CI) was 3.6% (95% CI 1.3, 5.9).

In the ERT naïve population (n= 27) using the same model, the LS mean improvement was +28.5 m (95% CI 12.4, 44.7) in the 20 ERT-naïve subjects who received cipaglucosidase alfa/miglustat. In the alglucosidase alfa/placebo control group (n = 7) the LS mean improvement was 52.7 m (95% CI 23.2, 82.3). The LS mean treatment difference (95% CI) for the change to week 52 in 6MWD was -24.2 (-60.0, 11.7). The LS means for the change to week 52 in sitting % predicted FVC was -5.2 (95% CI -7.5, -2.9) for cipaglucosidase alfa/miglustat, and -2.4 (95% CI -6.7, 1.8). The LS mean treatment difference was -2.8 (95% CI -7.8, 2.3).

3.3. Uncertainties and limitations about favourable effects

Apart from 11 patients in study ATB200-02 who received a single dose of 5, 10 or 20 mg/kg cipaglucosidase alfa, no information on cipaglucosidase alfa monotherapy is available. Study ATB002-02 is of limited value for the evaluation of the dose response of cipaglucosidase alfa in combination with miglustat. Due to the non-randomised, open-label nature of study ATB002-02, and the limited number of patients (n= 29 divided over 4 cohorts), no definitive conclusions can be made with respect to a potential dose-response relationship for the endpoints measured.

The contribution of miglustat itself to the clinical effects of the co- administration of miglustat and cipaglucosidase alfa in human LOPD patients is unknown since cipaglucosidase alfa on its own has not been evaluated in human LOPD patients. Despite a lack of clear pharmacokinetic rationale for adding miglustat, the clinical relevance of the co-administration cipaglucosidase alfa and miglustat has been established based on the most adequate and reliable efficacy data (see above). An approximate 7% to 30% increases in AUC upon the addition of miglustat in rodent models were associated with a 50% increase in grip strength-wire hang in conducted non-clinical studies. These findings support, in theory, an additive value of miglustat to the clinical effects of cipaglucosidase alfa in human adult LOPD patients. However, the extent of this contribution is unknown.

The pivotal study has not met its primary objective. According to the planned hierarchical testing strategy, all other (key secondary and secondary) endpoints will be considered explorative.

Data on long-term efficacy are limited. Studies ATB200-02, ATB200-07) are still ongoing. Nearly all enrolled subjects with at least an additional 6 months of exposure to cipaglucosidase alfa after the end of the ATB200-03 study, and 33 subjects (approximately 30% of subjects) with no less than an additional 12 months of exposure to cipaglucosidase alfa have been included in the ongoing study ATB200-07 as of 3 August 2021.

3.4. Unfavourable effects

Considering the addition of miglustat to cipaglucosidase alfa had no or limited impact on the Cmax of cipaglucosidase alfa, the safety profile of miglustat in combination with cipaglucosidase alfa is not expected to be much different compared to that of cipaglucosidase alfa alone.

In general, the occurrence of treatment-emergent adverse events (TEAEs) tended to be higher at a longer treatment exposure time (mean 17.3 vs. 11.8 months). For example, the occurrence of severe treatment-emergent adverse events (9.4 vs. 13.2%), treatment-related adverse events (30.6 vs. 41.1%), anaphylactic reactions (20.0 vs. 29.1%), infusion-associated reactions (24.7 vs. 28.5%), and hypersensitivity reactions (17.6 vs. 21.9%) upon cipaglucosidase alfa/miglustat treatment tended to be lower in safety pool 1 (n=123) as compared to safety pool 2 (n=151) respectively.

However, the pattern of observed treatment-emergent adverse events from the analysed safety populations (pools 1 and 2) was comparable, and the data from the pivotal study ATB200-03 (pool 1) is consequently used to characterise the safety profile of the co-administration of cipaglucosidase alfa and miglustat.

The most common TEAEs in the cipaglucosidase alfa/miglustat group were fall (29.4%), headache (23.5%), nasopharyngitis (22.4%), and myalgia (16.5%).

The occurrence of anaphylactic reactions (20.0 vs. 28.9%), infusion-associated reactions (24.7 vs. 26.3%), and hypersensitivity reactions (17.6 vs. 36.8%) tended to occur less frequently upon cipaglucosidase alfa/miglustat compared to alglucosidase alfa/placebo treatment.

The anti-drug antibody prevalence tended to be higher for patients who were treated with cipaglucosidase alfa (93.9%) compared to those who were treated with alglucosidase alfa (86.8%) in studies ATB200-02 and ATB200-03. A similar trend was observed with respect to the anti-drug antibody incidence during the first year of treatment (65.8 vs. 34.2%). However, there was no clear trend in infusion-associated reaction occurrence with the incidence of anti-rhGAA immunoglobulin E (IgE) or total anti-rhGAA antibodies.

3.5. Uncertainties and limitations about unfavourable effects

Since cipaglucosidase alfa and miglustat were administered in combination in conducted clinical studies, it is not possible to determine the contribution of each active component to the overall safety profile.

The included number of Pompe disease patients is limited (n=151). This is expected since Pompe disease is rare. The majority of patients with Pompe disease were ERT-experienced, and hence the safety data in ERT-naïve population do not allow a full characterisation of the safety profile, however, it is not expected to be much different than the ERT experienced patients.

The available safety data at different dosages of cipaglucosidase alfa alone and with 20 mg/kg cipaglucosidase alfa with different dosages of miglustat in the conducted dose-response study in 11 patients with Pompe disease is too limited to draw appropriate conclusions regarding clinical safety.

In clinical studies, the Cmax of a cipaglucosidase alfa dosage of 20 mg/kg was 325 µg/ml. Upon administration of cipaglucosidase alfa in combination with miglustat, the Cmax ranged from 323-345 µg/ml. Considering the addition of miglustat to cipaglucosidase alfa had no or limited impact on the Cmax of cipaglucosidase alfa, the safety profile of miglustat in combination with cipaglucosidase alfa is not expected to be much different compared to that of cipaglucosidase alfa alone. This has, however, not been evaluated in conducted clinical studies.

Limited study data on the clinical effects of cipaglucosidase alfa/miglustat are available for a treatment period beyond 24 months. Additional data from the ongoing clinical studies ATB200-02 and ATB200-07 will provide some more insight into the long-term clinical safety of cipaglucosidase alfa/miglustat.

3.6. Effects Table

Table 17 Effects table for cipaglucosidase alfa/miglustat

Effect	Short Description	Unit	Cipaglucosidase alfa/miglustat (n= 85)	Alglucosidase alfa/placebo (n= 37)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in 6MWD Overall population	Change in distance walked in meters from baseline to week 52*	LS Mean (95% CI)	20.0 m (13.1, 26.9)	8.3 m (-2.2, 18.8)	**SoE;** statistical superiority was missed for the primary endpoint. LS Mean treatment difference is 11.7 m (95% CI -1.0, 24.4). **Unc:** Results in the subgroup of treatment experienced and naïve patients were different. In the treatment experienced patients treatment difference (LS mean (95% CI) was 14.9m (1.2, 28.6) For the treatment naïve patients the difference was -24.2m (-60.0, 11.7)	ATB200-03

Effect	Short Description	Unit	Cipaglucosidase alfa/miglustat (n= 85)	Alglucosidase alfa/placebo (n= 37)	Uncertainties/ Strength of evidence	References
%FVC Overall population	Change in sitting predicted %FVC from baseline to week 52*	LS Mean (95% CI)	-1.4% (-2.5, -0.3)	-3.7% (-5.4, -2.0)	**SoE:** Superiority tests for the secondary endpoints in the pre-specified hierarchy could formally not be carried out under adequate control of the overall type 1-error, since statistical superiority was missed for the primary endpoint. Treatment difference is 2.3% (95% CI 0.2, 4.4) **Unc:** Results in the subgroup of treatment experienced and naïve patients were different. In the treatment-experienced patients treatment difference (LS mean (95% CI) was 3.6% (1.3, 5.9). For the treatment naïve patients the difference was -2.8 (-7.8, 2.3).	ATB200-03
Unfavourable Effects						
Treatment-related TEAEs		%	30.6	36.8	**Unc:** treatment-relatedness difficult to determine for combined study treatments	Study ATB200-03
Infusion-associated reactions		%	24.7	26.3	**SoE:** infusion-associated, anaphylactic, and hypersensitivity reactions are related	Study ATB200-03
	Anaphylactic reactions	%	20.0	28.9		Study ATB200-03
	Hypersensitivity reactions	%	17.6	36.8		Study ATB200-03
ADA incidence	ADA incidence during study treatment	%	65.8	34.2	**SoE:** No adverse impact of ADA formation observed with respect to clinical safety	Study ATB200-03

Abbreviations: ADA: anti-drug antibody, LS: least squares, SoE: strength of evidence, TEAE: treatment-emergent adverse event, Unc: uncertainty
Notes:Based on the mixed-effect model for repeated measures and actual time point of assessments of study ATB200-03(ITT-OBS population excluding outlying subject).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Although the pivotal study failed to show the superiority of the co-administration of cipaglucosidase alfa and miglustat over alglucosidase alfa/placebo in adult LOPD patients as per the prespecified analysis, the change from baseline for the 6MWD in the cipaglucosidase alfa/miglustat group showed a clinically relevant effect, while the sitting %FVC indicated a stabilisation based on the most adequate and reliable MMRM analysis to further analyse the efficacy data. The clinical benefit of the co-administration of cipaglucosidase alfa and miglustat has thus been demonstrated in a patient population mainly consisting of subjects who are likely to slowly progress as already treated by ERT. The used MMRM analysis was based on the actual time point of assessments (ITT-OBS Population) and excluding the outlying (as requested by the CHMP), the estimated LS mean treatment differences for the 6MWD and the sitting % predicted FVC tended to be more favourable for cipaglucosidase alfa/miglustat than alglucosidase alfa/placebo, respectively.

In contrast with the ERT experienced population (mainly represented in the clinical development programme), the clinical efficacy was less clear in the treatment naïve patients with an observed clinically relevant improvement in 6MWD and a change in sitting % predicted FVC suggestive of a deterioration under cipaglucosidase alfa/miglustat co-administration. Treatment effects in naïve patients were more variable due to the smaller study population. There is no biologically plausible reason that the benefits from the generally more severe and difficult to treat ERT-experienced LOPD population would not be translatable to ERT-naïve LOPD patients. Therefore, the extrapolation of benefit from ERT-experienced to ERT-naïve LOPD patients is considered acceptable.

The inclusion criteria as well as the current indication limits the indicated population to adult LOPD patients.

Considering no or a limited increase in the Cmax and a lower AUC of miglustat in cipaglucosidase alfa-treated patients was observed, the safety profile of cipaglucosidase alfa and miglustat co-administration is not expected to be much different compared to that of cipaglucosidase alfa alone. In support of this, the safety profile of the cipaglucosidase alfa/miglustat co-administration appeared to be overall comparable to that of alglucosidase alfa. The occurrence of treatment-related adverse events tended to be lower upon cipaglucosidase alfa/miglustat treatment as compared to alglucosidase alfa/placebo treatment.

No unexpected safety concerns were observed in the intended use of miglustat and cipaglucosidase alfa co-administration. Infusion-associated reactions upon parenteral administration of LOPD treatment occur soon after administration and may be severe and life-threatening. Because of this, these safety concerns are an important identified risk of cipaglucosidase alfa treatment. The occurrence of infusion-associated reactions, anaphylactic reactions, and hypersensitivity reactions however tended to be less frequent upon cipaglucosidase alfa/miglustat compared to alglucosidase alfa/placebo treatment. This is considered an advantage of cipaglucosidase alfa infusions in combination with miglustat relative to alglucosidase alfa infusions, albeit long term data beyond 24 months are not yet available. Since these risks are considered manageable, the CHMP agreed to collect further data as part of the additional pharmacovigilance activities through the ongoing studies and a prospective and observational registry to be put in place by the applicant.

3.7.2. Balance of benefits and risks

Notwithstanding the lack of a superior result in the active comparison (co-administration of cipaglucosidase alfa and miglustat versus alglucosidase alfa and placebo), the CHMP considered that the observed improvements in treatment effects with cipaglucosidase alfa in combination with miglustat are clinically relevant. Together with the scientific evidence and supportive empirical clinical data with alglucosidase alfa these data demonstrate a positive benefit-risk balance in patients with LOPD Pompe disease (either ERT-experienced or naïve) and thus the co-administration of cipaglucosidase alfa and miglustat constitutes an alternative option to other existing and approved ERTs in this population.

The clinical safety profile of cipaglucosidase alfa in combination with miglustat is overall comparable to that of alglucosidase alfa.

Based on the totality of evidence, the benefit/risk balance of cipaglucosidase alfa in combination with miglustat is positive in the claimed indication.

3.7.3. Additional considerations on the benefit-risk balance

Being engaged in the EMA pilot "CHMP early contact with patient organisations", the following feedback was received.

- All patients expressed the need to be able to adjust the dose of their enzyme replacement therapy until the optimum levels are reached (personalised dosing).
- Most patients expect that a new treatment should stabilise the disease more than existing ones. Some recovery would be welcomed, but experience with alglucosidase alfa might limit this expectation.
- With miglustat, diarrhoea is reported the day the product is taken, which can exacerbate this symptom for people with Pompe disease suffering from gastrointestinal disorders. However, these episodes can be reasonably controlled (no carbohydrate products ingested the day before, and some medications can also help).
- As most patients are taking alglucosidase alfa already, the administration of miglustat in combination with cipaglucosidase alfa poses no problem. The switch might require returning to the hospital for a short period for those receiving infusions at home, which could be a concern during Covid-19 pandemic.
- Only if allergic reactions occurred in the past, then hospital infusions are preferred. However, it is also possible to train nurses for home infusions and to have a prescription for antihistamines at home.

3.8. Conclusions

The overall benefit/risk balance of Pombiliti is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pombiliti is favourable in the following indication(s):

Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Educational materials for home infusion

The MAH must agree on the content and format of the educational materials for use of Pombiliti in home infusion, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials for the use of Pombiliti in home infusion are aimed at providing guidance on how to manage the risk of infusion-related reactions including allergic-type hypersensitivity reactions in a home setting.

The MAH shall ensure that in each Member State where Pombiliti is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe, dispense, or use Pombiliti have access to/are provided with the following educational package:

- Home infusion guide for healthcare professionals
- Patient/caregiver's guide including an infusion diary

The home infusion guide should contain the following key elements:

- Details on the preparation and administration of Pombiliti, including all the steps of preparation, reconstitution, dilution, and administration;
- Guidance on the medical evaluation of the patient prior to administration of the infusion at home;
- Information on signs and symptoms related to IARs and recommended actions for the management of the adverse drug reactions (ADRs) when symptoms occur.

The patient/caregiver's guide should contain the following key elements:

- Information on signs and symptoms related to IARs and recommended actions for the management of the ADRs when symptoms occur.
- An Infusion Diary that can be used to record the infusions and document any product-related IARs, including allergic-type hypersensitivity reactions before, during or after the infusion.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that cipaglucosidase alfa is not to be qualified as a new active substance in itself.

Based on the review of the available data, the CHMP considers that cipaglucosidase alfa in comparison to previously authorised as medicinal product (alglucosidase alfa) in the European Union is not to be qualified as a new active substance as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.