26 April 2023
EMA/CHMP/794405/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Opfolda

International non-proprietary name: miglustat

Procedure No. EMEA/H/C/005695/0000

Note

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

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Table of contents

List of abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
AI	Acceptable intake
ALT	Alanine aminotransferase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AS	Active substance
ASMF	Active substance master file = drug master file
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
BCS	Biopharmaceutics classification system
BDL	Below the limit of detection
CEP	Certificate of suitability of the Ph. Eur.
CHG	Change from baseline
CHMP	Committee for Evaluation of Human Medicinal Products
CI	Confidence interval
CI-MPR	Cation-independent mannose 6-phosphate receptor
CK	Creatine kinase
CL/F	Apparent oral clearance
C_{max}	maximum observed plasma concentration
CMA	Conditional marketing authorisation
CMS	Concerned Member State
CoA	Certificate of analysis
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
CRADA	Cross-reactive alglucosidase alfa ADA
CRS	Chemical reference substance
CSR	Clinical study report

D1	Zero order absorption
DL	Detection limit
DLP	Data lock point
DMF	Drug master file = active substance master file, ASMF
DPH	Diphenhydramine
DSC	Differential scanning calorimetry
EBD	European birth date
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EFD	Embryo-fetal developmental
EMA	European Medicines Agency
EP	European Pharmacopoeia
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)
ESI	Electrospray ionization
EU	European Union
FEED	Fertility and early embryonic development to implantation
FID	Flame ionisation detection
FP	finished product
FT-IR	Fourier transmission infra-red (spectroscopy)
FVC	Forced vital capacity
GAA	Human acid α-glucosidase, may be specified as either GAA enzyme activity or GAA protein
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
GC	Gas chromatography
GCP	Good clinical practices
GD	Gestational day
GLP	Good laboratory practices
GMP	Good manufacturing practices
GOF	Goodness of fit
GSD	Glycogen storage disease

GSGC	Gait, climbing stairs, Gowers' maneuver, and rising from a chair test; a clinical outcome assessment scoring system to assess motor function in Pompe disease
HDPE	High density polyethylene
hERG	Human ether-à-go-go-related gene
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
HPLC	High performance liquid chromatography
HPLC-CAD	High performance liquid chromatography with charged aerosol detector
IAR	Infusion associated reaction
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IgE	Imunoglobulin E
IOPD	infantile-onset Pompe disease
IPC	In-process control test
IR	Infra-red spectroscopy
ITT	Intent-to-treat
ITT-OBS	Intent-to-treat–observed
IV	Intravenous(ly)
Ka	Absorption rate constant
Kd	Equilibrium dissociation constant
KF	Karl-Fischer titration
Ki	Inhibitor constant
KO	Knock-out
LAMP1	Lysosome-associated membrane protein 1
LC-MS/MS	Liquid chromatography mass spectrometry/mass spectrometry
LDPE	low density polyethylene
LLOQ	Lower limit of quantification
LMW	Low molecular weight impurities
LoA	Letter of access
LOCF	Last observation carried forward
LOD	Loss on drying
LoD	Limit of detection
LOPD	Late-onset Pompe disease
LS	Least squares carried forward
M6P	Mannose-6-phosphate
MAH	Marketing authorisation holder
MCID	Minimal clinically important difference

MDD	maximum daily dose
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
MO	major objection
MRHD	Maximum recommended human dose.
MRI	Magnetic resonance imaging
MRM	Multiple reaction monitoring
MS	Mass spectroscopy
Myozyme	Commercially available rhGAA; also referred to as alglucosidase alfa
N/A	Not applicable
NA	Not analysed
NAb	Neutralising antibody
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PBS	Phosphate-buffered saline
PBT	Persistence-bioaccumulation-toxicity
pcVPC	Prediction-corrected visual predictive checks
PD	Pharmacodynamic(s)
PDA	Photo diode array
PDE	Permitted daily exposure
PEC surface water	Predicted Environmental Concentration in surface water
PGE2	Prostanglandin E2
PGIC	Physician’s global impression of change
Ph. Eur.	European Pharmacopoeia
PIC	Powder in capsule
PIL	Patient information leaflet
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PL	Package leaflet
PND	Postnatal day
popPK	Population pharmacokinetics

PP	Per protocol
PRO	Patient-reported outcome
PROMIS	Patient-reported outcomes measurement information system
PSD	particle size distribution
PT	Preferred term
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
Q/F	Apparent intercompartmental clearance
QbD	quality by design
QL	Quantitation limit
QOD	Every other day
QoL	Quality of life
QOS	Quality overall summary
QOW	Every other week
QTcF	QT interval corrected using Fridericia's formula
QTPP	quality target product profile
RH	Relative humidity
rhGAA	Recombinant human acid α-glucosidase
rhGAA	Human recombinant acid A-glucosidase
RMP	Risk management plan
RMS	Reference member state
Rrt	Relative retention time
RSD	Relative standard deviation
Rt	Retention time
Rt	Room temperature
SAE	serious adverse event
SAP	Statistical analysis plan
SAR	structure activity relationship
SD	Standard deviation
SE	Standard error
SGIC	Subject global impression of change
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System organ class
SRT	Substrate reduction therapy
SVC	Slow vital capacity
SWFI	Sterile water for injections
$t_{1/2}$	Half-life

TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TGA	Thermo-gravimetric analysis
TK	Toxicokinetics
TLC	Thin layer chromatography
t_{max}	Time to reach the maximum observed concentration
TSE	Transmissible spongiform encephalopathy
TTC	threshold of toxicological concern
TUG	Timed up and go
ULN	Upper limit of normal
UPLC	Ultra-performance liquid chromatography
UV	Ultra violet spectrometry
V2/F	Apparent central volume of distribution
V3/F	Apparent peripheral volume of distribution (V3/F)
Vd	Volume of distribution
vs	Versus
XRD	X-ray diffraction
y	Years
γ-CD	gamma cyclodextrine

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 Opfolda, 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.

At initial submission, Opfolda was designated as an orphan medicinal product EU/3/18/2129 on 11 January 2019. Opfolda was designated as an orphan medicinal product in the following condition: Treatment of glycogen storage disease type II (Pompe's disease). In March 2023, Opfolda was withdrawn from the Union Register of orphan medicinal products upon request of the applicant.

The applicant initially applied for the following indication:

Opfolda is indicated in co-administration with cipaglucosidase alfa for use in 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:
Opfolda (miglustat) is an enzyme stabiliser of cipaglucosidase alfa long-term enzyme replacement therapy in 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:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Zavesca instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Zavesca, 100 mg hard capsules
- Marketing authorisation holder: Janssen Cilag International NV
- Date of authorisation: 20 November 2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/238/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Zavesca, 100 mg hard capsules
- Marketing authorisation holder: Janssen Cilag International NV

- Date of authorisation: 20 November 2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/238/001

1.3. Information on paediatric requirements

Not applicable

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. 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**
31 May 2018	EMEA/H/SA/3813/1/2018/II	*Dr Hans Ovelgönne and Dr Karl-Heinz Huemer*

The scientific advice pertained to the following non-clinical, and clinical aspects:

Non-clinical:

- Adequacy of the non-clinical safety programme to support a conditional marketing authorisation (CMA).

Clinical: Acceptability of the cipaglucosidase alfa/miglustat programme for a CMA.

- Acceptability of the confirmatory study design.
- Dose selection for the proposed confirmatory study.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Fátima Ventura

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 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 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	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	10 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 agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 December 2022
The applicant submitted the responses to the CHMP List of Outstanding	27 March 2023

Issues on	
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	12 April 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Opfolda on	26 April 2023

2. Scientific discussion

2.1. Problem statement

Zavesca miglustat 100 mg hard capsules are used as the reference miglustat medicinal product in the present application. This medicinal product has been authorised for marketing since 2002 (EU/1/02/238). It is currently authorised for type 1 Gaucher disease and Niemann-Pick type C disease as follows:

Type 1 Gaucher disease

Miglustat is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Miglustat may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

The recommended starting dose for the treatment of adult patients with type 1 Gaucher disease is 100 mg three times a day (i.e. 300 mg/day). Temporary dose reduction to 100 mg once or twice a day may be necessary in some patients because of diarrhoea.

Niemann-Pick type C disease

Miglustat is also indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease (see sections 4.4 and 5.1).

The recommended dose for the treatment of patients aged 12 years and above with Niemann-Pick type C disease is 200 mg three times a day (i.e. 600 mg/day). Dosing in patients under the age of 12 years should be adjusted based on body surface area. Temporary dose reduction may be necessary in some patients because of diarrhoea.

In the present application, miglustat, also referred to as N butyl-deoxynojirimycin [AT2221], is developed for co-administration with cipaglucosidase alfa (also referred to as ATB200, recombinant human acid α-glucosidase [rhGAA]) for the treatment of patients with Pompe disease. A capsule formulation with a lower strength (65 instead of 100 mg) and a lower total daily dose (195/260 mg versus up to 300-600 mg) compared to reference medicinal product has been developed for such intended use.

2.1.1. Disease or condition

The applicant initially applied for the following indication: Opfolda is indicated in co-administration with cipaglucosidase alfa for use in 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). Alglucosidase alfa, is globally approved for the treatment of all subsets of Pompe disease under the tradenames of Myozyme and Lumizyme. Avalglucosidase alfa (Nexviadyme) is also authorised with the same indication in the EU. 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

Miglustat (AT2221, N-butyl-deoxynojirimycin) is a small-molecule enzyme stabiliser that binds to and prevents inactivation of the cipaglucosidase alfa enzyme in the blood, indicated as long-term enzyme replacement therapy (ERT) for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency). Cipaglucosidase alfa is used in co-administration with miglustat. The clinical effectiveness and safety of the monotherapy of cipaglucosidase alfa have not been studied.

The selective binding between cipaglucosidase alfa and miglustat is transient. Dissociation of the cipaglucosidase alfa-miglustat bindings occurs in the acidic environment of the lysosome. 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, Gieke and Pompe disease).

As the major claimed role of miglustat is the stabilisation of cipaglucosidase alfa in the bloodstream and the improvement of the cellular uptake, miglustat is considered an inactive drug constituent of the 2-component therapy.

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.

The extent to which the medicinal product is expected to fulfil the unmet medical need is unclear, and the strength of evidence does not support a justification of major interest from the point of view of public health. 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 hard capsules containing 65 mg of miglustat as the active substance.

Other ingredients are:
- for capsule content: pregelatinised starch (maize), magnesium stearate (E470b), microcrystalline cellulose (E460i), sucralose (E955), colloidal silicon dioxide;

- for capsule shell: gelatin, titanium dioxide (E171), black iron oxide (E172);

- for printing ink: black iron oxide (E172), potassium hydroxide (E525), propylene glycol (E1520), shellac (E904), strong ammonia solution (E527).

The product is available in 40 ml high-density polyethene bottles with polypropylene child-resistant closures with induction seal as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical (IUPAC) name of the active substance miglustat is (2R,3R,4R,5S)-1-butyl-2-(hydroxymethyl) piperidine-3,4,5-triol. It has a relative molecular mass of 219.28 g/mol and the structure shown in Figure 1:

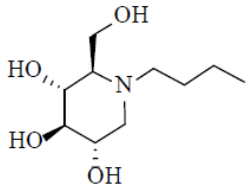


Figure 1: Active substance structure

The active substance (AS) was characterised by ^{1}H- and ^{13}C-NMR, IR, Mass Spectrometry, elemental analysis, DSC and XRPD Analysis. The obtained spectra are in agreement with the structure of the reference standard.

Miglustat is white to off-white crystalline powder, highly soluble in water, soluble in methanol, very slightly soluble in acetone.

It has 4 stereocentres which potentially can give rise to 16 different stereoisomers. Three of the chiral centres are introduced with the starting material already. The synthetic route applied by the manufacturer allows to obtain a single stereoisomer RRRS confirmed by specific optical rotation. The structure was confirmed by X-Ray powder diffraction data.

The AS exists as a single polymorph and no other polymorphs have been observed.

2.4.2.1. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

In the initial application there was a second ASMF proposed. However, there were major objections (MO) raised in relation to the selection of starting materials and the applied control strategy. During the procedure, this ASMF was withdrawn by the applicant therefore those MOs were not relevant anymore.

The manufacturing process consists of 5 steps using 2 starting materials. Both are acceptable and justified as per ICH Q11, and are controlled by agreed specifications.

The manufacturing process has been described in sufficient detail and critical process parameters and IPCs have been stated. Critical steps of the manufacturing process have been identified and verified during validation. Intermediates are clearly defined and controlled by suitable specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. In general, satisfactory information has been provided regarding the fate of potential genotoxic impurities, purging and levels in the final AS (below LoD).

The manufacturing process has been optimised during development in view of the scale up of the process, required for the industrial manufacturing. The introduced changes have been clearly described and adequately justified.

The AS is packaged in double LDPE bag with a desiccant of silica gel, placed inside Al bags and stored inside HDPE drums with HDPE lid. The container closure system complies with EC 10/2011 as amended.

2.4.2.2. Specification

The active substance specification includes tests for appearance (visual), identification (IR, HPLC), assay (HPLC-CAD), related substances (HPLC-CAD), trifluoroacetic acid content (HPLC-CAD), residual solvents (GC), water content (KF), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.), palladium content (ICP-MS) and specific optical rotation (Ph. Eur.).

Acceptable justification of specifications has been provided by the finished product (FP) manufacturer, in line with ICH Q6A recommendations. Limits for residual solvents, specified, unspecified impurities, and residual palladium complies with requirements of ICH Q3C, ICH Q3A or ICH Q3D (R1). Omission of certain parameters from the specification has been adequately justified and supported by relevant data..

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results for AS batches tested by the FP manufacturer were presented. In addition, results from batches tested by the ASMF holder were presented. The results are within the specifications and consistent from batch to batch.

2.4.2.3. Stability

Stability data from four commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, identification, water content, loss on drying, related substances, and assay. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specification limits.

Photostability study has been performed on one batch according to the ICH Q1B guideline. No degradation occurred after 48 hours of exposure.

Furthermore, a stress study has been performed under basic and acidic conditions; oxidative conditions; high temperature; exposure of the solution and the powder to sunlight and UV light. The study revealed the most significant degrading conditions to be basic and oxidising conditions (formation of N-oxide derivate) and demonstrated the related substances method is stability indicating.

Overall, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months without special storage conditions is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The FP is an immediate release, hard capsule for oral administration containing 65 mg miglustat. The capsules are size 2 with an opaque white body and grey opaque cap containing white to off-white powder. "AT2221" is printed with black ink on the capsule body.

The Opfolda 65 mg hard capsules application was submitted as hybrid marketing authorisation application in accordance with Article 10(3) of Directive 2001/83/EC with Reference Product Zavesca 100 mg capsules (centrally authorised product registration) for combined use of miglustat with cipaglucosidase alfa for the treatment of Pompe disease. The aim of the pharmaceutical development was to develop an immediate release oral dosage form, which contains 65 mg of miglustat as the active substance presented in the form of hard capsules. Different excipients are used in Opfolda in comparison with the reference product Zavesca. As Opfolda is developed in different strengths and for different indications and dosage regimens compared with reference product Zavesca direct comparison of main pharmaceutical characteristics with reference product Zavesca was not considered necessary.

The development has been performed according to the ICH Q8 using quality by design (QbD) approach. The dry blend formulation containing 65 mg of miglustat and widely used excipients (microcrystalline cellulose, pregelatinised starch, sucralose, magnesium stearate, and colloidal silicon dioxide) filled in the size 2, hard gelation capsule shells has been developed. The choice of excipients is justified, and their functions are explained. All excipients are compendial with a history of safe use in human medicine. There are no novel excipients. The list of excipients is presented in section 6.1 of the SmPC. and in paragraph 2.4.1 of this report.

The compatibility of the AS and the selected excipients was shown by a relevant study in binary mixtures and was further confirmed by FP forced degradation study, long-term and accelerated stability studies.

Except for the capsule shell colour and printing, the same quantitative composition as the intended commercial formulation was used throughout Phase 1/2 and Phase 3 clinical trials. The changes introduced during development have no impact on dissolution performance and bioavailability; therefore, the batches used throughout the clinical development are considered representative for the commercial product to be marketed. The FP quality target product profile (QTPP) and critical quality attributes (CQAs) of the FP have been evaluated, and an acceptable control strategy has been defined.

The CQAs that may be affected by the manufacturing process are appearance, identification, assay, related substances, content uniformity, dissolution, water content and microbial limits. Microbiological studies suggest no potential for microbial growth in the FP formulation.

The applicant has applied QbD principles to develop the manufacturing process; however, no design spaces were claimed for the manufacturing process of the finished product. The selected manufacturing process comprises screening/deagglomeration, blending, encapsulation and packaging. Through a risk-based approach, critical and non-critical process parameters have been defined. Their

impact on the FP CQAs has been discussed. These CQAs are routinely controlled in accordance with specification. Measures to mitigate the risks have been discussed and an updated risk assessment was presented. Parameters that were assessed as non critical will still be monitored and assessed throughout the commercial lifecycle of the product. During manufacturing, critical process parameters are maintained within established ranges determined by the applicable proven acceptable ranges or parameter setpoints.

During development the physicochemical characteristics of the AS, such as high aqueous solubility, hygroscopic properties, stability, particle size, polymorphism and biopharmaceutical class has been taken into consideration. The AS is classified as BCS Class I/III, hence the dissolution rate is not considered as a high risk factor.

Dissolution data showed that the FP dissolves rapidly (>80% in 15 minutes) in the physiological range. Lack of discriminative power for dissolution method has been justified based on the requirements of ICH Q6A Decision Tree #7 as it was demonstrated that dissolution does not affect bioavailability and changes in formulation and manufacturing variables do not affect dissolution in media over the range pH 1 – 6.8.

The container closure system is high density polyethylene (HDPE) 40 cc bottles, closed with induction sealed, polypropylene child resistant closure. The choice of packaging materials is properly justified. Moisture vapor permeation and light transmission tests on the bottles were evaluated. The container closure systems meet requirements of the EC Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. The risk of interaction between packaging components and a solid oral dosage form is considered low. The suitability of the container closure system for commercial use and compatibility of the container closure system with the finished product is demonstrated with satisfactory stability data provided. Compliance of the child resistant closure with ISO standard 8317:2015 is confirmed. Two pack sizes are proposed with 4 and 24 capsules.

2.4.3.1. Manufacture of the product and process controls

The manufacturing sites involved in the finished product manufacturing process have been stated and their GMP status has been confirmed.

The FP manufacturing process can be considered a standard process comprising a dry mixing process followed by encapsulation.

Manufacturing process has been described in sufficient detail. The process parameters that have been identified during development studies as critical, non-critical are controlled during the manufacturing process in ranges or set points.

The proposed blend hold time prior to encapsulation has been supported by an appropriate study. For bulk capsules the proposed hold time prior to packaging has been supported by relevant stability data and is thus acceptable . The CHMP requested and the applicant committed to provide additional stability data on another batch post approval (REC). The container closure system of bulk capsules has been described and compliance to EC Regulation (EU) No 10/2011 is confirmed for bulk packaging.

Although the manufacturing process is standard for this type of dosage form, process validation study has been conducted on three commercial scale batches. The results comply with the acceptance criteria; it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The commercial batch size has been stated. Opfolda has orphan status; therefore the proposed commercial batch size is considered justified in accordance with *EMA/CHMP/QWP/245074/2015 Guideline on manufacture of the finished dosage form.*

2.4.3.2. Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (TLC, HPLC), assay (HPLC-CAD), content uniformity (Ph. Eur.), dissolution (HPLC-CAD), related substances (HPLC-CAD), water content (Ph. Eur.), limit of nitrosamines (LC-MS/MS) and microbial examination (Ph. Eur.).

The proposed specification follows the ICH guidelines Q6A, Q3B and Ph. Eur. and reflects common quality specifications for this type of product (capsules). An acceptable justification of each specification parameter was provided.

The impurity limits were set as per the ICH Q3B taking into account the maximum daily dose following the SmPC is 260 mg and are, therefore, acceptable.

The dissolution acceptance criterion was set based on the historical performance of the product across the development program, including dissolution profiles at release and on stability. The dissolution rate is not considered as a high-risk factor. Some variability in dissolution results observed during stability studies has been satisfactorily discussed. The selected dissolution method is considered adequate. Furthermore, from in-vivo clinical performance data for the corresponding batches it was concluded that both batches were acceptable from C_{max} and AUC perspective. Considering the overall information, the dissolution limit is considered to be in-line with the principles described in the guidance document EMA/CHMP/CVMP/QWP/336031/2017 and, therefore, is accepted.

An elemental impurities (EIs) risk assessment was performed on the FP. The risk assessment was performed in line with the ICH Q3D(R1) guideline in batches of FP by a validated method. Based on the obtained results the applicant concludes that the tested elements are below 25% of the Option 1 limits. The submitted discussion on elemental impurities is considered sufficient and it is agreed that routine testing of FP for elemental impurities is not required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed. However the provided documentation was incomplete and a MO was raised by the CHMP on nitrosamine testing.

In response to the MO, the company presented a validated method for the control of these impurities. The calculated limits for each nitrosamine impurity and the limit for total impurities are acceptable considering the acceptable intakes (AI) and maximum daily dose. Considering the above stated and on risk-based approach the absence of the control of nitrosamines in the shelf-life specification is accepted.

In addition, in the updated risk evaluation submitted in response to the MO, a risk for potential formation of nitrosamine impurities was identified. The theoretical chemical pathway for N-nitrosation process of active substance and its impurities were provided; two possible nitrosamines were identified.

The applicant has conducted a structure activity relationship (SAR) analysis for chemistry, mutagenicity, and carcinogenicity risk assessments concerning the potential presence of above-mentioned nitrosamine impurities. The SAR approach was described, including the surrogate selection

process, and calculations of the acceptable intake (AI) and AI limit. The proposed AI limit is based on EMA/409815/2020 Rev. 14, Question 10 and on the maximum daily dose of 260 mg. The provided information is acknowledged, however, the acceptable intake based on SAR approach would normally have to be reviewed and adopted by the NCWP.

Nevertheless, the applicant has developed and validated a new highly sensitive test method that is able to detect and quantify these two nitrosamines. The proposed approach is considered acceptable. The method specificity has been shown. Furthermore, an acceptable detection (LoD) and quantitation limits (QL) have been demonstrated. The achieved QL is far below the 10% AI limit by SAR approach, but importantly, it is also 10% of the AI limit that is derived from the default class specific TTC/AI of 18 ng/day (based on MDD of 260 mg).

In addition the confirmatory testing of three finished product batches by the validated method has been performed as requested.

Since it is demonstrated that the presence of the potential nitrosamines is consistently below 10% of the acceptable limit based on AI of 18 ng/ml in the finished product, it can be concluded that intake of N-nitrosamine impurities does not exceed the threshold of toxicological concern (TTC) of 18 ng / day in the finished product. Based on provided assessment it can be concluded that there is no risk of active substance-related nitrosamines formation, and a test for these nitrosamines can be omitted from the specification.

Overall, the MO has been resolved; the updated risk evaluation concerning the presence of nitrosamine impurities is considered acceptable and is 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 Rev 14).

The analytical methods for all test parameters in the specification have been described in detail. Validations of in-house methods have been performed in accordance with ICH Q2 (R1) guideline. Stability indicating properties of the HPLC method used to determine assay and impurities was demonstrated by forced degradation studies. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analyses are provided for three commercial scale batches. All results are within the limits of the proposed specification. Batch analysis results confirm the consistency and uniformity of the product.

2.4.3.3. Stability of the product

Stability studies are performed on 3 commercial scale batches manufactured at the proposed commercial site using the commercial formulation and manufacturing process, and packaged in the same container closure system as proposed for marketing.

Samples were stored for 12 months under long term storage at 30°C /75% RH, and for 6 months accelerated storage conditions 4 °C /75% RH. It is noted that for long-term testing, the applicant uses more stringent humidity conditions such as 30°C /75% RH compared to long-term storage conditions 30°C /65% RH required by the ICH Q1A; such an approach is considered acceptable. The frequency of testing was in-line with the ICH Q1A requirements.

In addition, stability data was provided for another 3 batches manufactured at the same site according to the same process but packed in different colour capsules. The difference in composition between the

different capsule shells are negligible, and the impact on the stability due to the change of capsule colour is minimal. Thus, it is agreed that these batches are considered representative of the commercial product and may be used for FP stability evaluation. These batches, were stored for up to 36 months at 30°C /65% RH (2 batches) and for 6 months at 40°C /75% RH, in-line with the ICH Q1A requirements.

All results meet specification criteria at all tested conditions. A slight increase in water content was observed during storage. There is no trend that dissolution profile changes over time in any of the stability studies, but variability from time point to time point is observed in some batches as discussed previously. No other trends were observed in any of the parameters for any of the batches. The specifications and test methods (assay/related substances by HPLC/CAD) have changed during stability studies but details were described, and a comparison of methods was provided.

A photostability study in-line with ICH Q1B has been performed using on one batch. Based on the study results, it is demonstrated that Opfolda capsules are not sensitive to light and therefore no special precautions for storage are needed.

An in-use stability study was performed on one batch. The study design simulates the posology described in SmPC. The drug product demonstrates good stability in long-term and accelerated conditions; there are no signs that the FP might be susceptible to deterioration. According to the EMA Quality Q&A, in such cases, in-use stability studies do not need to be undertaken. Also, the performed in-use study of one batch does not show significant changes . According to the EMA Quality Q&A, since no relevant deterioration is observed, no in-use shelf life should be set in the SmPC.

Based on provided stability data, the proposed 36 months shelf-life without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.4.3.4. Adventitious agents

The gelatin used in the hard gelatin capsule shells is of animal origin. Valid certificates of Suitability granted by the EDQM for demonstrating TSE compliance for gelatin used in the production of the hard capsules have been provided. Gelatin complies with the current *"Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 rev. 3)."*

There are no other excipients of human or animal origin.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner.

The MOs raised during the procedure in relation to the selection of starting materials and the control strategy applied by one of the ASMF holders were resolved, as the ASMF was withdrawn by the applicant.

The MO raised during the procedure regarding the risk of nitrosamines impurities formation and their control strategy has been resolved by provision of additional information and suitable updating of the risk assessment required by the relevant guidance documents.

The FP manufacturer applied quality by design (QbD) concepts to develop the medicinal product however, no design-space is claimed.

The results of tests carried out indicate satisfactory 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 the clinic.

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, which pertain to bulk hold time. This point is put forward and agreed as recommendation 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.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- the applicant commits to perform a finished product bulk hold time study on one additional batch and submitted the results by 4Q 2023.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical dossier relies on the results of preclinical data from a reference medicinal product and/or applicant's own non-clinical data to support the intended use of miglustat in co-administration with cipaglucosidase alfa for the treatment of Pompe disease. Since the applicant has obtained a right-of-reference from the MAH for Zavesca to permit access to the product's data, cross references to relevant non-clinical data of the reference medicinal product are made below.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

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 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

Miglustat was tested for its inhibitory activity against selected key enzymes in carbohydrate metabolism: Isolated α-glucosidase from porcine liver, ß-glucosidase from almond and hexokinase from yeast. Ki's for miglustat were 0.22 µM for α-glucosidase and 1125 µM for ß-glucosidase. Miglustat did not inhibit hexokinase.

Fetal fibroblast and/or peritoneal macrophages were incubated for different periods of time with or without a dose dependent concentration of miglustat (up to 6 mg/ml). After the pre-incubation period, the cells were stimulated with bradykinin, ionophore and arachidonic acid to determine the effect of the compound on receptor-mediated vs receptor-independent release of PGE2. PGE2 was measured by available radio-immunoassays. Miglustat did not inhibit PGE2 synthesis. Hence, it was concluded that miglustat should not demonstrate any anti-inflammatory activity.

Miglustat does not inhibit key enzymes involved in carbohydrate metabolism, nor is it likely that miglustat will have anti-inflammatory activity.

2.5.2.3. Safety pharmacology programme

An *in vitro* GLP study was completed to determine the potential proarrhythmic effect of miglustat. The in vitro effects of AT2221 on ionic currents in voltage-clamped human embryonic kidney cells (HEK-293) that stably express the human ether-à-go-go-related gene (hERG) were determined. Two concentrations of AT2221 (100 µM and 1000 µM) were tested at near-physiological temperature.

AT2221 inhibited hERG current by (Mean ± SEM; n = 3) -3.1 ± 1.1% at 100 µM and -3.4 ± 2.2% at 1000 µM versus 1.1 ± 1.2% in control. hERG inhibition at 100 µM and 1000 µM were not statistically significant when compared to vehicle control values. The IC50 for the inhibitory effect of AT2221 on hERG potassium current was not calculated but was estimated to be greater than 1000 µM.

The positive control article terfenadine inhibited hERG potassium current by (Mean ± SD; n = 2) 88.9 ± 2.4% at 60 nM.

2.5.2.4. Pharmacodynamic drug interactions

No new studies have been conducted and this is considered acceptable by the CHMP.

2.5.3. Pharmacokinetics

A short overview of all pharmacokinetics studies performed with miglustat was submitted. These studies involved single-dose administration of miglustat in wild-type and *Gaa* KO mice, as well as cynomolgus monkeys.

Validation reports for the analytical methods used, demonstrating the suitability of the methods, storage and handling for the purpose of analysis of miglustat were submitted. Specific and sensitive bioanalytical assays were developed and validated for the quantitative determination of miglustat in rat, rabbit and monkey plasma. These methods utilised a solid-phase extraction procedure, followed by liquid chromatography (together with internal standard) using reversed-phase chromatography and subsequent LC-MS/MS analysis in the positive ESI-MRM mode.

Absorption

The absorption of miglustat was studied in wild-type and *Gaa* KO mice, as well as in cynomolgus monkeys.

Wild-type mice were dosed orally with 0, 1, 3, 10, and 30 mg/kg miglustat, which resulted in fast absorption, with t_{max} values ≤0.4 hours. C_{max} and AUC values showed dose-proportional increases. Finally, the mean plasma t½ of miglustat was quite short following oral administration for all doses tested (≤0.5 hours).

The plasma PK profile of miglustat was also evaluated following co-administration with cipaglucosidase alfa in *Gaa* KO mice. These mice were dosed with 20 mg/kg cipaglucosidase alfa intravenously and 0, 10 and 30 mg/kg miglustat orally. The plasma $t_{1/2}$ values obtained from this study were similar to the half-life obtained in the wild type mice dosed with miglustat only, with $t_{1/2}$ values of ≤0.6 hours for miglustat upon co-administration with cipaglucosidase alfa.

In cynomolgus monkeys dosed orally with 25, 250 and 1000 mg/kg miglustat, C_{max} and AUC values increased in a less-than dose-proportional manner, although emesis for the 250 and 1000 mg/kg groups could bias this observation. Absorption was fast, with t_{max} for all three groups observed from 1.0 to 1.5 hours. The plasma half-life observed for the various dosing groups ranged from 3.9-5.4 hours, indicating a longer half-life of miglustat in monkeys compared to mice.

Distribution

Distribution was studied in C57BL/6 wild-type mice dosed orally with 10 and 30 mg/kg miglustat, and tissue PK was assessed using quadriceps muscle. The maximum concentrations were observed after 0.45 and 0.90 hours, indicating fast distribution to muscle tissue. The exposure to miglustat increased linearly with an increase in dose for both C_{max} and AUC values. The tissue $t_{1/2}$ was calculated at 1.4 hours for 10 mg/kg dose and at 1.2 hours for 30 mg/kg dose, indicating increased half-life in muscle when compared to plasma, instead of the 24 hours reported in the non-clinical overview.

Metabolism

No new studies have been conducted and this is considered acceptable by the CHMP.

Excretion

No new studies have been conducted and this is considered acceptable by the CHMP.

Pharmacokinetic drug interactions

No new studies have been conducted and this is considered acceptable by the CHMP.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No new studies have been conducted and this is considered acceptable by the CHMP.

2.5.4.2. Repeat dose toxicity

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

No new studies have been conducted and this is considered acceptable by the CHMP.

2.5.4.4. Carcinogenicity

No new studies have been conducted and 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

Toxicokinetic studies for miglustat were performed in monkeys in a repeated-dose study.

Cynomolgus monkeys were dosed orally every other week up to 13 weeks with up to 175 mg/kg miglustat in the presence or absence of 100 mg/kg cipaglucosidase alfa (intravenously administered). There was no consistent effect of animal gender on miglustat TK parameters. The t_{max} ranged from approximately 2 to 4 hours post-dose. Miglustat exposure increased with doses between 25 and 175 mg/kg. The mean $t_{1/2}$ (males and females combined) was consistent on Days 1 and 85 and ranged from 6.7 to 8.2 hours. Little to no accumulation was observed with repeated once every other week oral administration. There was no observable effect of cipaglucosidase alfa co-administration on overall miglustat exposure (*i.e.*, AUC_{0-t}) or other TK parameters. The exposure multiples for miglustat monotherapy were ~10 for male and female, indicating sufficient exposure for toxicity testing. Co-administration resulted in similar or slightly higher exposure multiples.

Toxicokinetics were also performed as part of reproduction-toxicology studies. In a FEED study using rats that were dosed every other day with 60 mg/kg miglustat in the presence or absence of 400 mg/kg cipaglucosidase alfa, there was no evidence for accumulation in both the males (dosed up to day 28) and females (dosed up to GD7), based on AUC values. Also, there were no differences between the exposure of both sexes after day 1 dosing. The exposure multiples for miglustat monotherapy were ~9 and ~11 for male and female, respectively, indicating sufficient exposure for toxicity testing. Co-medication resulted in significantly higher exposure multiples.

Two EFD were performed, using rat and rabbit. In the rat EFD study, female rats were dosed with 60 mg/kg miglustat in the presence or absence of 400 mg/kg cipaglucosidase alfa. No accumulation of miglustat was observed after multiple doses in both groups. Co-administration with cipaglucosidase

alfa resulted in ~2-2.5-fold higher AUC_{0-24} values when compared to miglustat monotherapy on GD 6 and 18. The exposure multiple for the monotherapy and co-administration groups were ~14 and ~29, respectively, indicating sufficient exposure for toxicity testing. In the rabbit EFD study, female rabbits were dosed with 25 mg/kg miglustat in the presence or absence of 175 mg/kg cipaglucosidase alfa. No accumulation of miglustat was observed after multiple doses in pregnant rabbits. The mean C_{max} and AUC_{0-24} values for miglustat were slightly higher in the co-administration group as compared to the miglustat monotherapy group, with differences of less than 2-fold. The exposure multiple for the monotherapy and co-administration groups were ~13 and ~22, respectively, indicating sufficient exposure for toxicity testing.

Furthermore, the single-dose pharmacokinetic behaviour of miglustat was studied in mice and monkeys as an interspecies comparison. Based on the data, the half-life of miglustat ranged from 0.2-0.6 hours in mice to 3.9-5.4 hours in the monkey. Absorption was fast, ranging from 0.3-0.4 hours in mice to 1-1.5 hours in the monkey. No accumulation was also observed upon multiple-dosing for any of the species used for PK (mice and monkey) and toxicology (rat and rabbit) studies.

2.5.4.7. Local tolerance

No new studies have been conducted and this is considered acceptable by the CHMP.

2.5.4.8. Other toxicity studies

No new studies have been conducted and this is considered acceptable by the CHMP.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): Miglustat			
CAS-number (if available): 72599-27-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	D_{ow}: -2.92 (pH 5) D_{ow}: -1.15 (pH 7) K_{ow}: -1.38 (pH 9)	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater, refined}$	0.00028	µg/L	< 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

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.

Miglustat does not inhibit key enzymes involved in carbohydrate metabolism, nor is it likely that miglustat will have anti-inflammatory activity.

Miglustat did not show any potential to inhibit the hERG channel at the tested concentrations.

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.

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.

Miglustat $PEC_{surfacewater}$ is below the action limit of 0.01 µg/L and miglustat is not a PBT substance as log K_{ow} does not exceed 4.5.

Therefore, miglustat 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 miglustat 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	Safety and efficacy	N = 115[b] 47.9 (22 to 75) y[c]	20 mg/kg cipaglucosidase alfa IV + 195/260 mg

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
	Study ATB200-03 Phase 3		61 sites	miglustat oral capsules QOW[a]

d 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

No BCS based biowaiver has been applied for, nor a bioequivalence study was submitted. Instead, pharmacokinetic data after a single dose is compared between Opfolda (65 mg capsule) and Zavesca (100 mg capsule) to bridge to the general pharmacokinetics properties obtained for miglustat from Zavesca. Dose normalised data indicate that the pharmacokinetics are comparable after administration of Opfolda and Zavesca. However this was based on absolute values only, and therefore ranges/confidence intervals were requested to further support the bridging to the reference medicinal product. Comparing different studies and using an analysis of variance (ANOVA) on the dose-normalised Cmax and AUC, data showed that both formulations can be considered bioequivalent. Next to this bridging, specific pharmacokinetic data is obtained for Opfolda co-administered with cipaglucosidase alfa in patients with Pompe disease.

A popPK analysis was made in order to characterise the pharmacokinetics of miglustat when administered with cipaglucosidase alfa. For plasma miglustat, a 2-compartment popPK model provided the best and most parsimonious fit to the data. The base (and final) model was parameterised in terms

of CL/F, apparent intercompartmental clearance (Q/F), apparent central volume of distribution (V2/F), and apparent peripheral volume of distribution (V3/F). The oral absorption phase in the base model was characterised with a sequential zero- and first-order absorption model, where there was a zero-order input into the depot (dosing compartment) followed by first-order absorption into the central compartment. The model was parameterised in terms of absorption rate constant (ka) and duration of zero-order absorption (D1). The base (and final) model included a shared estimated weight effect on CL/F and Q/F and a shared estimated weight effect on V2/F and V3/F.

The final miglustat PK model expanded the base model to include covariate effects. As with the base model, the final model included a shared estimated weight effect on CL/F and Q/F, and a shared estimated weight effect on V2/F and V3/F. Additionally, the effects of age, race (ie, Asian versus non-Asian), sex (male versus female), and ERT history (naïve versus experienced) were estimated on CL/F. The final model resulted in acceptable fixed effect parameters estimates and random effect parameter estimates with acceptable Shrinkage. GOF plots were also acceptable without any major trends and the pcVPCs demonstrated that model-predicted miglustat concentrations were in reasonable agreement with observed concentrations. The median and 5^{th}/95^{th} percentiles of the observed data were in close agreement with the distributions summarised from 500 simulated replicates for all treatment groups. Overall, the method seems generally acceptable. Only data from study ABT200-03 and study ATB200-02 was used.

Body weight, age and race appeared to affect miglustat PK. The popPK analysis predicted a higher Vss/F and Cl/F (500 l and 5.7 l/h) compared to non-compartmental analysis (100 l and 11 l/h, respectively). Furthermore, only data were included from patients and not from healthy subjects. This should be clarified and justified, considering an update of the model. In a further justification it was shown that the model predicted the non-compartmental data from study ATB200-02 sufficiently, but that due to inclusion of data from study ATB200-03 it resulted in the shift in Vd and CL/F, which may be due to the numerical more data included from study ATB200-03 compared to study ATB200-2. This seems plausible. Furthermore, data from patients were retrieved already from dense sampling data, and it was considered that adding the healthy subject data would not have a relevant contribution, which can be agreed.

Co-administration of miglustat reduced cipaglucosidase alfa linear clearance by approximately 26% for the 130 mg dose and by 37% for > 130 mg doses (mainly 260 mg). Co-administration of miglustat increased cipaglucosidase alfa AUC by approximately 22% for the 130 mg dose and by 35% for > 130 mg dose.

Immunogenicity markers did not have an obvious impact on miglustat PK disposition.

Absorption

The absolute bioavailability after oral administration of miglustat has not been determined. Maximum plasma concentrations are reached about 3 hours after dosing.

The 100 mg capsule with a standard high fat meal decreased Cmax by 36% and AUC by 14%. Food delayed tmax by 2 hours.

At the clinical dose, 260 mg, plasma miglustat attained a Cmax of approximately 3000 ng/ml and an AUC0-∞ of approximately 25,000 ng h/ml.

Distribution

Miglustat does not bind to plasma proteins.

The volume of distribution after oral administration is about 78 to 103 l (terminal phase volume of distribution was approximately 90 l), which is greater than total body water (42 l).

Miglustat crosses the blood-brain barrier.

Elimination

Based on the reference medicinal product, miglustat is mainly eliminated by renal excretion, with the urinary recovery of unchanged drug accounting for 70-80% of the dose. Following administration of a single dose of 100 mg ^{14}C-miglustat to healthy volunteers, 83% of the radioactivity was recovered in urine and 12% in faeces. Several metabolites were identified in urine and faeces. The most abundant metabolite in urine was miglustat glucuronide accounting for 5% of the dose.

Miglustat clearance in patients with Pompe disease was about 10.5 l/h, independent of the dose or co-administered with cipaglucosidase alfa. The popPK estimated clearance was lower and estimated to be 5.7 l/h. This was additional clarified by the applicant, due to the numerical more data included from study ATB200-03 compared to study ATB200-2 (see before).

The miglustat elimination half-life was about 6 hours.

Dose proportionality and time dependencies

Plasma miglustat Cmax and AUC increased dose-proportional over the 130 – 260 mg dose range, co-administered with cipaglucosidase alfa.

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 miglustat exposure. Body weight appeared to be a covariate for miglustat exposure. An increase of body weight increases AUC and Cmax. AUC was 24% lower in a subject weighing 104 kg, while AUC was about 24% higher in a subject weighing 51 kg, compared to a reference non-Asian, ERT-naive, 70 kg, 50-year-old male. However, a lower dose is recommended for a subject weighing 40 – 50 kg.

Pharmacokinetic interaction studies

Literature data indicate that miglustat may inhibit intestinal disaccharidases such as sucrase, maltase and isomaltase in the gastrointestinal tract leading to reduced absorption of dietary disaccharides.

Pharmacokinetics using human biomaterials

Based on the reference medicinal product, a low potential for clinically relevant drug-drug interactions with CYP450 isoenzymes has been identified. However, a full panel of transporter-mediated in vitro studies has not been completed at the present time.

2.6.2.2. Pharmacodynamics

Mechanism of action

Miglustat was developed for oral administration in conjunction with cipaglucosidase alfa to ensure its stability at neutral pH and delivery of active enzymes to muscle and lysosomes. Miglustat concerns a pharmacokinetic enzyme stabiliser of cipaglucosidase alfa.

Miglustat binds selectively with cipaglucosidase alfa in the blood during infusion; thereby stabilising the conformation of cipaglucosidase alfa and minimising the loss of enzyme activity while in circulation. This selective binding between cipaglucosidase alfa and miglustat is transient with disassociation occurring in the lysosome. Miglustat alone has no effect on glycogen reduction.

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.

Based on the reference medicinal product, miglustat levels are likely to affect the production of glycosylceramide and glycosylceramide-derived glycosphingolipids as a secondary pharmacological effect. Although glycosphingolipid levels may decrease in the first hours post-dose at the recommended miglustat posology, a lasting physiologic effect is not expected in Pompe disease patients.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

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

Apparent differences in the pharmacokinetics of miglustat was observed in healthy volunteers and patients with Pompe disease, respectively. Non-compartmental analysis indicated a higher volume of distribution and elimination half-life in patients, 160 l vs. 100 l and 9.6 h vs. 6 h, respectively. This

may be explained by the difference in blood sampling scheme. Blood samples were collected for a longer period of time post-dose for healthy subjects compared to patients, leading to a different elimination half-life in healthy volunteers, which also resulted in a higher Vd.

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 ERT-experienced ambulatory patients, at the 260 mg miglustat dose level, early exposure (AUCtmax-24h) increased 43.6%, AUC0-inf increased 29.1%, and clearance decreased by 26.8%. In ERT-naïve ambulatory patients, early exposure (AUCtmax-24h) increased 47.5%, and AUC0-inf increased 31.7%. In addition, plasma levels were significantly increased at 12h and 24h after the start of infusion.

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. This is considered acceptable based on the above data.

Moreover, the SmPC indicates that patients should fast 2 hours before and 2 hours after taking Opfolda. 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.

Furthermore, the posology is based on body weight. For patients weighing ≥ 50 kg, the recommended dose is 4 capsules of 65 mg (260 mg total). For patients weighing ≥ 40 kg to < 50 kg, the recommended dose is 3 capsules of 65 mg (195 mg total).

During the procedure, additional popPK data showing comparable adult exposure were submitted to support the proposed dose of 195 mg in subjects weighing 40 - 50 kg and such posology was considered acceptable for this specific population. In subjects >100 kg, the exposure was 24% lower. At CHMP request, further simulation were performed to investigate the need for an increased dose. Additional data showed that % occupancy would not significantly increase in case a higher miglustat dose would be administered to subjects weighing >90 kg, compared to subjects weighing <90 kg. Thus the CHMP recommended a normal dose of 260 mg for subjects weighing > 100 kg.

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

Modelling and simulation suggested that 260 miglustat QOW did not accumulate in subject with renal clearance ≥ 25 ml/min. Thus no dosing adjustment has been recommended by the CHMP for renal impaired patients, despite noting the reference medicinal product tid dosing is not recommended for subjects with severe renal impairment or end-stage renal disease.

In addition no dosing adjustment is necessary for the hepatic impaired patients since miglustat is not expected to be impacted by hepatic impairment and is not bound to plasma proteins, eliminated for 70 – 80% as an intact drug in the urine, and only 12% of a labelled dose was recovered in faeces.

Based on the reference medicinal product, a low potential for clinically relevant drug-drug interactions with CYP450 isoenzymes has been identified. However, a full panel of transporter-mediated in vitro studies has not been completed at the present time.

In the clinical studies, 2 formulations were used in phase I/II and phase III studies respectively. The formulation for phase I/II studies contains only miglustat powder and the phase III studies used the "to be marketed" formulation. Both formulations were shown bioequivalent under fasting conditions. In addition, bioequivalence was also shown for the "to be marketed" formulation when administered as

whole vs. reconstituted in 180 ml of water. Based on these data, the SmPC reflects that miglustat 65 mg capsule can be swallowed whole and taken on an empty stomach.

Pharmacodynamics

Miglustat bound to cipaglucosidase alfa stabilises cipaglucosidase alfa in the circulation. This increases the cipaglucosidase alfa exposure, possibly resulting in a more pronounced clinical effect.

Although glycosphingolipid levels may decrease in the first hours post-dose at the recommended miglustat posology, a lasting physiologic effect is not expected in Pompe disease patients. Based on the assumptions that the lysosomal bioavailability is increased by both the added M6P residues and the coadministration of miglustat, it is plausible that the combined pharmacological effects of cipaglucosidase alfa and miglustat will increase the clinical effects upon long-term treatment in patients with Pompe disease.

Miglustat is used as an enzyme stabiliser of cipaglucosidase alfa but exerts no pharmacodynamic effects itself. Observed pharmacodynamic effects are due to cipaglucosidase alfa of which the systemic availability is enhanced by miglustat.

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 additive effects of miglustat to cipaglucosidase alfa have not been evaluated in conducted clinical studies.

Two biomarkers were evaluated in studies ATB200-02 and ATB200-03. These were creatine kinase (CK), an indicator of muscle damage in Pompe disease, and urine Hex4, a disease substrate. 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.

A positive dose-response relationship was demonstrated for the combined use of cipaglucosidase alfa and miglustat with respect to pharmacodynamics (Hex4 and CK).

Miglustat-related QTc prolongation or changes in other ECG parameters were evaluated and did not suggest that miglustat and/or cipaglucosidase alfa induce clinically relevant QTc prolongations.

Regarding miglustat dosed at 260 mg every 2 weeks with cipaglucosidase alfa, plots of conditional weighted residual and normalised prediction distribution errors did not show obvious trends in effects

of immunogenicity markers on miglustat pharmacokinetics. The estimated covariate effects were generally close to the null value, with 95% CIs containing the null value. Overall, these immunogenicity markers did not impact miglustat PK in a clinically meaningful manner.

Subgroups

Miglustat-dosing is body weight-dependent in adult patients with late-onset Pompe disease. For patients weighing ≥ 40 kg to < 50 kg, the recommended miglustat dosing is 195 mg once every 2 weeks. For patients weighing ≥ 50 kg, the recommended miglustat dosing is 260 mg once every 2 weeks. The impact of body weight on biomarker (CK, Hex4) and functional endpoints at a particular miglustat dosage for late-onset Pompe disease in adults was initially unclear. Later, it was shown that there is little correlation between body weight and biomarker and functional endpoints in LOPD patients. Hence, similar pharmacodynamic and clinical effects are expected for patients with varying body weight. This supports the appropriateness of proposed single miglustat dosing regimen for all patients weighing 50 kg or more.

2.6.4. Conclusions on clinical pharmacology

Miglustat was developed for oral administration in conjunction with cipaglucosidase alfa to ensure its stability at neutral pH and delivery of active enzyme to muscle and lysosomes. Miglustat alone has no specific effects on glycogen reduction in Pompe disease. The individual contribution of the mannose enriched cipaglucosidase alfa, and miglustat to the observed combined pharmacodynamic effects has not been evaluated.

The available study data on pharmacodynamics support the pharmacodynamic effects of cipaglucosidase alfa in combination with miglustat in ERT-naïve and ERT-experienced late-onset Pompe disease patients.

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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- A full panel of transporter-mediated in vitro studies

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 6).

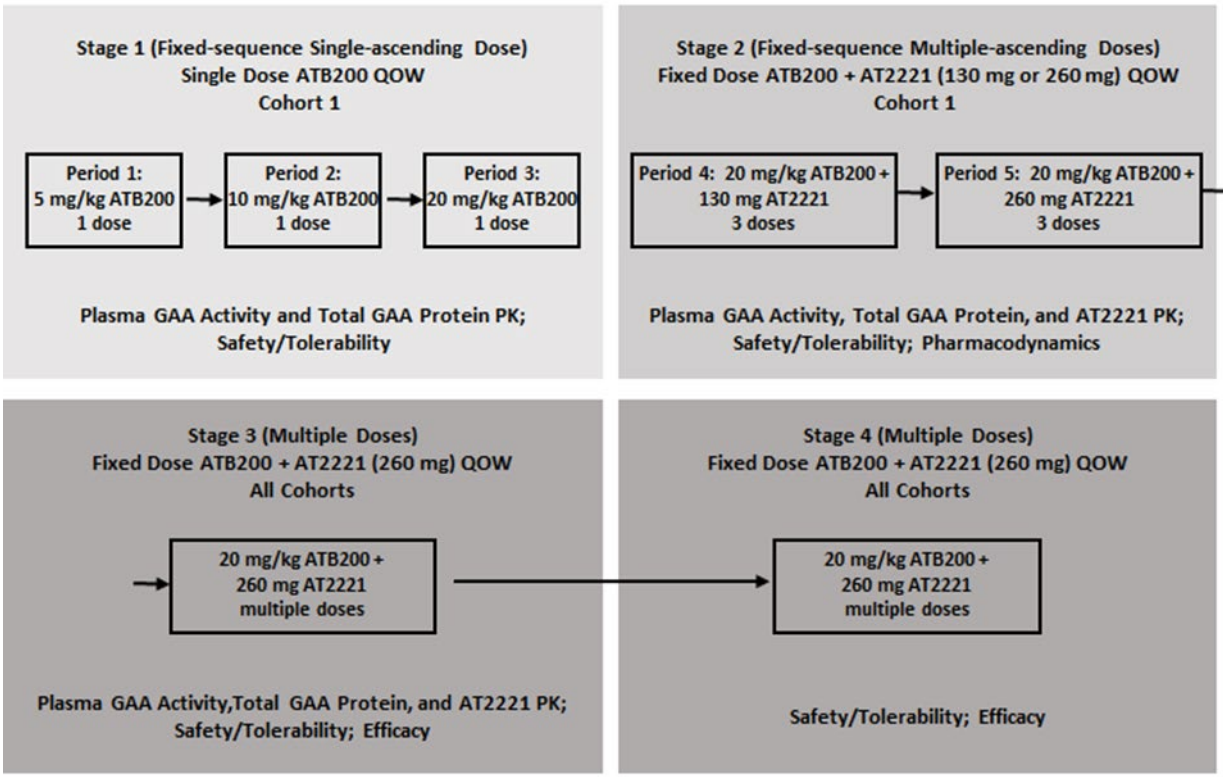


Figure 2. Study design of study ATB002-02

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 7.

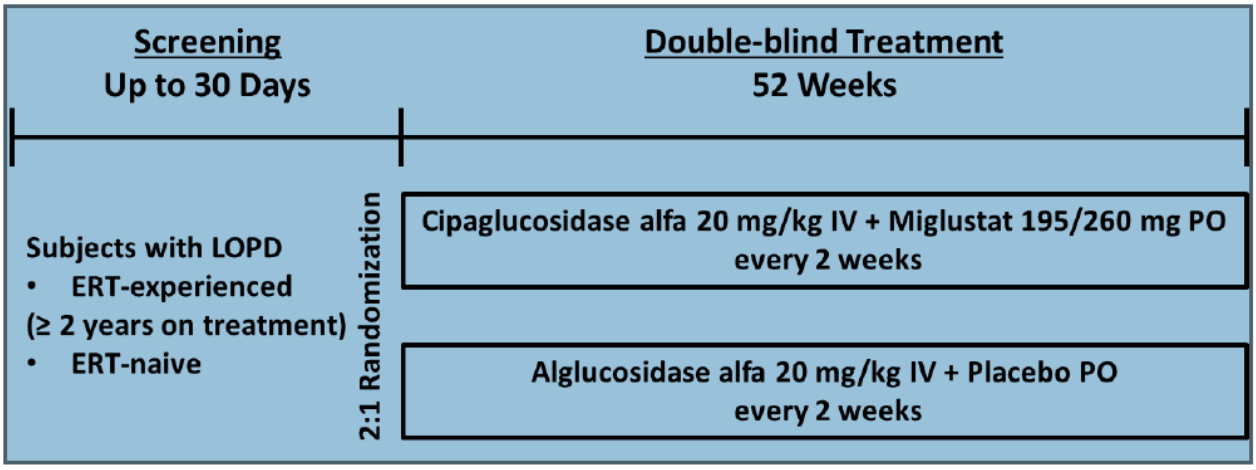


Figure 2. Study design

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.

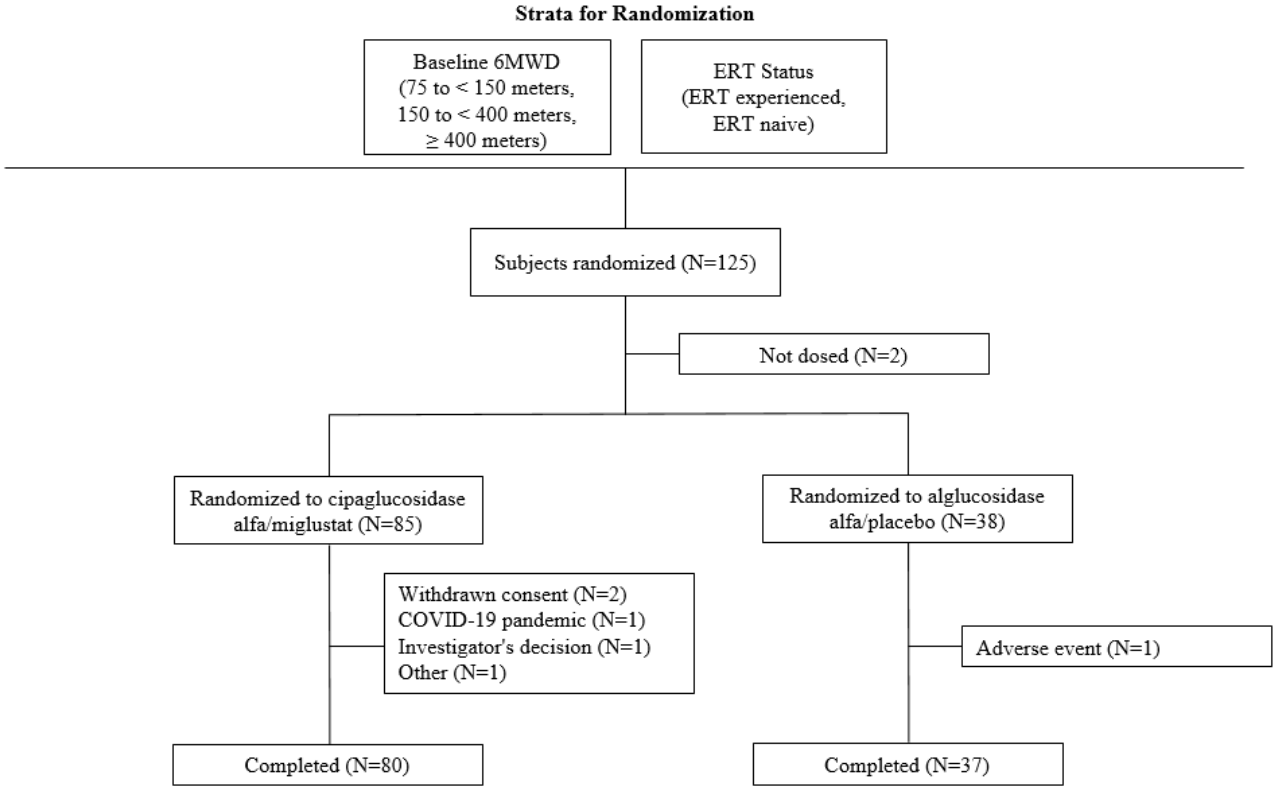
Delayed visits and make-up assessments that go beyond the stated visit windows were remapped to the planned study visit. Suppose a subject had a COVID-19 related situation leading to a delay in the week 26 assessment such that the delayed visit / make-up assessment for week 26 occurs on Day 261 (which 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 6.

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 7. 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**

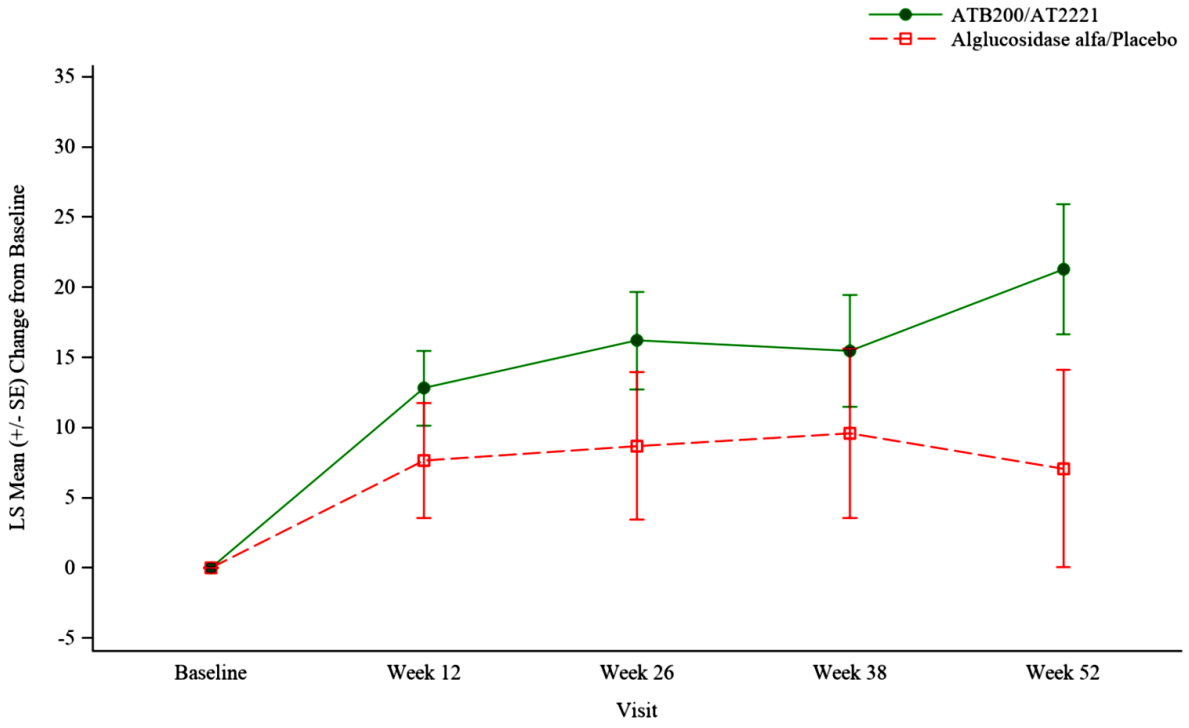
For all analyses, one outlying subject was excluded. Examination of the clinical data revealed that one subject, an ERT-naïve subject in the control arm, had previously been using an anabolic steroid and had deliberately underperformed its screening assessments to gain entry into the study. The study 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 8). 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



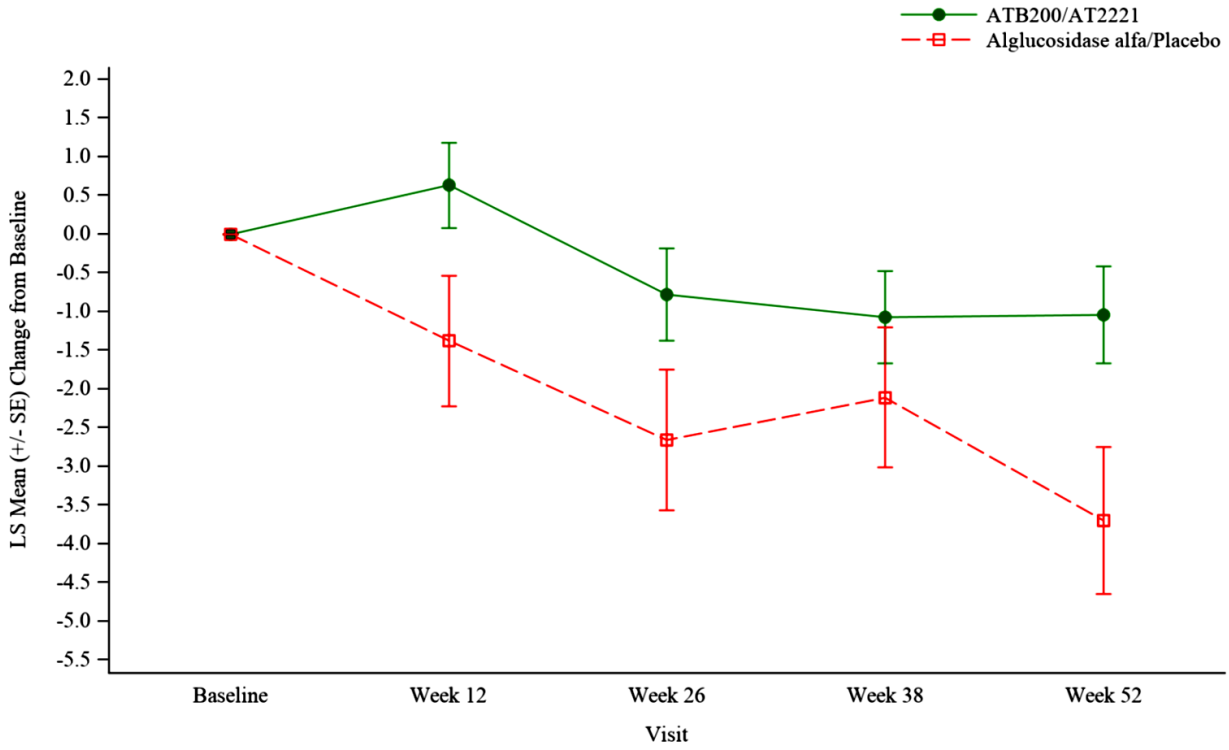
Abbreviations: 6MWD = 6-minute walk distance; AT2221 = miglustat; ATB200 = cipaglucosidase alfa; ITT-OBS = Intent-to-Treat Population that includes all available, observed data without any missing data imputation at Week 52; LS = least squares; MMRM = mixed-effect model repeated measures; SE = standard 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 9 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).

Table 8 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)
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 Table 9 and Table 10).

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 "Opfolda is indicated in co-administration with cipaglucosidase alfa for use in 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:

Opfolda (miglustat) is an enzyme stabiliser of cipaglucosidase alfa long-term enzyme replacement therapy in 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 program 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 12).

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 Table 13.

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 15 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 16).

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

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N = 85)	Alglucosidase alfa/placebo (N = 38)
Enteritis	1 (1.2)	0
Vomiting	1 (1.2)	0
General disorders and administration site conditions	1 (1.2)	0
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)

Table 17 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)

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)
Swollen tongue	0	0	0	0	1 (0.7)	1 (0.9)	0
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)

Table 18 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 19 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 Table 20.

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

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N = 85)			Alglucosidase alfa/placebo (N = 38)		
	Cipaglucosidase alfa	Miglustat	Total	Alglucosidase alfa	Placebo	Total
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
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

SOC PT – n (%)	Cipaglucosidase alfa/miglustat (N = 85)			Alglucosidase alfa/placebo (N = 38)		
	Cipaglucosidase alfa	Miglustat	Total	Alglucosidase alfa	Placebo	Total
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
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 (Table 21).

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 titres 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

No post marketing experience for the co-administration of cipaglucosidase alfa and miglustat treatment is known.

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

[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 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 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.

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.

There were no reports of paresthesia and peripheral neuropathy related to miglustat. Reports related to miglustat only were: abdominal discomfort, constipation, feeling jittery, and platelet count decreased and these are included as ADRs in the SmPC in addition to those reported in the clinical studies and attributable to the co-administration of cipaglucosidase alfa and miglustat.

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.

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.

Due to the nature of the product, it is not expected that drug abuse, withdrawal and rebound are likely to occur. No information on these aspects is available for the co-administration of cipaglucosidase alfa and miglustat and this is considered acceptable by the CHMP.

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	• None
Important potential risks	• None
Missing information	• Use in pregnant and lactating women • Long-term use (> 24 months)

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 (ie, Stage 3 and Stage 4) include evaluations of long-term efficacy, safety, and tolerability of cipaglucosidase alfa/miglustat in all subjects from Stage 3.	• 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.	• 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	• 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; 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
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 Opfolda in combination with cipaglucosidase alfa; • As stated in the PL (Section 2), Opfolda in combination with cipaglucosidase alfa 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), Opfolda in combination with cipaglucosidase alfa 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.

Safety concern	Risk minimisation activities	Pharmacovigilance activities
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: 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

Based on new indication and patient population for miglustat to be used only in combination with cipaglucosidase alfa, the PRAC is of the opinion that a separate entry in the EURD list for Opfolda is needed, as it cannot follow the already existing entry for miglustat. 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 request the alignment of the new PSUR cycle with the European Birth Date (EBD) for cipaglucosidase alfa. The new EURD list entry will therefore use the EBD for cipaglucosidase alfa 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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Opfolda (miglustat) is an enzyme stabiliser of cipaglucosidase alfa long-term enzyme replacement therapy in 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 every other week 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
%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

Effect	Short Description	Unit	Cipaglucosidase alfa/miglustat (n= 85)	Alglucosidase alfa/placebo (n= 37)	Uncertainties/ Strength of evidence	References
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 Opfolda 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 Opfolda is favourable in the following indication(s):

Opfolda (miglustat) is an enzyme stabiliser of cipaglucosidase alfa long-term enzyme replacement therapy in 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.