CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761204Orig1s000

INTEGRATED REVIEW

Office Director Review

Date	(electronic stamp)
From	Janet Maynard, MD, MHS
Review Type	Office Director Review
BLA # and NDA #	BLA 761204 and NDA 215211
Applicant	Amicus Therapeutics, Inc.
Date of Submission Receipt	7/29/2021
PDUFA Goal Date	10/29/2022 for BLA and 8/29/2022 for NDA (BLA impacted by COVID-related travel restrictions that delayed the pre-approval inspection)
Proprietary Name	Pombiliti and Opfolda
Established or Proper Name	Cipaglucosidase alfa-atga and miglustat
Dosage Form(s)	Cipaglucosidase alfa-atga: lyophilized powder for solution for intravenous infusion, 105 mg/mL Miglustat: capsules for oral administration, 65 mg/capsule
Applicant Proposed Indication)/Population	(b) (4)
Approved indication(s)/ population(s) (if applicable)	Treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha glucosidase [GAA] deficiency) weighing ≥40 kg and who are not improving on their current enzyme replacement therapy.
Action or Recommended Action:	*Approval*

This memo serves as the decisional memo to support the regulatory actions for BLA 761204 (cipaglucosidase alfa-atga) and NDA 215211 (miglustat). See the integrated review dated October 17, 2022, for detailed review of these applications. The applicant proposed the use of a novel biologic (cipaglucosidase alfa) co-administered with miglustat for the treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha glucosidase [GAA] deficiency).

Pompe disease (PD) is an autosomal recessive, lysosomal storage disease that results in deficient activity of acid alpha-glucosidase (GAA), the enzyme that degrades glycogen in lysosomes. GAA deficiency leads to myopathy, respiratory weakness, physical disability, and premature death.

Cipaglucosidase is a modified recombinant human GAA intended for use as enzyme replacement therapy (ERT) in patients with LOPD. Miglustat is an N-alkylated iminosugar (a synthetic analog of D-glucose) and is the active ingredient in Zavesca, which is approved for the treatment of adult patients with mild/moderate Type 1 Gaucher disease for whom ERT is not a therapeutic option. Given that cipaglucosidase and miglustat will be co-administered, we are taking action on these applications at the same time.

At the time of the PDUFA date for BLA 761204, there were restrictions on travel due to the COVID-19 pandemic and the pre-approval inspection (PAI) of the drug substance and drug product manufacturing facility WuXi, Biologics, Co., Ltd, China (FEI: 3010606982) could not be performed.

The Office of Pharmaceutical (OPQ), has completed the inspection and OPQ CDER, "recommends approval of BLA 761204 for Pombiliti manufactured by WuXi, Biologics, Co., Ltd, WuXi, China (FEI: 3010606982) for Amicus Therapeutics US, LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of Pombiliti is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert."

For cipaglucosidase, there will be product quality post marketing commitments that have been proposed and accepted by the Applicant. For miglustat, we are requiring postmarketing studies to evaluate the effects of miglustat on the QTc interval and to assess the CYP450 enzyme- and transporter-mediated drug-drug interaction (DDI) potential of miglustat. See the approval letters for additional details of these commitments.

The overall benefit/risk of these applications is favorable and the regulatory actions will be approval.

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/s/

JANET W MAYNARD
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Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA and NDA
Application number(s)	761204 and 215211
Priority or standard	Standard review with major amendment
Submit date(s)	7/29/2021
Received date(s)	7/29/2021
PDUFA goal date	10/29/2022 for BLA and 8/29/2022 for NDA
Division/office	Division of Rare Diseases and Medical Genetics (DRDMG)
Review completion date	See electronic stamp date
Established/proper name	Cipaglucosidase alfa-atga and miglustat
(Proposed) proprietary name	Pombiliti and Opfolda
Pharmacologic class	Hydrolytic lysosomal glycogen-specific enzyme and enzyme stabilizer
Code name	ATB200 and AT2221
Applicant	Amicus Therapeutics, Inc.
Dosage form(s)/formulation(s)	Cipaglucosidase alfa-atga: lyophilized powder for solution for intravenous infusion, 105 mg/mL Miglustat: capsules for oral administration, 65 mg/capsule
Dosing regimen	Cipaglucosidase alfa-atga: 20 mg per kg of actual body weight administered every other week as intravenous infusion. Miglustat: 260 mg for patients 50 kg and greater and 195 mg for patients weighing 40 kg and greater and less than 50 kg administered orally 1 hour prior to the intravenous infusion with cipaglucosidase alfa-atga.
Applicant proposed indication(s)/ population(s)	(b) (4) [redacted]
Proposed SNOMED indication	722343009, Glycogen storage disease type II late-onset (disorder)
Regulatory action	Approval, pending the results of the facility inspection for cipaglucosidase alfa
Approved dosage (if applicable)	Cipaglucosidase alfa-atga: 20 mg/kg (of actual body weight) administered every other week as an intravenous infusion over approximately 4 hours. Miglustat: 260 mg for patients 50 kg and greater and 195 mg for patients weighing 40 kg and greater and less than 50 kg administered orally in combination with cipaglucosidase alfa-atga every other week 1 hour prior to the intravenous infusion with cipaglucosidase alfa-atga.
Approved indication(s)/ population(s) (if applicable)	Treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha glucosidase [GAA] deficiency) weighing ≥40 kg and who are not improving on their current enzyme replacement therapy.
Approved SNOMED term for indication (if applicable)	722343009, Glycogen storage disease type II late-onset (disorder)

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Glossary

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BSA	body surface area
BUN	blood urea nitrogen
CE	confirmatory evidence
CI	confidence interval
CK	creatinine phosphokinase
CL	clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CYP	cytochrome P450
EAER	exposure-adjusted event rate
ECG	electrocardiogram
ER	emergency room
E-R	exposure-response
ERT	enzyme replacement therapy
FVC	forced vital capacity
GD	gestation day
GAA	acid alpha-glucosidase
GSGC	Gait, Stairs, Gowers' maneuver, and Chair test
Hex4	hexose tetrasaccharide
IAR	infusion-associated reaction
IND	investigational new drug
IOPD	infantile-onset Pompe disease
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
KO	knockout
LD	lactation day
LOAEL	lowest observed adverse effect level
LOCF	last observation carried forward
LOPD	late-onset Pompe disease
M6P	mannose-6-phophate
MMRM	mixed model for repeated measures
NDA	new drug application

NOAEL	no observed adverse effect level
PAS	periodic acid-Schiff
PD	Pompe disease
PK	pharmacokinetic
PKS	Pharmacokinetics Subcommittee
PMR	postmarketing requirement
PROMIS	Patient-Reported Outcome Measurement Information System
QC	quality control
qow	every other week
rhGAA	recombinant human acid alpha-glucosidase
RI	renal impairment
RRA	remote regulatory assessment
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
UTI	urinary tract infection

I. Executive Summary

1. Summary of Regulatory Action

Amicus (Applicant) submitted this biologics license application (BLA) for cipaglucosidase alfa (tradename Pombiliti) and new drug application (NDA) for miglustat (tradename Opfolda), seeking approval of this enzyme replacement therapy for late-onset Pompe disease (LOPD), a rare lysosomal storage disorder. Patients with LOPD have an enzyme deficiency that leads to glycogen accumulation in skeletal and cardiac muscle, causing muscle weakness, respiratory failure, and heart failure. The BLA and NDA were reviewed by a multidisciplinary review team. Each discipline recommends approval for adult patients with LOPD weighing ≥40 kg who are not improving on their current enzyme replacement therapy (ERT), with one exception. Although OPQ does not note any product quality deficiencies that would preclude approval at this time, the OPQ recommendation for BLA 761204 is pending final determination of the compliance status of WuXi, Biologics, Co., Ltd, WuXi, China (FEI: 3010606982). Due to COVID-19 related travel restrictions, the pre-license inspection cannot be performed at this time. The signatory authority for this application concurs with these recommendations.

Substantial evidence of effectiveness for cipaglucosidase alfa coadministered with miglustat in patients with LOPD was established using data from one adequate and well-controlled trial with confirmatory evidence (CE). A single trial in treatment-experienced and treatment-naive patients 18 years of age and older with LOPD showed a clinically meaningful numerical improvement in motor and lung function compared to treatment with a non-U.S.-approved alglucosidase alfa product coadministered with placebo. CE providing strong mechanistic support includes the well-established etiology of the disease, the mechanism of action of the therapy, and animal studies in G*aa* knockout (KO) mice showing reduced glycogen in tissues and improved muscle function. While the one adequate and well-controlled trial with CE were adequate to establish substantial evidence of effectiveness, the data were not adequate to support use as first-line therapy given the lack of statistical significance for superiority and the inherent increased risk of two products over one.

The available safety data show that cipaglucosidase alfa coadministered with miglustat is safe for its intended use. Common adverse reactions included headache, fatigue, diarrhea, nausea, arthralgia, dizziness, myalgia, pruritus, vomiting, dyspnea, erythema, paresthesia, and urticaria. Serious adverse reactions include anaphylaxis, a known class effect for enzyme replacement therapies (ERTs). A Boxed Warning for hypersensitivity reactions, including anaphylaxis, infusion-associated reactions, and risk of acute cardiorespiratory failure in susceptible patients will be included in the product labeling to mitigate these known risks with ERTs. All the identified safety risks for cipaglucosidase alfa and miglustat can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance.

The BLA and NDA include appropriate preapproval nonclinical studies, and no additional nonclinical studies will be conducted as postmarketing requirements. We are requiring postmarketing studies to evaluate the effects of miglustat on the QTc interval and to assess the CYP450 enzyme- and transporter-mediated drug-drug interaction (DDI) potential of miglustat.

In addition, the Applicant committed to additional chemistry, manufacturing, and controls postmarketing studies.

As described in the Benefit/Risk Framework below, we conclude that the improvement in motor and lung function observed with use of cipaglucosidase alfa coadministered with miglustat outweighs the risks when these coadministered products are used as a second-line therapy according to recommendations in the approved labeling.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pompe disease (PD) is an autosomal recessive, lysosomal storage disease that results in deficient activity of acid alpha-glucosidase (GAA), the enzyme that degrades glycogen in lysosomes. GAA deficiency leads to myopathy, respiratory weakness, physical disability, and premature death. • The incidence of PD in the United States is approximately 1:40,000 births. • There are two forms of PD caused by deficiency of the same enzyme: infantile-onset and late-onset. Infantile-onset Pompe disease (IOPD) is associated with severe left ventricular hypertrophy and a high mortality rate within the first year of life. Late-onset Pompe disease (LOPD) is associated with limb girdle and respiratory muscle weakness and premature death due to respiratory insufficiency(Gupta et al. 2020). • During a Patient-Focused Drug Development meeting, the major difficulties in daily life identified by patients with Pompe disease included progressive muscle weakness, loss of mobility, inability to participate in or perform daily activities, difficulty eating, inability to work or go to school, difficulty communicating, and fatigue. The most important targets for drug treatment included improving mobility, muscle strength, and ease of breathing, as well as stabilizing or slowing loss of muscle function.	• PD is a rare and serious disease that can lead to death from cardiac or respiratory failure if untreated in the infantile-onset form and to motor impairment and premature death from respiratory failure in the late-onset form.
Current Treatment Options	• Enzyme replacement therapy (ERT) with recombinant GAA (alglucosidase alfa or avalglucosidase alfa) is the only approved therapy. However, the improvements seen with alglucosidase alfa are not sustained. Patients can regress	• Improvements seen with alglucosidase alfa are not sustained.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	back to their baseline pulmonary function within 3 years(Schoser et al. 2017). It is unknown if the improvements seen with recently approved avalglucosidase alfa are sustained. • Patients with LOPD have shown improvement in forced vital capacity and 6-minute walk test with both available ERTs. • Patients with IOPD have shown improvement in cardiac variables, such as left ventricular hypertrophy and improved survival, with alglucosidase alfa if treatment is initiated before 6 months of age.	• The treatment and cure of Pompe disease continue to represent unmet needs.
Benefit	• Cipaglucosidase alfa is a modified recombinant human GAA intended for use as ERT in patients with LOPD. • The cipaglucosidase alfa sequence is identical to endogenous human GAA, after the removal of the initial 56 residues comprising the signal peptide and precursor. • Cipaglucosidase alfa contains complex-type N-glycan structures with two M6P on the same glycan. • The in vitro data from both Pompe patient fibroblasts and rat myoblasts suggest that it is likely that cipaglucosidase alfa is more efficiently internalized into lysosomes than alglucosidase alfa. • Miglustat is an N-alkylated iminosugar (a synthetic analog of D-glucose) and is the active ingredient in Zavesca, which is approved for the treatment of adult patients with mild/moderate Type 1 Gaucher disease for whom ERT is not a therapeutic option. • Miglustat is a small-molecule pharmacological chaperone that binds and stabilizes cipaglucosidase alfa to improve enzyme uptake. When cipaglucosidase alfa is coadministered with miglustat, in vitro and animal studies showed improved dose-dependent stability of cipaglucosidase alfa and studies in *Gaa* knockout mice showed significant reduction in glycogen. Miglustat has no direct treatment effect on patients with LOPD.	• The distance walked (6MWD), the primary endpoint, in adult patients with LOPD treated with cipaglucosidase alfa coadministered with miglustat showed numerical improvement compared to the comparator, but it did not reach statistical significance for superiority. • Lung function assessed as FVC (% predicted), the key secondary endpoint, in adult patients with LOPD treated with cipaglucosidase alfa coadministered with miglustat showed numerical improvement that was comparable to what was observed in the trials supporting approval of alglucosidase alfa and avalglucosidase alfa, particularly considering that in those trials all patients were treatment naïve. The estimated treatment difference of 2.3% is considered clinically meaningful. • Confirmatory evidence supports the finding of effectiveness in adult patients with LOPD treated with cipaglucosidase alfa coadministered with miglustat by showing improvement in muscle function, which supports the improvement in distance walked and lung function seen in patients with LOPD. • In the subgroup analysis, treatment-experienced patients seemed to benefit from treatment more than treatment-naïve patients in the 6MWT and FVC (% predicted), but the small number of treatment-naïve patients prevents conclusive interpretation of the data. The review team

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The efficacy of cipaglucosidase alfa coadministered with miglustat was evaluated in one adequate and well-controlled trial (ATB200-03) in patients with LOPD. Changes in the distance walked in the 6-minute walk test (6MWT) were assessed in patients with LOPD randomly assigned to coadministration of cipaglucosidase alfa 20 mg/kg and miglustat 260 mg every other week (qow; N=85) or a non-U.S.-approved alglucosidase alfa product at 20 mg/kg and placebo qow (N=38). • The observed mean change from baseline in 6MWD was 20.5 meters for cipaglucosidase alfa coadministered with miglustat and 17.4 meters for a non-U.S.-approved alglucosidase alfa product coadministered with placebo. The estimated treatment difference in the mean change in 6MWD (meters) from baseline to Week 52 was 5.3 meters (95% confidence interval [CI]: -15.2 to 25.9), favoring cipaglucosidase alfa coadministered with miglustat; however, the difference did not reach statistical significance for superiority over a non-U.S.-approved alglucosidase alfa product coadministered with placebo (p=0.61). • A treatment-naïve patient outlier in the comparator arm was identified after the trial was concluded. This outlier significantly impacted the primary endpoint analysis. This patient had an observed improvement of 355 meters at 52 weeks from baseline in the 6MWD, which is deemed clinically implausible. When excluding the outlier, the estimated treatment difference increases from 5.3 to 14.2 meters and the p-value decreases from 0.61 to 0.10. • The observed mean change from baseline in the lung function (sitting forced vital capacity [FVC] % predicted), a key secondary endpoint in ATB200-03, was -1.1% for cipaglucosidase alfa coadministered with miglustat and -3.3% for a non-U.S.-approved alglucosidase alfa product coadministered with placebo. The estimated treatment difference was 2.3% (CI: 0.02 to 4.62; p=0.05), favoring cipaglucosidase alfa coadministered with miglustat and supporting improved lung function. The 2.3% change in FVC	recommended that treatment with cipaglucosidase alfa coadministered with miglustat should be limited to adult patients who are not to improving on their current ERT. • There are insufficient data to support labeling claims (b) (4) [redacted] • The nonclinical data provided evidence that miglustat increases the bioavailability of cipaglucosidase alfa. (b) (4) [redacted] A three-arm trial was discussed with the Sponsor during the drug development, and the Division agreed to the two-arm design, comparing cipaglucosidase alfa coadministered with miglustat to the comparator, due to the unfeasibility of a three-arm trial in this rare disease. • The review team concluded it was reasonable to approve cipaglucosidase alfa coadministered with miglustat for chronic us (b) (4) [redacted]

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	is clinically significant and is similar to the change observed in the trials that led to the approval of avalglucosidase alfa (2.4%). • Post hoc global test performed on the 6MWT and FVC (% predicted) endpoints showed a greater improvement, in either one of the endpoints, in the cipaglucosidase alfa coadministered with miglustat group than the non-U.S.-approved alglucosidase alfa product coadministered with placebo group (p=0.02). The global test p-value decreases from p=0.02 to p=0.01 when excluding the outlier. • Subgroup analysis showed a numerical improvement in the 6MWT (estimated treatment difference 16 meters; p=0.07) and FVC (% predicted) (estimated treatment difference 4%; p<0.01) in the treatment-experienced group. • Confirmatory evidence (CE) of the effectiveness of the coadministration of cipaglucosidase alfa and miglustat in LOPD is derived from mechanistic evidence in the setting of well-established disease etiology, the mechanism of action of each component in vitro, and studies showing that cipaglucosidase alfa coadministered with miglustat reduces glycogen levels in tissues and improves muscle function in *Gaa* knockout mice, compared to alglucosidase alfa, consistent with the mechanism of action and pathophysiology of the disease. • (b) (4) In a nonclinical model (*Gaa* knockout mice), the contribution of miglustat to the effectiveness of cipaglucosidase alfa (reduction of glycogen levels) was not observed after 2 months of treatment. No increase in GAA activity with miglustat pretreatment was observed at 3- or 6-months post-treatment and improvement in grip strength with miglustat was observed only at one time point (5 months). Nonclinical studies where cipaglucosidase reached steady state and miglustat was removed were not conducted. (b) (4)	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4)	
Risk and Risk Management	• Safety was assessed in 151 patients 18 years of age and older with LOPD who received cipaglucosidase alfa coadministered with miglustat. This included both treatment-naïve (34) and treatment-experienced (117) patients. • Total cumulative duration of exposure was 218 patient-years; 108 patients (71.5%) had 52 weeks or more of exposure, and 22 patients (14.6%) had 104 weeks or more of exposure. • There were no deaths in any of the trials or the expanded access program. • Serious adverse events (SAEs) were reported in 14.6% (22/151) of patients treated with cipaglucosidase alfa coadministered with miglustat; 6 of those patients had SAEs assessed as related to treatment with cipaglucosidase alfa coadministered with miglustat. SAEs reported in 2 or more patients were pneumonia and urticaria. • The most common adverse reactions (ARs) were nausea, abdominal pain, abdominal distension, flatulence, diarrhea, arthralgia, oropharyngeal pain, muscle spasms, musculoskeletal pain, asthenia, dyspnea, tachycardia, blood pressure increased, headache, fatigue, dizziness, pyrexia, chills, flushing, pruritus, rash, flushing, dysgeusia, tremor, paresthesia. • Three patients treated with cipaglucosidase alfa coadministered with miglustat met the clinical criteria for anaphylaxis, and all three patients developed symptoms within one hour of the initiation of the infusion. One patient had anaphylaxis during their first infusion. An additional patient with anaphylaxis was identified in the 120-day safety report.	• Safety risks of hypersensitivity, including anaphylaxis, and infusion-associated reactions are known risks with ERT. These risks with cipaglucosidase alfa coadministered with miglustat appear similar to those of the non-U.S.-approved alglucosidase alfa product and can be addressed through labeling and routine pharmacovigilance. The review team recommended changes to the Applicant's proposed prescribing information to provide additional details about the symptoms and treatment of hypersensitivity reactions. • There is a potential risk for cardiac birth defects in fetuses exposed to cipaglucosidase alfa coadministered with miglustat during pregnancy based on findings in nonclinical studies. Patients undergoing ERT develop antidrug antibodies (ADAs) to the recombinant enzyme; switching patients between enzymes could increase immunogenicity concerns. Therefore, the review team recommended contraindicating use of cipaglucosidase alfa coadministered with miglustat in pregnancy. • Cipaglucosidase alfa and miglustat are likely to be present in breast milk. The review team recommended that breastfeeding should be avoided during treatment with cipaglucosidase alfa coadministered with miglustat. • The review team concluded that an evaluation of the effects of miglustat on the QTc interval is required as a postmarketing requirement to evaluate the risk of electrocardiogram changes and potential for cardiac arrhythmias. • The review team concluded that the CYP450 enzyme- and transporter-mediated DDI potential of miglustat should be evaluated as a postmarketing requirement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Three patients treated with cipaglucosidase alfa coadministered with miglustat had infusion-associated reaction (IAR) SAEs. The most frequently reported IARs were conjunctivitis, rash, urticaria, pruritus, asthma, flushing, and mouth ulceration. • Four patients discontinued from the trials due to IARs. • Anti-cipaglucosidase alfa antibodies (ADA) prevalence was 92% (81/88) in treatment-experienced patients and 100% (26/26) in treatment-naïve patients following the 52-week treatment period in trials ATB200-02 and ATB200-03. • Electrocardiograms (ECGs) did not show clinically meaningful changes over time; however, the data were insufficient to adequately evaluate for potential ECG changes and cardiac arrhythmias, because the ECGs were only performed before the miglustat dose was administered. • Reproductive toxicology studies in rabbits exposed to cipaglucosidase alfa co-administered with miglustat showed great vessel and cardiac malformations. During human embryogenesis, organ formation, including the heart, occurs during weeks 3-8 following fertilization, which is likely to be prior to a woman knowing she is pregnant. • There are no data on the presence of cipaglucosidase alfa or miglustat in human milk, its effect on the breastfed infant, or its effect on milk production. Cipaglucosidase alfa and miglustat were present in rat milk.	

Abbreviations: ADA, antidrug antibodies; AR, adverse reaction; CE, confirmatory evidence; CI-MPR, cation-independent M6P receptor; ERT, enzyme replacement therapy; FVC, forced vital capacity; GAA, acid alpha-glucosidase; IAR, infusion-associated reaction; IOPD, Infantile-onset Pompe disease; LOPD, Late-onset Pompe disease; M6P, mannose-6-phosphate; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; PD, Pompe disease; PK, pharmacokinetic; SAE, serious adverse event

2.2. Conclusions Regarding Benefit-Risk

Pompe disease (PD) is a rare and serious lysosomal storage disease caused by autosomal recessive variants in the acid alpha-glucosidase (*GAA*) gene. The resulting enzyme deficiency of GAA results in accumulation of glycogen in cells and leads to myopathy, respiratory weakness, and physical disability, and can lead to premature death. The two forms of PD present differently:

infantile-onset PD is associated with severe left ventricular hypertrophy and high mortality within the first year of life, whereas late-onset PD (LOPD) is associated with limb girdle and respiratory muscle weakness; respiratory failure is the most common cause of death. Currently, the approved therapies are recombinant human acid alpha-glucosidases, alglucosidase alfa and avalglucosidase alfa. Alglucosidase alfa does not lead to a sustained improvement in muscle weakness, and thus, patients tend to develop progressive disease, which can lead to respiratory failure. (b) (4) Therefore, treatment and cure of PD continue to represent unmet needs.

The benefit of cipaglucosidase alfa, a hydrolytic lysosomal glycogen-specific enzyme, coadministered with miglustat, a chaperone protein that stabilizes the enzyme, is based on comparison of distance walked on the 6-minute walk test, the primary endpoint, and forced vital capacity (% predicted), a key secondary endpoint, in 123 treatment-experienced (n=95) and treatment-naïve (n=28) patients greater than 18 years of age with LOPD randomized either to cipaglucosidase alfa 20 mg/kg coadministered with miglustat 260 mg every other week (n=85) or 20 mg/kg of a non-U.S.-approved alglucosidase alfa product coadministered with placebo every other week (n=38). The estimated treatment difference in the mean change from baseline to Week 52 in the 6-minute walk test was 5.3 meters (95% confidence interval: -15.2 to 25.9) and in forced vital capacity (% predicted) was 2.3% (95% confidence interval: 0.02 to 4.6), favoring the cipaglucosidase alfa coadministered with miglustat arm. The primary endpoint results were driven by the treatment-experienced subgroup; the estimated treatment difference was 16.1 meters (95% CI: -1.3, 33.4). Confirmatory evidence of effectiveness for LOPD is derived from mechanistic support including the mechanism of action of the therapy and animal studies that show cipaglucosidase alfa coadministered with miglustat reduces glycogen levels in tissues and improves muscle architecture and function in *Gaa* knockout mice.

Safety concerns for enzyme replacement therapies include hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions. The safety profile of cipaglucosidase alfa coadministered with miglustat as assessed in 151 patients with LOPD appears to be similar to that of the currently available therapies, alglucosidase alfa and avalglucosidase alfa. Despite the high incidence of adverse events (93% of patients), most patients (97%) did not discontinue due to adverse events. The most common adverse reactions were hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions, which presented most often as nausea, abdominal pain, abdominal distension, flatulence, diarrhea, arthralgia, oropharyngeal pain, muscle spasms, musculoskeletal pain, asthenia, dyspnea, tachycardia, blood pressure increased, headache, fatigue, dizziness, pyrexia, chills, flushing, pruritus, rash, flushing, dysgeusia, tremor, paresthesia. Safety concerns identified as possibly related to miglustat in the safety population include tremor and a mild increase in creatinine level. The risk of hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions can be addressed through labeling and routine pharmacovigilance.

Great-vessel and cardiac malformations were identified in the nonclinical studies in rabbits during treatment with cipaglucosidase coadministered with miglustat. Thus, there is a potential risk of cardiac birth defects in fetuses of pregnant women who receive cipaglucosidase coadministered with miglustat. Other safety concerns include uncertainties regarding risk to infants during lactation for coadministered cipaglucosidase alfa and miglustat and the risk of electrocardiogram changes and potential for cardiac arrhythmias

for miglustat. Labeling will note the potential risk to the fetus and the lack of data regarding lactation. A postmarketing study will assess the uncertainties related to risk of electrocardiogram changes and potential for cardiac arrhythmias.

In summary, we conclude that the benefits of cipaglucosidase alfa coadministered with miglustat on lung function, an important target for drug treatment for patients with LOPD, outweigh its risks when used according to the agreed-upon labeling. We are recommending cipaglucosidase alfa coadministered with miglustat as a second-line therapy because of the potential increased risk when receiving two drugs instead of only one drug and the availability of two other approved enzyme replacement therapies for the treatment of Pompe disease. The availability of cipaglucosidase alfa coadministered with miglustat provides a second-line enzyme replacement therapy for adult patients with LOPD weighing ≥40 kg who are not improving on their current enzyme replacement therapy.

II. Interdisciplinary Assessment

3. Introduction

Pompe disease (PD), also known as acid maltase deficiency or glycogen storage disease type II, is a rare, autosomal recessive disease caused by the deficiency of lysosomal acid alpha-glucosidase (GAA). GAA cleaves alpha-1,4 and alpha-1,6 linkages in glycogen under the acidic conditions of the lysosome. In this lysosomal disorder, glycogen accumulation in affected tissue (skeletal and/or cardiac muscle) can result in progressive hypotonia, respiratory failure, and cardiomyopathy. The disease spectrum ranges from the severe, rapidly progressive infantile-onset Pompe disease (IOPD) to the slowly progressive, heterogeneous late-onset Pompe disease (LOPD).

During a virtual Externally-Led Patient-Focused Drug Development meeting on July 13, 2020, sponsored by the Muscular Dystrophy Association in partnership with the Acid Maltase Deficiency Association and the United Pompe Foundation, over 100 members of the Pompe patient community (both patients and caregivers) shared their perspectives on disease symptoms and daily impacts of IOPD and LOPD, as well as current experiences with treatment and expectations for potential future treatments (Muscular Dystrophy Association 2022). The age of diagnosis for most meeting participants with Pompe disease was 0 to 5 years of age (35%) or 19 to 50 years of age (50%), only 5% were diagnosed through newborn screening. The majority of meeting participants with Pompe disease were patients with LOPD; only 16% were patients with IOPD. The major difficulties in daily life identified by patients with Pompe disease included progressive muscle weakness, loss of mobility, inability to participate in or perform daily activities, difficulty eating, inability to work or go to school, difficulty communicating, and fatigue. Eighty-six percent of patients and caregivers reported using enzyme replacement therapy. Over 50% of patients reported participating in a clinical trial of an experimental treatment, and the most important targets for drug treatment included improving mobility, muscle strength, and ease of breathing, and stabilizing or slowing further progression from current level of muscle function. The patient community emphasized the importance of maintaining their current respiratory capabilities and, that respiratory outcomes should be paid particular attention.

First-generation enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme, biologics license application [BLA] 125141) was approved in April 2006 for patients diagnosed with IOPD, based upon improvement in ventilator-free survival compared to the well-described natural history of the disease. Lumizyme (BLA 125291) was approved for patients with LOPD in May 2010 based on improvements in lung function (forced vital capacity [FVC, % predicted]) and 6-minute walk distance compared to placebo. Lumizyme and Myozyme are both alglucosidase alfa products manufactured by the same Applicant at different bioreactor scales. The indication for Lumizyme was subsequently extended to all patients with PD (SUPPL-136 in August 2014) based on the physicochemical comparability of Myozyme and Lumizyme. Currently, alglucosidase alfa (Lumizyme; Myozyme is no longer manufactured in the United States) is an approved therapy for PD.

Second-generation ERT with avalglucosidase alfa (Nexviazyme, BLA 761194) was approved in August 2021 for patients 1 year of age and older with LOPD, based on a noninferiority comparison of FVC (% predicted) in treatment-naïve patients randomized to avalglucosidase alfa or alglucosidase alfa.

Patients with LOPD treated with alglucosidase alfa experience lung function improvement within the first few months of treatment, but this gradually returns to baseline at 36 months, with a slight decline after 36 months(Schoser et al. 2017). Similarly, in a prospective study, 30 patients with LOPD who had been treated with alglucosidase alfa had improved walking distances on the 6-minute walk test (6MWT) during the first 3 years of treatment (Harlaar et al. 2019). After the first 3 years, the patients experienced a decline; at the 10-year assessment, the average 6MWT distance was shorter than the distance walked at the start of treatment. Patients with LOPD treated with avalglucosidase alfa performed better in the 6MWT than patients who received alglucosidase alfa in a 49-week trial (COMET). More long-term data are necessary to determine whether patients treated with avalglucosidase alfa will experience a similar decline in effectiveness over time or whether the gains they achieved initially with avalglucosidase alfa treatment will persist after 1 year. The two treatments had similar safety results.

Cipaglucosidase alfa provides an exogenous source of GAA. Cipaglucosidase alfa has the same amino acid sequence as the endogenous GAA enzyme, but contains complex-type N-glycan structures with two mannose-6-phosphate (M6P) moieties on the same glycan. The Applicant hypothesizes that the complex structure with increased numbers of M6P moieties may lead to increased affinity and binding to the M6P receptor on cell surfaces, specifically the cation independent M6P receptor; this receptor mediates the internalization of exogenous GAA to lysosomes.

Miglustat is a small-molecule enzyme stabilizer that binds to exogenous GAA, thereby preventing inactivation of cipaglucosidase alfa in blood, which is unstable at neutral pH, and improving exposure of the enzyme to muscle cells. In the acidic environment of the lysosome, cipaglucosidase alfa and miglustat dissociate. Although miglustat is cleared from the muscle within approximately 24 hours, cipaglucosidase alfa was detected in the muscle for approximately 7 to 10 days. The Applicant proposes that coadministration of miglustat (orally) with cipaglucosidase alfa (intravenously [IV]) promotes enzyme stability and, therefore, greater bioavailability of the enzyme for uptake by muscle cells.

In terms of regulatory history, the Applicant submitted the investigational new drug opening protocol (127387) to FDA in November 2015. The program was developed to compare cipaglucosidase alfa coadministered with miglustat to a non-U.S.-approved alglucosidase alfa product. In September 2017, cipaglucosidase alfa coadministered with miglustat was granted Orphan Drug designation, followed by Breakthrough Therapy designation in February 2019. A rolling review submission request was granted in April 2020. The type B pre-BLA teleconference was held in April 2021.

The application encompasses three clinical trials of patients with LOPD. The pivotal trial, ATB200-03, was a randomized, double-blind, comparator-controlled trial in ERT treatment-experienced and -naïve patients 18 years of age and older with LOPD, comparing cipaglucosidase alfa coadministered with miglustat to a non-U.S.-approved alglucosidase alfa product coadministered with placebo.

3.1. Review Issue List

The review team identified the key review issues listed in Sections 3.1.1 and 3.1.2 to be relevant to the evaluation of benefit and risk, respectively. In-depth assessments of these benefit and risk issues can be found in Sections 6.3 and 7.7, respectively.

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- Evidence of effectiveness from ATB200-03.
- Confirmatory evidence.
- Evidence of miglustat contribution to effectiveness of cipaglucosidase alfa.

(b) (4)

3.1.2. Key Review Issues Relevant to Evaluation of Risk

- Hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions.
- Risk to fetus during pregnancy and infant during lactation.
- Risk of electrocardiogram changes and potential for cardiac arrhythmias for miglustat at the proposed dosage.

3.2. Approach to the Review

The Applicant submitted data from three trials that included patients 18 years of age and older with LOPD (summarized in Table 3) that form the basis of the benefit-risk assessment of cipaglucosidase alfa/miglustat in patients diagnosed with LOPD. The review of BLA 761204 and new drug application (NDA) 215211 is based on the current understanding of LOPD as described in the literature.

Determination of Efficacy

To evaluate the efficacy of cipaglucosidase alfa coadministered with miglustat, the review team primarily evaluated data originating from 123 patients with LOPD who received either cipaglucosidase alfa coadministered with miglustat or a non-U.S.-approved alglucosidase alfa product coadministered with placebo in clinical trial ATB200-03. We evaluated the 6MWT and the sitting FVC (% predicted) at 1 year in treatment-experienced and -naïve patients in trial ATB200-03 (pivotal trial) in comparison to patients who received a non-U.S.-approved alglucosidase alfa product coadministered with placebo. Although data from trial ATB200-02 evaluating clinical domains of LOPD (motor and pulmonary function, and muscle strength) at 12 months were submitted as supporting data for trial ATB200-03, these data were not used by the review team to assess efficacy, because ATB200-02 was an open-label trial.

Determination of Safety

Data from three trials were reviewed to determine the safety of cipaglucosidase alfa coadministered with miglustat in patients with LOPD. The safety data from these trials were pooled by the Applicant and presented as the Integrated Summary of Safety. This population of 151 patients with LOPD who received cipaglucosidase alfa coadministered with miglustat, including 85 patients from ATB200-03, 37 patients from ATB200-07, and 29 patients from ATB200-02. Two pools of data were reviewed separately: pool 1 (ATB200-03) and pool 2 (ATB200-03, ATB200-02, and ATB200-07).

The analysis of general safety—assessment of adverse events, laboratory evaluations, vital signs, and electrocardiograms—was based on descriptive summaries and review of source data. Case report forms and patient narratives were reviewed for serious adverse events, anaphylaxis, death, discontinuations, and withdrawals. Clinical trial data were independently analyzed using JMP, JMP Clinical, and Python software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

Note

For ease of reading, we will use, from this section onward, the terms *cipa-mig* to refer to *cipaglucosidase alfa coadministered with miglustat* and *comparator* to refer to the *non-U.S.-approved alglucosidase alfa product coadministered with placebo*.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Cipa-Mig

Trial Identifier (NCT Number)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
ATB200-02 (NCT02675465, ongoing)	Treatment-naïve and treatment-experienced adult (≥18 years of age) patients with LOPD	Control type: Uncontrolled Randomization: Actual enrolled Blinding: None Biomarkers: PD biomarkers and immune system activation Innovative design features: Open-label, fixed sequence, single and multiple ascending doses with IV infusions of cipaglucosidase alfa alone and coadministered with oral miglustat. There were four stages and four cohorts.	Drug: Cipaglucosidase alfa and Miglustat Stage 1 Dosage: cipaglucosidase alfa: 5, 10, 20 mg/kg single dose mg Stage 2 Dosage: cipaglucosidase alfa: 20 mg/kg qow miglustat: 130, 260 mg qow Stages 3 and 4: cipaglucosidase alfa: 20 mg/kg qow miglustat: 260 mg qow Number treated: 29 Duration (quantity and units): 4 y	Primary: Assess safety, tolerability, and efficacy of cipaglucosidase alfa alone and coadministered with miglustat and characterize PK and pharmacodynamic parameters in patients with LOPD Secondary: Not applicable	18-34, 29	17 centers in 6 countries

Trial Identifier (NCT Number)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
ATB200-03 (NCT03729362)	Treatment-naïve and treatment-experienced adult (≥18 years of age) patients with LOPD	Control type: Active Randomization: Randomized Blinding: Double-blind Biomarkers: Skeletal muscle glycogen content (Hex4) and muscle injury (CK) Innovative design features: 12-month trial, randomization was stratified by baseline 6MWT and ERT treatment status (naïve or experienced)	Drug: cipaglucosidase alfa and miglustat Dosage: cipaglucosidase alfa: 20 mg/kg qow miglustat:195, 260 mg qow Number treated: 85 Duration: 2 y Drug: a non-U.S.-approved alglucosidase alfa product and placebo Dosage: alglucosidase alfa: 20 mg/kg qow placebo qow Number treated: 38 Duration: 2 y	Primary: Assess effect of cipaglucosidase alfa coadministered with miglustat treatment on 6MWT compared to a non-U.S.-approved alglucosidase alfa product and placebo Secondary: Assess effect on FVC (% predicted), 6MWT at 26 Weeks, lower extremity muscle strength, PROMIS-physical function, PROMIS-fatigue, and GSGC	110, 123	61 centers in 24 countries

Trial Identifier (NCT Number)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
ATB200-07 (NCT04138277, ongoing)	Treatment-naïve and treatment-experienced adult (≥18 years of age) patients with LOPD from trial ATB200-03	Control type: Uncontrolled Randomization: Actual enrolled Blinding: None Biomarkers: Skeletal muscle glycogen content and injury Innovative design features: Open-label extension trial with patients who finished trial ATB200-03	Drug: Cipaglucosidase alfa with miglustat Dosage: 20 mg/kg qow Miglustat 195, 260 mg qow Number treated: 118 Duration: 4 y	Primary: Assess long-term safety and tolerability of cipaglucosidase alfa coadministered with miglustat, Secondary: Long-term effect on 6MWT, FVC (% predicted), muscle strength, PROs, motor function, overall clinical impression, biomarkers of muscle injury and disease substrate, immunogenicity, and PK	117, 118 (efficacy population) and 115 (safety population)	61 centers, 24 countries

Source: Review team.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: BID, twice daily; CK, creatinine phosphokinase; DB, double-blind; ERT, enzyme replacement therapy; FVC, forced vital capacity; GSGC, Gait, Stairs, Gowers' maneuver, and Chair test; Hex4, hexose tetrasaccharide; IV, intravenous; LTE, long-term extension study; LOPD, late-onset Pompe disease; MC, multicenter; 6MWT, 6-minute wa k test; NCT, National Clinical Trial; N, number of subjects; OL, open-label; PC, placebo-controlled; PD, Pompe disease; PG, parallel group; PK, pharmacokinetic; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; qow, every other week; R, randomized

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	3.2 and 6.2
☐	Observer-reported outcome	
☒	Clinician-reported outcome	3.2
☒	Performance outcome	3.2, 6.2, and 6.3
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting summary report	6.3 and 3
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The pharmacologic activity, pharmacokinetics, and clinical pharmacology of cipaglucosidase alfa and miglustat that are relevant to the interpretation of benefit and risk are summarized in Table 5 and Table 9, respectively.

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics for Cipaglucosidase Alfa

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	A hydrolytic lysosomal glycogen-specific enzyme.
Mechanism of action	Pompe disease is an inherited disorder of glycogen metabolism caused by the deficiency of acid alpha-glucosidase (GAA), an enzyme that degrades lysosomal glycogen to glucose. Cipaglucosidase alfa provides an exogenous source of GAA. The M6P on cipaglucosidase alfa mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported into lysosomes where it undergoes proteolytic cleavage that results in increased GAA enzymatic activity. Cipaglucosidase alfa then exerts enzymatic activity in cleaving glycogen.
Active moieties	Cipaglucosidase alfa is a recombinant human GAA with 1.3 moles of bis-mannose-6-phosphate (bis M6P) per mole of enzyme. Cipaglucosidase alfa undergoes proteolytic cleavage and N-glycan trimming in the lysosome to the mature, most active form of the enzyme.
QT interval prolongation	Cipaglucosidase alfa is a glycoprotein with a molecular weight of approximately 110 kDa. No TQT studies have been performed to evaluate the QT internal prolongation potential for cipaglucosidase alfa.
	General Information
Bioanalysis	Plasma concentrations of cipaglucosidase alfa were determined using two independently validated assays: (1) LC-MS/MS assay that measures plasma total GAA protein concentration by signature peptide T09; and (2) an enzymatic activity 4-MU-α-Glc assay. The plasma total GAA protein concentration assay measures both active and inactive cipaglucosidase alfa moieties while the enzyme activity assay measures and accounts only for active cipaglucosidase alfa. Analysis of variance (ANOVA) of the AUC_{0-t} determined by GAA protein and GAA activity suggest that the differences in exposure observed were not significant. Population PK and exposure-response (E-R) analysis utilized total protein concentrations.
Healthy subjects versus patients	The PK of cipaglucosidase alfa has not been assessed in healthy subjects.

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)</td><td>Table 6 shows pharmacokinetics of cipaglucosidase alfa following single ascending doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg in ATB200-02 in ERT treatment-experienced patients by measuring plasma total GAA protein concentrations.

Table 6. Pharmacokinetics of Cipaglucosidase Alfa
<table><tr><th>Parameter</th><th>5 mg/kg (N=10)</th><th>10 mg/kg (N=11)</th><th>20 mg/kg (N=11)</th></tr><tr><td>C_{max} (µg/mL)</td><td>58.4 (19.1)</td><td>135 (18.3)</td><td>325 (13.5)</td></tr><tr><td>$AUC_{0\text{-}24h}$ (µg·h/mL)</td><td>208 (9.6)</td><td>533 (23.7)</td><td>1405 (16.2)</td></tr><tr><td>$AUC_{0\text{-}\infty}$ (µg·h/mL)</td><td>209 (18.0)</td><td>538 (23.9)</td><td>1410 (15.9)</td></tr></table>Source: ATB200-02 CSR Table 13; values are geometric means (coefficients of variation [%]).
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration.

The pharmacokinetics of cipaglucosidase alfa 20 mg/kg coadministered with miglustat 260 mg every other week was characterized in ERT treatment-experienced and treatment-naïve patients in Studies ATB200-02 and ATB200-03. The pharmacokinetic parameters from population analysis are summarized in Table 7.

Table 7. Pharmacokinetics of Cipaglucosidase Alfa Coadministered With Miglustat
<table><tr><th>Parameter</th><th>Treatment-Experienced</th><th>Treatment-Naïve</th></tr><tr><td></td><td>Day 1(N=56)</td><td>Day 1 (N=18)</td></tr><tr><td>C_{max} (µg/mL)</td><td>279.9 (51.9)</td><td>272.8 (49.3)</td></tr><tr><td>AUC (µg·h/mL)</td><td>1395.0 (299.7)</td><td>1343.1 (344.7)</td></tr><tr><td></td><td>Day 364 (N=44)</td><td>Day 364 (N=16)</td></tr><tr><td>C_{max} (µg/mL)</td><td>296.2 (58.8)</td><td>272.9 (49.3)</td></tr><tr><td>AUC (µg·h/mL)</td><td>1476.1 (321.9)</td><td>1457.1 (279.8)</td></tr></table>Source: AMC206-Pop-PK Report Table A2; values are means (standard deviation).
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration.</td></tr>
<tr><td>Range of effective dosage(s) or exposure</td><td>The recommended dosage regimen for cipaglucosidase alfa is 20 mg/kg every other week administered as an IV infusion coadministered with miglustat.</td></tr>
<tr><td>Maximally tolerated dosage or exposure</td><td>A maximally tolerated dose of cipaglucosidase alfa has not been determined. The highest evaluated dose was 20 mg/kg every other week in clinical trials in patients with LOPD.</td></tr>
<tr><td>Dosage proportionality</td><td>Greater than dose proportional increase in exposure was observed across the doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg in ATB200-02. AUC increased 6.7-fold and C_{max} increased 5.6-fold when dose increased 4-fold from 5 mg/kg to 20 mg/kg.</td></tr>
<tr><td>Accumulation</td><td>No accumulation in plasma concentration of cipaglucosidase alfa was observed at the recommended dose administered every other week.</td></tr>
<tr><td>Bridge between to-be-marketed and clinical trial formulations</td><td>The Applicant scaled up [redacted] (b) (4) from (b) (4) L in ATB200-02 to (b) (4) L for ATB200-03 and future commercial use. The clinical trial formulation composition is quantitatively identical to the proposed commercial product formulation. A PK bridge between the to-be-marketed formulation and clinical trial formulations is not needed.</td></tr>
<tr><td></td><td>Absorption</td></tr>
<tr><td>Bioavailability</td><td>Bioavailability is 100% because cipaglucosidase alfa is administered as an intravenous infusion.</td></tr>
<tr><td>T_{max}</td><td>C_{max} is expected to be achieved at the end of IV infusion.</td></tr>
</table>

Characteristic	Drug Information
	Distribution
Plasma protein binding	Plasma protein binding has not been characterized for cipaglucosidase alfa.
Volume of distribution	2.0 to 4.7 L
	Elimination
Clearance	The mean total body clearance (CL) of cipaglucosidase alfa when coadministered with miglustat was 0.8 and 1 L/h in treatment-experienced and treatment-naïve patients, respectively.
Half-life	The mean half-life of cipaglucosidase alfa when coadministered with miglustat was 2.1 and 2.2 h in treatment-experienced and treatment-naïve patients, respectively.
Metabolic pathway(s)	Metabolic pathway of cipaglucosidase alfa has not been characterized. Cipaglucosidase alfa is expected to be degraded into small peptides and amino acids via catabolic pathways.
	Intrinsic Factors and Specific Populations
Body weight	The recommended dose of cipaglucosidase alfa is based on body weight; the impact of body weight on exposure was not clinically meaningful.
Age	Based on population PK analysis from ATB200-02 and ATB200-03, age did not have clinically meaningful effects on the PK of cipaglucosidase alfa.
Renal impairment	No dedicated trial of the impact of renal impairment on the PK of cipaglucosidase alfa has been conducted.
Hepatic impairment	No dedicated trial of the impact of hepatic impairment on the PK of cipaglucosidase alfa has been conducted.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	No drug-drug interaction studies were conducted for cipaglucosidase alfa. This does not constitute a knowledge gap since cipaglucosidase alfa as a recombinant protein is unlikely to be involved in CYP450-mediated drug interactions.
Inhibition/induction of transporter systems	No drug-drug interaction studies were conducted for cipaglucosidase alfa. This does not constitute a knowledge gap since cipaglucosidase alfa as a recombinant protein is unlikely to be involved in transporter-mediated drug interactions.
	Immunogenicity
Bioanalysis	The immunogenicity of cipaglucosidase alfa was assessed in studies ATB200-02 and ATB200-03. A validated electrochemiluminescent assay was used to detect anti-cipaglucosidase alfa antibodies (total ADA assay) in plasma. An assay identical to the total ADA assay was qualified to detect cross-reactive with anti-alglucosidase alfa antibodies by method bridging. Three validated assays were used to determine the neutralizing activity of ADAs: (1) the inhibition of enzyme activity in hydrolysis of 4-MU-α-Glc; (2) the inhibition of enzyme activity in hydrolysis of glycogen; and (3) the inhibition of cellular uptake measured as inhibition of binding to cation-independent M6P receptor. A validated assay was used to detect anti-cipaglucosidase alfa IgE antibodies.

Characteristic	Drug Information
Incidence	Incidence of anti-cipaglucosidase alfa antibodies (ATB200-02 and ATB200-03):

Table 8: Incidence of Anti-Cipaglucosidase Alfa Antibodies

Antidrug Antibodies	Treatment-Experienced Patients	Treatment-Naïve Patients
ATB200-02	N = 23	N = 6
ADA at Baseline	n = 21 (91.3%)	n = 2 (33.3%)
ADA at Week 52	n = 23 (100%)	n = 6 (100%)
Inhibition of enzyme activity†	n = 12 (52.2%)	n = 0 (0%)
Inhibition of enzyme activity‡	n = 8 (34.8%)	n = 0 (0%)
Inhibition of CI-MPR binding§	n = 17 (73.9%)	n = 1 (16.7%)
ATB200-03	N = 65	N = 20
ADA at Baseline	n = 55 (85%)	n = 3 (15%)
ADA at Week 52	n = 58 (89%)	n = 20 (100%)
Inhibition of enzyme activity†	n = 26 (40%)	n = 4 (20%)
Inhibition of enzyme activity‡	n = 24 (37%)	n = 5 (25%)
Inhibition of CI-MPR binding§	n = 53 (82%)	n = 13 (65%)

Source: Compiled from Tables 8.1.1, 8.1.2 Descriptive Analysis Summaries of the Impact of Anti-Drug Antibodies on PK, PD, Efficacy, and Safety. Response to February 23, 2022 IR.
Abbreviations: ADA, antidrug antibody
† Enzyme activity measured as 4-methylumbelliferone-α-D-glucopyranoside (4-MU-α-Glc) hydrolysis
‡ Enzyme activity measured as glycogen hydrolysis
§ Inh bition of cation independent mannose-6-phosphate receptor (CI-MPR) binding

Clinical impact	There was no identified clinically significant effect of ADA on pharmacokinetics or pharmacodynamics (urinary Hex4 and CK) of cipaglucosidase alfa coadministered with miglustat over the treatment duration of 52 weeks. Because of the small number of patients with negative ADA, the effect of ADA on the effectiveness of cipaglucosidase alfa coadministered with miglustat is unknown. Antidrug antibody cross-reactivity studies showed that antibodies to cipaglucosidase alfa were cross-reactive to alglucosidase alfa. Patients who experienced anaphylaxis and infusion-associated serious adverse reactions had high peak ADA titers. IARs in treatment-experienced were also associated with high baseline ADA titers. There was no clear trend in IAR occurrence with the development of anti-cipaglucosidase alfa IgE antibodies.

Table 9. Summary of General Clinical Pharmacology and Pharmacokinetics for Miglustat

Characteristic	Drug Information
	Pharmacologic Activity

Characteristic	Drug Information
Established pharmacologic class	Enzyme stabilizer.
Mechanism of action	Miglustat binds with and stabilizes cipaglucosidase alfa while in circulation in the blood after infusion. The bound miglustat is disassociated from cipaglucosidase alfa after it is internalized and transported into lysosomes. Miglustat alone has no pharmacological activity in cleaving glycogen.
Active moieties	The parent drug miglustat is the active moiety. No active metabolite of miglustat has been identified.
QT prolongation	The Applicant has not conducted a thorough QT/QTc study to assess the effect of miglustat on QT interval prolongation. The clinical ECGs collected in studies ATB200-02 and ATB200-03 are not informative of the QTc prolongation potential due to the timing of ECG collection relative to peak miglustat concentration. We are requiring a postmarketing study rather than a preapproval study so as not to delay access of this drug that has shown a favorable benefit/risk profile for a rare disease condition.
	General Information
Bioanalysis	Miglustat concentrations in human plasma were quantified using a validated LC-MS/MS assay. The sensitivity of the assay was 0.50 ng/mL.
Healthy subjects versus patients	The PK of miglustat coadministered with cipaglucosidase alfa has not been assessed in healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	The geometric mean (CV%) results for $AUC_{0\text{-}inf}$ and C_{max} were 5908 (17.8%) ng·h/mL and 692 (26.5%) ng/mL, respectively, following a single dose oral administration of 65 mg miglustat (to-be-marketed formulation) in adult healthy subjects. At the recommended 260 mg dose in patients with LOPD, the mean (SD) C_{max} was 3 (0.9) µg/mL and the mean (SD) AUC was 25 (6.5) µg·h/mL.
Range of effective dosage(s) or exposure	Miglustat is dosed once every other week 1 h prior to the start of cipaglucosidase alfa infusion. The recommended dosage regimen for miglustat is based on patient's actual body weight: Patients weighing ≥40 kg to <50 kg: 195 mg Patients weighing ≥50 kg: 260 mg
Maximally tolerated dosage or exposure	A maximum tolerated dose has not been determined.
Dosage proportionality	The PK of miglustat is linear and dose proportional within the range of 130 mg to 260 mg.
Accumulation	No accumulation is expected at the recommended dosage administered once every other week.
Time to achieve steadystate	Not applicable as miglustat is dosed once every other week.
Bridge between to-be-marketed and clinical trial formulations	The phase 3 trial used the to-be-marketed 65 mg capsule (new); therefore, a PK bridging study between the to-be-marketed formulation and clinical trial formulation is not needed.
	Absorption
Bioavailability	The absolute bioavailability of miglustat following oral administration has not been determined.
T_{max}	Approximately 2-3 h.
Food effect (fed/fasted)	The effect of food on the PK of the to-be-marketed miglustat 65 mg capsule has not been conducted.

Characteristic	Drug Information
Geometric least square mean and 90% CI	The effect of food on the PK of miglustat was evaluated with Zavesca 100 mg. When taken with a high-fat meal, plasma C_{max} decreased by 36%, $AUC_{0\text{-}inf}$ decreased by 14% and T_{max} was delayed by approximately 2 h. Zavesca 100 mg capsule, fed:fasted ratios of least-square means (90% CI) C_{max} (ng/mL): 0.64 (0.57, 0.71) $AUC_{0\text{-}inf}$ (ng·h/mL): 0.86 (0.81, 0.91)
	Distribution
Volume of distribution (V/F)	The apparent volume of distribution is approximately 94 L in adult patients with LOPD.
Plasma protein binding	Miglustat does not bind to plasma proteins.
Drug as substrate of transporters	Miglustat is not a substrate of P-gP.
	Elimination
Mass balance results	Based on the Zavesca PI, the primary route of excretion of miglustat is via the kidney. Following a single oral dose of 100 mg [^{14}C]-labeled miglustat to healthy subjects, 83% of the radioactivity was recovered in urine and 12% in feces. In healthy subjects, 67% of the administered dose was excreted as unchanged miglustat in urine over 72 h. The most abundant metabolite in urine was miglustat glucuronide, which accounted for 5% of the dose. The terminal half-life of radioactivity in plasma was 150 h, suggesting the presence of one or more unidentified metabolites with a prolonged half-life.
Clearance (CL/F)	The apparent clearance is 10.4 L/h in adult patients with LOPD.
Half-life	The half-life is approximately 6 to 7 h.
Metabolic pathway(s)	The most abundant metabolite in urine was miglustat glucuronide.
Primary excretion pathways (% dosage)	Renal excretion.
	Intrinsic Factors and Specific Populations
Body weight	Body weight was identified as a significant covariate on the clearance of miglustat. Subjects with higher body weight had higher clearance and lower plasma miglustat concentrations. The proposed weight-based doses of 260 mg for patient weighing ≥50 kg and 195 mg for patient weighing ≥40 kg to <50 kg resulted in similar plasma miglustat concentrations.
Age	Age (19 to 74 years) was not identified as a significant covariate on the clearance of miglustat.
Renal impairment	The apparent clearance of miglustat decreased with decreasing renal function. A dedicated renal impairment (RI) study with Zavesca showed that subjects with moderate to severe RI had 60% to 70% decrease in miglustat CL/F, compared to subjects with normal renal function and mild RI. PK modeling and simulation results showed that $UC_{0\text{-}24hr}$ of miglustat increased by 21%, 32%, and 41% in patients with mild (CLcr 60 to 89 mL/minute, estimated by Cockcroft-Gault), moderate (CLcr 30 to 59 mL/minute), and severe (CLcr 15 to 29 mL/minute) RI, respectively, compared to patients with normal renal function. The effect of end stage renal disease on miglustat PK is unknown.
Hepatic impairment	No studies have been performed to assess the pharmacokinetics of miglustat in patients with hepatic impairment.

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Miglustat is not a substrate or inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A11. We are requiring a postmarketing study to assess whether miglustat is a substrate, inhibitor, or inducer of other metabolizing enzymes.
Inhibition/induction of transporter systems	Miglustat is not an inhibitor or a substrate of P-gP. We are requiring a postmarketing study to assess whether miglustat is a substrate, inhibitor, or inducer of other transporters.

Source: Applicant's Summary of Clinical Pharmacology Studies.
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated to infinity; CI, confidence interval; CL, clearance; CL/F, clearance after oral administration; C_{max}, maximum plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; GAA, acid alpha-glucosidase; GMR, geometric mean ratio; HPLC, high performance liquid chromatography; MS, mass spectrometry; MTD, maximum tolerated dose; PI, prescribing information; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration; TQT, thorough QT

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Cipaglucosidase Alfa

See Section 6.3.2

5.1.2. Miglustat

See Section 6.3.2

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. Cipaglucosidase Alfa Dosage

Cipaglucosidase alfa is administered as an IV infusion and is to be coadministered with oral miglustat. The proposed dosage regimen for cipaglucosidase alfa is 20 mg/kg administered every other week. The proposed dosage regimen was evaluated in ERT treatment-experienced and treatment-naïve patients in trials ATB200-02 and ATB200-03. The proposed cipaglucosidase alfa dosage is acceptable.

6.1.2. Miglustat Dosage

Miglustat is proposed to be coadministered with cipaglucosidase alfa. Miglustat is administered orally one hour prior to the start of IV infusion of cipaglucosidase alfa every other week. The proposed dosage regimens are 260 mg for patients weighing 50 kg and greater and 195 mg for patients weighing 40 kg and greater and less than 50 kg. The proposed dosage regimens were evaluated in ERT treatment-experienced and treatment-naïve patients in trials ATB200-02 and ATB200-03. The proposed miglustat dosage is acceptable. See Section 8.1.2.2 for dose adjustment in patients with moderate or severe renal impairment.

6.1.3. Dose Selection for the Clinical Studies

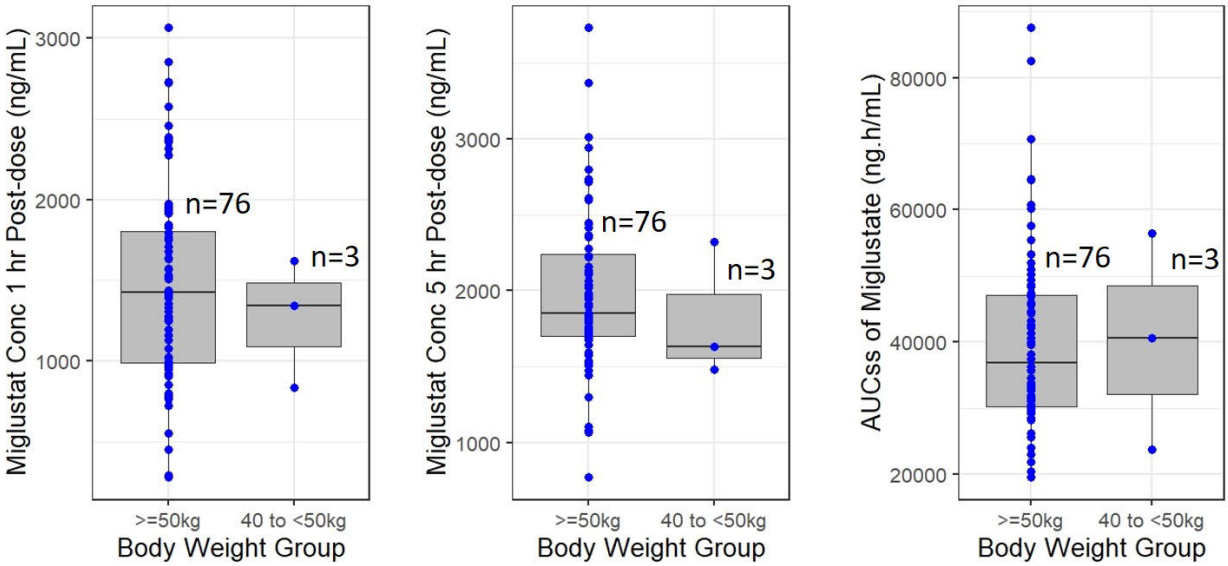
ATB200-02 was the first-in-human evaluation of cipaglucosidase alfa. It evaluated single ascending doses of cipaglucosidase alfa 5 mg/kg to 20 mg/kg and cipaglucosidase alfa 20 mg/kg coadministered with ascending doses of miglustat 130 mg and 260 mg in ERT treatment-experienced and treatment-naïve patients.

The starting dose of 5 mg/kg cipaglucosidase alfa was based on the no observed adverse effect level (200 mg/kg, the highest dose tested) in 6-month toxicity studies in rats and nonhuman primates, and the no observed adverse effect level for coadministered cipaglucosidase alfa and

miglustat, 100 mg/kg for cipaglucosidase alfa and 175 mg/kg for miglustat (the highest doses tested) in a 3-month toxicity study in nonhuman primates. The predicted safety margin for 5 mg/kg cipaglucosidase alfa starting dose was 31- to 55-fold in area under the concentration-time curve (AUC) and 23- to 55-fold in maximum concentration (C_{max}). The predicted safety margin for the starting 130 mg miglustat dose was 20-fold in AUC and C_{max}. The predicted safety margins for cipaglucosidase alfa and miglustat supported the starting doses in ATB200-02. Cipaglucosidase alfa 20 mg/kg and miglustat 260 mg (195 mg for patients weighing 40 kg and greater and less than 50 kg) doses administered every 2 weeks were selected for evaluation in the pivotal trial, ATB200-03.

The proposed and evaluated miglustat dose levels in Study ATB200-03 were 260 mg for patients weighing 50 kg and above, and 195 mg for patients weighing 40 to less than 50 kg, followed approximately 1 h later by cipaglucosidase alfa IV infusion every other week. The Applicant did not provide justification for the proposed body weight-tiered dosing regimen. Thus, the FDA review team conducted independent analysis to evaluate whether the proposed body weight-based dosing regimens for miglustat are reasonable. Miglustat concentrations at 1 and 5 h post dose were derived based on a population pharmacokinetic (PK) model for each subject in Study ATB200-03. One- and five-hour time points were selected because 1 hour post dose is the start of the infusion of cipaglucosidase alfa, and 5 h post dose is the end of the infusion of cipaglucosidase alfa. The miglustat concentrations at 1 and 5 h post dose and the AUC at steady state were compared between the body weight groups of 40 to <50 kg and ≥50 kg. Overall, the exposures in these two body weight groups largely overlapped (Figure 1), supporting the proposed miglustat dosing adjustment for patients weighing 40 to <50 kg. However, it should be noted that there were only three patients in the body weight group of 40 to <50 kg.

Figure 1. Miglustat Exposure in Patients Weighing ≥50 kg and 40 to <50 kg



Source: Review team.
Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state; conc, concentration

6.1.4. Pharmacodynamics

Urinary hexose tetrasaccharide (Hex4), a product of intravascular degradation of glycogen from damaged tissue and biomarker of glycogen accumulation, and serum creatine kinase (CK), a biomarker of muscle damage, were evaluated in patients with Pompe disease in ATB200-03. Urinary Hex4 was measured using a validated liquid chromatography-mass spectrometry method and serum CK was measured as part of standard serum chemistry by the Clinical Laboratory Improvement Amendments-certified central lab and not validated by the Applicant. Reductions in CK and Hex4 were significantly greater with cipa-mig than with the comparator. A summary of baseline and changes from baseline at Week 52 is shown in Table 10.

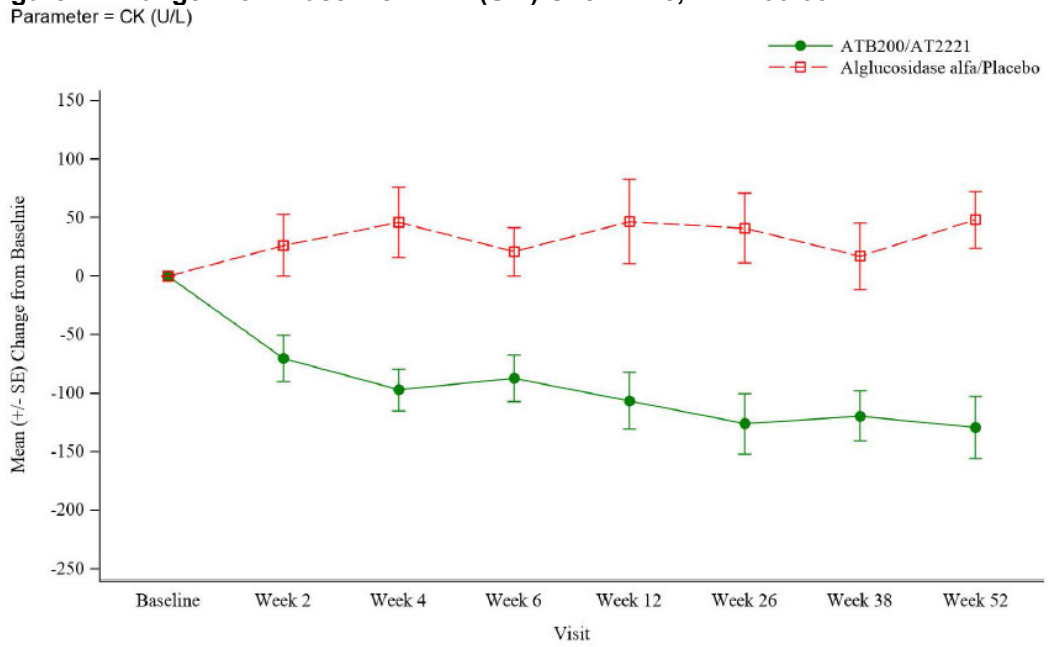
Table 10. Absolute Baseline Values and Change From Baseline at Week 52 LOCF Values in Serum CK and Urinary Hex4

	Cipa-Mig (N=85)		Comparator (N=37)	
Parameter	Baseline Mean (SD)	CFBL Mean (SD)	Baseline	CFBL Mean (SD)
CK (U/L)	447.0 (399.52)	-130.5 (231.18)	527.8 (426.57)	60.2 (159.49)
Treatment-experienced (N=95*)	441.8 (402.90)	-118.0 (228.79)	492.3 (442.73)	79.6 (147.46)
Treatment-naïve (N=27**)	464.1 (398.11)	-171.3 (240.17)	680.3 (333.13)	-23.1 (193.76)
Hex4 (mmol/mol creatinine)	4.61 (3.37)	-1.88 (2.38)	6.92 (6.94)	1.22 (4.43)
Treatment-experienced (N=94#)	4.55 (3.50)	-1.69 (2.41)	7.17 (7.62)	1.89 (4.61)
Treatment-naïve (N=27**)	4.81(2.99)	-2.48 (2.25)	5.84 (2.50)	-1.64 (1.80)

Source: Tables 47, 48, and 49 ATB200-03 CSR. Subject (b) (6) has been excluded.
*Cipa-mig N=65; comparator N=30, ** cipa-mig N=20; comparator N=7; # cipa-mig N=64; comparator N=30. Baseline was defined as the last available result on or prior to the first dose date.
Abbreviations: CFBL, change from baseline; cipa-mig, cipaglucosidase alfa coadministered with miglustat; CK, creatinine kinase; Hex4, hexose tetrasaccharide; LOCF, last observation carried forward; N, number of patients in group; SD, standard deviation

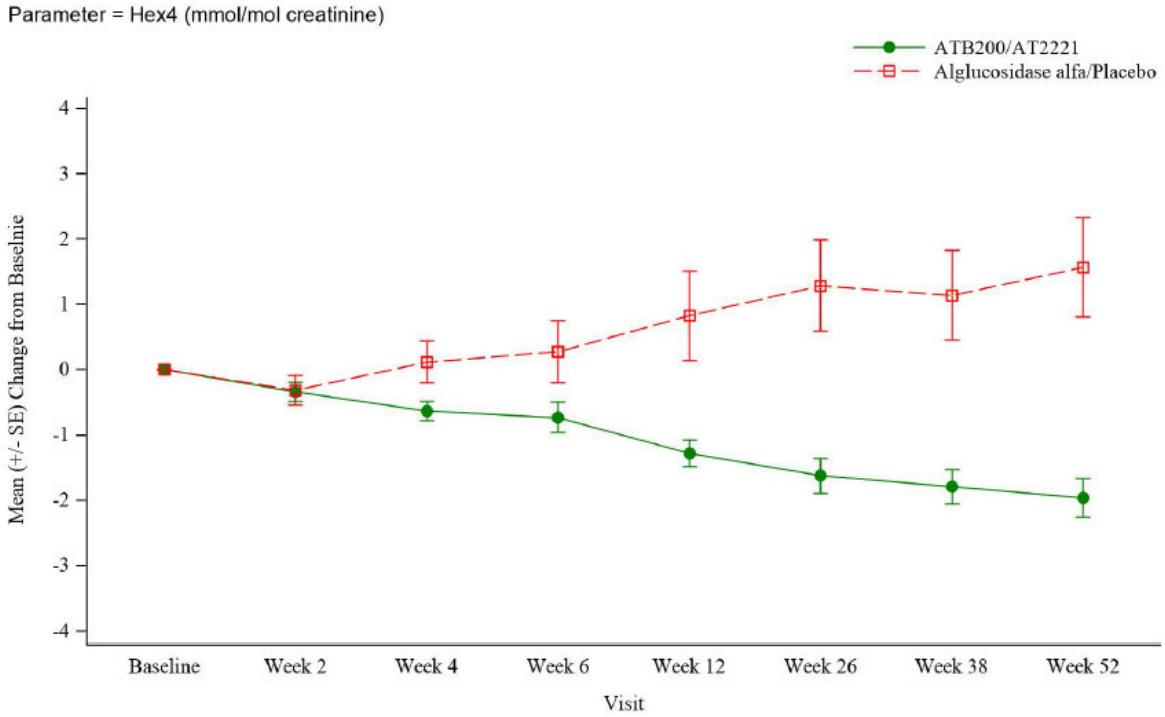
Serum CK measurements over the 52-week study period in cipa-mig treated patients showed significant reductions starting at Week 2, and reduced serum CK levels were sustained to Week 52 (Figure 2). Reduced urinary Hex4 was also observed from baseline to Week 52 (Figure 3). In comparison with ERT treatment-experienced patients (65 of 85 patients in the cipa-mig group), treatment-naïve patients (20 of 85 patients in the cipa-mig group) showed greater reductions in CK and Hex4.

Figure 2. Change From Baseline in CK (U/L) Over Time, ATB200-03



Source: ATB200-03 CSR Figure 14.4.1.1. Baseline was defined as the last available result on or prior to the first dose date.
Abbreviations: ATB200/AT2221, cipa-mig; CK, creatinine phosphokinase; SE, standard error

Figure 3. Change From Baseline in Hex4 (mMol/Mol Creatinine) Over Time, ATB200-03



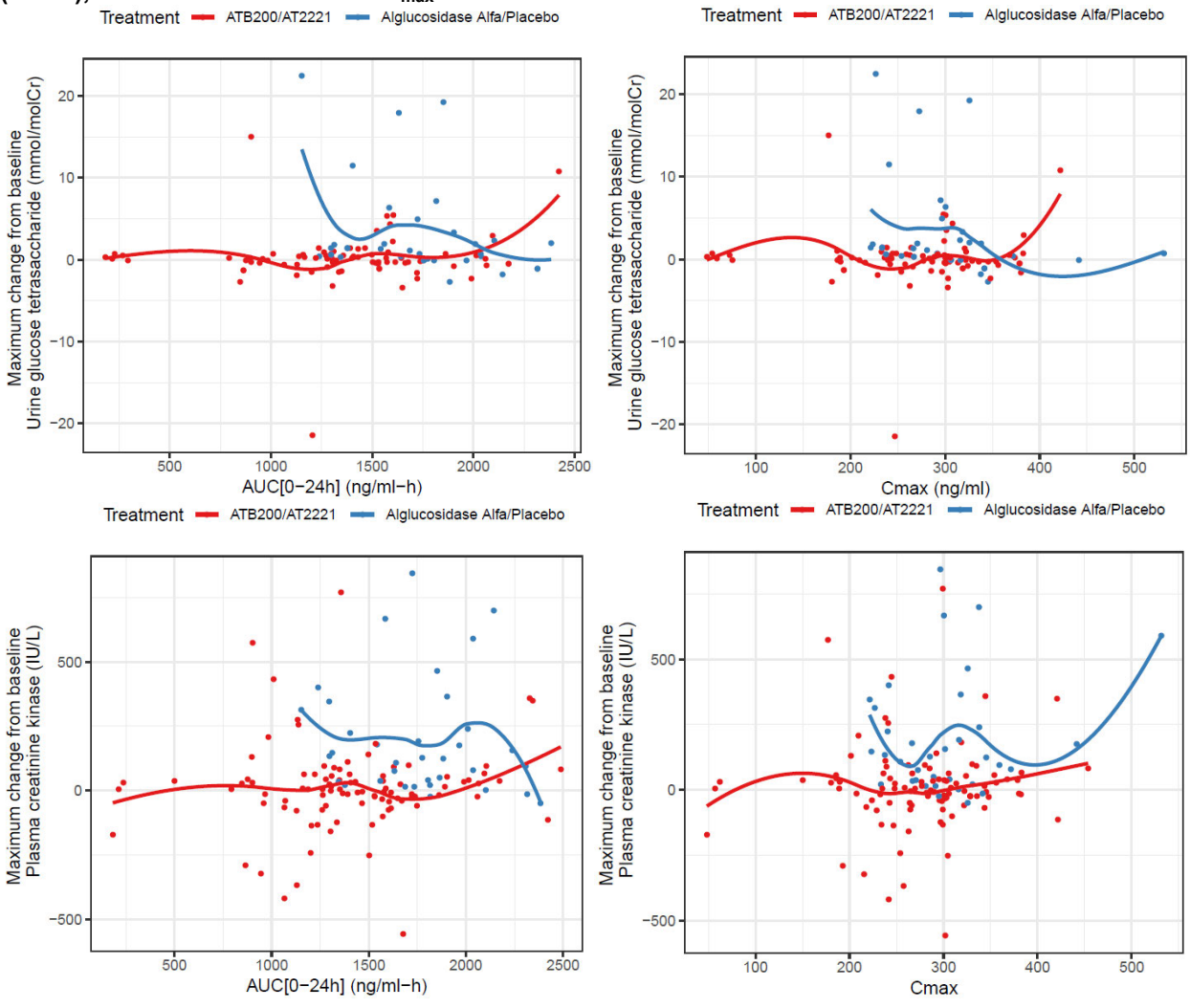
Source: ATB200-03 CSR Figure 14.4.1.1. Baseline was defined as the last available result on or prior to the first dose date.
Abbreviations: ATB200/AT2221, cipa-mig; SE, standard error

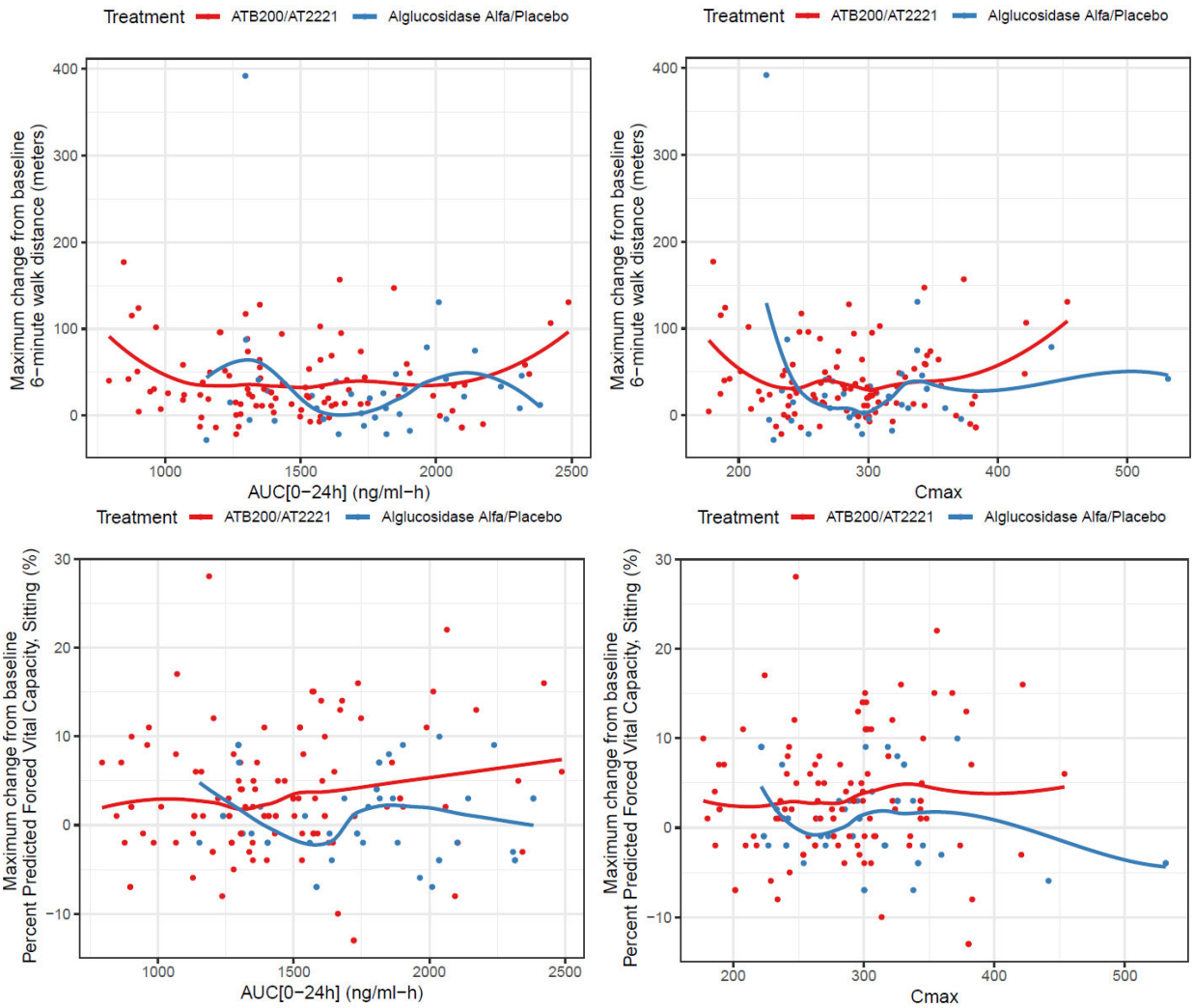
6.1.5. Exposure-Response

6.1.5.1. Exposure-Response for Efficacy

The Applicant conducted exposure-response (E-R) analyses for efficacy based on the data from all subjects with at least one observation and associated time-point available or reliably assumed. Two biomarker endpoints (serum CK and urinary Hex4) and two efficacy endpoints (6MWT and FVC%) were evaluated. Overall, no apparent E-R relationship was identified for both the biomarker endpoints and efficacy endpoints using AUC or C_{max} as the exposure metrics (Figure 4). Of note, because cipaglucosidase alfa exerts its pharmacological activity in lysosomes after its cellular internalization, plasma concentration may not be the most relevant driver of efficacy.

Figure 4. Maximum Change From Baseline of Creatinine Kinase (CK), Urinary Tetrasaccharide (HEX4), 6MWT and FVC Versus C_{max} or AUC





Source: Applicant's population PK and PK/PD study report.
Abbreviations: AT2221, miglustat; ATB220, cipaglucosidase alfa; AUC, area under the concentration-time curve; CK, creatinine kinase; C_{max}, maximum concentration; PD, pharmacodynamic; PK, pharmacokinetic

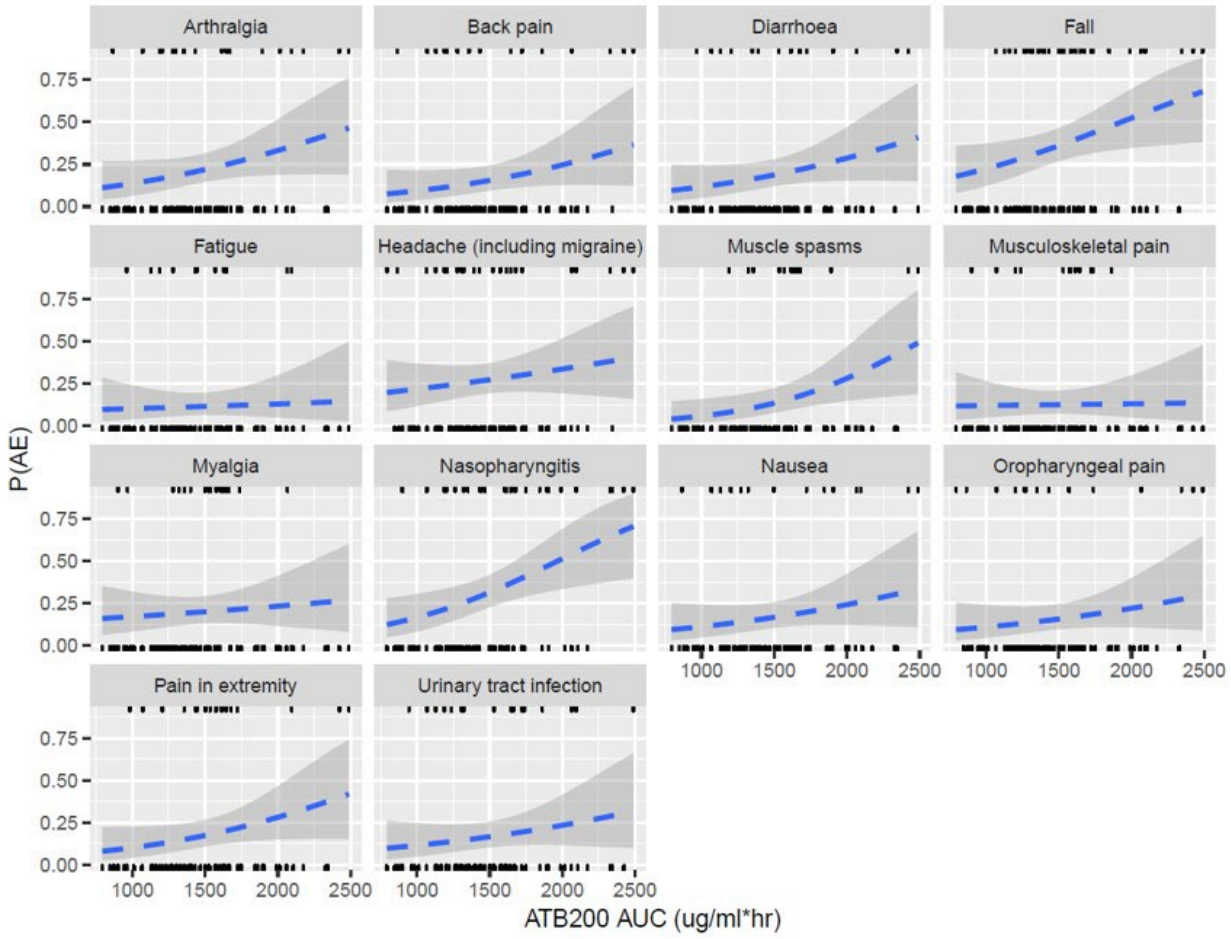
6.1.5.2. Exposure-Response for Safety

6.1.5.2.1. Cipaglucosidase Alfa

Upon FDA's request, the Applicant conducted multivariate E-R analysis for safety endpoints for cipaglucosidase alfa using the data from Studies ATB200-02 and ATB200-03. The analysis population were subjects who had cipaglucosidase alfa PK data following the treatment of cipa-mig. The most frequent treatment-emergent adverse events (TEAEs) (≥10%) included in the analyses were fall, headache, nasopharyngitis, arthralgia, back pain, myalgia, nausea, diarrhea, pain in extremity, urinary infection, fatigue, musculoskeletal pain, oropharyngeal pain, and muscle spasms (for details, refer to Section 14.4). The covariates included age, race (Asian/non-Asian), gender and ERT status (treatment-experienced and treatment-naïve). The results of the analysis identified positive E-R relationships for nasopharyngitis, pain in extremity, and muscle spasms (Figure 5).

Muscle spasms was identified by the Applicant as an adverse drug reaction. Pain in extremity was addressed by the adverse drug reactions of pain, arthralgia, and myalgia. For nasopharyngitis, while the positive E-R relationship was observed, the number of subjects were limited. In addition, none of the reported TEAEs of nasopharyngitis was considered related to study drugs.

Figure 5. Exposure-Response Analysis for Safety for Cipaglucosidase Alfa, ATB200-03 and ATB200-02 (Cohorts 1 and 3)



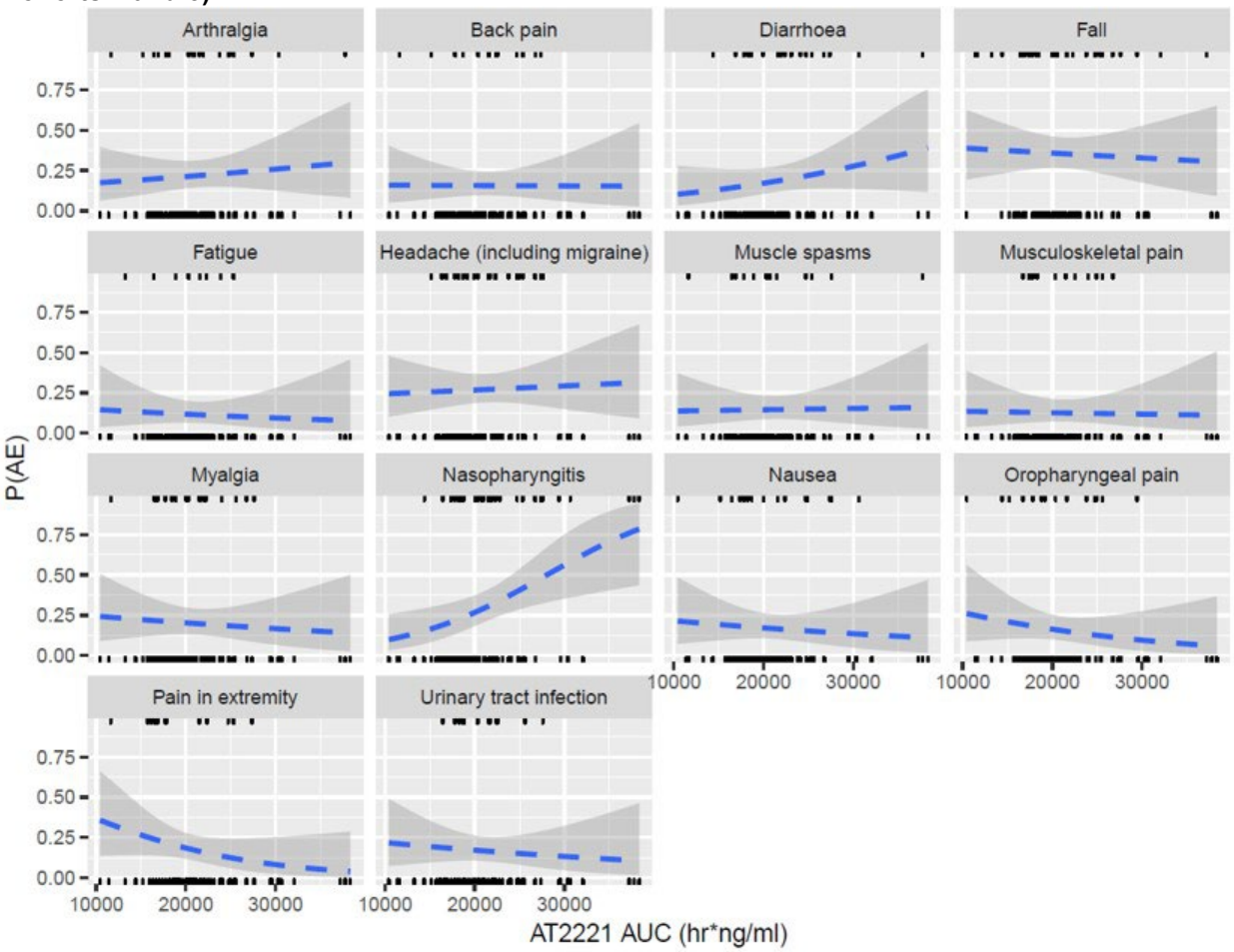
Source: Applicant's response to a September 9, 2021 Information Request.
Abbreviations: AE, adverse event; ATB220, cipaglucosidase alfa; AUC, area under the concentration-time curve

6.1.5.2.2. Miglustat

Upon FDA's request, the Applicant conducted E-R analysis for safety endpoints (Figure 6) for miglustat. The most frequent TEAEs (≥10%) included in the analyses were fall, headache, nasopharyngitis, arthralgia, back pain, myalgia, nausea, diarrhea, pain in extremity, urinary infection, fatigue, musculoskeletal pain, oropharyngeal pain, and muscle spasms. As shown in Figure 6, overall, no significant E-R relationship was identified between the incident rate of adverse events versus AUC of miglustat based on the data from Study ATB200-03 and ATB200-02 (Cohorts 1 and 3), except for nasopharyngitis. Per the Applicant, none of the reported TEAEs of nasopharyngitis was considered related to miglustat. In addition, because no monotherapy arm of miglustat was included in the Study ATB200-03, the E-R analysis could be confounded by the

effect of cipaglucosidase alfa. Based on analysis of the currently available data, the proposed body weight-tiered dosing regimen of miglustat appears appropriate.

Figure 6. Exposure-Response Analysis for Safety for Miglustat, ATB200-03 and ATB200-02 (Cohorts 1 and 3)



Source: Applicant's response to an October 1 2021 Information Request.
Abbreviations: AE, adverse event; AT2221, miglustat; AUC, area under the concentration-time curve

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. ATB200-03

6.2.1.1. Design, ATB200-03

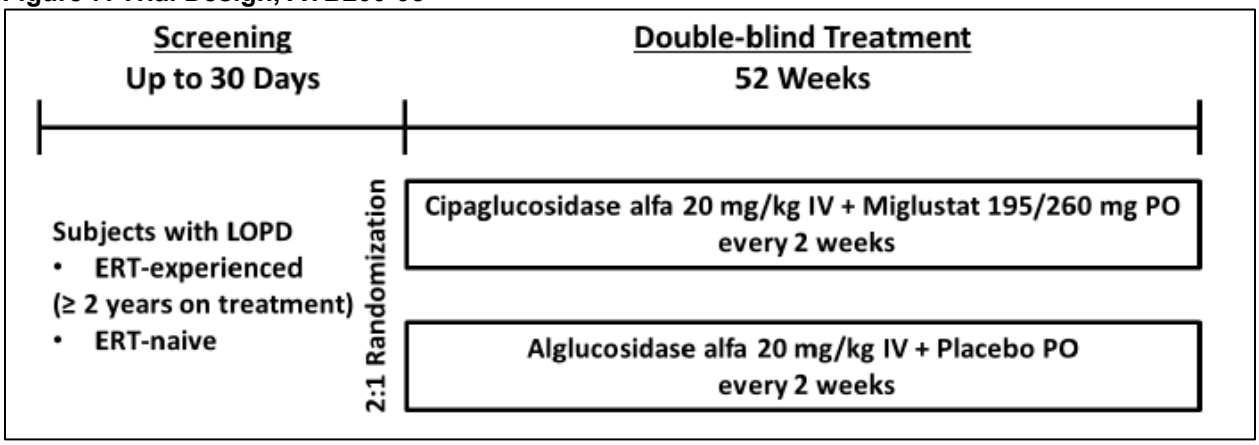
The pivotal trial, ATB200-03, conducted in 61 centers in 24 countries, was a randomized, double-blind, comparator-controlled study in treatment-naïve and treatment-experienced patients 18 years of age or older with LOPD (Figure 7). The primary objective of this trial was to determine the effectiveness of cipa-mig treatment on functional endurance as measured by the 6MWT at 52 weeks compared to the comparator. The key secondary objectives included

evaluation of respiratory muscle strength as measured by FVC (% predicted) in the sitting position, as well as on functional endurance (measured as 6MWT at 26 weeks), muscle strength (assessed using the Gait, Stairs, Gowers' maneuver, and Chair test [GSGC]), lower extremity muscle strength (measured via manual muscle testing using a hand-held dynamometer), and health-related quality of life (assessed using the Patient-Reported Outcomes Measurement Information System [PROMIS]-physical function and PROMIS-fatigue).

A total of 123 patients was randomized 2:1 to receive cipaglucosidase alfa 20 mg/kg coadministered with miglustat 195 mg (for patients weighing ≥40 kg to <50 kg) or 260 mg (for patients weighing >50 kg) every other week (qow) or a non-U.S.-approved alglucosidase alfa product at 20 mg/kg coadministered with placebo qow for a 12-month double-blind treatment period (Figure 7). Upon completion of the trial, the patients continued treatment in trial ATB200-07, an open-label extension trial designed for patients from ATB200-03, during which patients in the cipa-mig group continued to receive cipa-mig and patients in the comparator group started to receive cipa-mig. Randomization was stratified by baseline 6MWT (75 to <150 m, 150 to <400m, or ≥400 m) and ERT status (treatment-experienced and treatment-naïve).

The duration of the trial included a 30-day screening period, a 52-week blinded treatment period, and a 30-day follow-up period.

Figure 7. Trial Design, ATB200-03



Source: Figure 1 of the Clinical Study Report for trial ATB200-03.
Abbreviations: ERT, enzyme replacement therapy; IV, intravenous(ly); LOPD, late-onset Pompe disease; PO, by mouth

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline to Week 52 in the 6MWT to measure functional endurance.

Secondary Efficacy Endpoint

The key secondary efficacy endpoint was the change from baseline to Week 52 in FVC (% predicted) in the sitting position to measure respiratory muscle strength.

Additional secondary efficacy endpoints include the following (also see Sections 6.2.1.3.2, 6.2.1.3.3, and 6.2.1.4.3):

- 6MWT (at 26 weeks): functional endurance.
- GSGC: muscle strength.

- Manual muscle testing (neurological assessment and a hand-held dynamometer): lower extremity muscle strength (upper extremity muscle for non-ambulatory patients).
- PROMIS-physical function and PROMIS-fatigue: health-related quality of life.

6.2.1.2. Eligibility Criteria, ATB200-03

Key eligibility criteria are summarized in this section.

Inclusion Criteria

- Males and females with confirmed GAA enzyme deficiency or two confirmed *GAA* gene variants.
- Patients were 18 years of age or older and weighed 40 kg or more at screening.
- Patients ERT status was one of the following:
  - Treatment-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product) at the recommended dose and regimen (i.e., 20 mg/kg dose every 2 weeks) for ≥24 months
  - Treatment-naïve, defined as never having received investigational or commercially available ERT
- Patient had a sitting FVC ≥30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III) at screening.
- Patient performed two 6MWTs at screening that meet all the following criteria:
  - Both screening values of 6-minute walk distance (6MWD) were ≥75 m
  - Both screening values of 6MWD were ≤90% of the predicted value for healthy adults
  - The lower value of 6MWD was within 20% of the higher value of 6MWD

Exclusion Criteria

- Previous treatment with any investigational therapy or pharmacological treatment for Pompe disease, other than alglucosidase alfa, within 30 days or five half-lives of the therapy or treatment, whichever is longer, before Day 1.
- Previous treatment with gene therapy for Pompe disease.
- Current use of any of the following medications within 30 days before Day 1: miglitol (e.g., Glyset), miglustat (e.g., Zavesca), acarbose (e.g., Precose, Glucobay), or voglibose (e.g., Volix, Vocarb, Volibo).
- Dependence on invasive or noninvasive ventilation support for more than 6 h per day while awake.
- Hypersensitivity to any of the excipients in cipaglucosidase alfa or miglustat.

6.2.1.3. Statistical Analysis Plan, Trial ATB200-03

The statistical analysis plan (SAP; version 3) was finalized on January 14, 2021 and submitted to the Agency on January 19, 2021. The SAP-defined primary estimand for the primary efficacy endpoint is a treatment-policy estimand which is estimated by a mixed model for repeated measures (MMRM). The MMRM analysis relies on two assumptions: (1) the primary endpoint has a normal distribution and (2) the missing data are missing at random. The Agency reviewed this SAP and stated that the treatment-policy estimand is acceptable and the final acceptability of its estimation based on the MMRM would be a review issue. Note: according to the clinical study report, the first patient enrollment date was December 3, 2018 and the last patient completion date was December 15, 2020.

6.2.1.3.1. Analysis of the Primary Endpoint

The SAP-defined primary analysis used an MMRM to evaluate the mean change from baseline in 6MWD at Week 52. The MMRM included treatment group, time (i.e., study visit), an interaction between time and treatment, ERT experience status, sex, age, baseline 6MWD, weight, and height. Study visit was a categorical variable with four levels (12, 26, 38, and 52 weeks). The unstructured covariance structure was used to account for the within-subject correlations for the repeated measures. The estimate of the effect of the interaction between treatment and time at the 52-week timepoint was used to estimate the treatment effect for the primary endpoint.

The primary analysis was performed on the intent-to-treat population, defined as all randomized patients who received at least one dose of the study drug. Five patients did not have a measurement at the 52-week timepoint, though all previous observations for those patients were included in the MMRM.

Superiority of cipa-mig to the comparator was tested using a two-sided alpha level of 0.05.

After the database lock, the Applicant identified one patient as an outlier, due to having a "clinically implausible" improvement in the 6MWT at 52 weeks (for details see Section 6.3.1). This outlier had a significant impact on the estimation and testing of the primary endpoint. To evaluate the robustness of the efficacy results, nonparametric analyses and analyses excluding the outlier were conducted to further evaluate the primary endpoint by both the Applicant and the review team.

The nonparametric analyses included a Wilcoxon rank-sum test, which tests for a difference of the distributions, as well as a global rank-sum test combining information from the primary and key secondary endpoints.

Handling of Missing Data

The MMRM analysis assumed that the missing data were missing at random. This analysis method utilized all observed data without imputation for missing postbaseline data, referred to as the intent-to-treat (ITT) observed population. As shown in Figure 93, five patients (four patients (5%) in the cipa-mig arm and 1 (3%) in the comparator arm) had missing data for the primary endpoint. Note: according to the Applicant's response to the Agency's information request dated December 17, 2021, Subject (b) (6) in the cipa-mig arm received her last study treatment on Day 223 and decided she did not want to visit the study site again due to the COVID-19

pandemic. But she was willing to return for the early termination assessments, which occurred on Day 326. Since her early termination assessments fell within the 52-week analysis visit window defined in the SAP, her efficacy data collected on Day 326 were included in the primary efficacy analysis at Week 52.

By examining the causes of the missing data and the observed data of these patients, the review team found the missing at random assumption reasonable.

Sensitivity and Supportive Analyses

The normality assumption required of the MMRM method was violated, so nonparametric tests were also performed to assess sensitivity to this assumption. Per the SAP, if the assumption of normality was strongly violated, determined by a $p<0.01$ by Shapiro-Wilk test, a nonparametric analysis of variance approach was performed for the primary endpoint.

As supportive analysis, analysis of covariance (ANCOVA) was performed using the last available measurement to impute missing data, given that there was at least one postbaseline observation. This approach to handle missing postbaseline data will be referred to as last observation carried forward (LOCF).

Per the SAP, an ANCOVA with LOCF imputation for missing data at 52 weeks would be performed after removal of outliers, defined by "externally studentized residuals that are large (>3)," if outliers were present.

For the nonparametric analyses, the LOCF approach was also used to impute missing data at 52 weeks.

Subgroup Analyses

The SAP specified subgroup analyses of the following subgroups for the primary endpoint: ERT status (treatment-experienced versus treatment-naïve), ERT duration (2 to 3, 3 to 5, ≥5 years), age, gender, race, baseline 6MWD (75 to 150, 150 to 400, and ≥400 m and by median), baseline FVC (by median), regions (North and South America, Europe, and Asia Pacific), and history of infusion-associated reactions (IARs).

Important Post Hoc Analyses

Several important post hoc analyses were performed, largely due to the identification of a highly influential outlier after the time of database lock. In addition to predefined analyses for addressing outliers, the Applicant reproduced all the analyses defined for the primary endpoint while excluding the detected outlier. These analyses are justified given that the integrity of observations from the outlier are in question in addition to statistically appearing as an outlier.

Additionally a Wilcoxon rank-sum global test for the primary endpoint and key secondary endpoint, FVC (% predicted), was performed using the Wilcoxon rank-sum test (O'Brien 1984). The Wilcoxon rank-sum global test was performed by first ranking each endpoint for all patients. The ranks were then summed across endpoints for each patient. The distributions of the sum of the ranks for the two treatment groups were compared using a Wilcoxon rank-sum test.

6.2.1.3.2. Analysis of the Key Secondary Endpoint

The key secondary efficacy endpoints include FVC (% predicted) change at Week 52 from baseline, change in manual muscle test for the lower extremities, change in 6MWD at Week 26 from baseline, change in the total score for the PROMIS-physical function, change in total score for the PROMIS-fatigue, and change in the total score for the GSGC. The secondary endpoints were analyzed using ANCOVA on the ITT population and LOCF for missing Week 52 observations. The following covariates were adjusted for: baseline FVC, ERT status (treatment-experienced versus treatment-naïve), baseline age, gender, baseline height, and baseline weight. A stepwise testing procedure was specified in the SAP in order to control the Type I error rate, specifying that the key secondary endpoints only be tested if all previous endpoints in the hierarchical order succeeded in rejecting the null hypothesis at the alpha level of 0.05.

Subgroup analyses similar to those for the primary endpoint were performed for the key secondary endpoint.

6.2.1.3.3. Analysis of Other Secondary Endpoints

Other secondary endpoints include the manual muscle test for the lower extremities, 26-week change from baseline of 6MWD, total score for the PROMIS-physical function, PROMIS-fatigue total score, and total score for GSGC. Each of these will be analyzed using ANCOVA with LOCF imputation for missing values at the 52-week timepoint and adjusting for the following covariates: baseline value of respective endpoint, ERT status (treatment-experienced versus treatment-naïve), baseline age, gender, baseline height, and baseline weight. Again, these will be tested according to the stepwise testing procedure specified in the SAP in order to control the Type I error rate, specifying that the secondary endpoints only be tested if all previous endpoints in the hierarchical order succeeded in rejecting the null hypothesis at the α=0.05.

6.2.1.4. Results of Analyses, Trial ATB200-03

This section presents patient disposition, baseline demographics, and results of the efficacy analyses for the primary and secondary efficacy endpoints.

Baseline Demographics

Patient demographic information is presented in Table 11. Baseline demographics were similar in the two arms. The mean age at enrollment was 47.6 years for the cipa-mig group and 45.1 years for the comparator group. The majority of patients were white in both groups; 87.1% in the cipa-mig group and 78.9% in the comparator group. This is not representative of the overall population with PD, which has an incidence of 1:14,000 among African Americans (Leslie and Bailey 1993). However, this imbalance was also present in the alglucosidase alfa and avalglucosidase alfa trials. Most patients were enrolled in sites in the United States, Australia, and France. Overall, 77.3% of patients were treatment-experienced, and 22.7% were treatment-naïve.

Table 11. Baseline Demographic and Clinical Characteristics, ATB200-03

Characteristic	Cipa-Mig 20 mg/kg N=85	Comparator 20 mg/kg N=38
Sex, n (%)		
Female	49 (57.6)	18 (47.4)
Male	36 (42.4)	20 (52.6)
Age, years		
Mean (SD)	47.6 (13.3)	45.1 (13.3)
Median (minimum, maximum)	48 (19, 74)	46 (22, 66)
Age group, years, n (%)		
≥18 to <35 years	17 (20.0)	10 (26.3)
≥35 to <50 years	27 (31.8)	13 (34.2)
≥50 to <65 years	30 (35.3)	12 (31.6)
≥65 years	11 (12.9)	3 (7.9)
Race, n (%)		
White	74 (87.1)	30 (78.9)
Asian	3 (3.5)	1 (2.6)
Black or African American	0 (0)	1 (2.6)
American Indian or Alaska Native	0 (0)	1 (2.6)
Japanese	2 (2.4)	4 (10.5)
Native Hawaiian or Other Pacific Islander	1 (1.2)	0 (0)
Other	5 (5.9)	1 (2.6)
Country of participation, n (%)		
United States	24 (28.2)	13 (34.2)
Australia	12 (14.1)	6 (15.8)
France	8 (9.4)	3 (7.9)
Hungary	7 (8.2)	0 (0)
Great Britain	6 (7.1)	3 (7.9)
Denmark	6 (7.1)	0 (0)
Spain	3 (3.5)	0 (0)
Germany	3 (3.5)	2 (5.3)
Japan	2 (2.4)	4 (10.5)
Italy	2 (2.4)	0 (0)
Belgium	1 (1.2)	2 (5.3)
Canada	1 (1.2)	2 (5.3)
Argentina	1 (1.2)	0 (0)
Austria	1 (1.2)	0 (0)
Bosnia and Herzegovina	1 (1.2)	1 (2.6)
Greece	1 (1.2)	0 (0)
Korea	1 (1.2)	0 (0)
Netherlands	1 (1.2)	0 (0)
Poland	1 (1.2)	1 (2.6)
Slovakia	1 (1.2)	0 (0)
Sweden	1 (1.2)	0 (0)
Taiwan	1 (1.2)	1 (2.6)
Clinical characteristics, n (%)		
Treatment-naïve	20 (23.5)	8 (21.1)
Treatment-experienced	65 (76.5)	30 (78.9)
ERT Duration (years) for ERT-experienced patients		
Mean (SD)	7.5 (3.4)	7.1 (3.6)
Median (min, max)	7.6 (2.0, 13.7)	7.1 (2.1, 13.2)

Source: adsl.xpt.
Abbreviations: Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Patient Disposition

A total of 125 patients was randomized (Table 12). Two patients were not dosed because their genotyping did not confirm LOPD. Five patients in the cipa-mig arm and one patient in the comparator arm prematurely discontinued the trial. Of the five patients in the cipa-mig arm, three patients discontinued the trial due to adverse events and two patients withdrew consent due to travel. The patient in the comparator arm discontinued the trial due to an adverse event (Table 13). All 117 patients who completed the trial entered the open-label extension trial ATB200-07, during which they received cipa-mig. One patient who discontinued ATB200-03, enrolled in ATB200-07. At the time of data cut-off (April 1, 2021), 118 patients continued to receive cipa-mig in the ongoing ATB200-07 trial.

Table 12. Patient Screening and Randomization, ATB200-03

Screening Disposition	ATB200-03
Number of patients screened	130
Number of screening failures	5
Number of patients randomized	125

Source: adds.xpt and Clinical Study Report.

Table 13. Patient Disposition, ATB200-03

Disposition Outcome	Cipa-Mig N=85	Comparator N=38	Risk Difference (%) (95% CI)
Patients randomized	85	38	NA
ITT population	85	38	NA
Safety population	85	38	NA
Discontinued study, n (%)	5 (5.9)	1 (2.6)	3.3 (-3.9, 10.4)
Withdrawal of consent by subject	2 (2.4)	0	2.4 (-0.9, 5.6)
Adverse event[a]	3 (3.6)	1 (2.6)	0.9 (-5.5, 7.3)

Source: ds.xpt, adsl.xpt.
[a] Recoded COVID-19 infection from "other" to adverse event; "withdrawal of consent by subject" (due to anaphylaxis) to AE, "investigator's decision" (due to infusion associated reaction) to AE.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; COVID-19, coronavirus disease 2019; ITT, intent-to-treat; N, number of patients in treatment arm; n, number of patients in specified population or group; NA, not applicable; qow, every other week

Baseline Key Efficacy Variables

Baseline data of the key efficacy variables are presented in Table 14. The mean 6MWD was slightly higher in the cipa-mig arm compared to the comparator arm, and the medians were similar in the two arms. All the secondary endpoints appear well balanced across the treatment arms.

Table 14. Baseline Data of Key Efficacy Variables, ATB200-03

Parameter Statistic	Cipa-Mig N=85	Comparator N=38	Total N=123
Distance in 6MWT (m)			
N	85	38	123
Mean (SD)	357.9 (111.8)	350.1 (119.8)	355.5 (113.9)
Median	359.5	358.5	359.5
Minimum, maximum	79.0, 575.0	112.5, 623.0	79, 623

Parameter Statistic	Cipa-Mig N=85	Comparator N=38	Total N=123
FVC (% predicted)			
N	85	38	123
Mean (SD)	70.7 (19.6)	70.0 (21.3)	70.5 (20.0)
Median	70.0	71.3	70.0
Minimum, maximum	30.5, 132.0	31.5, 122.0	30.5, 132.5
MMTL			
N	84	35	119
Mean (SD)	28.0 (5.8)	27.9 (6.3)	27.9 (5.9)
Median	28	28	28.0
Minimum, maximum	15, 39	14, 40	14, 40
PROMIS – Physical Function			
N	84	38	122
Mean (SD)	66.9 (12.3)	68.2 (13.0)	67.3 (12.5)
Median	67	67	67
Minimum, maximum	37, 96	44, 97	37, 97
PROMIS-Fatigue			
N	85	38	123
Mean (SD)	22.3 (8.3)	21.2 (6.0)	21.9 (7.7)
Median	22	21	21
Minimum, maximum	8, 40	8, 34	8, 40
GSGC			
N	74	33	107
Mean (SD)	14.5 (5.2)	14.2 (4.9)	14.4 (5.1)
Median	16	16	16
Minimum, maximum	4, 24	4, 22	4, 24

Source: Tables 11 and 14.1.3.3 of Clinical Study Report. This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
Abbreviations: Cipa-mig, cipaglucosidase alfa coadministered with miglustat; FVC, forced vital capacity; GSGC, Gait, Stairs, Gowers' maneuver, and Chair; MMTL, manual muscle testing lower extremities; 6MWT, six-min walk test; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation

6.2.1.4.1. Efficacy Results for 6MWT

The observed mean change from baseline in the 6MWD (m) to Week 52 was higher in the cipa-mig arm (Table 26, Section 6.3.1): 20.6 m (cipa-mig) versus 17.4 m (comparator). The median change from baseline in 6MWD to Week 52 was 12.5 m in the cipa-mig arm and 4.9 m in the comparator arm. The estimated treatment difference was 5.33 (95% confidence interval [CI]: -15.2 to 25.9; p=0.608) favoring the cipa-mig arm. The p-value for the superiority test was 0.61, larger than the prespecified significance level of 0.05. The primary efficacy results were heavily influenced by the presence of an outlier in the comparator arm. The results excluding Subject (b) (6) continue to favor the cipa-mig arm (Table 27, Section 6.3.1). The estimated treatment difference is 14 m (95% CI: -2.6, 31; p=0.1 based on the MMRM analysis), and the p-value based on the Wilcoxon rank-sum test is 0.07. Although these results did not meet the conventional statistically significance threshold of 0.05, they do provide convincing evidence that cipa-mig provides a clinically meaningful numerical improvement compared to treatment with an active comparator.

Refer to Section 6.3.1 for details of the primary efficacy results.

6.2.1.4.2. Efficacy Results for FVC (% Predicted)

The estimated mean change from baseline in FVC (% predicted) to Week 52 was higher in the cipaglucosidase alfa arm (Table 15): -1.6% (cipa-mig) versus -4.0% (comparator). The estimated treatment difference was 2.3% (95% CI: 0.02 to 4.6; p=0.0484) favoring the cipa-mig arm. These results suggest that cipa-mig is effective in improving pulmonary function (FVC % predicted). However, as the superiority test for the primary endpoint did not meet the significance level of 0.05, no formal superiority test was conducted for the FVC (% predicted) endpoint.

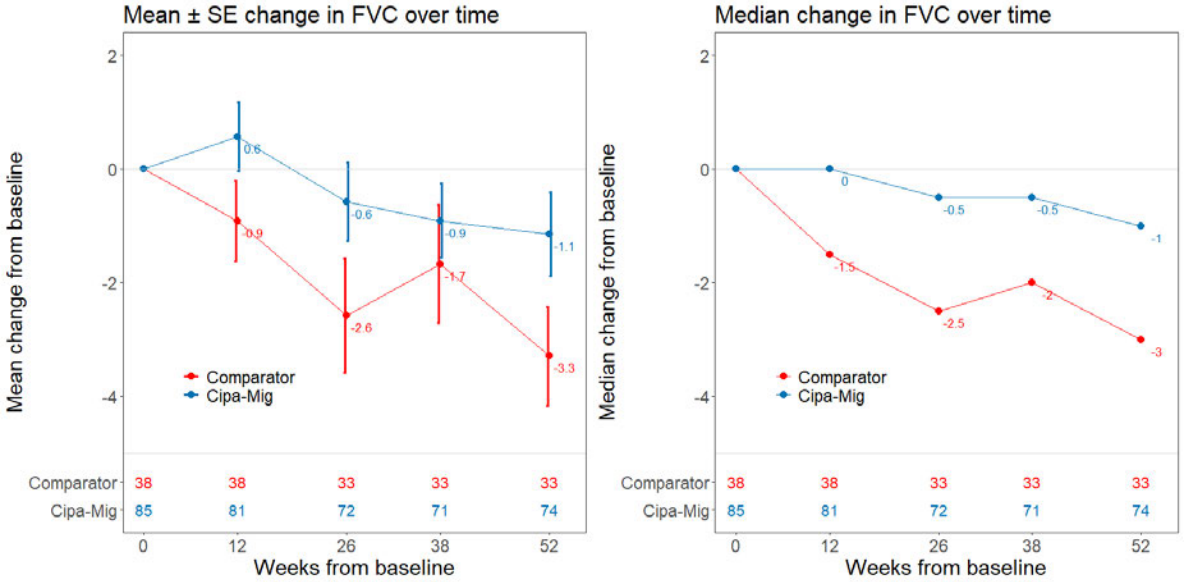
Table 15. Baseline and Change in FVC (% Predicted) From Baseline to Week 52, ITT Population, ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=85	N=38		
Mean (SD)	70.7 (19.6)	70.0 (21.3)		
Median (min, max)	70.0 (30.5, 132.5)	71.2 (31.5, 122.0)		
Week 52	N=74	N=33		
Mean (SD)	69.8 (20.2)	63.7 (20.8)		
Median (min, max)	69.0 (30.0, 137.0)	56.0 (28.0, 96.0)		
Change from baseline to Week 52	N=74	N=33		
Mean (SD)	-1.1 (6.3)	-3.3 (5.0)		
Median (min, max)	-1.0 (-17.0, 14.0)	-3.0 (-19.5, 7.5)		
Estimated change form baseline to Week 52	N=84	N=38		
LS mean change[2]	-1.64 (0.72)	-3.96 (1.02)	2.32 (0.02, 4.62)	0.0484
Wilcoxon rank-sum				0.0287

Source: Tables 16 and 14.2.3.1.1 of the Clinical Study Report. This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig − comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 estimated by analysis of covariance (ANCOVA) model including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline FVC (% predicted), age (continuous), weight, and height; an unstructured covariance matrix was used. Missing data were imputed using the last available values (this method was also used for the Wilcoxon rank-sum test).
Abbreviations: CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; FVC, forced vital capacity; ITT, intent-to-treat; LS, least squares; max, maximum; min, minimum; SD, standard deviation

Figure 8 depicts the mean change in FVC (% predicted) over time by the randomized arms. A difference between the two groups was observed at Week 12 (the time of the first postbaseline assessment) and maintained through Week 52.

Figure 8. Mean (±SE) and Median Change From Baseline in FVC (% Predicted) Over Time

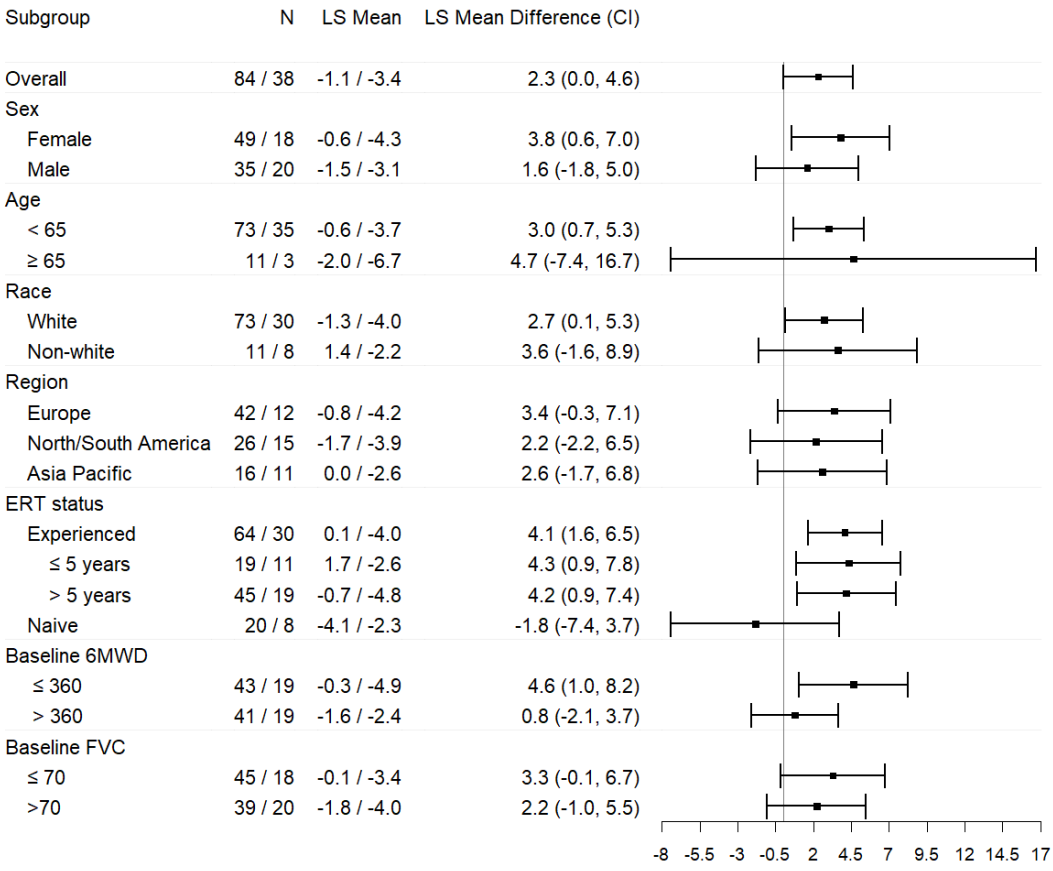


Source: Review team using the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
At each time point, the vertical bar presents ± standard error.
Blue and red lines show the mean or median change from baseline over time in the cipa-mig arm and the comparator arm, respectively.
The rows "Cipa-Mig and "Comparator" present the number of patients with available FVC (percent predicted) value at each time point for the cipa-mig arm and the comparator arm, respectively.
Abbreviation: FVC, forced vital capacity

Subgroup Analyses

The estimated treatment difference favors cipa-mig across most subgroups, with the exception of males, ERT naïve, baseline 6MWD greater than the median, and baseline FVC greater than the median. The results of the other subgroups are consistent with the analysis including all patients for FVC (Figure 9).

Figure 9. Estimated Mean Treatment Difference in FVC Across Subgroups



Source: Review team using the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets. The estimates corresponding to 'Overall' come from am ANCOVA model including: treatment, baseline 6MWD, ERT status, sex, age, baseline weight, and baseline height and the other models include only baseline 6MWD and treatment. Missing data were imputed using the last available values.
Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; FVC, forced vital capacity; LS, least squares

Among ERT-experienced patients, the estimated treatment difference for FVC is 4.1% (95% CI: 1.6, 6.5; p<0.01) in favor of cipa-mig (Table 16). Among ERT-naïve patients, the estimated treatment difference favors the comparator (estimated difference of -1.8%; CI: -7.4, 3.7; p=0.50; Table 17).

Table 16. Change in FVC (% Predicted) From Baseline to Week 52, ERT-Experienced Subgroup, ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=65	N=30		
Mean (SD)	67.8 (19.1)	67.5 (21.0)		
Median (min, max)	68.0 (30.5, 132.5)	69.0 (31.5, 122.0)		
Week 52	N=55	N=26		
Mean (SD)	67.4 (20.0)	60.6 (19.6)		
Median (min, max)	66.0 (30.0, 137.0)	54.5 (28.0, 96.0)		

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Change from baseline to Week 52	N=55	N=26		
Mean (SD)	0.1 (5.9)	-3.5 (4.7)		
Median (min, max)	0.5 (-17.0, 14.0)	-2.5 (-19.5, 2.0)		
Estimated change from baseline to Week 52	N=64	N=30		
LS mean change[2]	0.06 (0.70)	-4.02 (1.02)	4.08 (1.62, 6.54)	0.0014
Wilcoxon rank-sum				0.0016

Source: Table 22 of the Clinical Study Report. This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig − comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 estimated by analysis of covariance (ANCOVA) model including treatment and baseline FVC (% predicted). Missing data were imputed using the last available values (this method was also used for the Wilcoxon rank-sum test).
Abbreviations: CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; FVC, forced vital capacity; ITT, intent-to-treat; LS, least squares; max, maximum; min, minimum; SD, standard deviation

Table 17. Change in FVC (% Predicted) From Baseline to Week 52, ERT-Naïve Subgroup, ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=20	N=8		
Mean (SD)	80.2 (18.7)	79.6 (21.0)		
Median (min, max)	82.2 (48.0, 111.0)	88.5 (46.5, 98.0)		
Week 52	N=19	N=7		
Mean (SD)	76.8 (19.5)	75.3 (22.5)		
Median (min, max)	80.0 (36.0, 104.0)	88.0 (42.0, 94.0)		
Change from baseline to Week 52	N=19	N=7		
Mean (SD)	-4.7 (6.2)	-2.4 (6.3)		
Median (min, max)	-4.5 (-12.5, 10.0)	-3.0 (-13.0, 7.5)		
Estimated change from baseline to Week 52	N=20	N=8		
LS mean change[2]	-4.10 (1.45)	-2.26 (2.29)	-1.84 (-7.41, 3.74)	0.5031
Wilcoxon rank-sum				0.4003

Source: Table 22 of the Clinical Study Report. This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig − comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 estimated by analysis of covariance (ANCOVA) model including treatment and baseline FVC (% predicted). Missing data were imputed using the last available values (this method was also used for the Wilcoxon rank-sum test).
Abbreviations: CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; FVC, forced vital capacity; ITT, intent-to-treat; LS, least squares; max, maximum; min, minimum; SD, standard deviation

6.2.1.4.3. Results for Other Secondary Endpoints

The mean change from baseline to Week 52 or Week 26 of other key secondary endpoints is presented in Table 18. Numerically, all the differences favor the cipa-mig arm. Note that in the GSGC scale a lower score indicates better outcomes.

Table 18. Mean Change From Baseline for Other Secondary Endpoints, ATB200-03

Parameter	Cipa-Mig	Comparator	Difference1 (95% CI)	P-Value
MMTL				
Mean (SD) at baseline	28.0 (5.8)	27.9 (6.3)		
Estimated change (SE)	1.6 (0.4)	0.6 (0.6)	0.99 (-0.43, 2.41)	0.1680
6MWD 26-Week change				
Mean (SD) at baseline	357.9 (111.8)	350.1 (119.8)		
Estimated change (SE)	16.6 (3.5)	11.2 (5.3)	5.46 (-7.39, 18.30)	0.4018
PROMIS-Physical Function				
Mean (SD) at baseline	66.9 (12.3)	68.2 (13.0)		
Estimated change (SE)	2.0 (0.9)	0.6 (1.4)	1.37 (-2.03, 4.77)	0.4258
PROMIS-Fatigue				
Mean (SD) at baseline	22.3 (8.3)	21.2 (6.0)		
Estimated change (SE)	-1.9 (0.6)	-2.0 (0.9)	0.13 (-2.00, 2.27)	0.9026
GSGC				
Mean (SD) at baseline	14.5 (5.2)	14.2 (4.9)		
Estimated change (SE)	-0.6 (0.3)	0.7 (0.4)	-1.30 (-2.34, -0.26)	0.0147

Source: Produced by the review team based on adeff.xpt and adqs.xpt. They are located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Difference was estimated using the ANCOVA models described in Section 6.2.1.3.3.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; GSGC, Gait, Stairs, Gowers' maneuver, and Chair test; 6MWD, 6-minute walk distance; MMTL, manual muscle testing lower extremities; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SE, standard error

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Evidence of Effectiveness From ATB200-03

Issue

Results of the randomized, double-blind, controlled trial (ATB200-03) comparing cipa-mig to the comparator (a first generation ERT) failed to meet the threshold for statistical significance for superiority on the primary endpoint of 6MWD (p=0.608) according to the predefined analysis.

Background

In trial ATB200-03, changes in 6MWD and FVC (% predicted) from baseline at 52 weeks were defined as the primary and the first secondary endpoints, respectively. Both FVC (% predicted) and 6MWD were assessed in trials of the two approved drugs for LOPD, alglucosidase alfa and avalglucosidase alfa. FVC (% predicted) was used as the primary endpoint in the approval of alglucosidase alfa (Lumizyme, estimated treatment difference compared to placebo of 3.4% at 78 weeks) and avalglucosidase alfa (Nexviazyme, estimated treatment difference compared to alglucosidase alfa of 2.4% at 49 weeks). The 6MWD was used as the first secondary endpoint in the approval of both Lumizyme and Nexviazyme. Note that the results of trials used in the approval of Lumizyme and Nexviazyme are not directly comparable to ATB200-03 given two major differences in the trials: 1) use of an active comparator arm in ATB200-03 versus placebo in the trial for Lumizyme and 2) including only treatment-naïve patients in the trials for Lumizyme and Nexviazyme. Only 23% (n=28; 8 patients in the comparator group and 20 in the

cipa-mig group) of patients in ATB200-03 were treatment-naïve, whereas all patients in the trials for Lumizyme and Nexviazyme were treatment-naïve. In the meeting on October 30, 2018, the Division recommended that the Applicant place FVC (% predicted) as the first secondary efficacy endpoint and that the analysis should be for superiority relative to the comparator. According to the Division, improvement on this endpoint would provide stronger evidence of efficacy than the other endpoints proposed. The Applicant followed this recommendation.

One patient in ATB200-03 (b) (6) was identified after database lock as an outlier in the 6MWD at 38 and 52 weeks per the SAP criteria and was further investigated due to having a "clinically implausible" improvement in the 6MWT at 52 weeks. After this identification, "the subject revealed to the principal investigator that he deliberately underperformed on the 6MWT and PFT to ensure that he would meet inclusion criteria and gain entry into the study" (Clinical Study Report Section 11.5.2, p. 91; PFT: pulmonary function testing). Given this finding the Applicant performed additional post hoc analyses described in Section 6.2.1.3.1, including repeating the prespecified primary analysis excluding this subject.

Assessment

For the primary endpoint of 6MWT, the predefined primary MMRM analysis yielded a treatment difference of 5 m (95% CI: -15, 26; p=0.608; Table 19). These analysis results were significantly impacted by patient (b) (6) a treatment-naïve patient in the comparator arm. After excluding this outlier, the estimated treatment difference was 14 m (95% CI: -3, 31; p=0.100; Table 20).

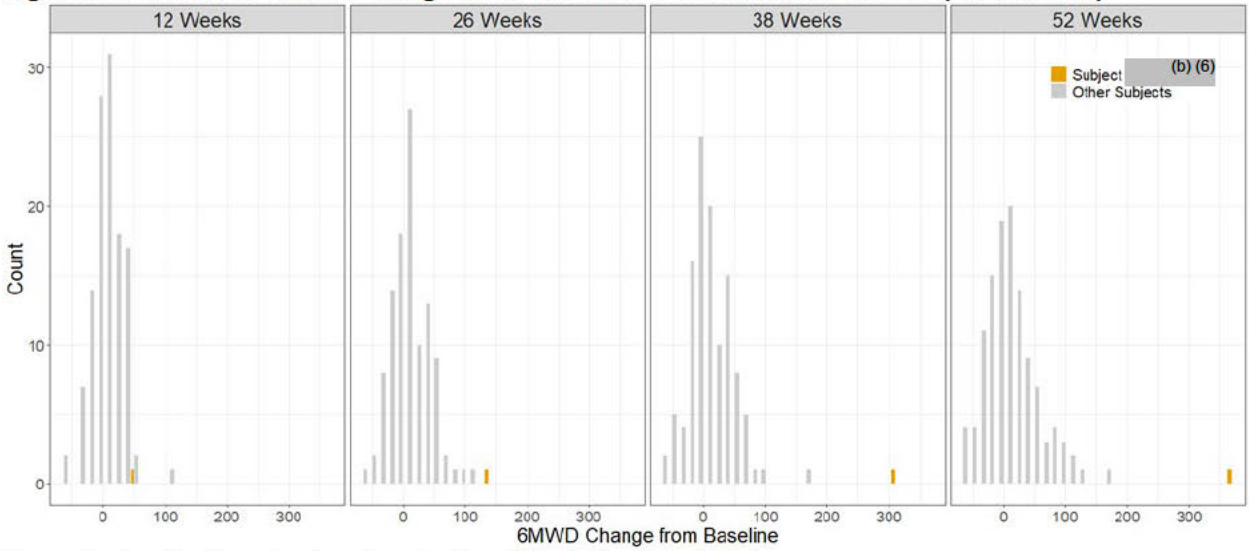
Table 19. Baseline and Change in 6MWT (Meters) From Baseline to Week 52, ITT Population (All Patients), ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=85	N=38		
Mean (SD)	357.9 (111.8)	350.1 (119.8)		
Median (min, max)	359.5 (79.0, 575.0)	358.4 (112.5, 623.0)		
Week 52	N=81	N=37		
Mean (SD)	376.4 (122.9)	368.2 (145.0)		
Median (min, max)	380.5 (79.6, 601.5)	373.5 (67.0, 675.4)		
Change from baseline to Week 52	N=81	N=37		
Mean (SD)	20.6 (42.3)	17.4 (69.7)		
Median (min, max)	12.5 (-59.5, 173.5)	4.9 (-55.5, 355.2)		
Estimated change from baseline to Week 52				
MMRM[2]	21.44 (5.75)	16.11 (8.58)	5.33 (-15.21, 25.88)	0.608
ANCOVA[3]	21.26 (5.49)	15.34 (8.33)	5.91 (-14.17, 26.00)	0.561
Wilcoxon rank-sum				0.116

Source: Tables 16 and 14.2.2.1.1 of the Clinical Study Report. This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig − comparator) and 95% confidence interval.
[2] LS mean change from baseline to Week 52 estimated by mixed model for repeated measures (MMRM) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height; an unstructured covariance matrix was used.
[3] Estimated mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (this method was also used for the Wilcoxon rank-sum test).
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; LS, least squares; max, maximum; min, minimum; MMRM, mixed model for repeated measures; 6MWT, 6-minute walk test; qow, every other week; SD, standard deviation

Patient (b) (6) (comparator group) was a statistical outlier with an improvement of 355 m at 52 weeks from baseline in the 6MWD. He received an investigational anabolic steroid (ostarine) for approximately 9 months after his diagnosis with LOPD; he discontinued ostarine 2 to 4 weeks before enrolling in ATB200-03. An assessment of his pulmonary function at 8 months before the trial showed that his FVC (% predicted) was 93%. Sixteen weeks before his trial enrollment his 6MWT was 585 m. However, at the two screening visits, his 6MWT was 337 and 303 m and his FVC (% predicted) was 83% and 84%. At Week 52, his 6MWD and FVC (% predicted) were 657 m and 91%, representing an improvement of 355 m and 7.5%, respectively. This patient had the largest improvement from baseline in both 6MWD and FVC (% predicted) among the patients in the comparator group. Figure 10 shows the deviation of the patient's 6MWD observations from the range of improvement in the other patients. In previous trials of Lumizyme and Nexviazyme, the maximum improvement in 6MWD was 268 m at 52 weeks and 262 m at 49 weeks, respectively, providing further evidence that a change exceeding 350 m is likely implausible. Clinical site inspections conducted by the FDA did not raise concerns for data integrity/quality issues for other patients.

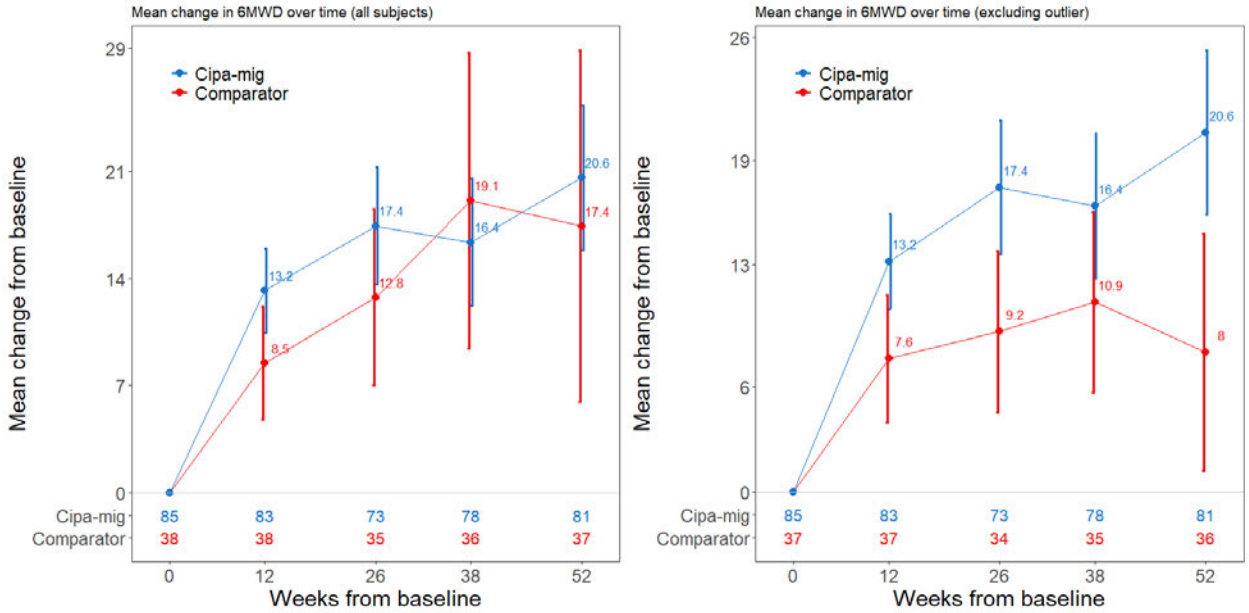
Figure 10. Observed 6MWD Change From Baseline Over Time, ATB200-03 (All Patients)



Source: Produced by the review team based on the adeff.xpt dataset, located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets
Abbreviation: 6MWD, 6-minute walk distance

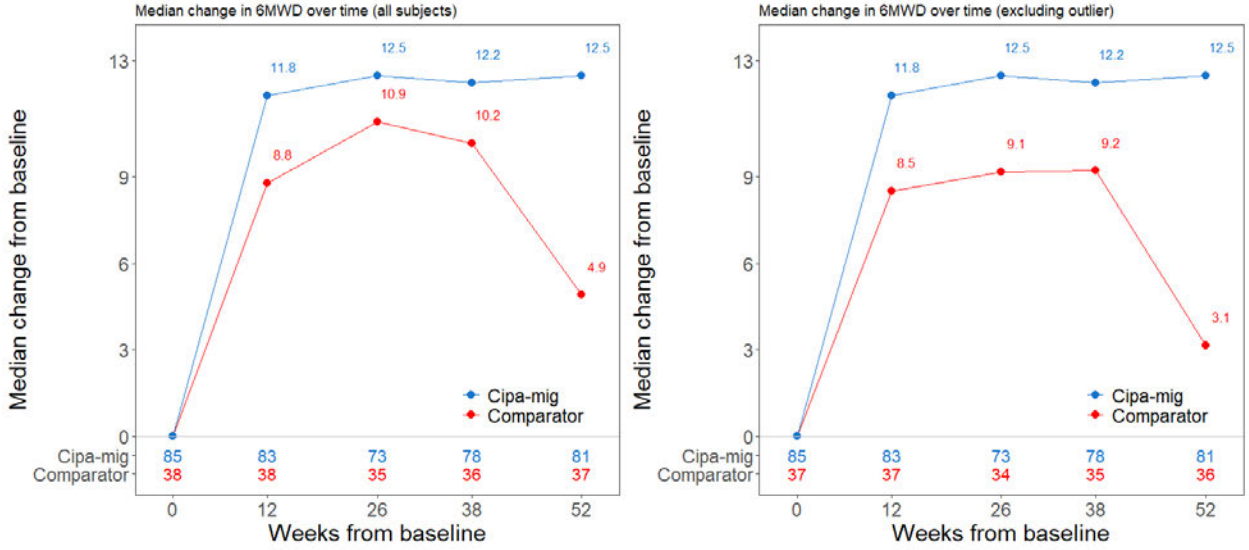
Inclusion of this patient's data leads to a highly skewed distribution, which violates the normality assumption relied on by the predefined MMRM analysis. A nonparametric approach would be more suitable for detecting a treatment difference when the assumption of normality is violated. The Wilcoxon rank-sum test was performed to test a difference in the distribution of the two treatment groups. This test, when including data from the outlier, yielded p=0.116 which is substantially smaller than the p=0.608 yielded by the primary analysis. In addition, the mean change in 6MWD when excluding the outlier and the median change in 6MWD over time reveal clear separation between the treatment groups, providing supportive evidence in favor of the cipa-mig group (Figure 11 and Figure 12). Even with the inclusion of the outlier, the primary endpoint numerically favors the cipa-mig group over the comparator group (estimated treatment difference of 5.33 m at Week 52).

Figure 11. Mean Change in 6MWD From Baseline Over Time, ATB200-03



Source: Produced by the review team based on the adeff.xpt dataset, located at
\\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets
Abbreviations: 6MWD, 6-minute walk distance

Figure 12. Median Change in 6MWD From Baseline Over Time, ATB200-03



Source: Produced by the review team based on the adeff.xpt dataset, located at
\\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets
Abbreviation: 6MWD, 6-minute walk distance

Additionally, the review team concluded that exclusion of the outlier may be reasonable given the questions of integrity of the subject's efforts. When excluding data from the outlier, the 6MWD estimated treatment difference increases from 5.3 m to 14.2 m, and although statistical significance is not achieved at the conventional threshold of 0.05, the p-value decreases from 0.608 to 0.097 using MMRM (Table 20). With exclusion of the outlier, the testing results are consistent regardless of the choice of analysis method. A change of 14 m is a clinically

meaningful difference compared to an active control, given the estimated treatment difference of Lumizyme was 28 m compared to placebo.

Table 20. Baseline and Change in 6MWD From Baseline to Week 52, Excluding Outlier, ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=85	N=37		
Mean (SD)	357.9 (111.8)	351.0 (121.3)		
Median (min, max)	359.5 (79.0, 575.0)	365.5 (112.5, 623.0)		
Week 52	N=81	N=36		
Mean (SD)	376.4 (122.9)	359.7 (137.4)		
Median (min, max)	380.5 (79.6, 601.5)	371.8 (67.0, 648.5)		
Change from baseline to Week 52	N=81	N=36		
Mean (SD)	20.6 (42.3)	8.0 (40.6)		
Median (min, max)	12.5 (-59.5, 173.5)	3.1 (-55.5, 127.0)		
Estimated change from baseline to Week 52				
MMRM[2]	21.31 (4.65)	7.10 (7.04)	14.21 (-2.60, 31.02)	0.0967
ANCOVA[3]	20.91 (4.52)	6.95 (6.95)	13.96 (-2.72, 30.64)	0.1002
Wilcoxon rank-sum				0.0665

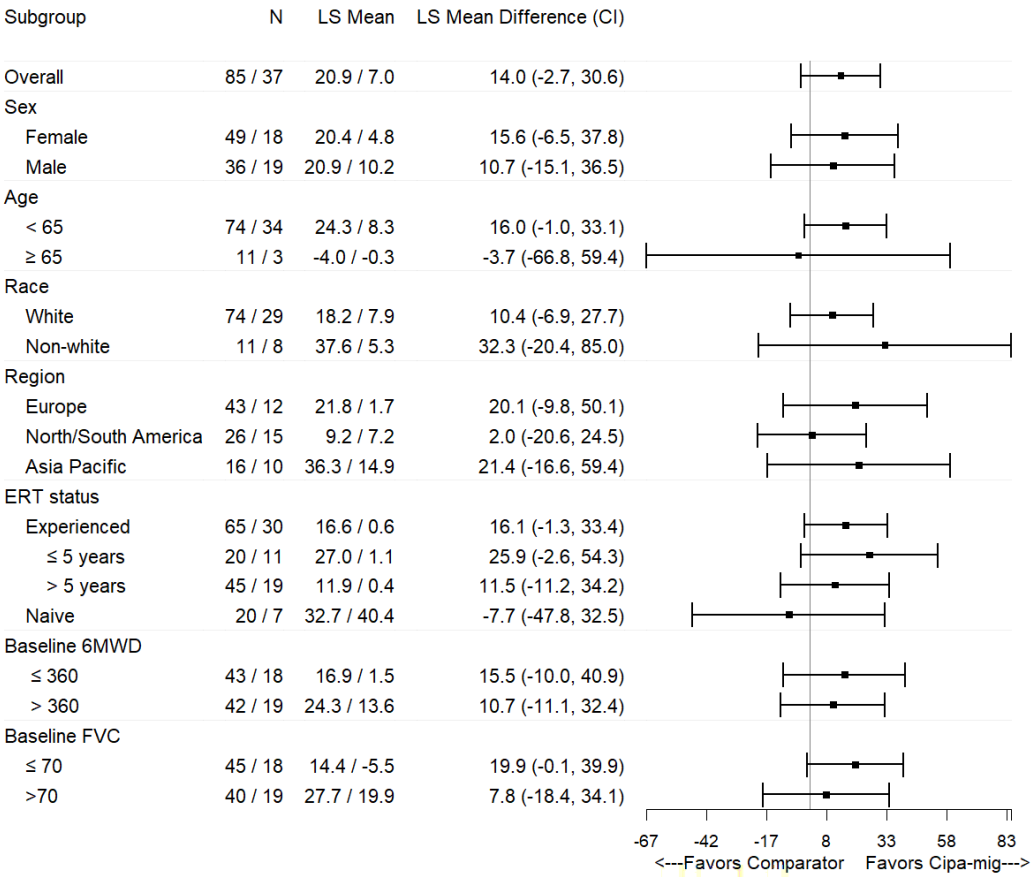
Source: Table 20 of the Clinical Study Report. Produced by the review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig − comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 estimated by mixed model for repeated measures (MMRM) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height; an unstructured covariance matrix was used.
[3] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (this method was also used for the Wilcoxon rank-sum test).
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; LS, least squares; max, maximum; min, minimum; MMRM, mixed model for repeated measures; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; SD, standard deviation

The key secondary endpoint, FVC (% predicted) reached nominal statistical significance, with an estimated treatment difference of 2.32% in favor of cipa-mig (2.32%; 95% CI: 0.02 to 4.62; nominal p=0.048), suggesting effectiveness of cipa-mig in the treatment of patients with LOPD in FVC (% predicted). Additionally, all the other secondary endpoints favored cipa-mig.

A post hoc Wilcoxon rank-sum global test performed on the 6MWD and FVC (% predicted) endpoints showed evidence that overall, the cipa-mig group performed better than the comparator group (p=0.022).

The subgroup analyses are presented in Figure 13 for all ITT patients excluding the outlier. Most subgroups show a consistent result to the overall analysis when excluding the outlier, with the exception of two subgroups of patients age ≥65 years and patients who were ERT native. Note that all non-white race subgroups were combined into one group, due to a limited sample size of non-white patients (n=19).

Figure 13. Estimated Mean Treatment Difference Across Subgroups, Excluding Outliner 0



Source: Produced by the review team based on the adeff.xpt dataset, located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets. The estimates corresponding to 'Overall' come from a model including: treatment, baseline 6MWD, ERT status, sex, age, baseline weight, and baseline height and the other models include only treatment and baseline 6MWD. LOCF was used to impute missing values at week 52.
Abbreviations: Cipa-mig, cipaglucosidase alfa coadministered with miglustat; CI, confidence interval; ERT, enzyme replacement therapy; FVC, forced vital capacity; LS, least squares; 6MWD, 6-minute walk distance

The majority of patients in ATB200-03 are treatment-experienced (N=90, 76%). For the treatment-experienced patients, the estimated treatment difference for 6MWD is 16 m (95% CI: -1.29, 33.42) (Table 21). Among treatment-experienced patients, the estimated treatment difference was smaller (11.50 m; 95% CI: -11.16, 34.16) for patients with greater than 5 years of ERT duration compared to those with 2 to 5 years of ERT experience (25.85 m; 95% CI: -2.57, 54.27). The outlier belongs to the treatment-naïve subgroup, and thus does not impact the results of the treatment-experienced subgroup.

Table 21. Baseline and Change in 6MWD (Meters) From Baseline to Week 52, Treatment-Experienced Subgroup, ATB200-03

Time Point Parameter	Cipa-Mig	Comparator Group	Difference[1] (95% CI)	P-Value
Baseline	N=65	N=30		
Mean (SD)	346.9 (110.2)	334.6 (121.3)		
Median (min, max)	352.5 (79.0, 557.5)	343.5 (112.5, 532.2)		

Time Point Parameter	Cipa-Mig	Comparator Group	Difference[1] (95% CI)	P-Value
Week 52	N=61	N=29		
Mean (SD)	363.8 (123.5)	334.6 (129.5)		
Median (min, max)	363.5 (79.6, 601.5)	339.0 (67.0, 576.0)		
Change from baseline to Week 52	N=61	N=29		
Mean (SD)	16.3 (39.5)	0.7 (39.8)		
Median (min, max)	9.6 (-57.0, 173.5)	-8.9 (-55.5, 127.0)		
Estimated change from baseline to Week 52	N=65	N=30		
ANCOVA[2]	16.62 (4.91)	0.56 (7.23)	16.06 (-1.29, 33.42)	0.0693
Wilcoxon rank-sum				0.0194

Source: Produced by the review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig − comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment and baseline 6MWT. Missing data at Week 52 values ware imputed using last observed value (this method was also used for the Wilcoxon rank-sum test).
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; LS, least squares; max, maximum; min, minimum; 6-minute walk distance; standard deviation

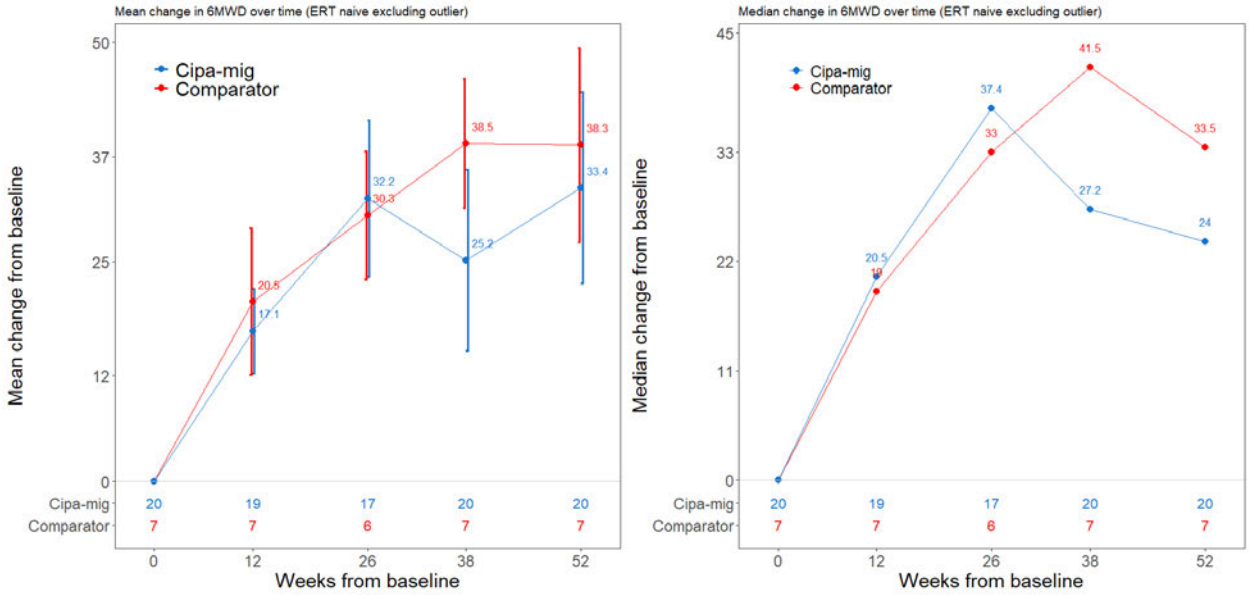
Among treatment-naïve patients, there is no evidence that the cipa-mig group performs better than the comparator. It is difficult to draw conclusions given the small number of patients (8 patients in the comparator group and 20 in the cipa-mig group) and the presence of an outlier. The observed 52-week mean change in 6MWD when excluding the outlier is 33 m for those receiving cipa-mig and 38 m for those on the comparator (Table 22). Figure 14 presents the observed mean and median changes from baseline over time for the treatment-naïve subgroup.

Table 22. Baseline and Change in 6MWT (Meters) From Baseline to Week 52, Treatment-Naïve Subgroup Excluding Outlier, ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	P-Value
Baseline	N=20	N=7	
Mean (SD)	393.6 (112.4)	420.9 (135.7)	
Median (min, max)	375.1 (154.0, 575.0)	385.5 (201.0, 623.0)	
Week 52	N=20	N=7	
Mean (SD)	427.1 (112.5)	459.3 (121.7)	
Median (min, max)	452.6 (166.5, 599.2)	446.5 (284.5, 648.5)	
Change from baseline to Week 52	N=20	N=7	
Mean (SD)	33.4 (48.7)	38.3 (29.3)	0.6071
Median (min, max)	24.0 (-59.5, 120.0)	33.5 (-4.2, 83.5)	

Source: Produced by the review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
Abbreviations: Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; max, maximum; min, minimum; 6MWD, 6-minute walk distance; SD, standard deviation

Figure 14. Observed Mean and Median Change From Baseline of 6MWD, Treatment-Naïve Subgroup Excluding Outlier



Source: This figure was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
Abbreviations: 6MWD, 6-minute walk distance

Though we should be cautious about cross trials comparisons, it may be useful to note the observed change in 6MWD among treatment-naïve patients in the pivotal trials for Lumizyme and Nexviazyme (Table 23). In the trial for Lumizyme approval, 57 treatment-naïve patients received Lumizyme and the mean change at 52 weeks from baseline was 27 m. In the trial for Nexviazyme approval, 49 treatment-naïve patients received Lumizyme (which was the comparator in that trial, as well as ATB200-03) and the mean change at 49 weeks was -1.7 m. In ATB200-03, 8 treatment-naïve patients received Lumizyme and the mean change at Week 52 was 78 m when including the outlier and 38 m when excluding the outlier, larger than that observed in either of the other trials that had much larger samples.

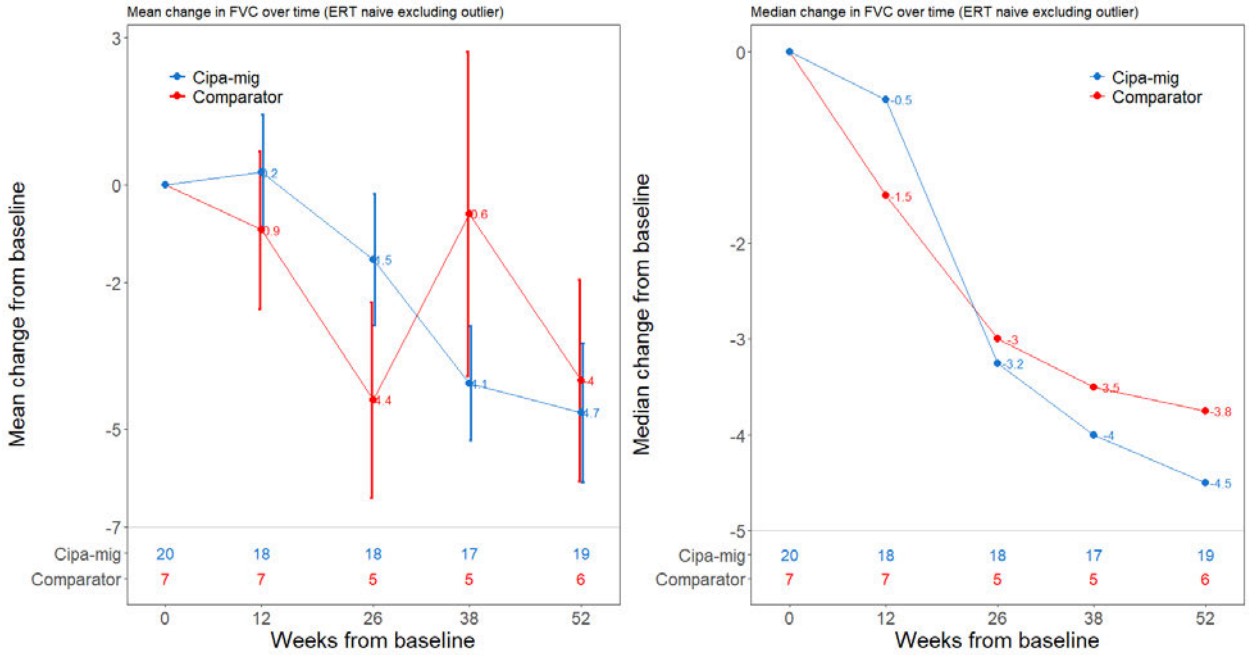
Table 23. Summary Statistics for 6MWD Among ERT-Naïve Patients Who Were Randomized to Receive Lumizyme Treatment in Three Pivotal Trials

				Change in 6MWD (meters)	
Trial	**Weeks From Baseline**	**N**	**Baseline Mean/Median**	**Mean (SD)**	**Median (Min, Max)**
LOTS (Lumizyme, 2010)	52	57	332/360	27 (55)	17 (-48, 268)
COMET (Nexviazyme, 2021)	49	43	378/387	-1.7 (85)	16 (-394, 193)
ATB200-03 (including outlier)	52	8	408/384	78 (115)	41 (-4, 355)
ATB200-03 (excluding outlier)	52	7	421/386	38 (29)	34 (-4, 84)

Source: Produced by the review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets and the efficacy data submitted in the applications for Lumizyme and Nexviazyme.
Abbreviations: 6MWD, 6-minute walk distance; N, number of patients in group; SD, standard deviation

FVC similarly shows a substantial treatment difference of 4.1% (95%CI: 1.62, 6.54) in favor of cipa-mig for the treatment-experienced subgroup. Among treatment-naïve patients, similar to the 6MWD finding, there is no evidence that cipa-mig performs better than the comparator with decline observed in both groups (mean 52-week change of -4.7% for cipa-mig and -4.0% for the comparator, Figure 15).

Figure 15. Mean and Median Change From Baseline of FVC, Treatment-Naïve Subgroup



Source: Produced by the review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
Abbreviations: FVC, forced vital capacity

In summary, due to the small sample size, the review team cannot draw a conclusion on whether cipa-mig performs as well as the comparator among treatment-naïve patients.

Conclusion

Although the results from ATB200-03 do not show statistical superiority compared to the comparator on the primary endpoint, 6MWD, the numerically favorable results of this endpoint and the positive results from the first key secondary endpoint, FVC (% predicted), demonstrate meaningful effectiveness of cipa-mig on adult patients with LOPD weighing ≥40 kg and who have previously received enzyme replacement therapy for at least two years. However, given the lack of sufficient data to support superiority over the standard of care for treatment-naïve patients and the inherent increased risk of two products over one, we do not recommend cipa-mig be used as a first-line therapy. Although there are no available data for patients with PD to determine the threshold at which a change in FVC (% predicted) estimated treatment difference becomes relevant, research using anchor-based methods in idiopathic pulmonary fibrosis (du Bois et al. 2011), indicates that differences between 2 to 6% are clinically meaningful. In addition, assessment of FVC (% predicted) in treatment experienced patients over time showed a slower rate of decline in FVC in the treatment group compared to the comparator group. The observed improvement in FVC (% predicted) is relative to an effective active comparator and is similar to the change observed in the trials that led to the approval of avalglucosidase alfa (2.4%). LOPD is

a serious condition with limited treatment options, and the overall results are numerically favorable to cipa-mig. Therefore, the review team concluded that cipa-mig shows evidence of effectiveness in trial ATB200-03 to support its use as a second-line therapy.

6.3.2. Confirmatory Evidence

Issue

Providing confirmatory evidence to support effectiveness of cipa-mig in the treatment of patients 18 years of age and older with LOPD in addition to the results from one adequate and well-controlled trial (ATB200-03).

Background and Assessment

When FDA determines that data from one adequate and well-controlled clinical investigation and confirmatory evidence (CE) is sufficient to establish effectiveness, FDA can consider such data and evidence to constitute substantial evidence under Section 505(d) of the Federal Food, Drug, and Cosmetic Act. FDA's guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (FDA 2019) describes data that provide strong mechanistic support as a possible source of CE.

To support the effectiveness of cipaglucosidase alfa, CE is derived from the well-established etiology of the disease, the mechanism of action of the therapy, and mechanistic evidence from studies in vitro and in vivo (in the mouse model of disease).

Pompe disease is caused by variants in the *GAA* gene that result in absence or reduction of lysosomal GAA. GAA enzyme deficiency leads to glycogen accumulation in the lysosome, resulting in cellular dysfunction. Cipaglucosidase alfa provides an exogenous source of GAA. The mouse model of Pompe disease (acid alpha glucosidase knock out mice; *Gaa* knockout [KO] mice) are genetically engineered to be unable to produce Gaa and are the most widely used animal model of Pompe disease; the review team considers this an acceptable animal model.

To support the effectiveness of coadministering miglustat with cipaglucosidase alfa, CE is derived from mechanistic evidence from studies in vitro and in vivo (in the mouse model of disease).

Nonclinical Confirmatory Evidence

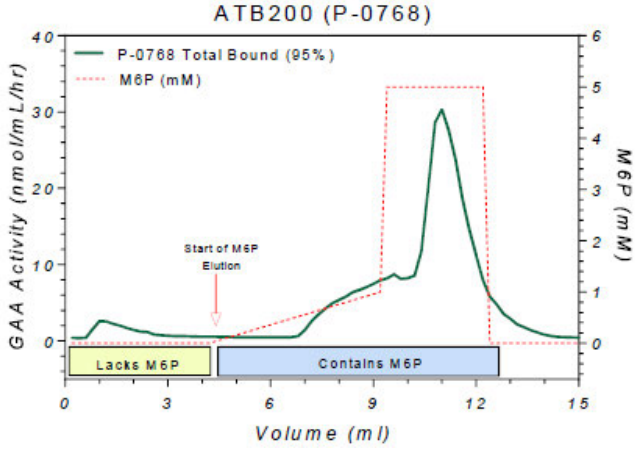
Nonclinical evidence to support the effectiveness of co-administered cipaglucosidase alfa and miglustat compared to alglucosidase alfa included in vitro studies of the mechanisms of action, and studies in a mouse model of disease.

In Vitro Mechanism of Action

Cipaglucosidase alfa contains bis-phosphorylated mannose 6-phosphate (bis-M6P) groups that have a high affinity for the cation independent mannose 6-phosphate receptor (CI-MPR), which is an integral membrane glycoprotein that forms part of the trans-Golgi network. The CI-MPR is responsible for internalization of newly synthesized lysosomal hydrolases. Cipaglucosidase alfa contains higher amounts of M6P than alglucosidase alfa and in a CI-MPR affinity chromatography assay, bound CI-MPR with a higher affinity than alglucosidase alfa (Figure 16,

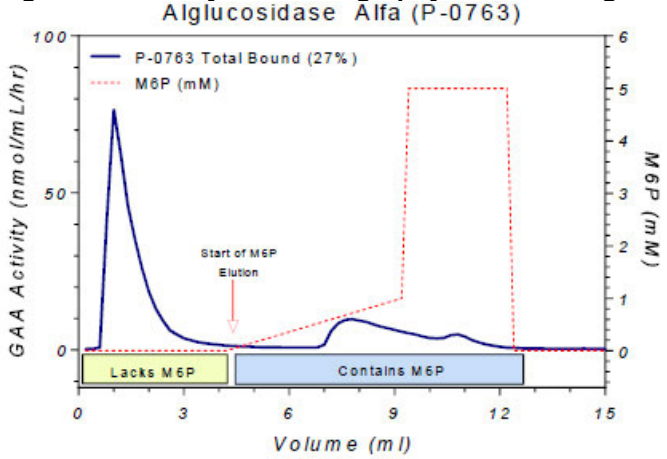
Figure 17, and Table 24) (Study No. RRB200-043), suggesting a higher propensity for cipaglucosidase uptake in cells that contain the CI-MPR.

Figure 16. Affinity Chromatography Profile of Cipaglucosidase Alfa



Source: Applicant's figure from Pharmacology Study No. RRB200-043, page 13.
ATB200 (1 µg) containing mannose-6-phosphate (M6P) was applied to a 1 mL mannose phosphate receptor (CI-MPR) affinity column. The bound material was eluted using a linear gradient of free M6P (dashed red line). The red arrow indicates initiation of the gradient.

Figure 17. Affinity Chromatography Profile of Alglucosidase Alfa



Source: Applicant's figure from Pharmacology Study No. RRB200-043, page 12.
Alglucosidase alfa (1 µg) was applied to a 1 mL mannose phosphate receptor (CI-MPR) affinity column. The bound material was eluted using a linear gradient of free M6P (dashed red line). The red arrow indicates initiation of the gradient.

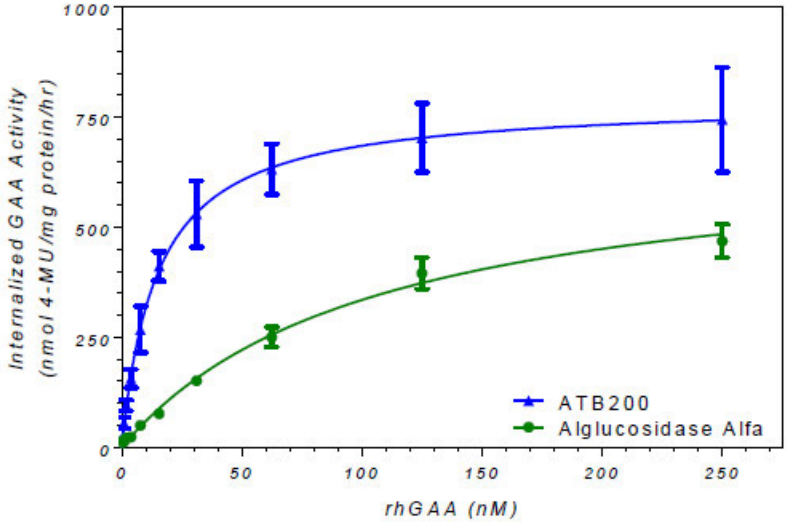
Table 24. Summary of CI-MPR Profile of ATB200 and Alglucosidase Alfa

Parameter	ATB200	Alglucosidase Alfa
Percentage unbound (lacks M6P)	5	73
Percentage bound (contains M6P)	95	27

Source: Applicant's table from Pharmacology Study No. RRB200-043, page 13.
Abbreviations: M6P, mannose-6-phosphate

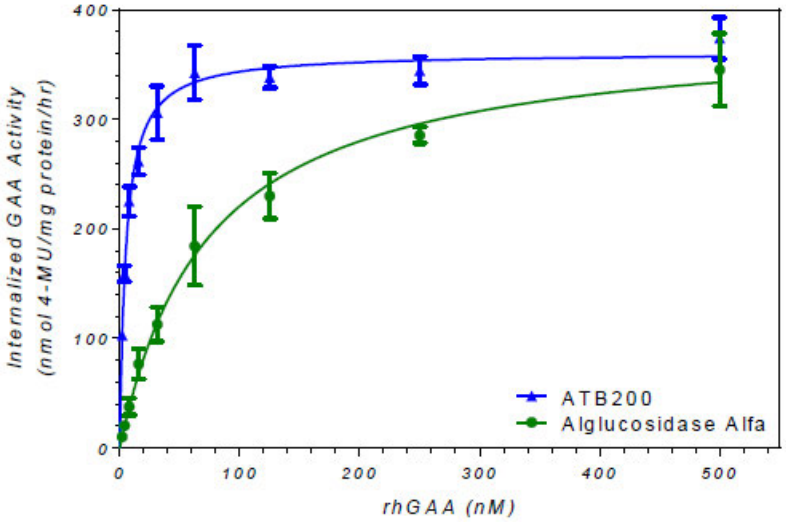
The optimized M6P glycosylation structure of cipaglucosidase alfa resulted in more efficient internalization of the enzyme into rat myoblast cells (Figure 18) and Pompe patient fibroblasts (Figure 19) than alglucosidase alfa (Study No. RRB200-009).

Figure 18. Internalization of Cipaglucosidase Alfa Versus Alglucosidase Alfa in L6 Rat Myoblasts



Source: Applicant's figure from Pharmacology Study No. RRB200-009, page 12.
Michaelis–Menten curve fit showing greater internalization of cipaglucosidase alfa in comparison to alglucosidase alfa in rat myoblasts.

Figure 19. Internalization of Cipaglucosidase Alfa Versus Alglucosidase Alfa in Pompe Patient Fibroblasts



Source: Applicant's figure from Pharmacology Study No. RRB200-009, page 13.
Michaelis–Menten curve fit showing greater internalization of cipaglucosidase alfa in comparison to alglucosidase alfa in Pompe patient f broblasts.
Abbreviations: GAA, acid alpha-glucosidase

In Vivo Evidence

In a *Gaa* KO mouse model of Pompe disease(Raben et al. 2005), coadministration of miglustat (AT2221) with cipaglucosidase alfa (ATB 200) was compared to alglucosidase alfa for enzyme activity, glycogen levels, muscle architecture and pathology, and muscle function (Study Nos. RRB200-004, RRB200-005, RRB200-025, RRB200-039, RRB200-006, RRB200-055, RRB200-056, and RRB200-017). Male *Gaa* KO mice were administered up to 12 biweekly (i.e., every other week) IV bolus injections of vehicle, 20 mg/kg ATB200 alone, 20 mg/kg alglucosidase alfa

alone (standard of care treatment/positive control), or 20 mg/kg ATB200 coadministered with 10 mg/kg AT2221 (miglustat, oral gavage 30 min before IV ATB200).

Table 25 shows the glycogen level in muscles of *Gaa* KO mice following biweekly treatments for 1, 2, 3 or 6 months. The coadministration of ATB200/AT2221 significantly reduced glycogen levels in quadriceps for up to 3 months, in triceps and gastrocnemius at 3 months, and in heart at 3 and 6 months, compared to alglucosidase alfa. Standard deviations increased at the 6-month time point, potentially obscuring a treatment effect.

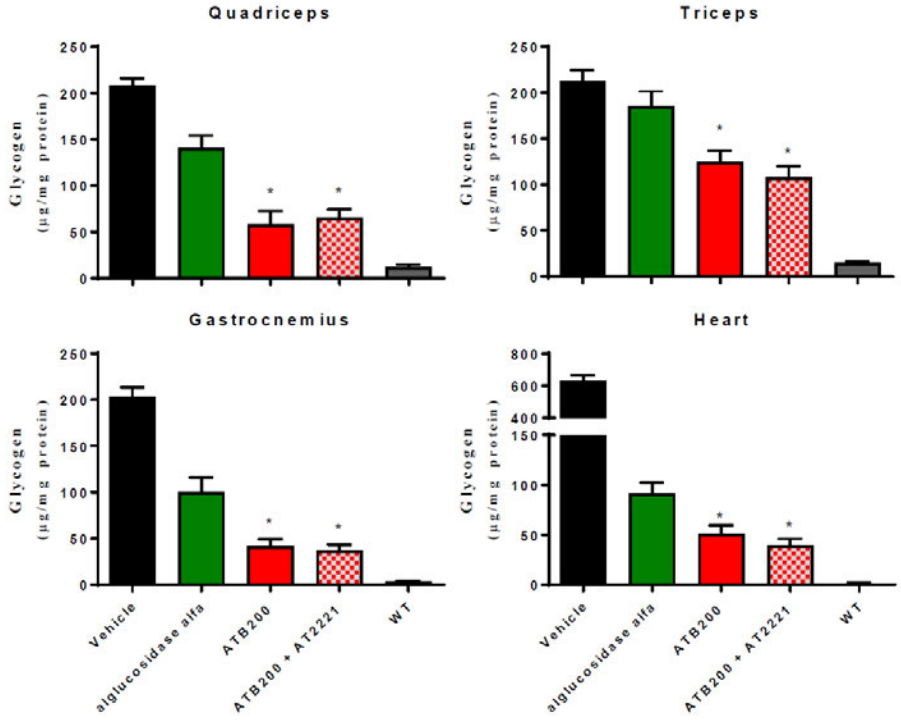
Table 25. Glycogen Levels (µg/g) in KO Mice Following 1, 2, 3, or 6 Months of Treatment With ATB200 (20 mg)/AT2221 (10 mg) or Alglucosidase Alfa (20 mg)

	1 Month			2 Months	3 Months		6 Months
	[b]296	[b]320	[b]328	[a]294B	[a]294A	c	c
Biweekly Treatments	2			4	6		12
Muscle Type							
Quadriceps							
ATB200/AT2221	101.8*	112.4*	196.3	51.2*	66.5	65.4*	141.0
alglucosidase alfa	299.5	207.5	301.2	208.9	135.2	140.8	209.5
Triceps							
ATB200/AT2221				142.1	106.1	107.7*	136.8
alglucosidase alfa				308.4	220.8	185.4	238.8
Heart							
ATB200/AT2221				19.3	31.5	39.5*	95.1*
alglucosidase alfa				17.6	32.4	91.5	288.8
Gastrocnemius							
ATB200/AT2221						37.2*	61.4
alglucosidase alfa						100.6	178.5

[a] Study #RRB200-004 studies 294A and 294B, p. 30.
[b] Study #RRB200-005 studies 296, 320 and 328, p. 32.
[c] Study #RRB200-017, p. 52.
[a, c] An amyloglucosidase-based biochemical method and a high-pH anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) chromatography method were used. [a] Glycogen was digested and evaluated by glucose assay.
* CDER statistical analysis. Statistical significance was determined by two-sided t-test; * $p<0.05$ versus alglucosidase alfa.
Abbreviations: KO, knockout, pH, potential of hydrogen

Figure 20 depicts the glycogen levels in quadriceps, triceps, heart, and gastrocnemius of *Gaa* KO mice at the maximum treatment effect level of 3 months (ABT200 (20 mg/kg)/AT221 (10 mg/kg), alglucosidase alfa (20 mg/kg).

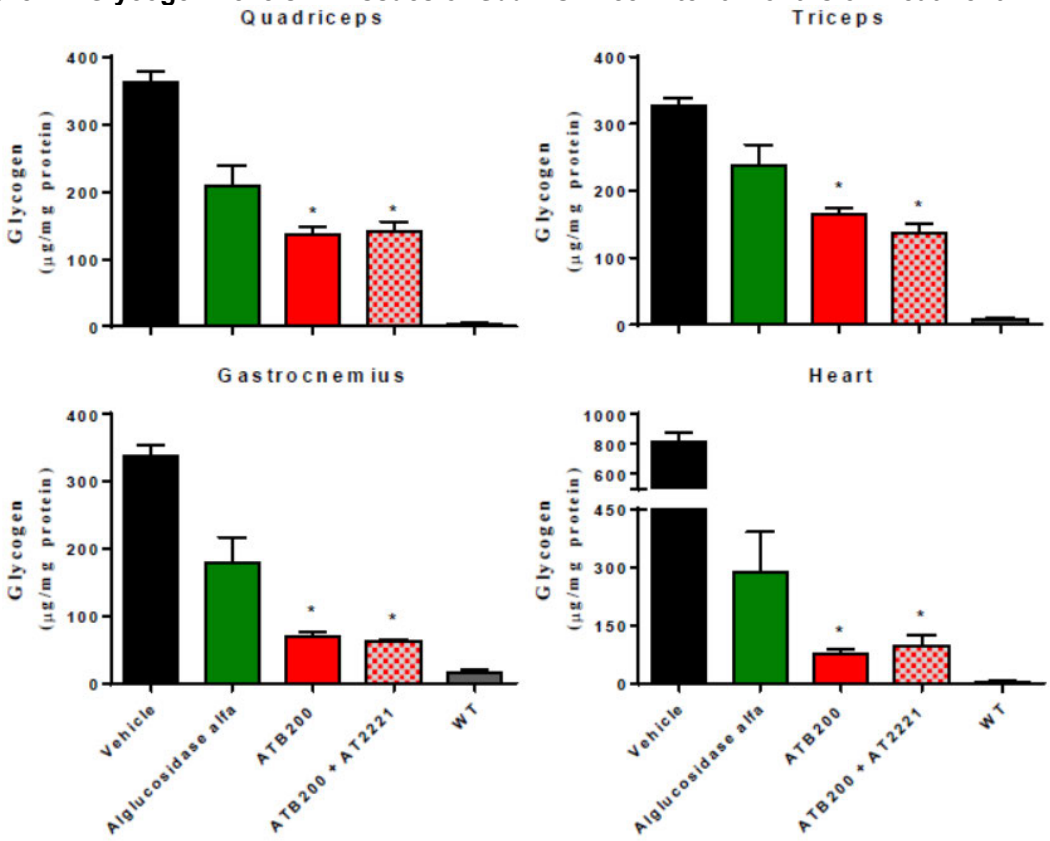
Figure 20. Glycogen Levels in Tissues of *Gaa* KO Mice After 3 Months of Treatment



Source: Applicant's figure from Pharmacology Study #RRB200-017, p. 23
Glycogen levels were measured 14 days after the sixth administration. About half of the animals in each group were sacrificed with tissues collected. Each column represents mean ± SEM of six or seven animals. Statistical significance was determined using Dunnett's multiple comparison test under one-way ANOVA; * $p<0.05$ versus alglucosidase alfa.
Abbreviations: ANOVA, analysis of variance; *Gaa*, acid alpha-glucosidase gene; KO, knockout

Figure 21 depicts glycogen levels in quadriceps, triceps, heart, and gastrocnemius of *Gaa* KO mice at 6 months (ATB200 [20 mg/kg]/AT221 [10 mg/kg], alglucosidase alfa [20 mg/kg]).

Figure 21. Glycogen Levels in Tissues of *Gaa* KO Mice After 6 Months of Treatment



Glycogen levels were measured as described in Section 6.4, 14 days after the 12th administration from remaining animals in each group. Each column represents mean ± SEM of the 5-8 animals. Statistical significance was determined using Dunnett's multiple comparison under one-way ANOVA, where * represents $p<0.05$ vs. alglucosidase alfa.
Source: Applicant's figure from Pharmacology Study #RRB200-017, p. 25.
Abbreviations: ANOVA, analysis of variance; *Gaa*, acid alpha-glucosidase gene; KO, knockout

ATB200 alone decreased glycogen in the quadriceps, triceps, gastrocnemius, and heart relative to alglucosidase alfa at both 3 and 6 months. Coadministration of with AT2221 did not further enhance the glycogen reduction.

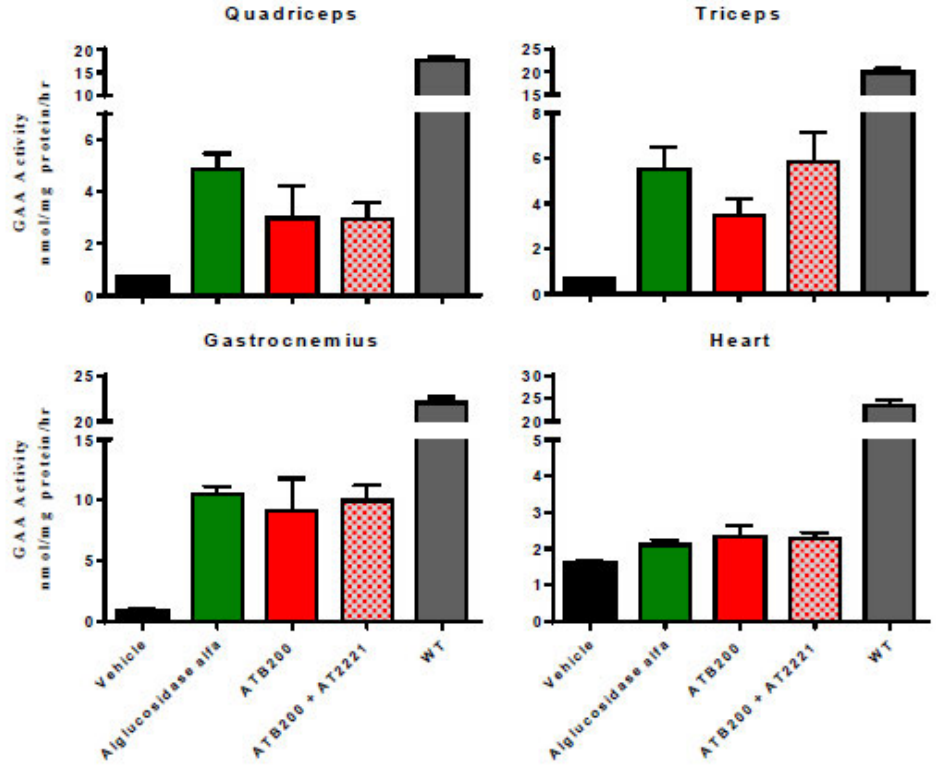
Table 26, Table 27, Figure 22, and Figure 23 show GAA enzyme activity levels in muscles of *Gaa* KO mice following biweekly treatments for 3 or 6 months. The coadministration of ATB200/AT2221 did not increase GAA enzyme activity levels in quadriceps, triceps, gastrocnemius, or heart at 3 or 6 months, compared to alglucosidase alfa.

Table 26. GAA Enzyme Activity (nmol/mg Protein/Hour) Following 3 Months of Treatment

Muscle Type	Vehicle	Alglucosidase Alfa 20 mg/kg	ATB200 20 mg/kg	ATB200 20 mg/kg AT2221 10 mg/kg	Wild Type
Quadriceps	0.70	4.87	2.97	2.96*	17.6
Triceps	0.69	5.50	3.45	5.86	19.9
Heart	1.60	2.10	2.33	2.27	23.3
Gastrocnemius	0.95	10.5	9.17	9.97	22.0

Source: Study No. RRB200-017, pages 54 to 55.
GAA activity was measured as digestion of 4-MU-α-Glc 4-methylumbeliferrone (4-MU) compared to a standard curve of 4-MU. The absolute GAA activity in each lysate was normalized by its protein concentration, and the final specific activity was expressed as nanomoles of released 4-MU per milligram of total protein per hour (nmol/mg protein/hour).
* CDER statistical analysis. Statistical significance was determined by two-sided t-test; * p<0.05 versus alglucosidase alfa.
Abbreviations: GAA, acid alpha-glucosidase

Figure 22. GAA Enzyme Activity in Tissues After 3 Months of Treatment



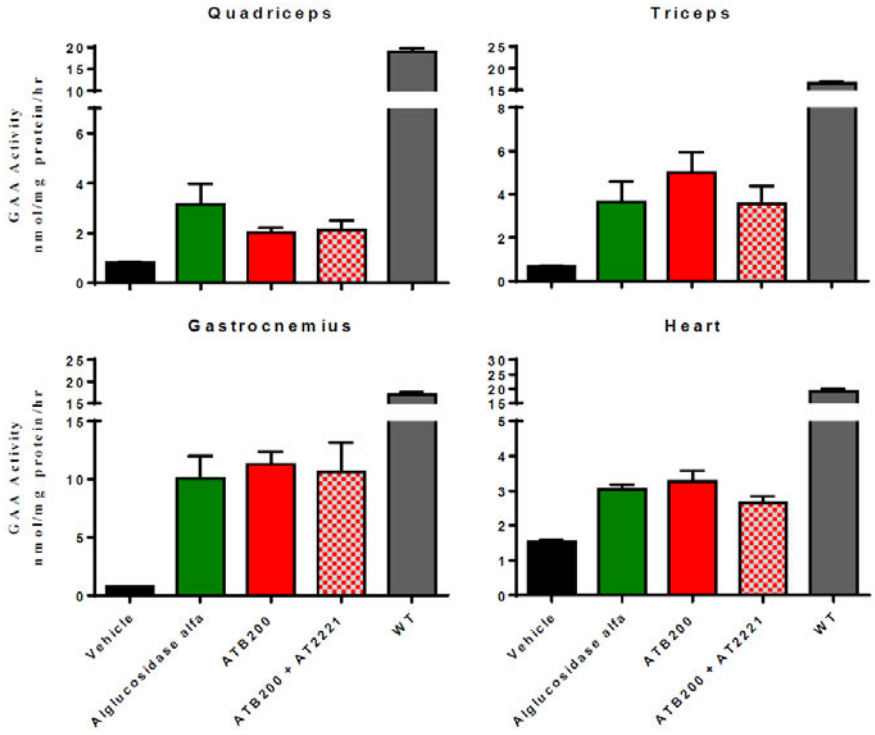
Source: Applicant's figure from Pharmacology Study # RRB200-017, p.24
GAA enzyme activities were measured 14 days after the sixth administration in mice. Each column represents the mean ± SEM of six or seven animals. There were no differences in measured GAA activities between treatment groups in knockout mice.
Abbreviations: GAA, acid alpha-glucosidase

Table 27. GAA Enzyme Activity (nmol/mg Protein/Hour) Following 6 Months of Treatment

Muscle Type	Vehicle	Alglucosidase Alfa 20 mg/kg	ATB200 20 mg/kg	ATB200 20 mg/kg AT2221 10 mg/kg	Wild Type
Quadriceps	0.81	2.74	2.04	2.13	18.9
Triceps	0.67	3.64	5.02	3.56	16.6
Heart	1.52	3.03	3.27	2.65	19.0
Gastrocnemius	0.70	10.1	11.3	10.6	17.1

Source: Pharmacology Study #RRB200-017, pages 58-59.
Abbreviations: GAA, acid alpha-glucosidase

Figure 23. GAA Activity in Tissues of *Gaa* KO Mice After 6 Months of Treatment



Source: Applicant's figure from Pharmacology Study #RRB200-017, p. 24.
GAA activities were measured 14 days after the 12th administration from remaining animals in each group. Each column represents the mean ± SEM of six or seven animals.
Abbreviations: GAA, acid alpha-glucosidase; KO, knockout

Table 28 and Table 29 show measures of muscle function (grip strength and wire hang time) in *Gaa* KO mice following biweekly treatments for 3 or 6 months.

Table 28. Grip-Strength (g) in *Gaa* KO Mice

Parameter	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Alglucosidase	112.2	99.5	103.8	102.5	104.5	102.8	126.2
ATB200/AT2221	103.9	111.4	117.7*	121.3*	138.6*	139.08*	151.5*
ATB200	106.9	109.3	123.1	118.8	128.0	122.0	152.3
Wild type	152.5	162	158	141.3	157	143	160.9
Vehicle	110.1	91.5	95.9	93.1	95.6	85.0	94.4

Source: Pharmacology Study #RRB200-017, Appendix C, pages 40 to 45.
Muscle function was assessed once per month. The wire-hang assay was conducted once on two consecutive days, with the data shown being the average of two assessments, while the grip-strength assay was repeated thrice on the same day, with the data shown being the average of those three assessments. Each point represents the mean ± SEM of 15 animals/group up to 3 months, and 8 animals/group for the remaining 3 months (seven animals sacrificed after 3 months). CDER statistical analysis by two-sided t-test; * $p<0.05$ versus alglucosidase alfa. WT, wild-type (untreated).
Abbreviations: *Gaa*, acid alpha-glucosidase gene; KO, knockout

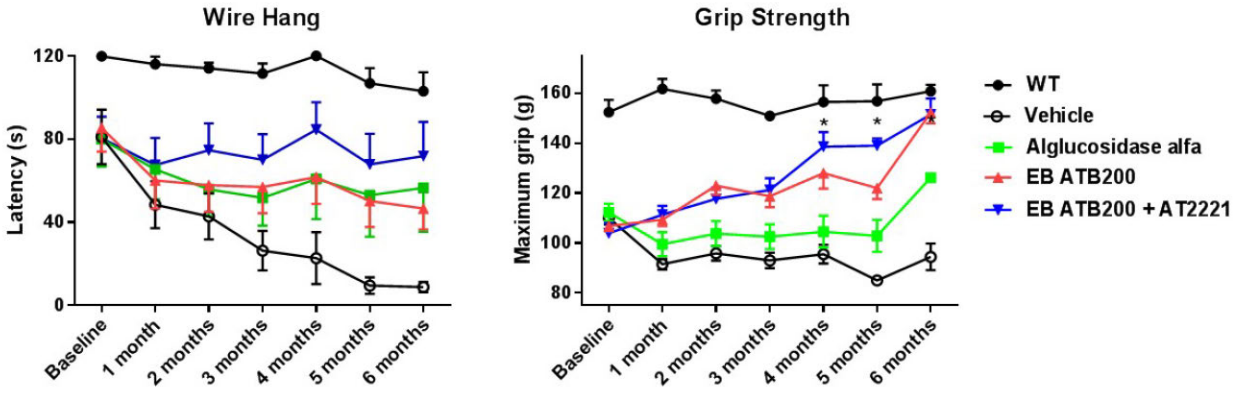
Table 29. Wire Hang Latency (Seconds) in *Gaa* KO Mice

Parameter	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Alglucosidase	79.9	65.4	55.6	51.8	60.8	53.1	56.6
ATB200/AT2221	80.4	67.4	74.6	70.1	84.5	67.8	71.8
ATB200	85.4	60.0	57.7	57.0	61.8	50.3	46.7
Wild type	119.9	116.1	114.1	115.5	105.8	94.8	103
Vehicle	81.0	48.4	42.8	26.4	22.7	9.6	8.9

Source: Pharmacology Study #RRB200-017, appendix C, pages 46 to 51.
Abbreviations: *Gaa*, acid alpha-glucosidase gene; KO, knockout

Figure 24 shows the results of the wire hang and grip strength assays in *Gaa* KO mice.

Figure 24. Muscle Function Assessments by Wire Hang and Grip Strength Assays (RRB200-017)



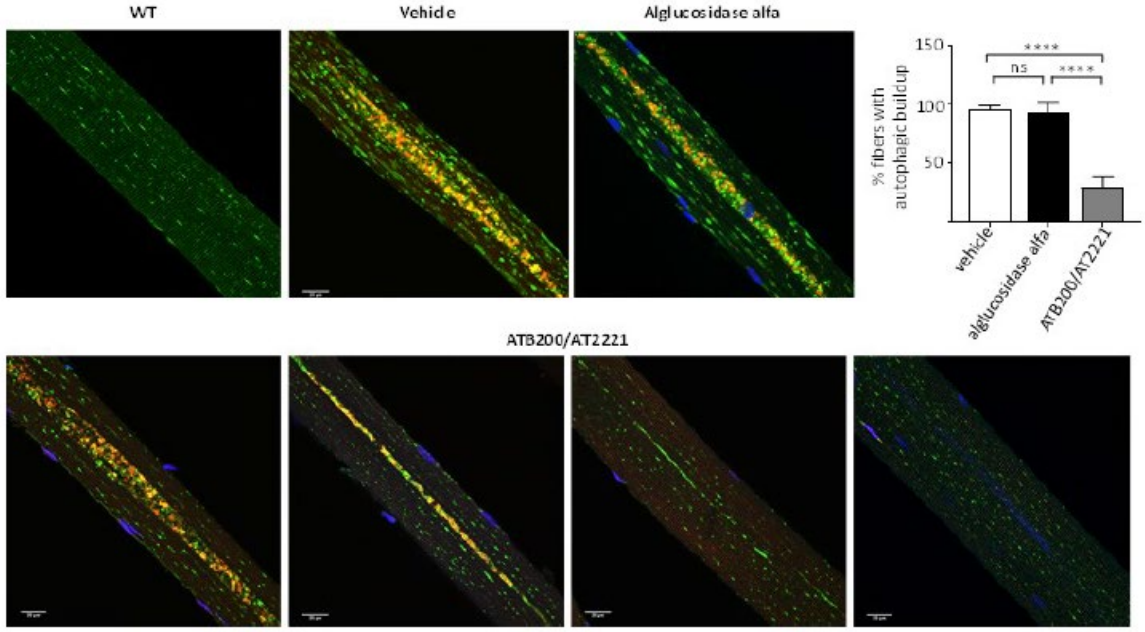
Source: Study RRB200-017
The wire-hang assay was conducted once on two consecutive days, with the data shown being the average of two assessments, while the grip-strength assay was repeated (three times) on the same day, with the data shown being the average of those three assessments (the Applicant considered the possibility of a systematic error during the sixth assessment for grip-strength). Each point represents the mean ± SEM of 15 animals/group up to 3 months, and 8 animals/group for the remaining 3 months (7 animals sacrificed after 3 months). Statistical significance was determined by two-sided t-test; * $p<0.05$ versus alglucosidase alfa.
Abbreviations: AT2221, miglustat; ATB200, cipaglucosidase alfa; IV, intravenous; QOW, every other week; SEM, standard error of means; WT, wild type

Treatment of *Gaa* KO mice with ATB200/AT2221 significantly improved grip strength from month 2 to month 6, relative to alglucosidase alone. Over 6 months, treatment of *Gaa* KO mice with ATB200/AT2221 showed a trend for increased hang time (wire hang latency) in the wire-hang assay compared to those treated with alglucosidase alfa; however, the pairwise comparisons showed no statistical difference between ATB200/AT2221 and alglucosidase alfa. In the wire hang assay, the trend reflects an apparent decrease in function in the alglucosidase-treated animals, particularly at months 1 and 2, whereas ATB200/AT2221-treated animals maintained function.

Muscle Architecture and Pathology

Co-immunofluorescence staining of single gastrocnemius fibers for LAMP1 (green, biomarker of lysosomes) and LC3 (red, biomarker of autophagy) show the presence of lysosomes and the absence of autophagy in wild-type (WT) muscle fibers relative to vehicle-treated (Vehicle) muscle fibers from *Gaa* KO mice (Figure 25). Fourteen days following the last treatment of male *Gaa* KO mice with four biweekly administrations 20 mg/kg cipaglucosidase alfa coadministered with a 10 mg/kg oral dose of miglustat, LAMP1 and LC3 fell to less than 30%, compared to untreated (vehicle) KO mice, suggesting a reduction of skeletal muscle fiber autophagic build up. In contrast, a 20 mg/kg dose of alglucosidase alfa showed more than 95% of muscle fibers with LAMP1/LC3-postive areas and autophagic build up (Figure 25 bar graph). Per the Applicant, the lower panel of Figure 25 shows different stages of resolution of autophagic build up in single muscle fibers observed at the end of treatment, indicating a high level of variability in these muscle fibers. A group treated with 20 mg cipaglucosidase alone was described in the study report methods section, but no data were included for this group in the study report.

Figure 25. Co-IF Staining for LAMP1 and LC3 in Single Muscle Fibers From White Gastrocnemius



Source: Applicant's figure from Pharmacology Study #RRB200-055, page 16.
Abbreviation: Co-IF, co-immunofluorescence; LAMP1, lysosomes-associated membrane protein 1; LC3, light chain 3

When the thick muscle filaments of the gastrocnemius muscles of the untreated *Gaa* KO mice were observed by fluorescence microscopy, small and large vacuolations representing autophagic debris were seen interrupting muscle architecture. Following treatment with coadministration of cipaglucosidase alfa (20 mg/kg) and miglustat (10 mg/kg), the fibers appeared qualitatively more normal than those in mice treated with alglucosidase alfa and in untreated mice.

The review team concluded from the in vivo studies that cipaglucosidase alfa coadministered with miglustat in male *Gaa* KO mice resulted in significant decreases in muscle tissue glycogen, significant increases in muscle function as measured by grip strength, reduced autophagic buildup and more normal muscle architecture, compared to alglucosidase alfa, the standard of care for Pompe disease. The effects of cipaglucosidase alfa coadministered with miglustat on glycogen reduction in heart and on grip strength persisted for at least 6 months.

Conclusion

In addition to the one single adequate and well-controlled clinical investigation (ATB200-03), the available CE for the efficacy of cipa-mig are provided by the well-established etiology of the disease and adequate mechanistic and animal model evidence and support approval.

6.3.3. Evidence of Miglustat Contribution to Effectiveness of Cipaglucosidase Alfa

Issue

Miglustat alone has no specific effects on glycogen reduction in patients with Pompe disease; therefore, with respect to glycogen reduction, miglustat is an inactive drug coadministered with

cipaglucosidase alfa to increase the stability of cipaglucosidase alfa. The persistent contribution of miglustat to the effectiveness of cipaglucosidase alfa is not established.

Background

The coadministration of miglustat (at doses of 130 mg and 260 mg administered orally, approximately 1 h before cipaglucosidase alfa infusion) with 20 mg/kg cipaglucosidase alfa in ATB200-02 showed a dose-dependent increase in cipaglucosidase alfa exposure as measured by AUC for total plasma GAA protein in ERT treatment-experienced patients. The $AUC_{0\text{-}t}$ from time 0 to the last measurable concentration for total GAA protein increased by 16.2% and 26.5% with coadministration of miglustat 130 mg and 260 mg, respectively. Greater increases in cipaglucosidase alfa exposure were observed in the elimination phase of the PK profiles with 27.7% and 43.7% increase in the $AUC_{tmax\text{-}24h}$ from the time of maximum concentration to 24 h with coadministration of miglustat 130 mg and 260 mg, respectively (Table 30).

The impact of miglustat on cipaglucosidase alfa exposure was also assessed based on cipaglucosidase activity (GAA activity) in plasma. The impact of miglustat on cipaglucosidase alfa exposure based on GAA activity was comparable between the two doses. The cipaglucosidase alfa PK profiles based on GAA activity indicated <10% increase in cipaglucosidase alfa $AUC_{0\text{-}t}$ when coadministered with 130 mg or 260 mg miglustat (Table 30). The $AUC_{tmax\text{-}24h}$ of cipaglucosidase alfa showed 24% and 21.3% increases with coadministration of miglustat 130 mg and 260 mg, respectively (Table 30).

Table 30. GAA Protein and GAA Activity PK Parameters of Cipaglucosidase Alfa 20 mg/kg With Coadministration of Miglustat Relative to 20 mg/kg Cipaglucosidase Alfa Alone

Parameter	Cipaglucosidase Alfa 20 mg/kg +130 mg Miglustat	Cipaglucosidase Alfa 20 mg/kg +260 mg Miglustat
GAA protein C_{max}	↑1.2%	↑4.3%
GAA protein $AUC_{0\text{-}t}$	↑16.2%	↑26.5%
GAA protein $AUC_{tmax\text{-}24h}$	↑27.7%	↑43.7%
GAA activity C_{max}	↓16.5%	↓17.2%
GAA activity $AUC_{0\text{-}t}$	↑7.1%	↑3.7%
GAA activity $AUC_{tmax\text{-}24h}$	↑24%	↑21.3%

Source: Review team derived from Table 13 and Table 19 in the ATB200-02 CSR.
Abbreviations: $AUC_{tmax\text{-}24h}$, AUC from time at maximum concentration to 24 h after start of cipaglucosidase alfa dose administration; C_{max}, maximum concentration; GAA, acid alpha-glucosidase; PK, pharmacokinetic

Overall, the PK results showed that coadministration of cipaglucosidase alfa with miglustat resulted in increases in plasma levels of total GAA protein and GAA activity compared to cipaglucosidase alfa administered alone, which supported that miglustat stabilized cipaglucosidase alfa and reduced the loss of enzyme activity while in circulation. However, given the relatively small PK enhancement effect of miglustat (<50% increase in cipaglucosidase alfa exposure across the PK metrics assessed) and the lack of exposure-response relationships between plasma cipaglucosidase alfa concentration and clinical efficacy, the clinical PK data alone (while supportive) are not considered adequate to demonstrate the contribution of miglustat to the effectiveness of cipaglucosidase alfa.

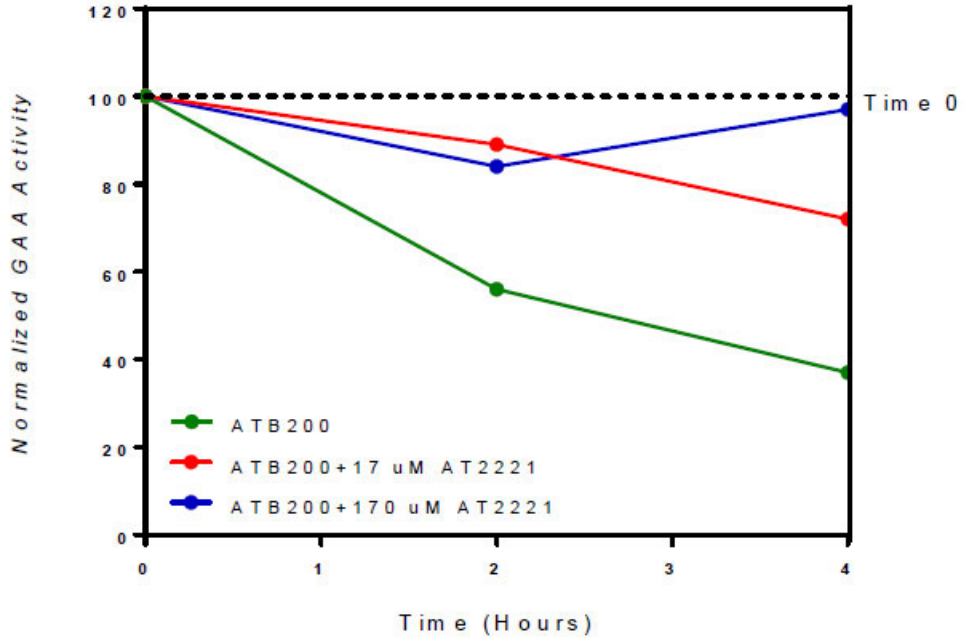
Nonclinical Assessment

Nonclinical evidence for the assessment of the contribution of miglustat to the effectiveness of cipaglucosidase alfa was obtained from mechanistic studies in vitro and from studies in a mouse model of disease.

In Vitro Evidence

Miglustat (17 and 170µM) was added to 3µM cipaglucosidase alfa in human blood at pH 7.4 and resulted in a dose-dependent increase in the stabilization of cipaglucosidase alfa with very little loss in enzyme activity (Figure 26). In contrast, when cipaglucosidase alfa alone was incubated with whole human blood for 4 h, it lost 70% of its enzymatic activity.

Figure 26. Stabilization of ATB200 by AT2221 in Human Blood (Study RB200-040)



Source: Applicant's Figure from Pharmacology Study #RRB200-040, page 12.

Miglustat stabilized cipaglucosidase alfa in neutral pH buffer and increased enzyme activity (Study No. RRB200-010).

Miglustat 10, 30 or 100µM dose-dependently stabilized 3 µg cipaglucosidase alfa or a reference compound of alglucosidase alfa incubated in a physiological buffer at pH 7.4, at which the enzymes are rapidly degraded (Table 31). Miglustat increased the melting pH of cipaglucosidase alfa from 56.2 to 61.6 in vitro.

Table 31. Melting Temperatures of rhGAA

Buffer	Melting Temperatures (°C)	
	Alglucosidase Alfa	ATB200
pH 7.4	56.7	56.2
pH 7.4 + 10 µM AT2221	62.9	61.6
pH 7.4 + 30 µM AT2221	64.9	62.9
pH 7.4 + 100 µM AT2221	66.5	66.0
pH 5.2	67.4	67.3

Source: Applicant's table from Pharmacology Study #RRB200-010, page 13.
Abbreviations: pH, potential of hydrogen; rhGAA, recombinant human acid alpha-glucosidase

In Vivo Evidence

Male *Gaa* KO mice were administered up to 12 biweekly (i.e., every other week) IV bolus injections of vehicle, 20 mg/kg ATB200 alone, 20 mg/kg alglucosidase alfa alone, or 20 mg/kg ATB200 coadministered with 10 mg/kg AT2221 (oral gavage 30 min before IV ATB200).

Table 32 shows glycogen levels in the muscles of *Gaa* KO mice following biweekly treatments for 1, 2, 3 or 6 months. The coadministration of ATB200/AT2221 significantly reduced glycogen levels in quadriceps for up to 2 months, compared to ABT200 alone. There were no differences in skeletal or heart muscle at 3 or 6 months.

Table 32. Glycogen Levels (µg/g) in *Gaa* KO Mice Following 1, 2, 3, or 6 Months of Treatment With ATB200 (20 mg)/AT2221 (10 mg) or ATB200 (20 mg) Alone.

	1 Month			2 Months	3 Months		6 Months
Number of Biweekly	[b]296	[b]320	[b]328	[a]294B	[a]294A	c	C
Treatments	2			4	6		12
Muscle Type							
Quadriceps							
ATB200/AT2221	101.8*	112.4*	196.3	51.2*	66.5	65.4	141.0
ATB200 alone	165.2	186.2	224.7	101.9	81.9	58.3	136.4
Triceps							
ATB200/AT2221				142.1	106.1	107.7	136.8
ATB200 alone				187.0	100.7	124.9	164.6
Heart							
ATB200/AT2221				19.3	31.5	39.5	95.1
ATB200 alone				16.2	39.2	50.6	74.9
Gastrocnemius							
ATB200/AT2221						37.2	61.4
ATB200 alone						42.1	70.4

[a] Study #RRB200-004 studies 294A and 294B, p. 30
[b] Study #RRB200-005 studies 296, 320, and 328, p. 32
[c] Study #RRB200-017, p. 52
[a, c] An amyloglucosidase-based biochemical method and a high-pH anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) chromatography method were used. [a] Glycogen was digested and evaluated by glucose assay.
* CDER statistical analysis was determined using the two-sided t-test; * p<0.05 versus ABT200 alone.
Abbreviations: KO, knockout, pH, potential of hydrogen

Table 33 shows GAA enzyme activity levels in muscles of KO mice following biweekly treatments for 1, 2, 3, or 6 months. The coadministration of ATB200/AT2221 did not increase GAA enzyme activity levels in quadriceps, triceps, gastrocnemius or heart compared to ABT200 treatment alone.

Table 33. GAA Enzyme Activity (nmol/mg Protein/Hour) in *Gaa* KO Mice Following 1, 2, 3, or 6 Months of Treatment With ATB200 (20 mg)/AT2221 (10 mg) or ATB200 (20 mg) Alone (RRB200-017)

	1 Month		2 Months	3 Months		6 Months
Number of Biweekly	c	b	b	a	d	D
treatments	2		4	6		12
Muscle Type						
Quadriceps						
ATB200/AT2221	8.35	5.22	13.3	2.90	2.96	2.13
ATB200 alone	4.68	3.56	4.21	1.68	2.97	2.04
Triceps						
ATB200/AT2221	4.35		11.5	3.90	5.86	3.56
ATB200 alone	4.89		5.35	2.95	3.45	5.02

	1 Month		2 Months	3 Months		6 Months
Number of Biweekly treatments	**c**	**b**	**b**	**a**	**d**	**D**
	2		**4**	**6**		**12**
Muscle Type						
Heart						
ATB200/AT2221	3.80		5.45	3.01	2.27	2.65
ATB200 alone	3.62		4.42	5.99	2.33	3.27
Gastrocnemius						
ATB200/AT2221					9.97	10.6
ATB200 alone					9.17	11.3

[a] Study report #RRB200-004, studies 294A and 294B, p32 and 31
[b] Study report #rrb200-005, study 296, page 33
[c] Study report #rrb200-014. Page 37
[d] Study report #RRB200-017, page 54-55
*CDER statistical analysis by two-sided t-test; * p<0.05 versus ABT200 alone.
Abbreviations: GAA, acid alpha-glucosidase; KO, knockout

Table 34 and Table 35 were constructed from muscle function tests in *Gaa* KO mice following biweekly treatments for 1 to 6 months. In the grip-strength assay, the pairwise comparisons showed no differences for the coadministration of ATB200/AT2221, when compared to ABT200 treatment, for grip strength, except in Month 5.

Table 34. Grip-Strength (g) in *Gaa* KO Mice

Compound	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
ATB200/AT2221	103.9	111.4	117.7	121.3	138.6	139.0*	151.5
ATB200	106.9	109.3	123.1	118.8	128.0	122.0	152.3

Source: Pharmacology Study #RRB200-017, Appendix C, pp. 40 to 45
Muscle function was assessed once per month. The wire-hang assay was conducted once on two consecutive days, with the data shown being the average of two assessments, while the grip-strength assay was repeated thrice on the same day, with the data shown being the average of those three assessments. Each point represents the mean ± SEM of 15 animals/group up to 3 months, and 8 animals/group for the remaining 3 months (7 animals sacrificed after 3 months). Statistical significance determined by two-sided t-test; * p<0.05 versus ABT200 alone.
Abbreviations: *Gaa*, acid alpha-glucosidase gene; KO, knockout

Over 6 months, treatment of *Gaa* KO mice with ATB200/AT2221 did not increase wire hang time compared to those treated with ABT200 alone.

Table 35. Wire Hang Latency (Seconds) in *Gaa* KO Mice

Compound	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
ATB200/AT2221	80.4	67.4	74.6	70.1	84.5	67.8	71.8
ATB200	85.4	60.0	57.7	57.0	61.8	50.3	46.7

Source: Pharmacology Study #RRB200-017, Appendix C, pp. 46 to 51.
Abbreviations: *Gaa*, acid alpha-glucosidase gene; KO, knockout

In in vivo PK studies to assess $t_{1/2}$ and AUC of IV cipaglucosidase alfa (5, 10, 20, or 100 mg/kg) or alglucosidase alfa (20 mg/kg), and the effects of oral coadministration of miglustat (10 or 30 mg/kg) in the plasma of *Gaa* KO mice, the half-life of cipaglucosidase alfa was modestly increased by miglustat from 0.73 to 0.93 with 10 mg/kg miglustat and from 0.73 to 0.97 at 30 mg/kg. (Study no. RRB200-10).

(b) (4)

Although ATB200/AT2221 treatment in a mouse model of disease (*Gaa* KO mice) resulted in decreased glycogen levels in tissues compared to ATB200 alone up to 2 months of treatment, no improvement in glycogen levels was seen thereafter. No improvement of ATB200/AT222 over ATB200 alone in GAA enzyme activity was observed at 3 or 6 months. Improvement in muscle

function (grip strength) following ATB200/AT2221 treatment was observed at 5 months only in *Gaa* KO mice, compared to ATB200 alone, but was not observed at earlier time points or at 6 months. Over a period of 6 months, treatment of *Gaa* KO mice with ATB200/AT2221 did not increase wire hang time compared to those treated with ABT200 alone.

Conclusion

The review team concluded that the nonclinical data for the contribution of AT2221 (miglustat) during coadministration with cipaglucosidase alfa did not demonstrate superiority or persistent improvement of cipa-mig coadministration compared to cipaglucosidase alfa alone. Glycogen levels initially improved with cipa-mig coadministration, compared to cipaglucosidase alfa alone; however, no further improvement was observed after 2 months of treatment in mice, no increase in GAA activity was observed at 3 or 6 months post-treatment, and improvement of grip strength was observed at only one time point (5 months). Overall, the nonclinical data do not demonstrate improved cipaglucosidase efficacy from chronically administered miglustat.

Given that the Division agreed that a three-arm clinical trial was not feasible, there are no clinical data to support the efficacy of cipaglucosidase alfa alone. In addition, no nonclinical or clinical studies were conducted to test whether removal of miglustat from dosing would result in reduced efficacy. The review team concluded that it is reasonable to approve cipa-mig for chronic use based on the available safety and efficacy dat (b) (4)

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7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

When cipaglucosidase alfa and miglustat were coadministered to pregnant rabbits every other day during organogenesis in this species, the incidences of great vessel and cardiac malformations were markedly increased: 15 fetuses from 6 of 18 litters were affected. The constellation of findings included malpositioned aorta; absent, dilated or retroesophageal aortic arch; absent or atretic ductus arteriosus; narrow/atretic pulmonary trunk; malpositioned or retroesophageal subclavian; abdominal situs inversus; dextrocardia; atrioventricular septal defects; ventricular septal defects; malpositioned atrium; three-chambered heart; small right ventricle; and enlarged left ventricle. A no observed adverse effect level (NOAEL) was not identified for the coadministered drugs.

When single AUC exposures in pregnant rabbits at the lowest observed adverse effect levels (LOAELs) of cipaglucosidase alfa and miglustat (175 mg/kg and 25 mg/kg, respectively) are compared to the clinical AUC values at the MRHD (1400 µg*h/mL and 20000 ng*h/mL, respectively), margins are 16.1 for cipaglucosidase alfa and 3.3 for miglustat. Single nonclinical AUC exposures are considered the most conservative estimates of margins, as these malformations are likely to initiate early in organogenesis (see Section 7.7.2).

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

7.2.1. Cipaglucosidase Alfa

Cipaglucosidase alfa is a hydrolytic lysosomal glycogen-specific enzyme developed as an enzyme replacement therapy. The potential risks with this class of drugs include hypersensitivity reactions including anaphylaxis, infusion-associated reactions, and immunogenicity (see Section 7.7.1).

7.2.2. Miglustat

Miglustat is an enzyme stabilizer coadministered with cipaglucosidase alfa. Miglustat is also a glucosylceramide synthase inhibitor and current risks identified in clinical trials for miglustat in

patients with Gaucher disease, administered orally 300 mg a day, include peripheral neuropathy, tremor, diarrhea, weight loss, and reductions in platelet count. Potential risks include Crohn's disease; adverse effects on spermatogenesis and sperm parameters and reducing fertility; reproductive toxicity, including dystocia; and increased incidence of large intestinal inflammation, adenoma and carcinoma. Effects on spermatogenesis are considered a potential risk based on nonclinical data included in NDA 021348 for Zavesca. Of note, the proposed dose regimen for miglustat for the treatment of patients with LOPD is higher than that used for patients with Gaucher disease, but is dosed only once every 2 weeks (260 mg qow in patients with LOPD versus 100 mg three times a day in patients with Gaucher disease).

7.3. Potential Safety Concerns Identified Through Postmarket Experience

7.3.1. Cipaglucosidase Alfa

This product has not been approved in the United States or in any foreign markets. Therefore, no postmarketing experience is available at the time of this review.

7.3.2. Miglustat

This product has been approved in the United States for treatment of adult patients with mild/moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option on July 31, 2003 (NDA 021348). Miglustat is also authorized in 55 other countries. The estimated total worldwide cumulative patient exposure to miglustat is 5073 person-years per the Periodic Benefit-Risk Evaluation from December 15, 2021 (period covered: October 20, 2018, to October 19, 2021). No new safety signals or concerns based on postmarket experience were reported in the Periodic Benefit-Risk Evaluation.

7.4. FDA Approach to the Safety Review

Safety data from the following trials were submitted to support the safety of cipa-mig:

- Trial ATB200-02 (29 patients)
- Trial ATB200-03 (123 patients)
- Trial ATB200-07 (117 patients who participated on ATB200-03)

The review team primarily assessed data from the comparator-controlled trial ATB200-03. This trial provided data to compare the incidences of adverse effects between cipa-mig and the standard of care at the time of the trial, alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product. In addition, data from each open-label trial (ATB200-02 and ATB200-07) and the pooled safety data from the three trials were reviewed to ensure completeness of the safety assessment. The combined safety population consisted of 151 patients 18 years of age and older from the three trials who received at least one dose of cipa-mig; of those 151 patients, 37 received the comparator in trial ATB200-03 and switched to cipa-mig in trial ATB200-07.

Patients treated under expanded-access protocols (eight patients) or enrolled in trial ATB200-04 (four pediatric patients) were not included in the pooled safety data.

The safety data are shown by events occurring in all patients; treatment-naïve and treatment-experienced patients; and each treatment arm within the ATB20-03 trial. Of the 151 patients, 34 patients were treatment-naïve and 117 were treatment-experienced, having received alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product alfa previously.

First, trial ATB200-03 and integrated summary of safety (ISS) datasets were examined for the required and standardized components and for completeness of the data. Then, the review team confirmed that the AEs reported by the Applicant accurately described the AEs reported by the investigators.

Once accuracy was confirmed, the frequencies of each AE were assessed and described both by occurrence and exposure-adjusted rates. The review team reviewed all adverse events of special interest (AESIs), serious adverse events (SAEs), discontinuations, withdrawals, and patients lost to follow-up.

7.5. Adequacy of Clinical Safety Database

The safety database was adequate for a sufficient safety assessment of cipa-mig for the indication of LOPD in patients 18 years of age and older. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review. No major issues were identified with respect to the coding of adverse events.

Table 37 shows the baseline demographics of the safety population consisting of 151 patients with LOPD in the ISS dataset (ATB200-02, ATB200-03, and ATB200-07) who received cipa-mig. The majority of the patients was female (53%), the mean age was 47 years, and most patients were white (80%).

Table 37. Baseline Demographic and Clinical Characteristics, Safety Population, Integrated Summary of Safety, ATB200-02, ATB200-03, and ATB200-07

Characteristic	Cipa-Mig Treatment-Experienced N=117	Cipa-Mig Treatment-Naïve N=34	Cipa-Mig Total N=151
Sex, n (%)			
Female	61 (52.1)	19 (55.9)	80 (53.0)
Male	56 (47.9)	15 (44.1)	71 (47.0)
Age, years			
Mean (SD)	47.2 (13.1)	45.9 (14.5)	46.9 (13.4)
Median (min, max)	48 (18, 74)	47.5 (19, 67)	48 (18, 74)
Age group, years, n (%)			
≥18 to <35 years	23 (19.7)	9 (26.5)	32 (21.2)
≥35 to <50 years	39 (33.3)	10 (29.4)	49 (32.5)
≥50 to <65 years	42 (35.9)	11 (32.4)	53 (35.1)
≥65 years	13 (11.1)	4 (11.8)	17 (11.3)

Characteristic	Cipa-Mig Treatment-Experienced N=117	Cipa-Mig Treatment-Naïve N=34	Cipa-Mig Total N=151
Race, n (%)			
Asian	4 (3.4)	0 (0)	4 (2.6)
Black or African American	1 (0.9)	0 (0)	1 (0.7)
Japanese	6 (5.1)	0 (0)	6 (4.0)
Native Hawaiian or other Pacific Islander	0 (0)	1 (2.9)	1 (0.7)
White	93 (79.5)	28 (82.4)	121 (80.1)
Other	6 (5.1)	0 (0)	6 (4.0)
Missing	7 (6.0)	5 (14.7)	12 (7.9)
Country of participation, n (%)			
Argentina	1 (0.9)	0 (0)	1 (0.7)
Australia	14 (12.0)	9 (26.5)	23 (15.2)
Austria	1 (0.9)	0 (0)	1 (0.7)
Belgium	2 (1.7)	1 (2.9)	3 (2.0)
Bosnia and Herzegovina	0 (0)	2 (5.9)	2 (1.3)
Canada	2 (1.7)	1 (2.9)	3 (2.0)
Germany	6 (5.1)	1 (2.9)	7 (4.6)
Denmark	6 (5.1)	0 (0)	6 (4.0)
Spain	3 (2.6)	0 (0)	3 (2.0)
France	8 (6.8)	3 (8.8)	11 (7.3)
Great Britain	8 (6.8)	4 (11.8)	12 (7.9)
Greece	1 (0.9)	0 (0)	1 (0.7)
Hungary	5 (4.3)	2 (5.9)	7 (4.6)
Italy	2 (1.7)	0 (0)	2 (1.3)
Japan	6 (5.1)	0 (0)	6 (4.0)
Korea	1 (0.9)	0 (0)	1 (0.7)
Netherlands	3 (2.6)	0 (0)	3 (2.0)
Poland	2 (1.7)	0 (0)	2 (1.3)
Slovakia	1 (0.9)	0 (0)	1 (0.7)
Sweden	1 (0.9)	0 (0)	1 (0.7)
Taiwan	2 (1.7)	0 (0)	2 (1.3)
United States	42 (35.9)	11 (32.4)	53 (35.1)

Source: adsl.xpt; software: R.
Abbreviations: Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Table 38 summarizes the cipa-mig exposure for the ISS dataset; the total exposure is 219 person-years. Of the 151 patients in the ISS dataset, 22 (14%) were treated with cipa-mig for 24 months or more. The largest cohort in the ISS dataset was treated with cipa-mig for 12 months or more, but less than 18 months (36%).

Table 38. Duration of Exposure, Safety Population, Integrated Summary of Safety, ATB200-02, ATB200-03, and ATB200-07

Variable	Cipa-Mig N=151
Duration of exposure, months	
Mean (SD)	17.3 (12.8)
Median (Q1, Q3)	14.8 (10.4,20.4)
Minimum, maximum	0, 52.2
Total exposure (person years)	219.2

Variable	Cipa-Mig N=151
Patients treated, by duration, n (%)	
<6 months	30 (19.9)
≥6 to <12 months	13 (8.6)
≥12 to <18 months	55 (36.4)
≥18 to <24 months	31 (20.5)
≥24 months	22 (14.6)

Source: adsl.xpt; software: R.
Individuals included in this analysis were receiving cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
For patients who were on cipa-mig in ATB200-03 and then continued in ATB200-07, the duration of exposure is calculated as the sum of durations in each study.
Abbreviations: Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation; Q1, first quartile; Q3, third quartile

Table 11, in Section 6.2.1.4, shows the baseline demographics for trial ATB200-03. Table 39 summarizes the cipa-mig exposure for trial ATB200-03. Patients treated for 9 months or more, but less than 12 months comprised the largest cohort (52.9%) in the cipa-mig group.

Table 39. Duration of Exposure, Controlled Safety Population, 52 Weeks, ATB200-03

Variable	Cipa-Mig N=85
Duration of treatment, months	
Mean (SD)	11.8 (1.8)
Median (minimum, maximum)	12 (1, 14.8)
Total exposure (person years)	83
Patients treated, by duration, n (%)	
<3 months	1 (1.2)
≥3 to <6 months	1 (1.2)
≥6 to <9 months	2 (2.4)
≥9 to <12 months	45 (52.9)
≥12 months	36 (42.4)

Source: adex.xpt; software: R.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow
Abbreviations: Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

Overall Summary

The demonstrated safety profile of cipaglucosidase alfa 20 mg/kg qow coadministered with miglustat 260 mg qow is acceptable in patients with LOPD. The most common adverse reactions from trial ATB200-03 (≥2%) were nausea, abdominal pain, abdominal distension, flatulence, diarrhea, arthralgia, oropharyngeal pain, muscle spasms, musculoskeletal pain, asthenia, dyspnea, tachycardia, blood pressure increased, headache, fatigue, dizziness, pyrexia, chills, flushing, pruritus, rash, dysgeusia, tremor, and paresthesia. No other adverse reactions were identified from the ISS dataset.

During the safety review, the review team also assessed AESIs; as with most ERTs, hypersensitivity events (including anaphylaxis) and IARs were identified with cipa-mig treatment. No data on pregnancy and lactation are available with cipa-mig. There were no deaths

during the trials. The review team concluded that labeling, including an updated boxed warning, and routine pharmacovigilance monitoring is adequate to monitor the identified safety risks.

7.6.1. Safety Findings and Concerns, ATB200-03

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, ATB200-03

During the ATB200-03 trial, 85 patients with LOPD received cipaglucosidase alfa 20 mg/kg coadministered with miglustat 260 mg qow, and 38 patients with LOPD received a non-U.S.-approved alglucosidase alfa product, the active comparator, at 20 mg/kg with placebo qow for 52 weeks. The safety data are displayed by treatment arm (cipa-mig or comparator group) and by prior treatment status (treatment-naïve or treatment-experienced).

Table 40 provides a summary of AEs reported in the ATB200-03 trial. One or more TEAEs were reported by 95% of the patients treated with cipa-mig compared to 97% of the patients treated with the comparator. Although approximately the same proportion of patients in both groups presented with AEs, SAEs, as well as AEs leading to dose modification or interruption, were reported more frequently in the cipa-mig group than in the comparator group, with risk differences of 6.8 (95% CI: -1.2, 14.8) and 8.0 (95% CI: -0.3, 16.2), respectively. However, most were not assessed as related to cipa-mig by the Applicant and the review team. No fatal outcome or life-threatening SAEs were reported for any of the 123 patients. The review team concluded that the safety profile is consistent with other enzyme replacement therapies and with the use of miglustat in Gaucher disease (Zavesca) and recommended routine pharmacovigilance monitoring.

Table 40. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, 52 Weeks, ATB200-03

Event Category	Cipa-Mig Treatment-Experienced N=65 N (%)	Cipa-Mig Treatment-Naïve N=20 n (%)	Cipa-Mig Total N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
SAE	6 (9.2)	2 (10.0)	8 (9.4)	1 (2.6)	6.8 (-1.2, 14.8)
AE leading to permanent discontinuation of study drug	3 (4.6)	0	3 (3.5)	1 (2.6)	0.9 (-5.5, 7.3)
AE leading to dose modification of study drug	7 (10.8)	2 (10.0)	9 (10.6)	1 (2.6)	8.0 (-0.3, 16.2)
AE leading to interruption of study drug	7 (10.8)	2 (10.0)	9 (10.6)	1 (2.6)	8.0 (-0.3, 16.2)
Any AE	62 (95.4)	19 (95.0)	81 (95.3)	37 (97.4)	-2.1 (-8.9, 4.7)
Severe	8 (12.3)	0	8 (9.4)	2 (5.3)	4.1 (-5.3, 13.6)
Moderate	26 (40.0)	11 (55.0)	37 (43.5)	19 (50.0)	-6.5 (-25.5, 12.6)
Mild	28 (43.1)	8 (40.0)	36 (42.4)	16 (42.1)	0.2 (-18.6, 19.1)

Source: adae.xpt; software: R.
Treatment-emergent adverse events defined as those events that were newly occurring or worsening on or after the first dose of study drug.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: AE, adverse event; CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment arm; n, number of patients with at least one event; qow, every other week; SAE, serious adverse event

7.6.1.2. Deaths, ATB200-03

There were no deaths reported.

7.6.1.3. Serious Adverse Events, ATB200-03

Table 41 lists the 12 SAEs reported in nine patients; eight (9%) patients in the cipa-mig group had an SAE compared to one (3%) patient in the comparator group (Table 40). However, only one SAE (in patient 2024-1103), an anaphylaxis reaction that led to study drug discontinuation, was assessed as related to cipa-mig by the review team. No SAE occurred in more than one patient.

Table 41. Serious Adverse Events by System Organ Class and Preferred Term, Controlled Safety Population, 52 Weeks, ATB200-03

Serious Adverse Event[1]	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Cardiac disorders (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Bradycardia	1 (1.2)	0	1.2 (-1.1, 3.5)
Gastrointestinal disorders (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Abdominal pain	1 (1.2)	0	1.2 (-1.1, 3.5)
Enteritis	1 (1.2)	0	1.2 (-1.1, 3.5)
Vomiting	1 (1.2)	0	1.2 (-1.1, 3.5)
Immune system disorders (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Anaphylactoid reaction	1 (1.2)	0	1.2 (-1.1, 3.5)
Infections and infestations (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Viral myositis	1 (1.2)	0	1.2 (-1.1, 3.5)
Injury, poisoning and procedural complications (SOC)	2 (2.4)	0	2.4 (-0.9, 5.6)
Contusion	1 (1.2)	0	1.2 (-1.1, 3.5)
Ilium fracture	1 (1.2)	0	1.2 (-1.1, 3.5)
Skin laceration	1 (1.2)	0	1.2 (-1.1, 3.5)
Nervous system disorders (SOC)	0	1 (2.6)	-2.6 (-7.7, 2.5)
Cerebrovascular accident	0	1 (2.6)	-2.6 (-7.7, 2.5)
Surgical and medical procedures (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Removal of internal fixation	1 (1.2)	0	1.2 (-1.1, 3.5)
Vascular disorders (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Aortic aneurysm	1 (1.2)	0	1.2 (-1.1, 3.5)

Source: adae.xpt; software: R.
[1] Coded as MedDRA preferred terms
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in group; n, number of patients with adverse event; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities, qow, every other week; SOC, system organ class

Narratives of Patients With SAEs

(b) (6) A 72-year-old male who was treatment-experienced at enrollment. The patient had a previous history of abdominal aorta sacular aneurysm. On Day 344, 7 days after the 25th infusion, during a routine cardiology visit, an ultrasound showed worsening of the aneurysm. The study drugs were interrupted on Day 362 due to this SAE. The patient underwent an endovascular stent graft surgery on Day 364; he was discharged 2 days later. The study drugs were interrupted on Day 376 due to worsening of a COVID-19 infection. He was discontinued from the trial on Day 394 due to investigator's decision; however, he subsequently enrolled in

the ATB200-07 trial. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 37-year-old male who was treatment-naïve at enrollment. On Day 177, 22 days after the 12th dosing with cipa-mig, the patient fell resulting in a fracture of the left os ilium. The patient was transferred to a hospital; on Day 179, the patient was discharged. No action was taken with the study drugs and the patient completed the trial. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 21-year-old female who was treatment-experienced at enrollment. On Day 305, 11 days after the 22nd dosing with cipa-mig, the patient was hospitalized for preplanned removal of internal fixation of the left femur as the pre-existing fracture, which had occurred 2 years prior, was healed. No action was taken with the study drugs and the patient completed the trial. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 44-year-old male who was treatment-experienced at enrollment. Past relevant medical history included cardiac flutter. On Day 183, 6 h after the 14th dosing with cipa-mig, the patient noted, on his smartwatch, that his heart rate was 37 beats per min (bpm), which then recovered to 80 bpm. The patient reported that for the past month, he had noted, on his smartwatch, dips in his heart rate down to the 40s with recovery with no overt symptoms. On Day 184, the patient developed fatigue. On Day 196, the patient experienced another episode of asymptomatic bradycardia (43 bpm). The patient was referred by the investigator to a cardiologist on Day 199 for episodic bradycardia; results of this evaluation were not provided. The patient had normal electrocardiograms (ECGs) at baseline, Days 84, 182, and 269. On Day 330, there was an ECG alteration classified as not clinically significant by the investigator. No corrective treatment medication or therapies were given to the patient. No action was taken with the study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team assessed the event as possibly related to cipa-mig.

(b) (6) A 44-year-old male who experienced anaphylaxis probably related to cipaglucosidase alfa during his 14th dosing with cipa-mig and was discontinued from the trial. See Section 7.6.1.3 for the patient narrative.

(b) (6) A 46-year-old male who was treatment-experienced at enrollment. On Day 242, 3 days after the 17th dosing with the comparator, the patient had a cerebrovascular stroke. On Day 273, the event was considered resolved and the patient was discharged to inpatient rehabilitation in stable condition. The study drugs were permanently discontinued. The investigator and the Applicant assessed the event as serious and unrelated to the comparator. The review team agreed with the assessment of this event.

(b) (6) A 38-year-old female who was treatment-experienced at enrollment. On Day 260, the patient was diagnosed with influenza A. On Day 267, the patient received the 20th dosing of cipa-mig. The patient experienced a fall on Day 271 and developed worsening muscle weakness on Day 272. On Day 279, the patient presented to the ER with worsening cough and was diagnosed with viral myositis, a complication from the influenza A infection. The patient was admitted to the hospital and presented elevated aspartate aminotransferase (AST) (515 U/L), elevated alanine aminotransferase (ALT) (547 U/L), elevated creatine kinase (CK) 12.638 U/L, and tested positive for myoglobin in urine. On Day 283, the patient was discharged from the

hospital with the diagnosis of viral myositis ongoing; the myoglobinuria had resolved. On Day 322, the patient reported to be improving, but still required assistance for completing daily activities; the CK, ALT, and AST levels were normal. The patient received approximately 2 months of physical therapy due to the myositis. On Day 426, the viral myositis was considered resolved. No action was taken with the study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 57-year-old female who was treatment-experienced at enrollment. On Day 43, 1 day after the fourth dosing with cipa-mig, the patient had abdominal pain and vomiting. Over the next 2 days, the patient's abdominal pain worsened. On Day 45, the patient had three episodes of vomiting. On Day 46, the patient's epigastric pain returned with diarrhea. On Day 48, the patient went to the ER. Computed tomography of the abdomen showed mucosal thickening and vascular engorgement of the ileum, which was concerning for ileitis. The patient received treatment for abdominal pain, hypokalemia, hypophosphatemia, hypomagnesemia, and urinary tract infection. A gastrointestinal pathogen panel was negative (including *Clostridium difficile)* and fecal leukocyte was not present. On Day 50, the abdominal pain and vomiting with ileitis resolved, and the patient was discharged from the hospital. No action was taken with the study drugs, and the patient completed the trial. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 30-year-old female who was treatment-naïve at enrollment. On Day 164, 9 days after the 12th dosing with cipa-mig, the patient fell off her bicycle and had contusions and skin lacerations in her face, chest, and extremities. The patient was taken to hospital and was admitted for overnight monitoring. No action was taken with the study drugs and the patient completed the trial. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, ATB200-03

Six patients in ATB200-03 discontinued participation during the clinical trial: three patients in the cipa-mig group and one patient in the comparator group discontinued due to AEs (Table 42), and two patients in the cipa-mig group withdrew due to the difficulty of visits.

Table 42. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Controlled Safety Population, 52 Weeks, Safety Population, ATB200-03

Adverse Event[1]	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
General disorders and administration site conditions (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Chills	1 (1.2)	0	1.2 (-1.1, 3.5)
Immune system disorders (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Anaphylactoid reaction	1 (1.2)	0	1.2 (-1.1, 3.5)
Infections and infestations (SOC)	1 (1.2)	0	1.2 (-1.1, 3.5)
Coronavirus disease 2019	1 (1.2)	0	1.2 (-1.1, 3.5)

Adverse Event[1]	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Nervous system disorders (SOC)	0	1 (2.6)	-2.6 (-7.7, 2.5)
Cerebrovascular accident	0	1 (2.6)	-2.6 (-7.7, 2.5)

Source: adae.xpt; software: R.
[1] Coded as MedDRA preferred terms
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: AE, adverse event; CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in group; n, number of patients with adverse event; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities; qow; every other week; SOC, system organ class

Of the four patients who discontinued the trial due to an AE, two patients' AEs were assessed by the review team as unrelated: one patient in the cipa-mig group with pneumonia as a complication from coronavirus disease 2019 infection and one patient in the comparator group with a cerebrovascular accident. Two patients were assessed as related to cipa-mig by the review team, which was consistent with the investigator's assessment. As described in the narratives below, these two patients had hypersensitivity events including anaphylaxis, chills, and urticarial rash.

Narratives of the two patients discontinuing due to AEs related to cipa-mig:

(b) (6) A 44-year-old male who experienced anaphylaxis probably related to cipaglucosidase alfa during his 14th dosing with cipa-mig and was discontinued from the trial. See Section 7.6.1.3 for the patient narrative.

(b) (6) A 38-year-old female in trial ATB200-03 who was treatment-experienced at enrollment. On Study Day 1 and Study Day 15, the patient experienced urticaria, lightheadedness, mild sleepiness, and moderate shivering; she had received pretreatment with oral cetirizine and paracetamol. The patient received treatment for the IARs, and the events resolved. On Study Day 29 (third infusion), the patient received premedication (oral cetirizine and paracetamol, and IV hydrocortisone), but developed severe urticarial rash over the whole body, followed by severe itchy extremities. Approximately 2.5 h after starting the infusion, the patient experienced severe chills, and the infusion was stopped. Following treatment with IV hydrocortisone, the urticarial rash of the whole body resolved approximately 3.5 h after stopping the infusion. The patient was discontinued from the trial on Study Day 43 due to investigator's decision. The investigator and the Applicant assessed the event as nonserious and related to cipaglucosidase alfa. The review team agreed with the assessment of these events.

7.6.1.5. Treatment-Emergent Adverse Events, ATB200-03

Table 43. lists the TEAEs that occurred in ≥2% of all patients who participated in the trial comparing the risk difference between those who received cipa-mig and those who received the comparator. The cipa-mig group presented a higher risk for several TEAEs than the comparator, most notably for pharyngitis, urinary tract infections, oropharyngeal pain, and muscle spasms. Only three TEAEs led to discontinuation of treatment in the cipa-mig group (Table 40); this may reflect the fact that most TEAEs were not severe.

Refer to Section 7.7.1 for a discussion of hypersensitivity (including anaphylaxis) and IARs.

Table 43. Common Adverse Events Occurring at ≥2% Frequency, Controlled Safety Population, 52 Weeks, ATB200-03

Preferred Term	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Any AE	81 (95.3)	37 (97.4)	-2.1 (-8.9, 4.7)
Pharyngitis	21 (24.7)	5 (13.2)	11.5 (-2.6, 25.7)
Urinary tract infection	12 (14.1)	2 (5.3)	8.9 (-1.4, 19.1)
Oropharyngeal pain	11 (12.9)	2 (5.3)	7.7 (-2.4, 17.7)
Muscle spasms	8 (9.4)	1 (2.6)	6.8 (-1.2, 14.8)
Cough	4 (4.7)	0	4.7 (0.2, 9.2)
Influenza-like illness	4 (4.7)	0	4.7 (0.2, 9.2)
Insomnia	4 (4.7)	0	4.7 (0.2, 9.2)
Muscle fatigue	4 (4.7)	0	4.7 (0.2, 9.2)
Muscle strain	4 (4.7)	0	4.7 (0.2, 9.2)
Dyspnea	6 (7.1)	1 (2.6)	4.4 (-3.0, 11.9)
Pain	6 (7.1)	1 (2.6)	4.4 (-3.0, 11.9)
Pyrexia	6 (7.1)	1 (2.6)	4.4 (-3.0, 11.9)
Hematuria	6 (7.1)	0	4.4 (-3.0, 11.9)
Diarrhea	12 (14.1)	4 (10.5)	3.6 (-8.7, 15.8)
Chills	3 (3.5)	0	3.5 (-0.4, 7.5)
Noncardiac chest pain	3 (3.5)	0	3.5 (-0.4, 7.5)
Rhinorrhea	3 (3.5)	0	3.5 (-0.4, 7.5)
Skin abrasion	3 (3.5)	0	3.5 (-0.4, 7.5)
Skin laceration	3 (3.5)	0	3.5 (-0.4, 7.5)
Tachycardia	3 (3.5)	0	3.5 (-0.4, 7.5)
Blood pressure increased	3 (3.5)	1 (2.6)	3.5 (-0.4, 7.5)
Vomiting	5 (5.9)	1 (2.6)	3.3 (-3.9, 10.4)
Bradycardia	2 (2.4)	0	2.4 (-0.9, 5.6)
Conjunctivitis	2 (2.4)	0	2.4 (-0.9, 5.6)
Depression	2 (2.4)	0	2.4 (-0.9, 5.6)
Dysgeusia	2 (2.4)	0	2.4 (-0.9, 5.6)
Dysuria	2 (2.4)	0	2.4 (-0.9, 5.6)
Ear pain	2 (2.4)	0	2.4 (-0.9, 5.6)
Face injury	2 (2.4)	0	2.4 (-0.9, 5.6)
Flushing	2 (2.4)	0	2.4 (-0.9, 5.6)
Hot flush	2 (2.4)	0	2.4 (-0.9, 5.6)
Influenza	2 (2.4)	0	2.4 (-0.9, 5.6)
Infusion site swelling	2 (2.4)	0	2.4 (-0.9, 5.6)
Malaise	2 (2.4)	0	2.4 (-0.9, 5.6)
Mouth ulceration	2 (2.4)	0	2.4 (-0.9, 5.6)
Musculoskeletal discomfort	2 (2.4)	0	2.4 (-0.9, 5.6)
Oedema peripheral	2 (2.4)	0	2.4 (-0.9, 5.6)
Presyncope	2 (2.4)	0	2.4 (-0.9, 5.6)
Spinal column injury	2 (2.4)	0	2.4 (-0.9, 5.6)
Tooth infection	2 (2.4)	0	2.4 (-0.9, 5.6)
Tremor	2 (2.4)	0	2.4 (-0.9, 5.6)
Viral rhinitis	2 (2.4)	0	2.4 (-0.9, 5.6)
Weight decreased	2 (2.4)	0	2.4 (-0.9, 5.6)
Arthralgia	13 (15.3)	5 (13.2)	2.1 (-11.1, 15.3)
Gastroenteritis	6 (7.1)	2 (5.3)	1.8 (-7.2, 10.7)
Rhinitis	6 (7.1)	2 (5.3)	1.8 (-7.2, 10.7)
Dizziness	8 (9.4)	3 (7.9)	1.5 (-9.1, 12.1)
Exercise tolerance decreased	3 (3.5)	1 (2.6)	0.9 (-5.5, 7.3)
Musculoskeletal stiffness	3 (3.5)	1 (2.6)	0.9 (-5.5, 7.3)
Paresthesia	3 (3.5)	1 (2.6)	0.9 (-5.5, 7.3)

Preferred Term	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Musculoskeletal pain	32 (37.6)	14 (36.8)	0.8 (-17.7, 19.3)
Abdominal distension	5 (5.9)	2 (5.3)	0.6 (-8.1, 9.3)
Nasal congestion	5 (5.9)	2 (5.3)	0.6 (-8.1, 9.3)
Burning sensation	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Hypoesthesia	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Joint injury	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Neuralgia	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Otitis media	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Rosacea	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Toothache	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Vertigo	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Contusion	6 (7.1)	3 (7.9)	-0.8 (-11.0, 9.3)
Asthma	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Bladder pain	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Epistaxis	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Fungal infection	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Gamma-glutamyltransferase increased	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Infusion site	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Muscle twitching	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Restlessness	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Road traffic accident	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Rotator cuff syndrome	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Sneezing	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Somnolence	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Thermal burn	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Tooth fracture	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Viral infection	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Headache	21 (24.7)	10 (26.3)	-1.6 (-18.3, 15.1)
Flatulence	3 (3.5)	2 (5.3)	-1.7 (-9.8, 6.4)
Limb injury	3 (3.5)	2 (5.3)	-1.7 (-9.8, 6.4)
Migraine	3 (3.5)	2 (5.3)	-1.7 (-9.8, 6.4)
Acne pustular	0	1 (2.6)	-2.6 (-7.7, 2.5)
Application site eczema	0	1 (2.6)	-2.6 (-7.7, 2.5)
Application site pruritus	0	1 (2.6)	-2.6 (-7.7, 2.5)
Application site rash	0	1 (2.6)	-2.6 (-7.7, 2.5)
Atrial fibrillation	0	1 (2.6)	-2.6 (-7.7, 2.5)
Blood iron decreased	0	1 (2.6)	-2.6 (-7.7, 2.5)
Bruxism	0	1 (2.6)	-2.6 (-7.7, 2.5)
Central venous catheterization	0	1 (2.6)	-2.6 (-7.7, 2.5)
Cerebrovascular accident	0	1 (2.6)	-2.6 (-7.7, 2.5)
Conjunctival hemorrhage	0	1 (2.6)	-2.6 (-7.7, 2.5)
Dacryostenosis acquired	0	1 (2.6)	-2.6 (-7.7, 2.5)
Disease progression	0	1 (2.6)	-2.6 (-7.7, 2.5)
Diverticulitis	0	1 (2.6)	-2.6 (-7.7, 2.5)
Dry mouth	0	1 (2.6)	-2.6 (-7.7, 2.5)
Ear infection	0	1 (2.6)	-2.6 (-7.7, 2.5)
Eosinophil count increased	0	1 (2.6)	-2.6 (-7.7, 2.5)
Erectile dysfunction	0	1 (2.6)	-2.6 (-7.7, 2.5)
Eye burns	0	1 (2.6)	-2.6 (-7.7, 2.5)
Feeling hot	0	1 (2.6)	-2.6 (-7.7, 2.5)
Gastritis	0	1 (2.6)	-2.6 (-7.7, 2.5)
Glycogen storage disease type II	0	1 (2.6)	-2.6 (-7.7, 2.5)
Glycosuria	0	1 (2.6)	-2.6 (-7.7, 2.5)

Preferred Term	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Groin abscess	0	1 (2.6)	-2.6 (-7.7, 2.5)
Hematochezia	0	1 (2.6)	-2.6 (-7.7, 2.5)
Herpes simplex	0	1 (2.6)	-2.6 (-7.7, 2.5)
Hordeolum	0	1 (2.6)	-2.6 (-7.7, 2.5)
Hyperthyroidism	0	1 (2.6)	-2.6 (-7.7, 2.5)
Infusion site pruritus	0	1 (2.6)	-2.6 (-7.7, 2.5)
Ingrown hair	0	1 (2.6)	-2.6 (-7.7, 2.5)
Iron deficiency	0	1 (2.6)	-2.6 (-7.7, 2.5)
Irritable bowel syndrome	0	1 (2.6)	-2.6 (-7.7, 2.5)
Joint swelling	0	1 (2.6)	-2.6 (-7.7, 2.5)
Lactose intolerance	0	1 (2.6)	-2.6 (-7.7, 2.5)
Laryngitis	0	1 (2.6)	-2.6 (-7.7, 2.5)
Lower gastrointestinal hemorrhage	0	1 (2.6)	-2.6 (-7.7, 2.5)
Lung cyst	0	1 (2.6)	-2.6 (-7.7, 2.5)
Malignant melanoma	0	1 (2.6)	-2.6 (-7.7, 2.5)
Motion sickness	0	1 (2.6)	-2.6 (-7.7, 2.5)
Nasal dryness	0	1 (2.6)	-2.6 (-7.7, 2.5)
Palpitations	0	1 (2.6)	-2.6 (-7.7, 2.5)
Pelvic fracture	0	1 (2.6)	-2.6 (-7.7, 2.5)
Pharyngeal swelling	0	1 (2.6)	-2.6 (-7.7, 2.5)
Prostatitis	0	1 (2.6)	-2.6 (-7.7, 2.5)
Proteinuria	0	1 (2.6)	-2.6 (-7.7, 2.5)
Sleep apnea syndrome	0	1 (2.6)	-2.6 (-7.7, 2.5)
Spinal compression fracture	0	1 (2.6)	-2.6 (-7.7, 2.5)
Testicular cyst	0	1 (2.6)	-2.6 (-7.7, 2.5)
Throat tightness	0	1 (2.6)	-2.6 (-7.7, 2.5)
Tinel’s sign	0	1 (2.6)	-2.6 (-7.7, 2.5)
Type 2 diabetes mellitus	0	1 (2.6)	-2.6 (-7.7, 2.5)
Vitamin D deficiency	0	1 (2.6)	-2.6 (-7.7, 2.5)
Vitreous floaters	0	1 (2.6)	-2.6 (-7.7, 2.5)
Wisdom teeth removal	0	1 (2.6)	-2.6 (-7.7, 2.5)
Dyspepsia	2 (2.4)	2 (5.3)	-2.9 (-10.7, 4.9)
Groin pain	2 (2.4)	2 (5.3)	-2.9 (-10.7, 4.9)
Panic attack	2 (2.4)	2 (5.3)	-2.9 (-10.7, 4.9)
Sinusitis	4 (4.7)	3 (7.9)	-3.2 (-12.9, 6.5)
Hypertension	6 (7.1)	4 (10.5)	-3.5 (-14.6, 7.7)
Balance disorder	1 (1.2)	2 (5.3)	-4.1 (-11.5, 3.4)
Infusion site bruising	1 (1.2)	2 (5.3)	-4.1 (-11.5, 3.4)
Abdominal pain	9 (10.6)	6 (15.8)	-5.2 (-18.5, 8.1)
Infusion site erythema	0	2 (5.3)	-5.3 (-12.4, 1.8)
Skin lesion	0	2 (5.3)	-5.3 (-12.4, 1.8)
Constipation	2 (2.4)	3 (7.9)	-5.5 (-14.7, 3.6)
Pruritus	2 (2.4)	3 (7.9)	-5.5 (-14.7, 3.6)
Dermatitis	1 (1.2)	3 (7.9)	-6.7 (-15.6, 2.2)
Rash	3 (3.5)	4 (10.5)	-7.0 (-17.5, 3.5)
Infusion site pain	0	3 (7.9)	-7.9 (-16.5, 0.7)
Respiratory tract infection	8 (9.4)	7 (18.4)	-9.0 (-22.8, 4.8)
Nausea	10 (11.8)	8 (21.1)	-9.3 (-23.9, 5.4)
Muscular weakness	3 (3.5)	5 (13.2)	-9.6 (-21.1, 1.8)
Fall	25 (29.4)	15 (39.5)	-10.1 (-28.4, 8.3)

Preferred Term	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Asthenia	9 (10.6)	8 (21.1)	-10.5 (-25.0, 4.1)

Source: adae.xpt; software: R.
Duration is 52 weeks.
Treatment-emergent adverse events defined as those events that were newly occurring or worsening on or after the first dose of study drug.
Coded as Medical Dictionary of Regulatory Activities preferred terms.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: AE, adverse event; CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment arm; n, number of patients with adverse event; qow, every other week

Table 44 shows the AEs according to system organ class based on FDA Medical Dictionary for Regulatory Activities queries. Within these systems, AEs related to hypersensitivity reactions and IARs were prevalent, suggesting that these are related to either cipaglucosidase alfa or to its administration. AEs that may be associated with hypersensitivity reactions include abdominal pain, anxiety, arthralgia, back pain, cough, diarrhea, dizziness, dyspepsia, dyspnea, erythema, fatigue, headache, local administration reactions, myalgia, nausea, paresthesia, peripheral edema, pruritus, pyrexia, rash, syncope, systemic hypertension, tachycardia, tremor, urticaria, and vomiting (see Section 7.7.1). Tremor, an adverse event associated with the approved miglustat (Zavesca), was reported in two patients in the cipa-mig group. One patient had mild tremor of hands during the infusion that resolved after 20 min. The Applicant assessed the event as an infusion-associated reaction. The review team agreed with the assessment of this event. The second patient had mild tremor of the hands, chronologically not associated with the infusion, that resolved in 1 day. The Applicant assessed the event as not related to cipa-mig. The review team disagreed and assessed the event as possibly related to miglustat. No cases of tremor were reported in the comparator group.

Table 44. FDA MedDRA Queries in the Controlled Safety Population, 52 Weeks, ATB200-03

System Organ Class FMQ (Narrow)	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)			
Leukopenia	3 (3.5)	0	3.5 (-0.4, 7.5)
Anemia	1 (1.2)	0	1.2 (-1.1, 3.5)
Cardiac disorders (SOC)			
Tachycardia	4 (4.7)	0	4.7 (0.2, 9.2)
Arrhythmia	5 (5.9)	1 (2.6)	3.3 (-3.9, 10.4)
Myocardial ischemia	1 (1.2)	0	1.2 (-1.1, 3.5)
Systemic hypertension	8 (9.4)	4 (10.5)	-1.1 (-12.7, 10.5)
Palpitations	0	1 (2.6)	-2.6 (-7.7, 2.5)
Ear and labyrinth disorders (SOC)			
Vertigo	2 (2.4)	1 (2.6)	-0.3 (-6.3, 5.7)
Gastrointestinal disorders (SOC)			
Diarrhea	12 (14.1)	4 (10.5)	3.6 (-8.7, 15.8)
Vomiting	5 (5.9)	1 (2.6)	3.3 (-3.9, 10.4)
Dyspepsia	5 (5.9)	3 (7.9)	-2.0 (-11.9, 7.9)
Dry mouth	0	1 (2.6)	-2.6 (-7.7, 2.5)
Abdominal pain	9 (10.6)	6 (15.8)	-5.2 (-18.5, 8.1)
Constipation	2 (2.4)	3 (7.9)	-5.5 (-14.7, 3.6)
Nausea	10 (11.8)	8 (21.1)	-9.3 (-23.9, 5.4)

System Organ Class FMQ (Narrow)	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
General disorders and administration site conditions (SOC)			
Pyrexia	6 (7.1)	1 (2.6)	4.4 (-3.0, 11.9)
Peripheral edema	3 (3.5)	0	3.5 (-0.4, 7.5)
Decreased appetite	1 (1.2)	0	1.2 (-1.1, 3.5)
Fatigue	11 (12.9)	8 (21.1)	-8.1 (-22.9, 6.7)
Local administration reactions	3 (3.5)	6 (15.8)	-12.3 (-24.5, -0.0)
Hepatobiliary disorders (SOC)			
Hepatic injury	1 (1.2)	0	1.2 (-1.1, 3.5)
Immune system disorders (SOC)			
Anaphylactic reaction	1 (1.2)	0	1.2 (-1.1, 3.5)
Infections and infestations (SOC)			
Nasopharyngitis	27 (31.8)	5 (13.2)	18.6 (4.0, 33.2)
Pneumonia	1 (1.2)	0	1.2 (-1.1, 3.5)
Musculoskeletal and connective tissue disorders (SOC)			
Myalgia	17 (20.0)	5 (13.2)	6.8 (-6.9, 20.5)
Arthralgia	13 (15.3)	5 (13.2)	2.1 (-11.1, 15.3)
Arthritis	1 (1.2)	0	1.2 (-1.1, 3.5)
Back pain	10 (11.8)	7 (18.4)	-6.7 (-20.8, 7.4)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)			
Malignancy	0	1 (2.6)	-2.6 (-7.7, 2.5)
Nervous system disorders (SOC)			
Dizziness	12 (14.1)	4 (10.5)	3.6 (-8.7, 15.8)
Dysgeusia	2 (2.4)	0	2.4 (-0.9, 5.6)
Tremor	2 (2.4)	0	2.4 (-0.9, 5.6)
Headache	22 (25.9)	10 (26.3)	-0.4 (-17.2, 16.4)
Paresthesia	6 (7.1)	3 (7.9)	-0.8 (-11.0, 9.3)
Somnolence	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Psychiatric disorders (SOC)			
Insomnia	5 (5.9)	0	5.9 (0.9, 10.9)
Depression	3 (3.5)	0	3.5 (-0.4, 7.5)
Parasomnia	1 (1.2)	0	1.2 (-1.1, 3.5)
Anxiety	5 (5.9)	2 (5.3)	0.6 (-8.1, 9.3)
Sexual dysfunction	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Reproductive system and breast disorders (SOC)			
Abnormal uterine bleeding	2 (2.4)	0	2.4 (-0.9, 5.6)
Excessive menstrual bleeding	1 (1.2)	0	1.2 (-1.1, 3.5)
Erectile dysfunction	0	1 (2.6)	-2.6 (-7.7, 2.5)
Respiratory, thoracic, and mediastinal disorders (SOC)			
Cough	5 (5.9)	0	5.9 (0.9, 10.9)
Dyspnea	6 (7.1)	1 (2.6)	4.4 (-3.0, 11.9)
Bronchospasm	1 (1.2)	1 (2.6)	-1.5 (-7.0, 4.1)
Skin and subcutaneous tissue disorders (SOC)			
Urticaria	2 (2.4)	0	2.4 (-0.9, 5.6)
Erythema	4 (4.7)	2 (5.3)	-0.6 (-9.0, 7.8)
Pruritus	2 (2.4)	4 (10.5)	-8.2 (-18.4, 2.1)
Rash	4 (4.7)	6 (15.8)	-11.1 (-23.5, 1.4)

System Organ Class FMQ (Narrow)	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Vascular disorders (SOC)			
Hemorrhage	15 (17.6)	7 (18.4)	-0.8 (-15.5, 14.0)

Source: adae.xpt; software: R.
Treatment-emergent adverse events defined as those events that were newly occurring or worsening on or after the first dose of study drug.
Duration is 52 weeks.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; qow, every other week; SOC, system organ class

7.6.1.6. Laboratory Findings, ATB200-03

Overall Summary

Routine safety monitoring blood work (hematology, clinical chemistry, creatine kinase, hepatic, and kidney function), and urinalysis were obtained throughout the trial. The mean values for most of these tests remained within expected ranges, and the review team does not feel that any laboratory findings warrant further investigation.

Hematological Analyses

The review team focused on the following hematological bloodwork obtained during this trial: hemoglobin, platelets, leukocytes, and neutrophils. The mean values for hemoglobin, platelets, neutrophils, eosinophils, and lymphocytes remained normal throughout the exposure to cipa-mig.

Liver Function

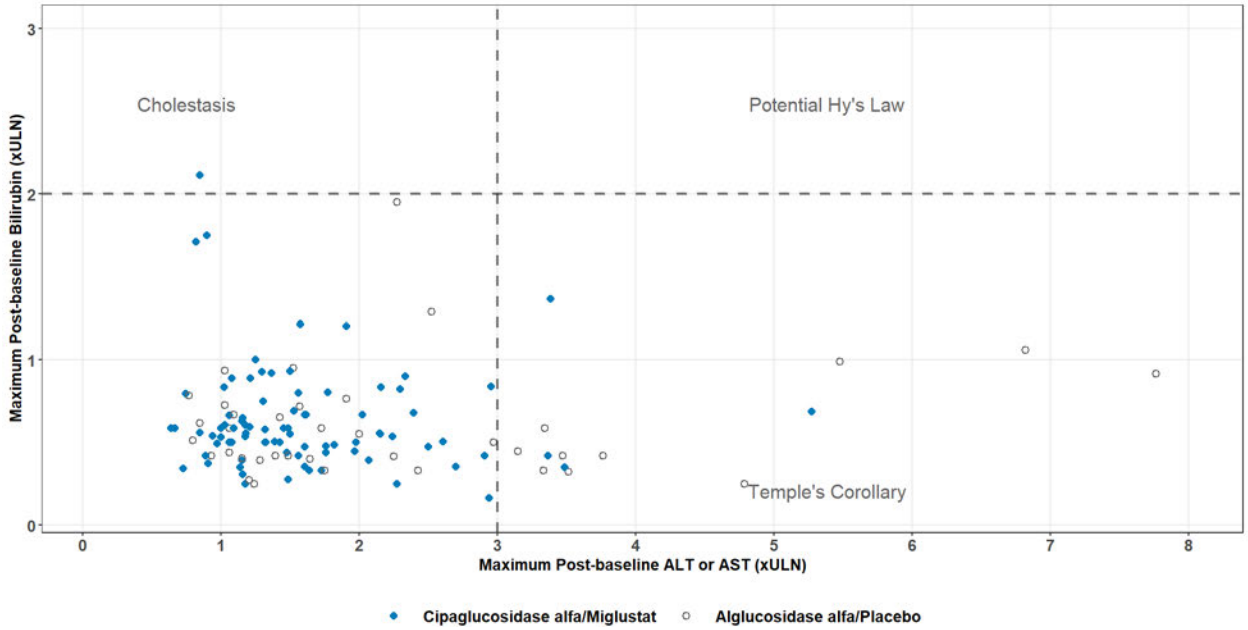
At baseline, 60 patients (70.6%) had AST or ALT above the upper limit of normal. Abnormal liver function at baseline could be reflective of muscle or general hepatocellular damage due to PD pathology (Kishnani et al. 2006). During the course of the ATB200-03 trial, AST and ALT levels decreased in the overall cipa-mig patient population.

Four patients (4.7%) in the cipa-mig group, compared to ten patients (26.3%) in the comparator group, had peak AST or ALT greater than or equal to 3× the upper limit of normal, which placed them in the Temple's Corollary quadrant (Figure 35), and thus at possible increased risk of drug-induced liver injury. No patient was placed in the Hy's Law quadrant. The review team performed additional analyses in those four patients in the cipa-mig group to discern the severity of the elevated liver enzyme levels during the trial. All four patients had abnormal liver enzymes at baseline; the peak level was between three- and five-fold the upper limit of normal, occurred between Day 10 and Day 43 of the trial, and resolved in 2 to 6 days. Three of these patients had normal total bilirubin levels throughout the trial; one patient had a total bilirubin peak level of 1.37 on Day 268, but AST and ALT levels were normal at that time. All four patients continued treatment until completion of the trial, and their liver enzymes normalized (one patient), remained the same (one patient), or were lower than baseline (two patients) at the end of the trial. There were no reported signs of liver failure.

One patient in the cipa-mig group had elevated bilirubin levels (>2× the upper limit of normal), which placed the patient in the cholestasis quadrant (Figure 35). The review team performed additional analysis of this patient to discern the severity of the elevated bilirubin levels during the trial. The patient had normal AST, ALT, and alkaline phosphatase levels from baseline throughout the trial. The patient discontinued the trial for reasons unrelated to liver function (see Section 7.6.1.4). The reason for the biliary disease is not described in the patient narrative, but because the high bilirubin levels were present from baseline and stable during the trial, the review team assessed that the bilirubin levels were not related to the treatment.

The observed elevations of liver enzymes from baseline were temporary, not associated with clinical symptoms of liver injury, not concomitant with elevation of bilirubin levels or other markers of liver failure; therefore, the review team concluded that cipa-mig is unlikely to cause hepatotoxicity.

Figure 35. Drug-Induced Liver Injury Case Screening Plot, Controlled Safety Population, 52 Weeks, ATB200-03



Source: adlb.xpt; software: R.
Each data point represents at least one visit (from a patient) with both ALT/AST and total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after maximum postbaseline ALT or AST ≥3× ULN, without findings of cholestasis (defined as ALP <2× ULN).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Kidney Function

Miglustat is substantially excreted by the kidney (80%) (Janssen 2020). The currently approved label for miglustat recommends monitoring of renal function and dose adjustments in patients with renal impairment. In addition, the Zavesca label recommends that patients with severe renal impairment should not use miglustat. Trials in patients with renal impairment were not conducted for cipa-mig.

Eight patients (9.4%) had a 1.5-fold increase from baseline for creatinine; only one of the eight patients had creatinine levels higher than a 2-fold increase from baseline. This patient's (b) (6) (b) (6) creatinine levels increased from 0.44 to 0.83 mg/dL (still within normal limits) with high

blood urea nitrogen (BUN) levels (28 mg/dL) at Week 38 (Table 45). The patient's creatinine and BUN levels returned to the patient's baseline (0.45 mg/dL and 15 mg/dL, respectively) by the next visit (Week 52, end of the trial). The review team assessed the laboratory findings in this patient as possibly related to treatment with miglustat. For five of the eight patients who had a 1.5-fold increase, the creatinine levels did not return to baseline levels by the end of the trial. For the other two patients, the creatinine levels returned to baseline levels; creatinine levels were within normal limits throughout the trial for these seven patients.

Twenty patients (23.5%) had elevated levels of BUN; however, only two patients had BUN levels higher than 31 mg/dL (level 3, cut-off defined by the CDS based on expert opinion) that decreased by Week 52, although they did not return to baseline. The increase in BUN could be due to dehydration; however, the review team did not observe a correlation with high hematocrit. Creatine kinase was elevated in some of the patients due to Pompe disease, which can also be associated with an increase in BUN levels. The review team assessed the BUN alterations as not clinically significant given that the increase did not lead to an intervention.

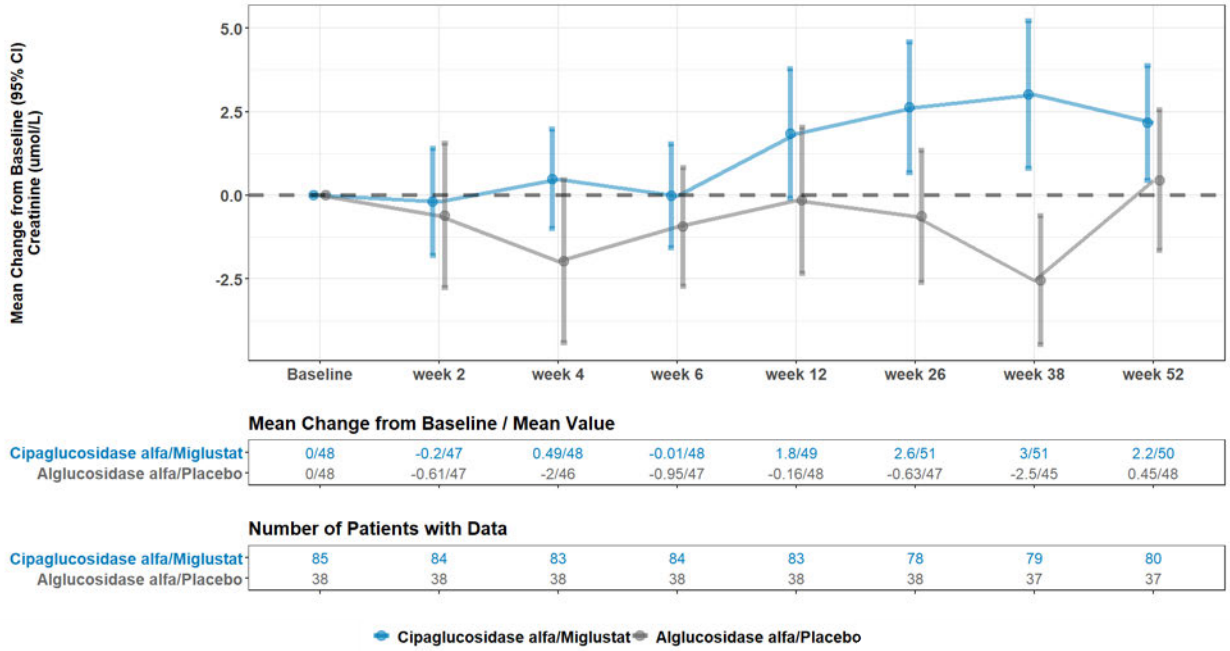
Table 45. Patients With One or More Kidney Function Analyte Values Outside Specified Levels, Controlled Safety Population, 52 Weeks, ATB200-03

Laboratory Parameter	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	20/85 (23.5)	5/38 (13.2)	10.4 (-3.7, 24.4)
Level 2 (>27)	6/85 (7.1)	0/38 (0)	7.1 (1.6, 12.5)
Level 3 (>31)	2/85 (2.4)	0/38 (0)	2.4 (-0.9, 5.6)
Creatinine, high (mg/dL)			
Level 1 (≥1.5× baseline)	8/85 (9.4)	3/38 (7.9)	1.5 (-9.1, 12.1)
Level 2 (≥2× baseline)	1/85 (1.2)	0/38 (0)	1.2 (-1.1, 3.5)
Level 3 (≥3× baseline)	0/85 (0)	0/38 (0)	0 (0,(0)

Source: adlb.xpt; software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 52 weeks.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment arm; n, number of patients meeting criteria

In the cipa-mig group, mean creatinine levels increased 1.8-fold at Week 12. At the end of the trial, the creatinine levels were increased 2.2-fold from baseline, but remained within normal limits. This increase in creatinine from baseline was not observed in the comparator group (Figure 36).

Figure 36. Mean Creatine Level Change From Baseline Over Time, Controlled Safety Population, 52 Weeks, ATB200-03



Source: adlb.xpt; software: R.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: CI, confidence interval

The review team reviewed the available data for the ongoing ATB200-07 trial (78 patients) that showed the mean creatinine and BUN levels decreased over the subsequent 26 weeks of available data. The review team also reviewed the data from the ongoing ATB200-02 trial (29 patients) that showed no significant changes from baseline over time (104 weeks in 23 patients) in the mean creatinine and BUN levels. The review team concluded that the changes in creatinine and BUN levels in ATB200-03 trial described above are possibly related to treatment with miglustat. However, no trend was identified based on data from ATB200-07 and ATB200-02 over a longer duration of exposure to cipa-mig to indicate that miglustat causes renal impairment at the proposed dose.

Electrolyte Trends

Sodium, potassium, chloride, calcium, phosphate, magnesium, bicarbonate, and blood glucose levels were followed throughout the trials. While several patients in the cipa-mig group had test results with abnormally high or low values, these results were not clinically significant in the majority of cases. The electrolyte profile was similar to the profile seen in the comparator group, especially with respect to bicarbonate, calcium, phosphate, and blood glucose (Table 46). The observed differences in electrolytes are discussed below.

Four patients (4.7%) had mild to moderate hyponatremia in the cipa-mig group compared to none in the comparator group; of them, three had low predicted FVC (% predicted less than 50.5%). Fourteen patients (16.5%) had mild hypernatremia, and all patients returned to baseline levels. Six patients presented mild to moderate hypokalemia, but none of those had persisting hypokalemia. Elevated levels of chloride, mostly mild, were observed in 27 (31.8%) patients in the cipa-mig group compared to 7 (18.4%) in the comparator group. Except for four patients in

the cipa-mig group, all other patients had normal levels at the end of the trial. Bicarbonate levels were low in six (7.1%) patients and high in nine (10.6%) patients. The cipa-mig group had a similar proportion of patients with low levels (10.5%), but a higher proportion with elevated levels (23.7%) of bicarbonate. The proportions of higher-than-normal magnesium and calcium levels were similar in the cipa-mig and comparator groups.

Some of these electrolyte changes can be potentially explained by the decline in pulmonary function in patients with LOPD, leading to hypoventilation and carbon dioxide retention, which can result in acute or chronic respiratory acidosis. Respiratory acidosis may cause slight elevations in calcium, bicarbonate, and potassium levels.

Some of the electrolyte changes can be explained as part of the natural history of the disease or caused by concomitant medications; the imbalances were mostly mild, the levels in most patients returned to those at baseline, and the precision of the estimates was lower due to the small sample sizes. Therefore, the review team concluded that the changes in electrolyte levels were likely not related to treatment with cipa-mig.

Table 46. Patients With One or More Chemistry Analyte Values Outside Specified Levels, Controlled Safety Population, 52 Weeks, ATB200-03

Laboratory Parameter	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Sodium, low (mEq/L)			
Level 1 (<134)	4/85 (4.7)	0/38 (0)	4.7 (0.2, 9.2)
Level 2 (<132)	3/85 (3.5)	0/38 (0)	3.5 (-0.4, 7.5)
Level 3 (<125)	0/85 (0)	0/38 (0)	0 (0, 0)
Sodium, high (mEq/L)			
Level 1 (>144)	14/85 (16.5)	2/38 (5.3)	11.2 (0.6, 21.8)
Level 2 (>150)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 3 (>155)	0/85 (0)	0/38 (0)	0 (0, 0)
Potassium, low (mEq/L)			
Level 1 (<3.6)	6/85 (7.1)	0/38 (0)	7.1 (1.6, 12.5)
Level 2 (<3.4)	4/85 (4.7)	0/38 (0)	4.7 (0.2, 9.2)
Level 3 (<3)	0/85 (0)	0/38 (0)	0 (0, 0)
Potassium, high (mEq/L)			
Level 1 (>5.5)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 2 (>6)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 3 (>6.5)	0/85 (0)	0/38 (0)	0 (0, 0)
Chloride, low (mEq/L)			
Level 1 (<95)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 2 (<88)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 3 (<80)	0/85 (0)	0/38 (0)	0 (0, 0)
Chloride, high (mEq/L)			
Level 1 (>108)	27/85 (31.8)	7/38 (18.4)	13.3 (-2.5, 29.2)
Level 2 (>112)	2/85 (2.4)	1/38 (2.6)	-0.3 (-6.3, 5.7)
Level 3 (>115)	2/85 (2.4)	1/38 (2.6)	-0.3 (-6.3, 5.7)
Bicarbonate, low (mEq/L)			
Level 1 (<20)	6/85 (7.1)	4/38 (10.5)	-3.5 (-14.6, 7.7)
Level 2 (<18)	3/85 (3.5)	1/38 (2.6)	0.9 (-5.5, 7.3)
Level 3 (<15)	0/85 (0)	0/38 (0)	0 (0, 0)
Bicarbonate, high (mEq/L)			
Level 1 (NA)	9/85 (10.6)	9/38 (23.7)	-13.1 (-28.1, 1.9)
Level 2 (NA)	9/85 (10.6)	9/38 (23.7)	-13.1 (-28.1, 1.9)
Level 3 (>30)	9/85 (10.6)	9/38 (23.7)	-13.1 (-28.1, 1.9)

Laboratory Parameter	Cipa-Mig N=85 n (%)	Comparator N=38 n (%)	Risk Difference (%) (95% CI)
Glucose, low (mg/dL)			
Level 1 (<70)	19/85 (22.4)	8/38 (21.1)	1.3 (-14.4, 17.0)
Level 2 (<54)	1/85 (1.2)	1/38 (2.6)	-1.5 (-7.0, 4.1)
Level 3 (<40)	0/85 (0)	0/38 (0)	0 (0, 0)
Glucose, high (mg/dL)			
Level 1 (>200)	1/85 (1.2)	1/38 (2.6)	-1.5 (-7.0, 4.1)
Level 2 (>250)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 3 (>500)	0/85 (0)	0/38 (0)	0 (0, 0)
Calcium, low (mg/dL)			
Level 1 (<8.4)	13/85 (15.3)	7/38 (18.4)	-3.1 (-17.6, 11.4)
Level 2 (<8)	5/85 (5.9)	3/38 (7.9)	-2.0 (-11.9, 7.9)
Level 3 (<7.5)	3/85 (3.5)	1/38 (2.6)	0.9 (-5.5, 7.3)
Calcium, high (mg/dL)			
Level 1 (>10.5)	2/85 (2.4)	0/38 (0)	2.4 (-0.9, 5.6)
Level 2 (>11)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 3 (>12)	0/85 (0)	0/38 (0)	0 (0, 0)
Magnesium, low (mg/dL)			
Level 1 (<1.5)	2/85 (2.4)	0/38 (0)	2.4 (-0.9, 5.6)
Level 2 (<1.2)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 3 (<0.9)	0/85 (0)	0/38 (0)	0 (0, 0)
Magnesium, high (mg/dL)			
Level 1 (>2.3)	24/85 (28.2)	12/38 (31.6)	-3.3 (-21.0, 14.3)
Level 2 (>4)	0/85 (0)	0/38 (0)	0 (0, 0)
Level 3 (>7)	0/85 (0)	0/38 (0)	0 (0, 0)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	4/85 (4.7)	1/38 (2.6)	2.1 (-4.7, 8.9)
Level 2 (<2)	2/85 (2.4)	0/38 (0)	2.4 (-0.9, 5.6)
Level 3 (<1.4)	0/85 (0)	0/38 (0)	0 (0, 0)

Source: adlb.xpt; software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide. Levels 2 and 3 are contained in level 1.
Duration is 52 weeks.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow
Abbreviations: CI, confidence interval; cipa-mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment arm; n, number of patients meeting criteria; ULN, upper limit of normal

Electrocardiogram Trends

Refer to Section 7.7.3 for a discussion of electrocardiogram trends.

Vital Signs Trends

Vital signs data were collected at every study visit. No clinically meaningful changes in vital signs were observed over time.

7.6.2. Safety Findings and Concerns, Integrated Summary of Safety (ATB200-02, ATB200-03, and ATB200-07)

7.6.2.1. Overall Treatment-Emergent Adverse Event Summary, Integrated Summary of Safety

During the ATB200-02, ATB200-03, and ATB200-07 trials, 151 patients with LOPD received cipaglucosidase alfa 20 mg/kg coadministered with miglustat 260 mg qow. TEAEs are displayed by prior treatment status (treatment-naïve or treatment-experienced).

Table 47 provides a summary of AEs reported in the ISS. One or more TEAEs were reported by 93% (140/151) of the patients. Of the six patients (4%) who had an AE that led to permanent discontinuation of cipa-mig, four patients' AEs were hypersensitivity reactions assessed by the review team as related to cipa-mig. Refer to Section 7.7.1 for the narratives.

Table 47. Overview of Treatment-Emergent Adverse Events, Safety Population, Integrated Summary of Safety, Pooled ATB200-02, ATB200-03, and ATB200-07

Event Category	Cipa-mig Treatment-Experienced N=117 n (%)	Cipa-mig Treatment-Naïve N=34 n (%)	Cipa-Mig N=151 n (%)
SAE	16 (13.7)	6 (17.6)	22 (14.6)
AE leading to permanent discontinuation of study drug	6 (5.1)	0	6 (4.0)
AE leading to dose modification of study drug	9 (7.7)	6 (17.6)	15 (9.9)
AE leading to interruption of study drug	8 (6.8)	5 (14.7)	13 (8.6)
AE leading to reduction of study drug	1 (0.9)	1 (2.9)	2 (1.3)
AE	108 (92.3)	32 (94.1)	140 (92.7)
Severe	17 (14.5)	3 (8.8)	20 (13.2)
Moderate	41 (35.0)	20 (58.8)	61 (40.4)
Mild	50 (42.7)	9 (26.5)	59 (39.1)

Source: adae.xpt; software: R.
Treatment-emergent adverse events defined as those events that were newly occurring or worsening on or after the first dose of study drug.
Individuals included in this analysis were receiving cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Abbreviations: AE, adverse event; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

In the 120-day safety update, the Applicant reported new SAEs that led to study drug discontinuation in two patients (b) (6) For patient (b) (6), the review team assessed the hypersensitivity reaction as related to cipa-mig. Refer to Section 7.7.1 for the narrative.

7.6.2.2. Deaths, Integrated Summary of Safety

No deaths were reported.

7.6.2.3. Serious Adverse Events, Integrated Summary of Safety

Table 48 lists the 41 SAEs reported in 22 of 151 patients receiving cipa-mig in the ISS. Of the 22 patients who had an SAE, 6 patients (b) (6) (b) (6) had SAEs assessed as hypersensitivities related to cipa-mig by the review team (refer to Section 7.7.1 for the narratives). Pneumonia and urticaria were the only SAEs that occurred in more than one patient.

Table 48. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Integrated Summary of Safety

System Organ Class Preferred Term	Cipa-Mig N=151 n (%)
Cardiac disorders (SOC)	2 (1.3)
Arrhythmia	1 (0.7)
Bradycardia	1 (0.7)
Gastrointestinal disorders (SOC)	1 (0.7)
Abdominal pain	1 (0.7)
Enteritis	1 (0.7)
Vomiting	1 (0.7)
General disorders and administration site conditions (SOC)	2 (1.3)
Chills	1 (0.7)
Pyrexia	1 (0.7)
Immune system disorders (SOC)	1 (0.7)
Anaphylactoid reaction	1 (0.7)
Infections and infestations (SOC)	5 (3.3)
Diverticulitis	1 (0.7)
Lower respiratory tract infection	1 (0.7)
Pneumonia	2 (1.3)
Postoperative wound infection	1 (0.7)
Urinary tract infection	1 (0.7)
COVID-19	1 (0.7)
Viral myositis	1 (0.7)
Injury, poisoning and procedural complications (SOC)	4 (2.6)
Limb injury	1 (0.7)
Traumatic hematoma	1 (0.7)
Contusion	1 (0.7)
Femur fracture	1 (0.7)
Fibula fracture	1 (0.7)
Ilium fracture	1 (0.7)
Skin laceration	1 (0.7)
Tibia fracture	1 (0.7)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.7)
Dupuytren's contracture	1 (0.7)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	1 (0.7)
Diffuse large B-cell lymphoma	1 (0.7)
Nervous system disorders (SOC)	2 (1.3)
Presyncope	1 (0.7)
Syncope	1 (0.7)

System Organ Class Preferred Term	Cipa-Mig N=151 n (%)
Respiratory, thoracic, and mediastinal disorders (SOC)	2 (1.3)
Cough	1 (0.7)
Dyspnea	1 (0.7)
Pharyngeal oedema	1 (0.7)
Wheezing	1 (0.7)
Skin and subcutaneous tissue disorders (SOC)	3 (2.0)
Urticaria	2 (1.3)
Angioedema	1 (0.7)
Surgical and medical procedures (SOC)	2 (1.3)
Femoral hernia repair	1 (0.7)
Removal of internal fixation	1 (0.7)
Vascular disorders (SOC)	4 (2.6)
Flushing	1 (0.7)
Hemorrhage	1 (0.7)
Aortic aneurysm	1 (0.7)
Hypotension	1 (0.7)

Source: adae.xpt; software: R.
Treatment-emergent adverse events defined as those events that were newly occurring or worsening on or after the first dose of study drug.
Individuals included in this analysis were receiving cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Abbreviations: Cipa-mig, cipaglucosidase alfa coadministered with miglustat; COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

The narratives for the seven (7/22) SAEs from ATB200-03 that were assessed as not related to cipa-mig are discussed in Section 7.6.1.3. The narratives for six (6/22) SAEs in the ISS related to cipa-mig that the review team considered hypersensitivity reactions are discussed in Section 7.7.1.

Narratives for SAEs in the other nine (9/22) patients from trials ATB200-02 and ATB200-07:

(b) (6) A 66-year-old male in trial ATB200-02 who was treatment-experienced at enrollment. On an unknown date, the patient had Dupuytren's contracture of digits 1 and 3 of the left hand, with intact blood circulation, motor function, and sensitivity. On Study Day 1324, approximately 3 months after the onset of the Dupuytren's contracture and 7 days after the 90th infusion, the patient had worsening of Dupuytren's contracture and was hospitalized; a resection of the cord formation was performed. The event resolved, and he was discharged 2 days later. No action was taken with study drug as a result of this event. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 56-year-old male in trial ATB200-02 who was treatment-experienced at enrollment. On Study Day 374, 7 days after the 27th infusion, the patient had pneumonia. The patient was hospitalized 5 days after the onset of pneumonia (on Study Day 379) due to worsening dyspnea. He was treated with antibiotics and was discharged 4 days later. The pneumonia resolved 14 days after onset. The study drugs were temporarily interrupted due to the hospitalization, but dosing was resumed on Study Day 395 with the 28th infusion, which was delayed by 2 weeks. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig and related to the subject's underlying condition. The review team agreed with the assessment of this event.

(b) (6) A 51-year-old male in trial ATB200-02 who was treatment-experienced at enrollment. On Study Day 603, the patient was hospitalized for an extirpation of an enlarged, right-side, supraclavicular lymph gland that was later diagnosed as diffuse large B-cell lymphoma; he was discharged from the hospital on the same day. The patient was discontinued from the trial due to the SAE. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) (also (b) (6) due to a study site transfer): A 53-year-old male in trial ATB200-02 who was treatment-experienced at enrollment. On Study Day 433, 14 days after the 31st infusion, the patient had vasovagal syncope. The patient reportedly had ingested several glasses of wine immediately prior to the syncope; he also had concurrent nonserious events of nausea, indigestion, and constipation. He was admitted to the hospital for observation; ECG was normal. He was discharged 1 day after with all events resolved. No action was taken with study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 44-year-old male in trial ATB200-02 who was treatment-experienced at enrollment. On Study Day 528, 6 days after the 38th infusion, the patient bumped his leg when getting out of his car. He developed a large hematoma and swelling in the left lower leg and was admitted to the hospital. He was treated with a bandage and discharged 1 day after. On Study Day 537, the patient's condition deteriorated; he was re-admitted to the hospital, received a blood transfusion, and excision of the left calf hematoma was performed. On Study Day 569, the patient fell and had a skin laceration and hemorrhage in the left-calf injury; he was admitted to hospital for 1 day. The SAEs of traumatic hematoma and traumatic leg injury resolved approximately 9 months after their onset. No action was taken with study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) (also (b) (6) due to a study site transfer): A 63-year-old female in trial ATB200-02 who was treatment-naïve at enrollment. On Study Day 12, 11 days after the first infusion, the patient was admitted to the hospital for a lower respiratory tract infection; chest x-ray showed no evidence of pneumonia, and she was discharged 1 day later. On Study Day 515, 10 days after the 37th infusion, the patient had lower abdominal pain and was admitted to the hospital. She was diagnosed with suspected diverticulitis and treated with enoxaparin, anti-embolism stockings, morphine, and paracetamol. The pain subsided, and the patient was discharged from hospital 2 days after, with the SAEs resolved. On Study Day 934, 11 days after the 66th infusion, the patient was hospitalized due to severe abdominal pain and diagnosed with diverticulitis. She was treated with antibiotics, and analgesics, and venous thromboembolism prophylaxis. She was discharged 1 day later with the event considered resolved. On Study Day 944, 7 days after the 67th infusion, the subject was hospitalized with severe abdominal pain and underwent a left femoral hernia repair. The patient was discharged from the hospital 3 days after onset, with the event resolved. The study drugs were temporarily interrupted. On Study Day 971, 5 days after the 68th infusion, the subject was hospitalized for a suspected postoperative wound infection; the subject was discharged on the same day without medication or concern for any infection, and the event was considered resolved. The investigator and the Applicant assessed the events as serious and unrelated to cipa-mig. The review team agreed with the assessment of these events.

(b) (6) A 74-year-old male in trial ATB200-07 who was treatment-experienced at enrollment in ATB200-03. On Study Day 86, 2 days after the sixth infusion in trial ATB200-07,

the patient had a fibular fracture and tibia fracture of the left leg due to a fall. The patient was hospitalized, and, on the same day, he underwent surgery. The patient was discharged from the hospital 3 days later with the events resolved. The seventh dose of treatment was delayed by 6 weeks (reason not provided), but no other action was taken with the study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 50-year-old male in trial ATB200-07 who was treatment-naïve at enrollment in trial ATB200-03. On Study Day 103, 7 days after the eighth infusion in trial ATB200-07, the subject had COVID-19 infection and moderate fever. On Study Day 108, the patient was admitted to the hospital with fever, cough, and fatigue and was diagnosed with COVID-19-related pneumonia. He was treated with antibiotics and corticosteroids; he was discharged on Study Day 122. The study drug was interrupted due to the SAE, but was reintroduced on Study Day 138. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 30-year-old female in trial ATB200-07 who was treatment-experienced at enrollment in ATB200-03. On Study Day 113, 7 days after the eighth infusion in trial ATB200-07, the patient went to the emergency room with worsening complaints of palpitations with dizziness, near-syncope episode, and dyspnea. She was hospitalized, and an ECG showed sinus tachycardia and nonspecific ST-T changes. On Study Day 115, the patient underwent elective cardiac ablation; she was discharged from the hospital on the next day with the event resolved. No action was taken with the study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

In the 120-day safety update, the Applicant reported five new SAEs in five additional patients; only patient (b) (6) had an SAE (anaphylaxis) related to cipa-mig. Narratives for SAEs from the 120-day Safety Update:

(b) (6) A 51-year-old female in trial ATB200-07 who was treatment-experienced at enrollment in ATB200-03. On Study Day 203, 2 days after the 15th infusion in trial ATB200-07, the patient had pain in his right hip diagnosed as lumbosacral radiculopathy. On Study Day 226, the patient was hospitalized with right hip and inguinal pain in the right upper and inner regions of the femur and was treated with guaifenesin, IV prednisone, and IV metamizole (no information provided on the discharge date). On Study Day 230, the SAE was reported as resolved with sequelae (chronic pain). No action was taken with study drugs. The investigator and the Applicant assessed the events as serious and unrelated to cipa-mig. The review team agreed with the assessment of these events.

(b) (6) A 25-year-old female in trial ATB200-07 who was treatment-experienced at enrollment in ATB200-03. On Study Day 472, 8 days after the 34th infusion, the patient had a car accident with right-lung contusion and traumatic right pneumothorax. The patient was hospitalized for observation and discharged 1 day later. No action was taken with study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) (also (b) (6) due to study site transfer): A 40-year-old male who was treatment-naïve at enrollment in trial ATB200-03. On Study Day 124, 13 days after the 9th infusion in trial ATB200-07, the patient had a grade 3 cholecystitis and grade 3 pancreatitis. The patient was hospitalized for a laparoscopic cholecystectomy and discharged on an unknown date. No action

was taken with study drugs. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 66-year-old male who was treatment-experienced at enrollment in trial ATB200-03. On Study Day 294, 13 days after the ninth infusion in trial ATB200-07, the patient had a hip fracture due to a fall. The patient was hospitalized for observation and discharged 2 days later. The study drugs were temporarily interrupted due to the SAE. The investigator and the Applicant assessed the event as serious and unrelated to cipa-mig. The review team agreed with the assessment of this event.

(b) (6) A 55-year-old male who experienced anaphylaxis definitely related to cipaglucosidase alfa during his fifth dosing with cipa-mig and was discontinued from the trial. See Section 7.6.1.3 for the patient narrative.

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, Integrated Summary of Safety

Six patients who received cipa-mig discontinued participation during the clinical trials due to TEAEs (Table 49). As described in the patient narratives in Section 7.7.1, four patients had hypersensitivity reactions: anaphylaxis (b) (6) urticarial rash (b) (6) anaphylaxis (b) (6) and chills and urticarial rash (b) (6) The review team assessed that the TEAEs for four of those patients (b) (6) were related to cipa-mig, which was consistent with the investigator's assessment. The other two patients (b) (6) discontinued due to SAEs not related to cipa-mig; refer to Section 7.6.2.3 for the patient narratives.

Table 49. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Integrated Summary of Safety, Pooled ATB200-02, ATB200-03, and ATB200-07

System Organ Class Preferred Term	Cipa-Mig N=151 n (%)
Vascular disorders (SOC)	1 (1.2)
Aortic aneurysm	1 (1.2)
General disorders and administration site conditions (SOC)	1 (0.7)
Chills	1 (0.7)
Immune system disorders (SOC)	1 (0.7)
Anaphylactoid reaction	2 (1.4)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	1 (0.7)
Diffuse large B-cell lymphoma	1 (0.7)
Skin and subcutaneous tissue disorders (SOC)	2 (1.4)
Urticaria	2 (1.4)

Source: adae.xpt; software: R.
Treatment-emergent adverse events defined as those events that were newly occurring or worsening on or after the first dose of study drug.
Individuals included in this analysis were receiving cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Per the request of the clinical review team, subject ATB200-03- (b) (6) is reported as discontinued due to AE COVID-19.
Abbreviations: AE, adverse event; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; COVID-19, coronavirus disease-2019; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Integrated Summary of Safety

Table 50 shows the AEs by treatment status and according to the system organ class based on FDA medical query (FMQ). Within these systems, AEs related to hypersensitivity reactions were prevalent, suggesting that these are related to cipaglucosidase alfa or to its administration. AEs that may be associated with hypersensitivity reactions include: tachycardia, diarrhea, nausea, abdominal pain, vomiting, dyspepsia, fatigue, pyrexia, local administration reactions, peripheral edema, angioedema, anaphylactic reaction, myalgia, arthralgia, dizziness, paresthesia, syncope, tremor, dyspnea, cough, bronchospasm, rash, pruritus, erythema, urticaria, and hypotension (see Section 7.7.1). Similar AEs were reported in the ATB200-03 and ISS datasets. The proportion of AEs was slightly higher in the ISS cohort compared to the ATB200-03 only cohort (Table 50); however this likely reflects the longer exposure to cipa-mig in the ISS cohort (up to 210 weeks) compared to the ATB200-03 cohort (52 weeks).

Patients who were treatment-naïve had higher proportions of arrhythmia, diarrhea, nausea, vomiting, dyspepsia, pyrexia, dizziness, pruritus, headache, and hemorrhage in terms of exposure-adjusted event rates.

Table 50. Exposure-Adjusted Treatment-Emergent Adverse Events by System Organ Class and FDA MedDRA Queries (Narrow), Safety Population, Integrated Summary of Safety

	Treatment-Experienced Person-Years =254.1		Treatment-Naïve Person-Years =74.7		Total Person-Years =328.8	
System Organ Class FMQ (Narrow)	N=117 n (%)	E =1823 n (EAER)	N=34 n (%)	E =879 n (EAER)	N=151 n (%)	E =2702 n (EAER)
Blood and lymphatic system disorders (SOC)						
Leukopenia	3 (2.6)	7 (2.8)	1 (2.9)	1 (1.3)	4 (2.6)	8 (2.4)
Thrombocytopenia	0	0	1 (2.9)	1 (1.3)	1 (0.7)	1 (0.3)
Anemia	3 (2.6)	4 (1.6)	0	0	3 (2.0)	4 (1.2)
Cardiac disorders (SOC)						
Systemic hypertension	10 (8.5)	27 (10.6)	8 (23.5)	10 (13.4)	18 (11.9)	37 (11.3)
Tachycardia	6 (5.1)	9 (3.5)	1 (2.9)	7 (9.4)	7 (4.6)	16 (4.9)
Arrhythmia	8 (6.8)	13 (5.1)	2 (5.9)	8 (10.7)	10 (6.6)	21 (6.4)
Myocardial ischemia	1 (0.9)	3 (1.2)	0	0	1 (0.7)	3 (0.9)
Palpitations	1 (0.9)	1 (0.4)	1 (2.9)	1 (1.3)	2 (1.3)	2 (0.6)
Ear and labyrinth disorders (SOC)						
Vertigo	4 (3.4)	5 (2.0)	4 (11.8)	6 (8.0)	8 (5.3)	11 (3.3)
Endocrine disorders (SOC)						
Hypoglycemia	1 (0.9)	2 (0.8)	1 (2.9)	4 (5.4)	2 (1.3)	6 (1.8)
Gastrointestinal disorders (SOC)						
Diarrhea	21 (17.9)	32 (12.6)	10 (29.4)	27 (36.1)	31 (20.5)	59 (17.9)
Abdominal pain	22 (18.8)	51 (20.1)	8 (23.5)	19 (25.4)	30 (19.9)	70 (21.3)
Nausea	25 (21.4)	47 (18.5)	9 (26.5)	31 (41.5)	34 (22.5)	78 (23.7)
Vomiting	8 (6.8)	11 (4.3)	5 (14.7)	14 (18.7)	13 (8.6)	25 (7.6)
Constipation	6 (5.1)	7 (2.8)	2 (5.9)	3 (4.0)	8 (5.3)	10 (3.0)
Dry mouth	1 (0.9)	1 (0.4)	0	0	1 (0.7)	1 (0.3)
Dyspepsia	4 (3.4)	7 (2.8)	3 (8.8)	7 (9.4)	7 (4.6)	14 (4.3)

System Organ Class FMQ (Narrow)	Treatment-Experienced Person-Years =254.1 N=117 n (%)	Treatment-Experienced Person-Years =254.1 E =1823 n (EAER)	Treatment-Naïve Person-Years =74.7 N=34 n (%)	Treatment-Naïve Person-Years =74.7 E =879 n (EAER)	Total Person-Years =328.8 N=151 n (%)	Total Person-Years =328.8 E =2702 n (EAER)
General disorders and administration site conditions (SOC)						
Fatigue	24 (20.5)	59 (23.2)	7 (20.6)	16 (21.4)	31 (20.5)	75 (22.8)
Peripheral oedema	6 (5.1)	9 (3.5)	4 (11.8)	7 (9.4)	10 (6.6)	16 (4.9)
Pyrexia	6 (5.1)	8 (3.1)	9 (26.5)	27 (36.1)	15 (9.9)	35 (10.6)
Decreased appetite	1 (0.9)	1 (0.4)	1 (2.9)	1 (1.3)	2 (1.3)	2 (0.6)
Local administration reactions	10 (8.5)	27 (10.6)	6 (17.6)	8 (10.7)	16 (10.6)	35 (10.6)
Hepatobiliary disorders (SOC)						
Hepatic injury	1 (0.9)	2 (0.8)	0	0	1 (0.7)	2 (0.6)
Immune system disorders (SOC)						
Anaphylactic reaction	1 (0.9)	1 (0.4)	0	0	1 (0.7)	1 (0.3)
Angioedema	2 (1.7)	3 (1.2)	0	0	2 (1.3)	3 (0.9)
Infections and infestations (SOC)						
Nasopharyngitis	41 (35.0)	74 (29.1)	12 (35.3)	26 (34.8)	53 (35.1)	100 (30.4)
Pneumonia	2 (1.7)	5 (2.0)	1 (2.9)	1 (1.3)	3 (2.0)	6 (1.8)
Musculoskeletal and connective tissue disorders (SOC)						
Arthralgia	28 (23.9)	44 (17.3)	7 (20.6)	17 (22.8)	35 (23.2)	61 (18.5)
Arthritis	4 (3.4)	5 (2.0)	0	0	4 (2.6)	5 (1.5)
Back pain	2 (1.7)	2 (0.8)	0	0	2 (1.3)	2 (0.6)
Myalgia	2 (1.7)	3 (1.2)	1 (2.9)	1 (1.3)	3 (2.0)	4 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	1 (0.9)	1 (0.4)	1 (2.9)	1 (1.3)	2 (1.3)	2 (0.6)
Nervous system disorders (SOC)						
Headache	38 (32.5)	122 (48.0)	12 (35.3)	82 (109.8)	50 (33.1)	204 (62.0)
Dizziness	18 (15.4)	41 (16.1)	8 (23.5)	18 (24.1)	26 (17.2)	59 (17.9)
Paresthesia	8 (6.8)	22 (8.7)	5 (14.7)	9 (12.0)	13 (8.6)	31 (9.4)
Tremor	4 (3.4)	5 (2.0)	2 (5.9)	3 (4.0)	6 (4.0)	8 (2.4)
Dysgeusia	1 (0.9)	1 (0.4)	1 (2.9)	4 (5.4)	2 (1.3)	5 (1.5)
Syncope	1 (0.9)	1 (0.4)	1 (2.9)	1 (1.3)	2 (1.3)	2 (0.6)
Somnolence	3 (2.6)	3 (1.2)	0	0	3 (2.0)	3 (0.9)
Psychiatric disorders (SOC)						
Insomnia	5 (4.3)	7 (2.8)	1 (2.9)	1 (1.3)	6 (4.0)	8 (2.4)
Depression	2 (1.7)	2 (0.8)	1 (2.9)	1 (1.3)	3 (2.0)	3 (0.9)
Parasomnia	2 (1.7)	2 (0.8)	0	0	2 (1.3)	2 (0.6)
Anxiety	6 (5.1)	6 (2.4)	3 (8.8)	3 (4.0)	9 (6.0)	9 (2.7)
Sexual dysfunction	1 (0.9)	1 (0.4)	1 (2.9)	1 (1.3)	2 (1.3)	2 (0.6)
Reproductive system and breast disorders (SOC)						
Abnormal uterine bleeding	1 (0.9)	3 (1.2)	2 (5.9)	3 (4.0)	3 (2.0)	6 (1.8)
Excessive menstrual bleeding	1 (0.9)	2 (0.8)	0	0	1 (0.7)	2 (0.6)
Erectile dysfunction	1 (0.9)	1 (0.4)	0	0	1 (0.7)	1 (0.3)

System Organ Class FMQ (Narrow)	Treatment-Experienced Person-Years =254.1 N=117 n (%)	E =1823 n (EAER)	Treatment-Naïve Person-Years =74.7 N=34 n (%)	E =879 n (EAER)	Total Person-Years =328.8 N=151 n (%)	E =2702 n (EAER)
Respiratory, thoracic and mediastinal disorders (SOC)						
Cough	9 (7.7)	12 (4.7)	4 (11.8)	8 (10.7)	13 (8.6)	20 (6.1)
Dyspnea	13 (11.1)	22 (8.7)	3 (8.8)	7 (9.4)	16 (10.6)	29 (8.8)
Bronchospasm	3 (2.6)	5 (2.0)	0	0	3 (2.0)	5 (1.5)
Skin and subcutaneous tissue disorders (SOC)						
Urticaria	7 (6.0)	19 (7.5)	0	0	7 (4.6)	19 (5.8)
Rash	17 (14.5)	44 (17.3)	8 (23.5)	15 (20.1)	25 (16.6)	59 (17.9)
Erythema	4 (3.4)	5 (2.0)	2 (5.9)	5 (6.7)	6 (4.0)	10 (3.0)
Pruritus	6 (5.1)	11 (4.3)	4 (11.8)	8 (10.7)	10 (6.6)	19 (5.8)
Vascular disorders (SOC)						
Hemorrhage	24 (20.5)	53 (20.9)	10 (29.4)	42 (56.2)	34 (22.5)	95 (28.9)
Hypotension	1 (0.9)	1 (0.4)	1 (2.9)	1 (1.3)	2 (1.3)	2 (0.6)

Source: adae.xpt; software: R.
Treatment-emergent adverse events defined as those events that were newly occurring or worsening on or after the first dose of study drug.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Individuals included in this analysis were receiving cipaglucosidase alfa 20 mg/kg + miglustat 260 mg
Abbreviations: Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class, E, number of events, EAER, exposure-adjusted event rate

7.6.2.6. Laboratory Findings, Integrated Summary of Safety

The laboratory findings for the ISS dataset were consistent with those from trial ATB200-03.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Hypersensitivity Reactions (Including Anaphylaxis) and Infusion-Associated Reactions

Issue

There is a risk of hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions (IAR) during treatment with cipaglucosidase alfa. ERTs, as a class, include a boxed warning in labeling for these risks. The Applicant included a boxed warning in the proposed labeling, but the warning does not differentiate IARs and does not provide anaphylaxis management.

Background

Among the patients treated with cipaglucosidase alfa, 22% (33 of 151) experienced hypersensitivity reactions. Exposure-adjusted event rates (EAER) show that hypersensitivity

reactions occurred in the same proportions in patients in the cipa-mig group (EAER: 30) and the comparator group (EAER: 31). In both groups, hypersensitivity was more common in treatment-naïve than in treatment-experienced patients (Table 51). The symptoms that occurred in more than one patient in the cipa-mig group consisted of conjunctivitis, rash, urticaria, pruritus, asthma, flushing, and mouth ulceration. Six patients in the cipa-mig group (6 of 151) had serious hypersensitivity reactions, including three patients who had anaphylaxis; four patients discontinued the study due to the hypersensitivity reactions.

Table 51. Hypersensitivity Reactions, Including Anaphylaxis, Safety Population, Integrated Summary of Safety

Parameter	Cipa-Mig Treatment-Experienced (N=117) n (%)	Cipa-Mig Treatment-Naïve (N=34) n (%)	Comparator* Treatment-Experienced (N=30) n (%)	Comparator* Treatment-Naïve (N=8) n (%)
Hypersensitivity (SMQ)	23(19.7)	10 (29.4)	10 (33.3)	4 (50.0)
Anaphylaxis (SMQ)	3 (2.6)	0	0	0
IAR SAEs	1 (0.8)	2 (5.9)	0	0

Source: adae.xpt; software: R.
Hypersensitivity and anaphylactic events defined as those events coded as standardized MedDRA query (SMQ) narrow and broad terms for anaphylactic reaction and hypersensitivity.
Doses: cipaglucosidase alfa: 20 mg/kg qow, miglustat: 360 mg qow, a non-U.S.-approved alglucosidase alfa product: 20 mg/kg qow.
Abbreviations: Cipa-mig, cipaglucosidase alfa coadministered with miglustat; N, number of patients in treatment arm; n, number of patients with adverse event

Assessment

Anaphylaxis

Based on the review team's assessment of patient narratives, three patients (3%) who received cipa-mig met Sampson's criteria (Sampson et al. 2006) for anaphylaxis: one patient from ATB200-02, one patient from ATB200-03 and one patient from ATB200-07. All three patients were treatment-experienced at enrollment. One patient had anaphylaxis on their first infusion with cipaglucosidase alfa; the other two patients had anaphylaxis after their 14th and 24th infusions. Their symptoms were considered moderate in severity and included hypotension, urticaria, pruritus, erythema, generalized erythematous hives, dyspnea, and flushing. The symptoms in these three patients are described in further detail in the narratives below.

Anaphylaxis Narratives

(b) (6) (also (b) (6) due to a study site transfer): A 23-year-old female in trial ATB200-02 who was treatment-experienced at enrollment. The patient had IARs from the 19th to the 21st infusions; these included fatigue, arthralgia, myalgia, abdominal pain, abdominal cramps, nausea, vomiting, diaphoresis, pallor, and urticarial rash. One hour after starting the 23rd infusion, having received premedication (diphenhydramine), the patient had chills, flushing, hives, shortness of breath, and wheezing. The infusion was discontinued immediately, and the patient was hospitalized and treated with prednisolone; the symptoms resolved 90 min after onset. For the 24th infusion, two premedications were added (IV solumedrol and oral paracetamol), but the patient had cough, shortness of breath, and wheezing 90 min after the infusion. The infusion was interrupted, and the patient was hospitalized and treated with albuterol via nebulizer and IV diphenhydramine; the symptoms resolved after 90 min and the infusion restarted and was completed. The subject continued in the trial with no further serious

hypersensitivity reactions. The investigator and the Applicant assessed the events as serious and definitely related to cipaglucosidase alfa. The review team agreed with the assessment of this event.

The review team sent an information request (December 10, 2021) to clarify why these concomitant AEs were not assessed as anaphylaxis. The Applicant re-evaluated the AEs for this patient and assessed the event as anaphylaxis.

(b) (6) A 44-year-old male in trial ATB200-03 who was treatment-experienced at enrollment. For the first 12 infusions, the patient did not experience any IARs. On the day of the 13th infusion, the patient experienced mild groin pruritus; no action was taken, and the infusion was completed. Fifty minutes after onset of the 14th infusion, the patient experienced pruritus and generalized erythematous raised, hive-like lesions all over their body. The infusion was stopped. The patient then had shortness of breath, dizziness, bradycardia, and hypotension; he was given IV epinephrine and oxygen via nasal canula and was transferred to the ER. At the ER, he was given IV hydrocortisone and diphenhydramine. All his symptoms resolved 49 min after onset of anaphylaxis. He was discharged from the ER, upon personal request, 9 h after onset of the events. The study drugs were permanently discontinued due to withdrawal of consent by the subject. The investigator and the Applicant assessed the event as serious and probably related to cipaglucosidase alfa. The review team agreed with the assessment of this event.

(b) (6) A 65-year-old female in trial ATB200-07 who was ERT treatment-experienced at enrollment into trial ATB200-03. She was treated with the comparator in Study ATB200-03. During the first dose infusion of cipaglucosidase alfa, the patient had urticaria of the upper limbs and trunk and hypotension. The infusion was stopped immediately. The diffuse erythema was predominantly in the arms and stomach and not on the face. There was no respiratory impairment, desaturation, or swelling of the tongue. Treatment included IV dexchlorpheniramine. The patient experienced an episode of hypotension (blood pressure 77/49 mm Hg), with an average blood pressure of 69 mm Hg. The events resolved on the same day of onset. The patient was hospitalized overnight for monitoring. The patient did not receive any further doses of the study drugs and was discontinued from the trial due to these anaphylactic events. The investigator and Applicant assessed the events as serious and related to cipaglucosidase alfa. The review team agreed with the assessment of this event.

In the 120-day safety update, the Applicant reported a new narrative that was assessed by the review team as anaphylaxis:

(b) (6) A 55-year-old male in trial ATB200-07 who was treatment-experienced at enrollment into trial ATB200-03. He was treated with the comparator in Study ATB200-03. The patient received premedications (oral prednisolone and fexofenadine) for all infusions. During the fifth infusion of cipaglucosidase alfa, 55 min after the onset, the patient had systemic rash, edema of the face, dyspnea, heartburn, tachycardia (heart rate 120 bpm), oxygen saturation of 88%, and wheezing. The infusion was interrupted, and the patient was treated with oxygen, IV methylprednisolone, IM epinephrine, procaterol (inhalation), and sodium cromoglicate (inhalation). All the symptoms resolved 2 h after onset. The patient was hospitalized for monitoring and was discharged on the following day. The patient did not receive any further doses of study drug and was discontinued from the trial due to anaphylaxis. The investigator and Applicant assessed the events as serious and definitely related to cipaglucosidase alfa. The review team agreed with the assessment of this event.

The review team sent an information request (December 10, 2021) requesting that the Applicant re-evaluate all infusion associated reactions and hypersensitivity AEs in the ISS using the Sampson criteria. The Applicant assessed the AEs in patients (b) (6) and (b) (6) 1 as anaphylaxis (IR response dated December 17, 2021). The review team sent a follow-up IR (January 5, 2022); the Applicant additionally assessed the AEs in the 120-day safety update data and assessed the AEs in patient (b) (6) as an additional case of anaphylaxis (IR response dated January 13, 2022).

AESI: IARs

Forty-three patients (28.5%) who received cipaglucosidase alfa had 241 IARs. The majority of these were mild to moderate in severity. The symptoms occurring in more than one patient consisted of abdominal distension, abdominal pain, flatulence, vomiting, diarrhea, nausea, chills, pyrexia, chest discomfort, dizziness, headache, dysgeusia, dyspnea, cough, pruritus, urticaria, rash, flushing, tachycardia, increased blood pressure, fatigue, and myalgia. Three (3%) patients had serious IARs—dyspnea, chest pain, tachycardia, increased blood pressure, fever, rash, pruritus, pyrexia, chills, urticaria, and nausea. The narratives are provided below.

AESI: IARs Narratives (SAEs only)

(b) (6) A 48-year-old female in trial ATB200-02 who was treatment-experienced at enrollment. During the third infusion, she developed rash, pruritus, and swollen tongue and hands; the infusion was temporarily interrupted. All subsequent infusions were administered following premedication with IV clemastine and IV hydrocortisone. During the fourth and fifth infusions no IARs occurred. During the sixth infusion, the patient experienced nasopharyngeal edema. During the seventh infusion, the patient experienced urticarial rash. During the eighth infusion, the patient presented urticarial rash in the right forearm, as well as itchy red palms of both hands. The infusion was discontinued immediately, the patient received paracetamol as treatment. One hour after onset, all symptoms resolved, and the infusion was restarted. After restarting the infusion, the urticarial rash reappeared, and the infusion was again stopped. All symptoms resolved and the infusion was restarted. After 1 h, the patient experienced the same symptoms, however the rash was more severe and widespread than the first and second times. The infusion was discontinued. The patient was discharged from the hospital on the same day with all symptoms resolved. The patient discontinued the trial. The investigator and the Applicant assessed the event as serious and probably related to cipaglucosidase alfa. The review team agreed with the assessment of this event.

(b) (6) A 53-year-old male in trial ATB200-02 who was treatment-naïve at enrollment. During the 95th infusion the patient had a low-grade fever. After completion of the 95th infusion (timing not provided), the patient continued to have fever and also had tachypnea, shortness of breath, tachycardia, increased blood pressure, chest pain, and palpitations. He was hospitalized and reported urinary symptoms over the past days; results of urinalysis and urine culture confirmed a urinary tract infection (UTI). He was treated for the fever and UTI, the fever resolved 1 day after onset, he was discharged 2 days after admission. The UTI resolved 11 days after treatment. The patient continued in the trial. The investigator and the Applicant assessed the event of fever and UTI as serious, the fever was assessed as possibly related to cipaglucosidase alfa and the UTI as unrelated to cipa-mig. The review team agreed with the assessment of these events.

(b) (6) (also (b) (6) due to study site transfer): A 24-year-old female in trial ATB200-02 who was treatment-naïve at enrollment. The patient had several nonserious IARs during 11 of the previous infusions including diaphoresis, tachycardia, chest tightness, chills, nausea, dyspnea, and pruritus. Approximately 2 h after starting the 69th infusion, after receiving premedication (paracetamol, cetirizine, and prednisolone), the patient had a presyncope event (lightheadedness) concurrently with mild nausea and chills. The infusion was stopped, and the patient had nausea, drowsiness, pallor, and low temperature (35.8°C), but other vital signs were normal. She was treated with an IV bolus of saline, and all symptoms resolved 25 min after onset. The patient continued in the trial with no further IARs reported. The investigator and the Applicant assessed the event as serious and probably related to cipaglucosidase alfa. The review team agreed with the assessment of this event.

Immunogenicity

Patients experiencing anaphylaxis and severe IARs had high peak ADA titers during treatment with cipa-mig. Of note, all four patients experiencing anaphylaxis were ERT-experienced at enrollment and had relatively high ADA titers before receiving treatment with cipa-mig (Table 52).

Severe IARs were more commonly observed in treatment-naïve patients, whereas anaphylaxis was more commonly observed in treatment-experienced patients, including one case of anaphylaxis to the first dose of cipa-mig. However, given the small number of events, these observations could be due to chance. Notably, ADA titers were elevated both for patients with severe IARs, including two-treatment-naïve patients, and for those with anaphylaxis. We speculate that development of ADA may contribute to IARs in treatment-naïve patients and that preexisting ADA may have contributed to the case of anaphylaxis observed with the first infusion of cipa-mig in a treatment-experienced patient.

Table 52. Summary of Antidrug Antibody Titers in Patients Experiencing SAEs of Analyphlaxis and Severe Infusion-Associated Reaction)

Subject ID	Study	Treatment Status; Trial Arm	Baseline Antibody Titer	Peak Antibody Titer
(b) (6)[a]	ATB200-02	Treatment-experienced; cipa-mig	25,600	409,600
[a]	ATB200-03	Treatment-experienced; cipa-mig	819,200	6,553,600
[a]	ATB200-07	Treatment-experienced; comparator in ATB200-03, cipa-mig in ATB200-07	400	6,400[b]
[a]	ATB200-07	Treatment-experienced; comparator in ATB200-03, cipa-mig in ATB200-07	25,600	102,400[b]
	ATB200-02	Treatment-experienced; cipa-mig	1,638,400	3,276,800
	ATB200-02	Treatment-naïve; cipa-mig	N/A	N/A
	ATB200-02	Treatment-naïve; cipa-mig	400	1,638,400

Source: Applicant's summary of immunogenicity and its relationship with safety report AMC0206-img.pdf.
[a] Patients with anaphylaxis.
[b] Peak titer observed during treatment in study ATB200-03.
Abbreviations: SAE, severe adverse effect

Conclusion

Hypersensitivity reactions (including anaphylaxis) and IARs are known risks with ERTs. The review team recommended changes to the Applicant's proposed boxed warning and to Sections 2 and 5 of the prescribing information to provide more detail on the symptoms of hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions.

7.7.2. Risk to Fetus During Pregnancy and Infant During Lactation

Issue

There are limited data available on the risks of cipaglucosidase alfa or miglustat on maternal and fetal health during pregnancy and on infants through their exposure to breast milk.

Background

Pregnant and lactating women were excluded from clinical trials with cipa-mig. One patient became pregnant during the ATB200-03 trial but had an elective pregnancy termination in the first trimester. Thus, there are no data to evaluate the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes in humans treated with cipa-mig. Additionally, there are no available data on the presence of cipaglucosidase alfa or miglustat in human milk, the effects on the breastfed infant, or the effects on human milk.

The Applicant proposed routine pharmacovigilance (b) (4) (b) (4) for cipa-mig for the treatment of adult patients with LOPD. The proposal was not submitted by the Applicant at the time of our review.

Assessment

Developmental toxicity and maternal and fetal mortality were observed following administration of ATB200/AT2221 to pregnant animals during the period of organogenesis.

In a rabbit study of embryo-fetal development, cipaglucosidase alfa was administered by infusion to pregnant rabbits, at doses of 30, 70, or 175 mg/kg every other day during organogenesis, beginning on gestation day (GD) 7 and ending on GD 19 (a total of seven doses) (N=20 dams/treatment group). One experimental group received only oral miglustat (25 mg/kg) every other day during organogenesis. Another received cipaglucosidase alfa (175 mg/kg) with oral miglustat (25 mg/kg); the latter was administered 30 min prior to infusion every other day beginning during organogenesis. Clusters of great vessel and cardiac malformations were increased in offspring when cipaglucosidase alfa (175 mg/kg) was coadministered with miglustat (25 mg/kg). A NOAEL for the coadministered products was not identified. One fetus treated with miglustat alone (25 mg/kg) and one fetus treated with cipaglucosidase alfa alone (175 mg/kg) each had a similar cluster of great-vessel and cardiac malformations. Whether these were related to cipaglucosidase and miglustat treatments alone is unclear. However, it was judged that coadministration of cipaglucosidase alfa and miglustat was synergistic. Possibly relatedly, under NDA 021348 (Zavesca), daily miglustat administration of doses ≥ 15 mg/kg increased the incidence of additional vessels emanating from the aortic arch. Rabbit maternal mortality was also reported in the Zavesca study.

In a rat study of embryo-fetal development, cipaglucosidase alfa was administered by infusion to pregnant rats, at doses of 70, 150, or 400 mg/kg every other day during organogenesis, beginning on GD 6 and ending on GD 18 (a total of seven doses) (N=22 dams/treatment group). One experimental group received miglustat (60 mg/kg) alone, every other day during organogenesis. One experimental group received cipaglucosidase alfa (400 mg/kg) with oral miglustat (60 mg/kg) every other day during organogenesis. No findings were observed at any dose of cipaglucosidase alfa, with miglustat, or with the coadministered products.

In a pre- and postnatal development study in rats, cipaglucosidase alfa was administered by infusion to pregnant rats, at doses of 70, 150, or 400 mg/kg every other day during pregnancy, beginning on GD 6 through GD 20, with a pause thereafter to permit parturition; then resuming on lactation day (LD) 1 and ending on LD 19. One experimental group received cipglucosidase alfa infusion (400 mg/kg) with oral miglustat (60 mg/kg) every other day during pregnancy and lactation; the latter was administered 30 min prior to ATB200 infusion. One experimental group received oral miglustat (60 mg/kg) alone every other day during pregnancy and lactation. Increases in maternal and fetal mortality were seen at the highest dose of cipglucosidase alfa (400 mg/kg), both alone and when coadministered with miglustat. The NOAEL for cipaglucosidase alfa for maternal and fetal mortality was 150 mg/kg/day.

A lactation study in rats showed minimal excretion of cipaglucosidase alfa in milk, measured 3 h after dosing; the milk:plasma ratio was 0.038. Conversely, miglustat excretion in rat milk, also measured 3 h after dosing, exceeded plasma levels (milk:plasma ratio 1.7). Since miglustat is likely present in breast milk and the use of Zavesca is not recommended during breast feeding, the review team agreed that no lactation study is required for the use of cipa-mig in patients with LOPD at this time and will follow the same recommendations as for Zavesca.

All developmental and reproductive toxicity (DART) studies were of similar design, with doses administered every other day, as compared to every other week in general toxicology studies and clinical studies, in order to ensure drug exposure during critical periods of fertility, pregnancy and lactation in animals. The Pharmacokinetics Subcommittee (PKS) of the Pharmacology and Toxicology Coordinating Committee recommended use of single exposures for margin calculations, because a single coadministration of cipaglucosidase alfa and miglustat could be responsible for the cardiac developmental effects observed in rabbits.

Summary exposure multiples for effects in developmental and reproductive toxicity (DART studies) for cipaglucosidase alfa and miglustat are provided in Table 53 and Table 54, respectively. The maximum recommended human dose (MHRD) of cipaglucosidase alfa is assumed to be 1200 mg (20 mg/kg × 60 kg), while the MHRD for miglustat is 260 mg. Clinical AUC values at the MRHD of cipaglucosidase alfa and miglustat at these doses were assumed to be 1400 µg*h/mL and 20000 ng*h/mL, respectively.

Table 53. Cipaglucosidase Alfa: Summary of DART Study Findings and Margins

Study	Parameter	Dose mg/kg	AUC_{0-24} (µg*h/mL)	Findings	Margin[a]
FEED	$NOAEL_{parental}$[b]	150	7190	-	5.1
	$LOAEL_{parental}$	400	Males: 62950 Females: 38050	Male and female-mediated increases in preimplantation loss	Males: 45 Females:27
EFD_{rat}	$NOAEL_{maternal\ and\ developmental}$	400	29250	-	20.6
EFD_{rabbit}	$NOAEL_{maternal}$	70	3665	-	2.6
	$LOAEL_{maternal\ and\ developmental}$	175	22,550	15 fetuses in 6 litters with great vessel and cardiac malformations, modest maternal toxicity	16.1
PPND[c]	$NOAEL_{maternal}$	150	7190	-	5.1
	$LOAEL_{maternal\ and\ developmental}$	400	29250	Excessive maternal and developmental mortality	20.9

Source: Review team.
[a] Margins calculated from AUC Comparisons
[b] NOAEL exposure derived from study 157387, Embryo-Fetal Development and Toxicokinetic Study for Effects with ATB200 Alone or Coadministered with AT2221 in Rats.
[c] NOAEL and LOAEL exposures derived from study 157387, Embryo-Fetal Development and Toxicokinetic Study for Effects with ATB200 Alone or Coadministered with AT2221 in Rats.
Abbreviations: AT2221, miglustat; ATB200, cipaglucosidase alfa; AUC, area under the curve; DART, developmental and reproductive toxicity; EFD, embryo-fetal development; FEED, fertility and early embryonic development; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

Table 54. Miglustat: Summary of DART Study Findings and Margins

Study	Parameters	Dose mg/kg	AUC_{0-24} (ng·h/mL)	Findings	Margin[a]
FEED[b]	$NOAEL_{parental}$	NA	NA	-	NA
	$LOAEL_{parental}$	60	84,300	Male and female-mediated increase in preimplantation loss	4.2
EFD_{rat}	$NOAEL_{maternal\ and\ developmental}$	60	84,300	-	4.2
EFD_{rabbit}	$NOAEL_{maternal}$	NA	NA	-	NA
	$LOAEL_{maternal\ and\ developmental}$	25	66,100	15 fetuses in 6/18 litters with great vessel and cardiac malformations	3.3
PPND[c]	$NOAEL_{maternal}$	NA	NA	-	NA
	$LOAEL_{maternal\ and\ developmental}$	60	84,300	Excessive maternal and developmental mortality	4.2

Source: Review team.
[a] Margins calculated from AUC Comparisons
[b] LOAEL exposures derived from study 157387, Embryo-Fetal Development and Toxicokinetic Study for Effects with ATB200 Alone or Coadministered with AT2221 in Rats.
[c] NOAEL and LOAEL exposures derived from study 157387, Embryo-Fetal Development and Toxicokinetic Study for Effects with ATB200 Alone or Coadministered with AT2221 in Rats.
Abbreviations: AT2221, miglustat; ATB200, cipaglucosidase alfa; AUC, area under the concentration-time curve; DART, developmental and reproductive toxicity; EFD, embryo-fetal development; FEED, fertility and early embryonic development; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development.

Considered together, the data from rabbits suggest that there is potential significant risk to the fetus following treatment with ABT200/AT2221 at low multiples of the clinical miglustat exposure. Of particular concern, there is no NOAEL for this coadministration of enzyme and chaperone.

Conclusion

The review team concluded that there is a potential significant risk to the fetus during treatment with cipa-mig in pregnant women based on nonclinical findings. Cipa-mig should not be used in pregnancy. Females of reproductive potential should use effective contraception during treatment with cipa-mig and for at least 60 days after the last dose. In addition, lactating females should avoid breastfeeding. The review team recommended adding the risk to the fetus as a Warning and Precaution and changing Sections 8 of the prescribing information to provide details about contraception, pregnancy testing, the risk to the fetus, and the risk to the infant during lactation and breastfeeding. The review team also recommended that the Applicant closely follow-up on pharmacovigilance reporting to capture detailed information on outcomes of any pregnancies; if there is demonstrated use in pregnant patients despite the Warning and Precaution, a future postmarketing requirement (PMR) may be requested.

7.7.3. Risk of Electrocardiogram Changes and Potential for Cardiac Arrhythmias for Miglustat at the Proposed Dosage

Issue

Limited data are available on the risks of miglustat on electrocardiogram changes and potential for cardiac arrhythmias. In the treatment of LOPD, miglustat will be dosed less frequently (every other week) than in Gaucher disease (TID); however, in the treatment of LOPD, each dose of miglustat will be higher, which may result in a higher acute exposure.

Background

Miglustat (Zavesca) is currently approved at a dose of 100 mg three times daily in the United States for the treatment of adult patients with mild to moderate Gaucher disease for whom enzyme replacement therapy is not a therapeutic option. There are currently no known concerns about QTc prolongation, sudden cardiac death, Torsades de Pointes, or other electrocardiogram (ECG) changes at the approved dosage of miglustat (Zavesca) for patients with Gaucher disease, based on the literature and Periodic Benefit-Risk Evaluation from December 15, 2021 (period covered: October 20, 2018, to October 19, 2021). A thorough QT study has not been conducted.

Because of the higher miglustat dose proposed, a lack of dedicated prior QT study for the approved miglustat (Zavesca), and a lack of convincing data from the nonclinical cardiac safety assessment, the review team previously recommended a dedicated QT study with miglustat as the only investigational drug (Meeting Min from October 23, 2020 and April 20, 2020). In addition, the data from the three clinical trials (ATB200-02, ATB200-03, and ATB200-07) offered limited clinical data regarding cardiac effects, because the ECGs were only performed before the miglustat dose was administered; therefore, the data do not provide information about QTc prolongation at the time of peak miglustat concentration.

A thorough QT study is not necessary for cipaglucosidase alfa, because, as a large protein, there is a low likelihood of direct ion channel interactions.

Assessment

The median time to reach maximum concentration (C_{max}) is 3 h for miglustat and its mean half-life is 6 h. Miglustat is not extensively metabolized and is not a known substrate for cytochrome P450 (CYP) enzymes. The steady state C_{max} for miglustat when dosed in patients for Gaucher disease (100 mg three times a day) is reported to be 1920 ng/mL (Zavesca label). The steady-state C_{max} for miglustat when dosed in patients with LOPD at the highest dose (260 mg qow) is 3176 ng/mL, therefore the C_{max} is approximately 50% higher compared to the approved miglustat (Zavesca). It is also noteworthy that miglustat is predominantly excreted by the kidneys, and patients with impaired renal function may be exposed to higher drug levels. However, given that miglustat will be dosed every other week in patients with LOPD, the risk of accumulation appears low.

The nonclinical QTc evaluation includes the results of a human ether-a-go-go related gene (hERG) assay (201027 (b) (4)) and ECGs collected in a 13-week repeat dose toxicity study in cynomolgus monkeys ((b) (4) -423-10). The hERG assay meets several of the best practice criteria (temperature; voltage protocol; concentration verification – though limited positive control data). The results of the Interdisciplinary Review Team for Cardiac Safety Studies analysis of the data were consistent with the Applicant's and showed that miglustat has a low potential to prolong the QT interval by inhibition of the hERG current at the anticipated therapeutic exposures (hERG safety margin >73 – no effect at 1000µM).

The in vivo QTc assessment in cynomolgus monkeys included ECGs collected pre and postdose on days 15 and 85 for each dose group; animals were sedated. The combined C_{max} for female and male cynomolgus monkeys for 100 mg/kg cipaglucosidase alfa and 175 mg/kg miglustat was 16,900 ng/mL. Based on the PK data collected in this study, the exposures at the timing of ECG collection postdose (0.5 to 1 h) covers approximately 5.6-fold the clinical exposure. No consistent increase in heart rate or QTcB was observed in this study when comparing pre to postdose on Days 1 and 71.

A standard 12-lead ECG was performed prior to dosing throughout the clinical trials. ECGs were transmitted to a central ECG core laboratory for a centralized and independent assessment. In the ATB200-03 trial, no patients presented with substantial increases in heart rate, PR interval, or QRS duration. One patient (b) (6) a 65-year-old male, in the treatment group presented with Fridericia's corrected QT interval prolongation (459 ms) at Week 38, which represented a change from the baseline value of 35 ms. This patient had a previous history of incomplete right bundle branch block. In contrast, 11 patients in the comparator group had at least one episode of Fridericia's corrected QT interval prolongation (>450 ms). In the ISS (including the 120-day update data), ECG data did not show clinically meaningful QTc prolongations (for predefined limits) or other ECG changes over time. Fourteen patients (14/151, 9.3%) in the cipa-mig group had a change from baseline in QT interval corrected using Fridericia's formula (QTcF) greater than 30 ms, and no subject experienced a change greater than 60 ms. Ten patients had an absolute QTcF greater than 450 ms; no patient in the cipa-mig had an absolute QTcF greater than 480 ms. No patients developed new right bundle branch block, new left bundle branch block, new myocardial infarction, or new ST segment depression.

Conclusion

The review team concluded that an evaluation of the effects of miglustat on the QTc interval is required as a PMR. See Section 22 for details of the PMR.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Cipaglucosidase Alfa

The recommended dosage regimen for cipaglucosidase alfa is based on an individual patient's actual body weight. The currently available data do not support a need for further therapeutic individualization based on other intrinsic factors.

8.1.1.1. Renal and Hepatic Impairment

No dedicated clinical pharmacology studies have been conducted to assess the impact of renal or hepatic impairment on PK of cipaglucosidase alfa. Intact cipaglucosidase alfa is unlikely to be filtered by the kidneys or excreted in urine. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of therapeutic proteins such as cipaglucosidase alfa.

8.1.2. Miglustat

The recommended dosage regimen of miglustat is based on an individual patient's actual body weight. Miglustat showed similar exposure at the recommended body weight-tiered dosage regimens, 260 mg for patients weighing ≥50 kg and 195 mg for patients weighing ≥40 to <50 kg. See Section 6.1.3 for details.

A dose adjustment is recommended in patients with moderate or severe renal impairment.

8.1.2.1. Hepatic Impairment

No dedicated clinical pharmacology studies have been conducted to assess the impact of hepatic impairment on PK of miglustat.

8.1.2.2. Renal Impairment

The apparent clearance of miglustat decreased with decreasing renal function. The renal impairment study conducted under the Zavesca NDA showed that subjects with moderate to severe renal impairment had a 60% to 70% decrease in miglustat CL/F, compared to subjects with normal renal function or mild renal impairment. For the proposed miglustat dosage regimen in the current NDA, the modeling and simulation estimated that the $AUC_{0\text{-}24h}$ of miglustat increased by 26% and 31% in subjects with moderate (CLcr 30 to 59 mL/min) and severe (CLcr

15 to 29 mL/min) renal impairment, respectively, compared to subjects with normal renal functions or mild renal impairment. See Section 14.4 for details. The recommended dosage of miglustat in patients with moderate or severe renal impairment is shown in Table 55. For patients with mild renal impairment (CLcr 60 to 89 mL/min), the recommended miglustat dosage is the same as for patients with normal renal function.

Table 55. Recommend Miglustat Dosage in Patients With Moderate or Severe Renal Impairment

Parameter	Moderate Renal Impairment (CLcr 30-59 mL/min)	Severe Renal Impairment (CLcr 15-29 mL/min)
Patients weighing ≥50 kg	195 mg	195 mg
Patients weighing ≥40 kg to <50 kg	130 mg	130 mg

Source: Review team.
Abbreviations: CLcr, creatine clearance

8.2. Drug Interactions

8.2.1. Cipaglucosidase Alfa

No specific drug-drug interaction studies were conducted with cipaglucosidase alfa.

8.2.2. Miglustat

Based on previous in vitro studies under the Zavesca NDA, miglustat does not inhibit CYP enzymes, including CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A11. We recommend the Applicant conduct a postmarketing study to further evaluate whether miglustat is a substrate, inhibitor, or inducer of metabolizing enzymes and transporters as outlined in the FDA guidance for industry *In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (FDA 2020).

8.3. Plans for Pediatric Drug Development

8.3.1. Cipaglucosidase Alfa Coadministered With Miglustat

Cipa-mig was granted orphan-drug designation in September 2017 for the treatment of patients with a confirmed diagnosis of Pompe disease. (b) (4)

[redacted]

Nonclinical

Nonclinical safety for pediatric patients was evaluated in repeat-dose toxicity studies conducted in juvenile rats for 10 weeks treated with cipa-mig every other day. The final report was submitted to the Agency on May 3, 2021, but has not been reviewed, since this study was not relevant in the context of the Applicant's proposed indication for adults with LOPD.

Clinical

Trial ATB200-04 is an ongoing open-label, phase 3 study of the pharmacokinetics, safety, efficacy, and pharmacodynamics of cipa-mig, in pediatric patients aged 0 to <18 years with LOPD. Safety data in four patients from this trial showed no deaths, discontinuations, IARs or serious adverse events (as of November 15, 2020; data cut-off).

8.4. Pregnancy and Lactation

8.4.1. Cipaglucosidase Alfa

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section 13.

Table 56. Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Labeling Section	Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation
8.1 Pregnancy	In a rabbit embryo-fetal development study, cipaglucosidase alfa-atga (30, 70, or 175 mg/kg) was administered intravenously every other day to pregnant females during organogenesis (Gestation Day (GD) 7 through GD 19). Additional experimental groups received 25 mg/kg oral miglustat alone, or (b) (4) (b) (4) with intravenous cipaglucosidase alfa-atga 175 mg/kg, with the same dosing frequency during organogenesis. Clusters of great vessel and cardiac malformations were increased in offspring of pregnant rabbits treated with (b) (4) of cipaglucosidase alfa-atga and miglustat. A NOAEL for the (b) (4) was not identified. (b) (4) One fetus treated with miglustat alone (25 mg/kg) and one fetus treated with cipaglucosidase alfa-atga alone (175 mg/kg), each showed a similar cluster of these great vessel and cardiac malformations. In a rat embryo-fetal development study, cipaglucosidase alfa-atga (75, 150, or 400 mg/kg) was administered intravenously every other day to pregnant rats during organogenesis (GD 6 through GD 18). Additional experimental groups received 60 mg/kg oral miglustat alone, or (b) (4) with intravenous cipaglucosidase alfa-atga 400 mg/kg, with the same dosing frequency during organogenesis. No evidence of adverse effects was noted in pregnant rats or their offspring in any experimental group. The margin for the NOAEL for cipaglucosidase alfa-atga (400 mg/kg) was 21-fold the POMBILITI MRHD based on plasma AUC exposure. The margin NOAEL for miglustat (60 mg/kg) was 4-fold the Opfolda MRHD based on plasma AUC exposure. In a pre-and post-natal development study in rats, cipaglucosidase alfa-atga (75, 150, or 400 mg/kg) was administered intravenously to pregnant females every other day from GD 6 through GD 18, and from Lactation Day (LD) 1 through LD 19. Additional experimental groups received 60 mg/kg oral miglustat alone, or (b) (4) (b) (4) with intravenous cipaglucosidase alfa-atga 400 mg/kg, with the same dosing frequency during pregnancy and lactation. Maternal and pup mortality were increased with (b) (4) and pup mortality was also increased with cipaglucosidase alfa-atga 400 mg/kg alone. The NOAEL for cipaglucosidase alfa-atga alone is 150 mg/kg (5-fold the POMBILITI MRHD margin). A NOAEL was not identified for the coadministered products, for which LOAEL margins at the MRHD of

Labeling Section	Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation
	POMBILITI and Opfolda were 21-fold and 4-fold, respectively, based on plasma AUC exposure.
8.2 Lactation	Evaluation of milk in rats from the pre- and post-natal development study of cipaglucosidase alfa-atga (b) (4) with miglustat (400 mg/kg and 60 mg/kg, respectively) showed excretion of cipaglucosidase alfa-atga and miglustat in rat milk. In this study, the ratio of cipaglucosidase alfa-atga exposure in rat milk to cipaglucosidase alfa-atga exposure in rat plasma was < 4%, and the ratio of miglustat exposure in rat milk to the miglustat exposure in rat plasma was 1.7.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Carcinogenesis Studies in animals to evaluate the carcinogenic potential of cipaglucosidase alfa-atga have not been conducted. For information on an evaluation of carcinogenicity of miglustat in animals, see the Opfolda Prescribing Information. Mutagenesis Studies to evaluate the mutagenic or genotoxic potential of cipaglucosidase alfa-atga have not been conducted. For information regarding the mutagenesis of miglustat, see the Opfolda Prescribing Information. Impairment of Fertility In a fertility study in rats, cipaglucosidase alfa-atga (75, 150, or 400 mg/kg) was administered intravenously to male and female rats every other day. Dosing in males was initiated 28 days prior to cohabitation with untreated females. Dosing in females was initiated 14 days prior to cohabitation with untreated males and continued through GD 7. Additional experimental groups received 60 mg/kg oral miglustat alone, or (b) (4) with intravenous cipaglucosidase alfa-atga 400 mg/kg, with the same frequency over the same pre-mating interval (males) or pre-mating and pregnancy interval (females). There was no effect on male or female rat fertility in any experimental group. Treatment of male rats with the (b) (4) was associated with increased preimplantation loss that was reversible. Treatment of female rats with the (b) (4) or with miglustat alone, resulted in preimplantation loss; whether this would be reversible if treatment were discontinued prior to cohabitation is unknown. NOAELs were not identified for the (b) (4) in either males or females. The LOAEL margins for these doses represent 21-fold and 4-fold the MRHD of POMBILITI and Opfolda, respectively, based on plasma AUC exposure.

Source: Review team.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; GD, gestation day; LD, lactation day; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PND, postnatal day; MRHD, Maximum recommended human dose

8.4.2. Miglustat

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section 13.

Table 57. Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Labeling Section	Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation
8.1 Pregnancy	In a rabbit embryo-fetal development study, (b) (4) (b) (4) every other day to pregnant females during organogenesis (Gestation Day (GD) 7 through GD 19). Additional experimental groups received (b) (4)

Labeling Section	Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation
	[redacted] with the same dosing frequency during organogenesis. Clusters of great vessel and cardiac malformations were increased in offspring of pregnant rabbits treated with [redacted] of cipaglucosidase alfa-atga and miglustat. A NOAEL for the [redacted] was not identified. [redacted] One fetus treated with miglustat alone (25 mg/kg) and one fetus treated with cipaglucosidase alfa-atga alone (175 mg/kg), each showed a similar cluster of these great vessel and cardiac malformations. In a rat embryo-fetal development study, cipaglucosidase alfa-atga (75, 150, or 400 mg/kg) was administered intravenously every other day to pregnant rats during organogenesis (GD 6 through GD 18). Additional experimental groups received 60 mg/kg oral miglustat alone, or when coadministered with intravenous cipaglucosidase alfa-atga 400 mg/kg, with the same dosing frequency during organogenesis. No evidence of adverse effects was noted in pregnant rats or their offspring in any experimental group. The margin [redacted] the NOAEL for cipaglucosidase alfa-atga (400 mg/kg) was 21-fold the POMBILITI MRHD based on plasma AUC exposure. The margin NOAEL for miglustat (60 mg/kg) was 4-fold the Opfolda MRHD based on plasma AUC exposure. In a pre-and post-natal development study in rats, [redacted] was administered [redacted] to pregnant females every other day from GD 6 through GD 18, and from Lactation Day (LD) 1 through LD 19. Additional experimental groups received [redacted] with the same dosing frequency during pregnancy and lactation. Maternal and pup mortality were increased with the [redacted] and pup mortality was also increased with cipaglucosidase alfa-atga 400 mg/kg alone. The NOAEL for cipaglucosidase alfa-atga alone is 150 mg/kg (5-fold the POMBILITI MRHD margin). A NOAEL was not identified for the [redacted] for which LOAEL margins at the MRHD of POMBILITI and Opfolda were 21-fold and 4-fold, respectively, based on plasma AUC exposure.
8.2 Lactation	Evaluation of milk in rats from the pre- and post-natal development study of miglustat [redacted] with cipaglucosidase alfa-atga (60 mg/kg and 400 mg/kg, respectively) showed excretion of miglustat and cipagluosidase alfa-atga in rat milk. In this study, the ratio of miglustat exposure in rat milk to the miglustat exposure in rat plasma was 1.7, and the ratio of cipaglucosidase alfa-atga exposure in rat milk to the cipaglucosidase alfa-atga exposure in rat plasma was < 4%.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	<u>Carcinogenesis</u> The carcinogenicity of OPFOLDA is based on studies from another miglustat product. Below are findings from the carcinogenicity studies with the other miglustat product. Two-year carcinogenicity studies have been conducted with miglustat in CD-1 mice at oral doses up to 500 mg/kg/day and in Sprague Dawley rats at oral doses up to 180 mg/kg/day. Oral administration of miglustat for 104 weeks produced mucinous adenocarcinomas of the large intestine at 210, 420, and 500 mg/kg/day (about 3, 5, and 6-fold the MRHD dose of OPFOLDA 260 mg, respectively, based on body surface area [BSA]) in male mice and at 420 and 500 mg/kg/day (about 5 and 6-fold the MRHD of OPFOLDA 260 mg, based on BSA) in female mice. The adenocarcinomas were considered rare in CD-1 mice and occurred in the presence of inflammatory and hyperplastic lesions in the large intestine of both males and

Labeling Section	Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation
	females. In rats, oral administration of miglustat for 100 weeks produced increased incidences of interstitial cell adenomas of the testis at 30, 60, and 180 mg/kg/day (about 1, 2, and 4-fold the MRHD of OPFOLDA 260 mg, respectively, based on BSA). Mutagenesis The mutagenicity of OPFOLDA is based on studies from another miglustat product. Below are findings from the carcinogenicity studies with the other miglustat product. Miglustat was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including the bacterial reverse mutation (Ames), chromosomal aberration (in human lymphocytes), gene mutation in mammalian cells (Chinese hamster ovary), and mouse micronucleus assays, in studies with another miglustat product. Impairment of Fertility In a fertility study in rats, oral miglustat (60 mg/kg) was administered alone, or (b) (4) with intravenous cipaglucosidase alfa-atga (400 mg/kg), to male and female rats every other day. Additional experimental groups received intravenous cipaglucosidase alfa-atga alone (75, 150, or 400 mg/kg/day) with the same frequency (b) (4) Dosing in males was initiated 28 days prior to cohabitation with untreated females. Dosing in females was initiated 14 days prior to cohabitation with untreated males and continued through GD 7. There was no effect on male or female rat fertility in any experimental group. Treatment of male rats with the (b) (4) was associated with increased preimplantation loss that was reversible. Treatment of female rats with the (b) (4) or with miglustat alone, resulted in preimplantation loss; whether this would be reversible if treatment were discontinued prior to cohabitation is unknown. (b) (4) The LOAEL margins for these doses represent 4-fold and 21-fold the MRHD of OPFOLDA and Pombiliti, respectively, based on plasma AUC. The impact of OPFOLDA on fertility is based, in part, on studies from another miglustat product. Below are findings from the fertility studies with the other miglustat product. Fertility studies conducted with another miglustat product showed that male rats, given 20 mg/kg/day miglustat (exposure less than that expected for the MRHD of OPFOLDA 260 mg, based on BSA comparisons, mg/m2) by oral gavage, 14 days prior to mating, had decreased spermatogenesis with altered sperm morphology and motility and decreased fertility. Decreased spermatogenesis was reversible following 6 weeks of miglustat withdrawal in this study. A higher dose of 60 mg/kg/day (2 times the MRHD of OPFOLDA, based on BSA comparisons, mg/m2) resulted in seminiferous tubule and testicular atrophy/degeneration. Female rats were given oral miglustat gavage doses of 20, 60, and 180 mg/kg/day beginning 14 days before mating and continuing through gestation in this study. Effects observed at 20 mg/kg/day (systemic exposure less than the human therapeutic systemic exposure, based on BSA comparisons) included decreased corpora lutea, increased post-implantation loss, and decreased live births.

Source: Review team.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; GD, gestation day; LD, lactation day; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PND, postnatal day; MRHD, recommended human dose

9. Product Quality

9.1. Device or Combination Product Considerations

9.1.1. Cipaglucosidase Alfa

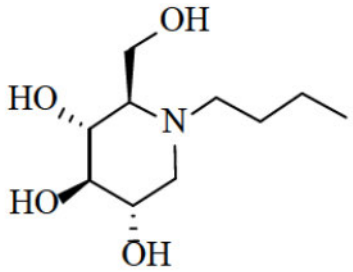
The Office of Pharmaceutical (OPQ), CDER, recommendation on approvability of STN 761204 for Pombiliti manufactured by Amicus Therapeutics US, LLC is pending final determination of the compliance status of WuXi, Biologics, Co., Ltd, WuXi, China (FEI: 3010606982) manufacturing site. From a product quality perspective, the Office of Pharmaceutical Quality, CDER, does not note any product quality deficiencies that would preclude approval of BLA 761204 for Pombiliti manufactured by Amicus Therapeutics US, LLC. at this time. The data and information submitted in this application are adequate to support the conclusion that the manufacture of Pombiliti is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. However, due to restrictions on travel during the ongoing COVID-19 pandemic, the pre-approval inspection (PAI) of the drug substance and drug product manufacturing facility WuXi, Biologics, Co., Ltd, China (FEI: 3010606982) cannot be conducted by the time of finalizing this memorandum. The outcome of the facility inspection will be documented in a future addendum. The chemistry, manufacturing, and controls postmarketing commitments between OPQ and the Applicant listed in Section 22 Postmarketing Requirements and Commitments will be included in the action letter if approval is recommended.

9.1.2. Miglustat Capsules, 65mg

Drug Substance:

The drug substance, miglustat is an N-alkylated iminosugar and a synthetic analog of D-glucose. It is a glucosylceramide synthase inhibitor which was first approved on July 31,2003 as the active ingredient of ZAVESCA (NDA 021348). Miglustat is a white to off-white solid which is readily soluble in water, soluble in methanol but insoluble in n-heptane, dichloromethane, and ethyl acetate.

Miglustat has the chemical name of (2R,3R,4R,5S)-1-butyl-2-(hydroxymethyl)piperidine-3,4,5-triol, a molecular formula of $C_{10}H_{21}NO_4$, a molecular weight of 219.28 and the chemical structure below:



Miglustat for this application is manufactured in accordance with current Good Manufacturing Process (cGMP) requirements [redacted] It is tested, released and accepted against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest period. The description of the manufacturing process for the miglustat manufactured [redacted] is provided in DMF [redacted] The description of the manufacturing process for the miglustat manufactured by [redacted] is provided in DMF [redacted]. Both DMF have been reviewed and found adequate.

Drug Product:

Each Opfolda is a size 2 hard gelatin capsule that contains 65mg of miglustat as the active ingredient and microcrystalline cellulose, starch (pregelatinized maize), sucralose, magnesium stearate, and colloidal silicone dioxide as inactive ingredients. The inactive ingredients including components of the hard gelatin capsule shells are all compendial materials. Iron oxide is used [redacted] The total iron content of each capsule is below the 5mg daily consumption by the patients per 21 CFR 73.1200 (c). The amounts of excipients used as the components of the drug product are below the currently approved limits listed in IID.

Opfolda capsules are manufactured [redacted] in accordance with cGMP requirements, packaged in HDPE bottles with child-resistant caps, and tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its expiration period of 24 months for 4-count and 100-count capsules packaging configuration and 36 months for 24-count capsules packaging configuration. Adequate stability data that supports the proposed expiration dating periods have been submitted to the application.

OPQ Recommendation:

The Applicant of this 505(b)(1) new drug application has provided sufficient CMC (chemistry, manufacturing, and controls) information to assure the identity, strength, purity, and quality of the drug substance, miglustat and the drug product, Opfolda (miglustat) Capsules, 65mg.

The Office Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.

The CMC issues on labels/labeling have been satisfactorily resolved.

The Applicant's request for the categorical exclusion from the preparation of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for approval with the expiration dating period of 24 months for 4-count and 100-count capsules packaging configurations and 36 months for 24-count capsules packaging configuration.

9.2. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Human Subjects Protections

As stated by the Applicant, the clinical trials were conducted in substantial conformance with International Council for Harmonisation good clinical practice requirements and with applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research. All studies submitted in this application were conducted according to FDA requirements, under investigational new drug 127387.

Clinical Site Inspections

FDA clinical site inspections were performed on-site at one site within the United States and at two sites remotely in Australia (refer to Section 20 for details).

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance *Financial Disclosure by Clinical Investigators*[1] (FDA 2013) (see Section 23), and by 21 Code of Federal Regulations 54.4. None of the investigators of the three studies were employed by the Applicant; five investigators disclosed financial interests with the Applicant that did not raise concerns for bias on the covered clinical studies results. In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not held for this application. It did not raise challenging efficacy or safety issues that needed external input.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

III. Appendices

12. Summary of Regulatory History

The Applicant, Amicus Therapeutics US, LLC (Amicus), doing business under their investigational new drug application (IND) as Amicus Therapeutics, Inc., has developed cipaglucosidase alfa (company code ATB200) coadministered with miglustat (company code AT2221) for the treatment of Pompe disease. Cipaglucosidase alfa is a second-generation recombinant human acid α-glucosidase (rhGAA) enzyme replacement therapy (ERT). Cipaglucosidase alfa is intended to be coadministered with an oral small molecule pharmacological chaperone, miglustat. Cipaglucosidase alfa coadministered with miglustat (referred to throughout the remainder of this document as cipa-mig) [redacted (b) (4)] was submitted as two separate marketing applications with each product intended to be labeled for use only in combination/coadministration with the other.

The first interaction between Amicus and the FDA regarding their development program for cipa-mig was during a Pre-IND meeting held on October 6, 2015. In that meeting, the FDA advised Amicus that both cipaglucosidase alfa and miglustat were considered active ingredients. Therefore, the proposed product, [redacted (b) (4)] would be considered a fixed combination drug product (FCDP) and each component would need to meet the regulatory requirements under 21 CFR §300.50(a) (i.e., the "combination rule"). The FDA advised that the clinical development program would need to independently demonstrate the efficacy and safety of cipaglucosidase alfa [redacted (b) (4)] and also demonstrate that miglustat enhanced the safety or effectiveness of cipaglucosidase alfa in the proposed patient population. The minutes for the Pre-IND meeting were issued on October 15, 2015.

Amicus submitted IND 127387 on November 20, 2015, which contained the protocol titled "An Open-label, Ascending-Dose, First-in-Human Study to Assess the Safety, Tolerability, and Pharmacokinetics of Intravenous Infusions of ATB200 Alone and ATB200 Coadministered with Oral AT2221 in Adult Subjects with Pompe Disease Who Were Previously Treated with Alglucosidase Alfa." A Study May Proceed letter was issued on December 31, 2015.

On March 4, 2016, Amicus Therapeutics submitted a meeting request to discuss their proposed plan for a cipaglucosidase alfa scale-up [redacted (b) (4)] and nonclinical and clinical pharmacology plans. The FDA issued written response on May 13, 2016.

On August 8, 2017, Amicus submitted a request for preliminary breakthrough therapy designation advice for cipa-mig. A teleconference between the FDA and Amicus took place on October 25, 2017, wherein the FDA advised Amicus that additional information would be needed for a breakthrough therapy designation request (BTDR). Additional FDA recommendations on the BTDR data were provided in an advice letter issued on November 13, 2017.

Amicus received orphan drug designation for cipa-mig for the treatment of Pompe disease on September 13, 2017.

Also on September 13, 2017, Amicus requested for a follow-up meeting to discuss its proposed plan for Development & Reproductive Toxicology (DART) studies and manufacturing scale-up of cipaglucosidase alfa production process to the (b) (4) L scale. The meeting was scheduled to take place on November 21, 2017. The FDA provided preliminary comments on November 17, 2017. After reviewing the preliminary comments, on November 20, 2017, Amicus cancelled the meeting.

On December 4, 2017, Amicus submitted a BTDR for cipa-mig. The FDA determined that the submitted clinical data did not support the criteria for a breakthrough therapy designation and issued a denied letter on February 2, 2018.

In an email on December 21, 2017, the FDA clarified that although the carcinogenicity studies are not needed for an ERT such as cipaglucosidase alfa, they are required for cipa-mig or miglustat alone. The FDA also advised that Amicus could consider obtaining right of reference for the commercially approved miglustat product to address these requirements.

On December 21, 2017, Amicus submitted a meeting request to obtain FDA feedback on a synopsis of their proposed pivotal clinical trial for cipa-mig, study ATB-003 titled "A Phase 3 Double-blind Randomized Study to Assess the Efficacy and Safety of Intravenous ATB200 Coadministered with Oral AT2221 in Adult Subjects with Late-Onset Pompe Disease Compared with Alglucosidase Alfa/Placebo Capsule." The FDA issued a written response on April 4, 2018. Additional clarification comments were provided during an informal teleconference with Amicus on April 5, 2018. On June 4, 2018, Amicus submitted a full protocol for study ATB200-03.

A type C meeting took place on July 16, 2018, to further discuss study ATB200-03 and Amicus' proposed plan to seek an approval for cipa-mig via the accelerated approval pathway. The FDA stated it did not have enough information on the proposed surrogate endpoint to make definitive comments but that it appeared that it would be most appropriate to demonstrate efficacy on an endpoint of known clinical meaningfulness. The FDA reiterated recommendations that Amicus demonstrate the efficacy of cipaglucosidase alfa by itself in addition to a demonstration of the contribution of miglustat to clinical efficacy when combined with cipaglucosidase alfa. In this meeting, Amicus informed the FDA that they (b) (4) intended to configure cipaglucosidase alfa and miglustat as two individual products that would be distributed separately, and that it intended to label each product specifically for use in coadministration with the other. The meeting minutes were issued on August 14, 2018.

Amicus submitted non-clinical study reports on July 3, 2018, and August 22, 2018, in support of their plan to not conduct cipaglucosidase alfa-only arm in the ATB200-03 clinical trial. On August 23, 2018, Amicus submitted a meeting request to continue the discussion their proposed ATB200-03 trial design. Based on the review of the non-clinical reports, the FDA issued an advice letter on August 28, 2018, which provided comments on design elements for trial ATB200-03 and stated that FDA's preliminary review of the non-clinical study reports suggested an AT200-only arm might not be necessary. In response, on September 26, 2018, Amicus updated their September 14, 2021, meeting background package with a revised protocol for ATB200-03. A type C meeting took place on October 30, 2018, with FDA providing comments on the clinical outcomes assessments endpoints, inclusion criteria, patient enrollment from 12 to 18 years of age, primary analysis, long-term effect of miglustat, immunogenicity, pharmacokinetic (PK) sampling, and product quality. Meeting minutes issued on November 15,

2018. Subsequent revisions of protocol ATB200-03 were received on November 2, 2018, February 1, 2019, and September 1, 2020.

On December 21, 2018, Amicus submitted a new BTDR. Cipa-mig was granted a breakthrough therapy designation for the treatment of late-onset Pompe disease (LOPD) on February 20, 2019.

On April 3, 2019, Amicus submitted protocols ATB200-04 titled "An Open-label Study of Pharmacokinetics, Safety, Efficacy, and Pharmacodynamics of ATB200/AT2221 in Pediatric Subjects Aged 12 to <18 Years with Late-onset Pompe Disease (Study ATB200-04)" and ATB200-07 titled "A Phase 3 Open-label Extension Study to Assess the Long-term Safety and Efficacy of Intravenous ATB200 Coadministered With Oral AT2221 in Adult Subjects With Late-onset Pompe Disease." (b) (4) A revised protocol for ATB200-07 was received on October 22, 2020. Protocol revisions for ATB200-04 were received on November 20, 2019, October 22, 2020, May 3, 2021, and September 30, 2021.

On May 14, 2019, the FDA issued type C written responses pertaining to Amicus' proposed preclinical study design and provided comments on the generation of toxicology data to support clinical trials of cipa-mig (b) (4)

An initial comprehensive multidisciplinary breakthrough therapy meeting took place on November 12, 2019, and included a discussion on Amicus' proposed alternative analysis plan (b) (4) The FDA stated its concerns (b) (4) (b) (4) and advised that evidence from ATB200-03 should serve as the primary basis for regulatory decision-making. Other advice was given on the Biopharmaceutics Classification System (BCS), bioavailability study (b) (4) The meeting minutes were issued on November 20, 2019.

(b) (4)

On February 24, 2020, Amicus requested a type C meeting to discuss the filing strategies for their future marketing applications, and included a request for a rolling review. Amicus also informed the FDA that they had obtained the right of reference for Zavesca (miglustat) capsules, an approved drug for the treatment of adult patients with type 1 Gaucher disease (NDA 021348, Actelion Pharmaceuticals US, Inc.). Therefore, Amicus stated its intent to submit its NDA for miglustat under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) and its original BLA for cipaglucosidase under section 351(a) of the Public Health Service Act (PHS Act). The FDA provided preliminary meeting comments and granted the requested rolling review on April 30, 2020. Amicus considered the FDA's preliminary comments satisfactory and on May 1, 2020, requested that the meeting be cancelled.

The Statistical Analysis Plan (SAP) for study ATB200-03 was submitted for FDA comments on March 2, 2020. The FDA provided comments on the SAP in advice letters issued on May 20,

2020, December 11, 2020, and February 22, 2021. Revised versions of the SAP were received on October 19, 2020, and on January 19, 2021.

(b) (4)

On November 9, 2020, the FDA issued an advice letter confirming that, based on Amicus' prior statements (b) (4)

A type B, pre-marketing meeting teleconference to discuss the CMC modules of the forthcoming BLA and NDA took place on November 10, 2020. The meeting minutes were issued on December 10, 2020.

A type B, pre-marketing meeting teleconference to discuss the clinical data package took place on April 20, 2021. The FDA noted that the primary analysis results of the primary endpoint from study ATB200-03 did not reach statistical significance (p-value>0.05) and therefore the data might not suffice to support efficacy for cipa-mig. Other potential review issues discussed included efficacy endpoints, (b) (4)

(b) (4) and the risk evaluation and mitigation strategy. The FDA also agreed to the Applicant's plan to conduct the QTc study as a postmarketing requirement (PMR). The meeting minutes were issued on April 27, 2021.

The marketing application for cipaglucosidase alfa, BLA 761204, was received as a three part rolling submission: the non-clinical module was received on November 20, 2020, the clinical module was received on June 30, 2021, and the quality module, additional clinical information, and other required application information were received on July 29, 2021, thereby completing the application. BLA 761204 received a standard review classification and was filed under section 351(a) of the PHS Act on September 27, 2021.

The marketing application for miglustat, NDA 215211, was received on July 29, 2021. On October 28, 2021, Amicus submitted a letter of authorization and right of reference from Janssen Research & Development, LLC, on behalf of Actelion Pharmaceuticals, Ltd., to allow for the incorporation by reference of modules 2, 4, and 5, and all other submissions containing safety reports, from NDA 021348 Zavesca (miglustat) into Amicus' NDA 215211. Therefore, NDA 215211 received a standard review classification and was filed under section 505(b)(1) of the FDCA on September 27, 2021.

On August 3, 2021, Amicus submitted proposed proprietary name requests for Opfolda for miglustat and Pombiliti for cipaglucosidase alfa, which were both found conditionally acceptable on October 29, 2021. In addition, on August 27, 2021, Amicus submitted to BLA 761204 a proposed nonproprietary name suffix for cipaglucosidase alfa. The proposed nonproprietary name cipaglucosidase alfa-atga was found conditionally acceptable on January 28, 2022. Because both cipaglucosidase alfa and miglustat are intended to be coadministered with each other and therefore are to be labeled only for use with each other, the Division of Rare Diseases and Medical Genetics (DRDMG) determined to conduct the review for BLA 761204 and NDA 215211 in parallel with the intent of taking an eventual concurrent action on both applications.

The mid-cycle communication was held between Amicus and FDA on February 1, 2022, during which the review issue of the primary endpoint in trial ATB200-03 not having reached statistical significance for superiority on the primary endpoint of 6-minute walk distance (6MWD) was discussed. Minutes for the mid-cycle communication were issued on February 7, 2022. Labeling negotiations for both BLA 761204 and NDA 215211 were opened on April 6, 2022, and the late-cycle meeting was held on April 7, 2022. During the late cycle meeting, the FDA discussed its recommendation that cipa-mig be indicated as a second-line therapy because of the lack of statistical significance for superiority over available enzyme replacement therapy since the applications are for the coadministration of two products when treatment with a single product is available. Nonclinical data pertaining to the use of the cipa-mig in pregnancy and women of reproductive potential was also discussed, as well as potential postmarketing requirements. Late cycle meeting minutes were issued on April 26, 2022. On April 29, 2022, Amicus submitted a major amendment to BLA 761204, and on May 4, 2022, Amicus submitted a major amendment to NDA 215211. On May 9, 2022, The FDA informed Amicus that the user fee goal date was being extended by three months for each application due to the major amendments.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

In Vitro Studies

ATB200/AT2221: Stabilization of ATB200 and Alglucosidase Alfa by Miglustat (AT2221) (Study #RRB200-010).

The study objective was to show that rhGAA, which is unstable in blood at physiological pH 7.4, can acquire improved thermal stability in the presence of Miglustat (N-butyldeoxynojirimycin; AT2221), a small molecule pharmacological chaperone that binds ATB200.

Methods

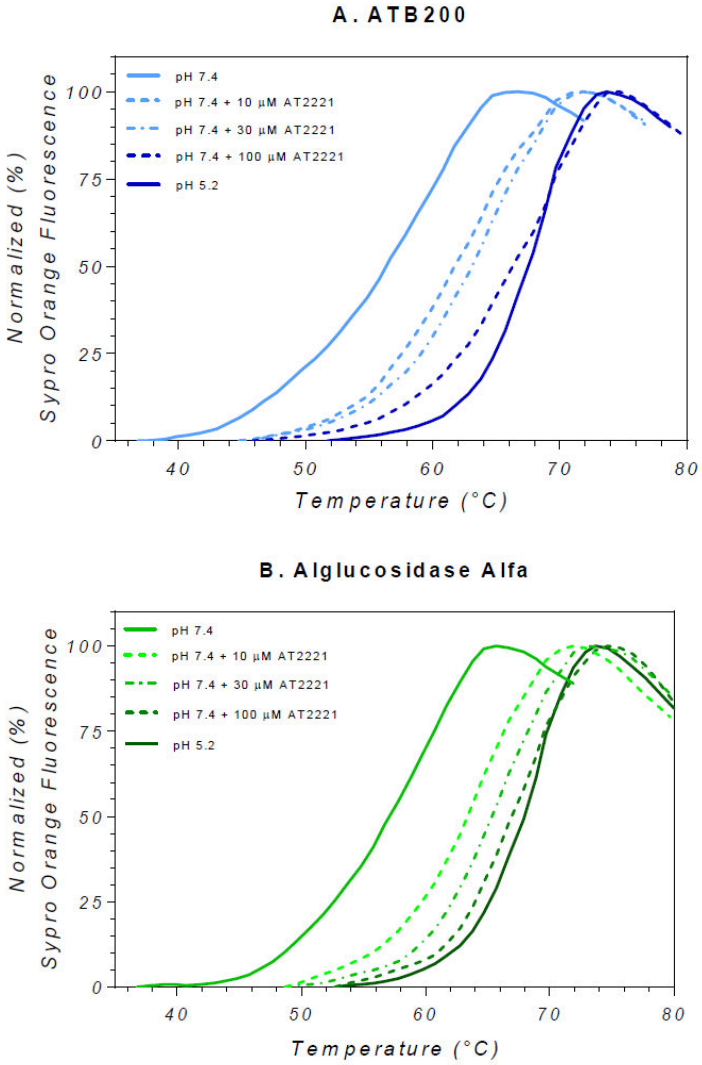
The thermal stability of ATB200 was measured by using a thermal gradient to determine the melting temperature of the protein. A modified fluorescence thermal stability assay using SYPRO orange to bind the exposed hydrophobic regions of unfolded proteins was used.

ATB200 (3 µg) or alglucosidase alfa (reference compound) were mixed with SYPRO orange in either an acidic (pH 5.2) or physiological (pH 7.4) media buffers containing either 0, 10, 30, or 100µM of miglustat (AT2221). The samples were subjected to a temperature gradient from 25 to 90 ^{o}C with a 1 ^{o}C increase per minute and the fluorescence signal recorded at each time point.

Results

The addition of miglustat, AT2221 stabilized ATB200 (Figure) and alglucosidase alfa (Figure) at pH 7.4 in a concentration-dependent manner. At 100µM AT2221, the protein stability of rhGAA at pH 7.4 was similar to its stability at pH 5.2 without the chaperone. The calculated melting temperature values are shown in Table 58 below.

Figure 37. AT2221 Stabilizes rhGAA at pH 7.4



Source: Applicant's figure from Pharmacology study RRB200-010, page 12.
Thermal stability assay data of ATB200 (A) and alglucosidase alfa (B) in the absence and presence of AT2221.
Unfolding/denaturation of ATB200 was monitored by the increase in SYPRO Orange fluorescence as a function of temperature.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; pH, potential of hydrogen

Table 58. Melting Temperatures of rhGAA

Buffer	Melting Temperatures (°C)	
	Alglucosidase Alfa	ATB200
pH 7.4	56.7	56.2
pH 7.4 + 10 µM AT2221	62.9	61.6
pH 7.4 + 30 µM AT2221	64.9	62.9
pH 7.4 + 100 µM AT2221	66.5	66.0
pH 5.2	67.4	67.3

Source: Applicant's table from Pharmacology study RRB200-010, page 13.
At physiological pH, ATB200 was significantly less stable (Tm =56.2°C) than at acidic pH 5.2 (Tm =67.3°C). Co-incubation of ATB200 with AT2221 at pH 7.4 resulted in a concentration-dependent stabilization of ATB200, with 100 µM AT2221 yielding a Tm close to that of enzyme alone at acidic pH.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; pH, potential of hydrogen

It was shown that the glucosidase enzymes, ATB200 and alglucosidase alfa are both less stable in physiological pH of 7.4, with a melting temperature of 56.7 and 56.2, respectively. However, the chaperone molecule, miglustat or AT2221 (10, 30 and 100µM) dose-dependently stabilized ATB200 or alglucosidase alfa with melting temperatures of 66.5 and 66.0, respectively, at pH 7.4, approaching their stability in the acidic environment of the lysosome.

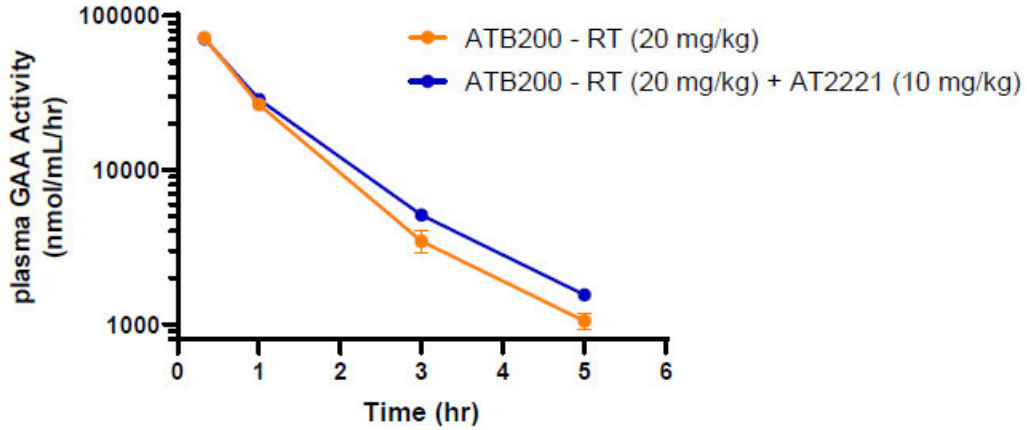
In conclusion, miglustat (AT2221) increased the stability of ATB200 at pH 7.4 (similar to blood pH), suggesting that AT2221 may protect rhGAA from irreversible unfolding and denaturation before its internalization to the acidic environment of the lysosome.

Study Number RRB200-056 (ATB200/AT2221: Pharmacokinetics and Glycogen reduction of ATB200 +/- AT2221 with Enzyme conditioned for 4 hours at Room Temperature)

The pharmacokinetics (PK) of ATB200 (measured by plasma GAA activity) and its efficacy (measured by tissue Glycogen level reduction), with or without Miglustat oral coadministration, was tested in *Gaa* knockout (KO) mice. Alglucosidase Alfa or ATB200 in dosing solutions were each kept at room temperature in infusion bags for 4 hours prior to IV administration to mice, to mimic dosing in patients in the clinical setting. KO mice were then dosed with Alglucosidase Alfa, ATB200, or ATB200 with oral Miglustat.

The results show that after preincubation at room temperature for 4 hours, the plasma GAA activity of ATB200 in plasma was increased by 25% with Miglustat coadministration, and glycogen levels in muscle (quadriceps, gastrocnemius and heart) were significantly decreased with Miglustat coadministration in comparison to ATB200 alone. In addition, ATB200 caused significantly decreased glycogen levels in muscle tissues compared to Alglucosidase Alfa. As observed in blood, Miglustat stabilized ATB200, increasing half-life in plasma and enzyme activity.

Figure 38. Plasma GAA Activities of IV ATB200 With or Without Oral Miglustat in Mice, With Enzyme Incubated for Four Hours at Room Temperature



Source: Applicant's Figure from Pharmacology Study No. RRB2000-56, Page 15.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; GAA, acid alpha-glucosidase; IV, intravenous, RT, room temperature

Table 59. Pharmacokinetic Summary of ATB200 With or Without Oral Miglustat in Mice

Description	ATB200 IV (mg/kg)	AT2221 PO (mg/kg)	AUC (x10^3 nmol 4-MU/mL/hr*hr)	$t_{½}$ (hr)
ATB200 alone	20	-	67	0.4
ATB200 + AT2221	20	10	74	0.5

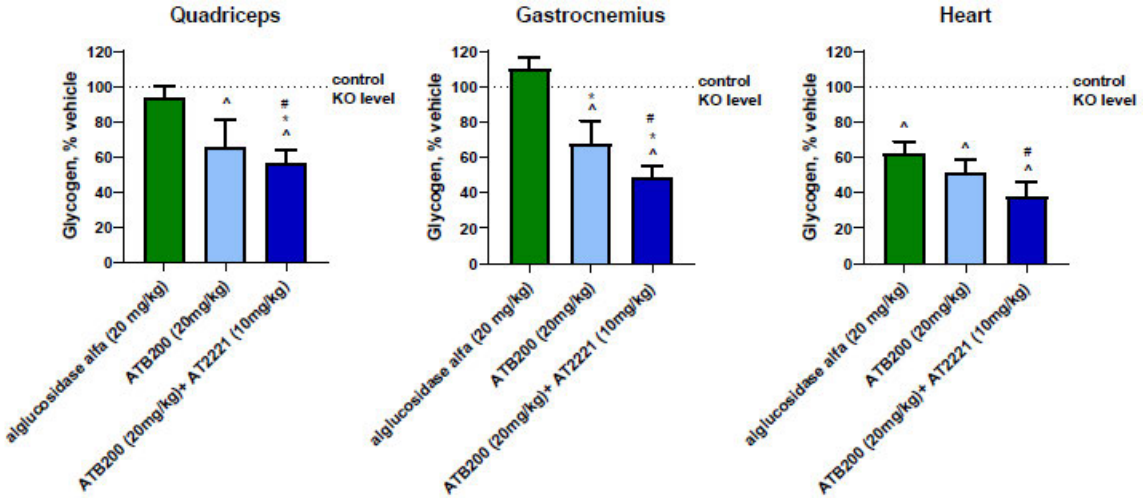
Source: Applicant's Table from Pharmacology Study No. RRB200-056, Page 16.
Abbreviations: AUC, area under the concentration-time curve; ATB200, cipaglucosidase alfa; AT2221, miglustat; IV, intravenous, PO, by mouth; RT, room temperature; $t_{1/2}$, elimination half life

Table 60. Glycogen Reduction Summary of ATB200 With or Without Oral Miglustat in Mice

Glycogen % reduction from vehicle (mean ±SEM)	Alglucosidase alfa	ATB200	ATB200 + AT2221
Quadriceps	7 ± 6	34 ± 15	43 ± 7*#
Gastrocnemius	No reduction	32 ± 13*	51 ± 6*#
Heart	38 ± 7^	49 ± 8^	62 ± 7^#

Source: Applicant's Table from Pharmacology Study No. RRB200-056, Page 18.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; SEM, standard error of means

Figure 39. Glycogen Levels (% of Vehicle) after 2-Biweekly Injections of ATB200 With and Without Miglustat with Enzyme Incubated for 4 Hour at Room Temperature



Source: Applicant's Figure from Pharmacology Study No. RRB200-056, Page 17.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; KO, knockout; SEM, standard error of means

Study Number RRB200-061 (AT2221: In Vitro Evaluation of the Inhibition of AT2221 towards Acid Alpha-Glucosidase at various pHs)

This study was conducted to show that the mechanism of action of AT2221 is to bind and inhibit ATB200 denaturation (endogenous and exogenous rhGAA) at a neutral pH of 7.0 (in blood and cytosol) with a high potency, and to bind to ATB200 to a lesser extent and with lower potency at an acidic pH of 4.0 (in the lysosomes). The difference in binding potency in the lysosomes is believed to enable the binding of ATB200 to the substrate glycogen in lysosomes. Inhibition curves demonstrating IC_{50}s, were constructed using nonlinear regression curves with a global fit.

The results show the IC_{50}s for different batches of AT2221. ATB200 demonstrated an IC_{50} at a neutral pH of 7.0 between 1.01 and 1.13µM and at an acidic pH of 4.0 between 6.9 and 7.2µM as shown in the Applicant's table below.

Table 61. IC_{50} of AT2221 Inhibition of rhGAA at pH 7.0

pH 7.0	Batch 6(A)	Batch 6(B)	Batch 7(A)	Batch 7(B)
IC50 (µM)	1.05	1.13	1.11	1.01
95% CI (µM)	1.00-1.10	1.05-1.20	1.00-1.23	0.95-1.08
R^2	0.9999	0.9997	0.9993	0.9998

Source: Applicant's Table from Pharmacology Study No. RRB200-061 Page 13.
Abbreviations: AT2221, miglustat; CI, confidence interval; IC_{50}, is the half maximal inh bitory concentration of the chaperone that reversibly binds and stabilizes rhGAA; pH, potential of hydrogen; R2, coefficient of determination; rhGAA, recombinant human acid α-glucosidase

Table 62. IC_{50} of AT2221 Inhibition of rhGAA at pH 4.0

pH 4.0	Batch 6(A)	Batch 6(B)	Batch 7(A)	Batch 7(B)
IC50 (μM)	7.2	7.3	7.4	6.9
95% CI (μM)	6.0-8.7	6.6-8.1	5.3-10.2	6.3-7.6
R^2	0.9970	0.9991	0.9950	0.9993

Source: Applicant's Table from Pharmacology Study No. RRB200-061 Page 12.
Abbreviations: AT2221, miglustat; CI, confidence interval; IC_{50}, is the half maximal inh bitory concentration of the chaperone that reversibly binds and stabilizes rhGAA; pH, potential of hydrogen; R2, coefficient of determination; rhGAA, recombinant human acid α-glucosidase

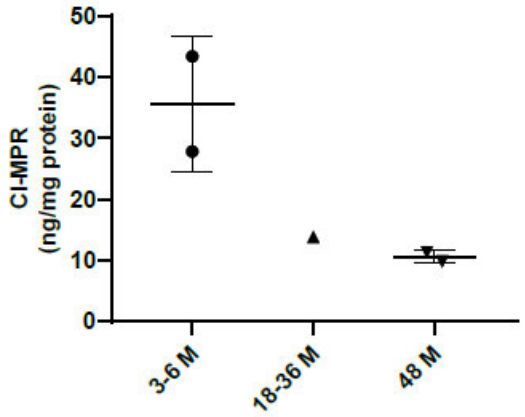
The results support the mechanism of action of miglustat in binding and stabilization of enzyme in blood and plasma, when coadministered with ATB200 in KO mice, followed by chaperoning of the enzyme to the lysosomal environment where it is released to bind and metabolize glycogen.

Study Number RRB200-060 (ATB200/AT2221: Ontogeny of CI-MPR and GAA levels in Monkey Muscles at Various Developmental Stages)

In this study, protein levels of cation independent-mannose phosphate receptor (CI-MPR) and GAA enzyme activity levels in cynomolgus monkey skeletal muscle were measured at various developmental stages: young, intermediate and adult 3 to 48 months old.

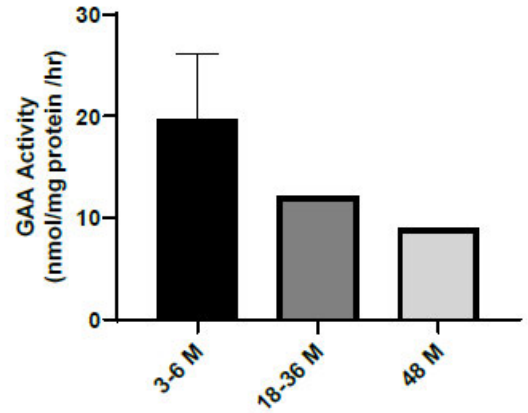
The result showed higher levels of CI-MPR and GAA in the skeletal muscle of young cynomolgus monkeys compared to skeletal muscles in adult monkeys, as shown in the Applicant's figures below.

Figure 40. Quantification of CI-MPR Levels in Monkey Quadriceps at Various Developmental Stages in Monkeys



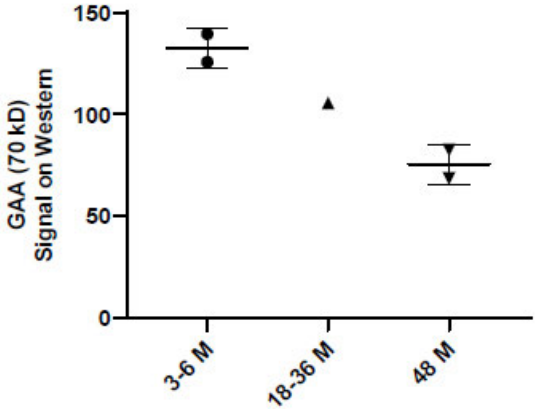
Source: Applicant's Figure from Pharmacology Study RRB200-60, Page 14.
Abbreviations: CI-MPR, cation independent-mannose phosphate receptor; M, months

Figure 41. GAA Enzyme Activity in Monkey Quadriceps at Various Developmental Stages in Monkeys



Source: Applicant's Figure from Pharmacology Study RRB200-60, Page 15.
Abbreviations: GAA, acid alpha-glucosidase; M, months

Figure 42. Quantification of GAA Enzyme Protein Levels in Monkey Quadriceps at Various Developmental Stages



Source: Applicant's Figure from Pharmacology Study RRB200-60, Page 16.
Abbreviations: GAA, acid alpha-glucosidase; M, months

Limited interpretation of the data are possible due to the small number of animals studied. The data appear to show higher levels of CI-MPR and GAA in the skeletal muscle of young monkeys in comparison to adult monkeys. The study groups were defined as young (N=2, 3-6 months old), intermediate age (N=1,18-36 months old) and adult (N=2, >48 months old). It was postulated that the higher levels of CI-MPR and GAA levels measured in young monkeys may be associated with increased metabolism and higher expression of proteins required in growth and development, compared with adult monkeys.

In Vivo Studies

ATB200: Effect of Repeat Intravenous Administration of ATB200 with or without AT2221 Coadministration on Glycogen Levels in *Gaa* KO Mice (Study #RRB200-004)

In this study, the effects of ATB200 and/or AT2221 on glycogen storage in tissues of *Gaa* KO mice and the effects anti-GAA IgG antibody on mouse plasma ATB200 and/or AT2221 were examined.

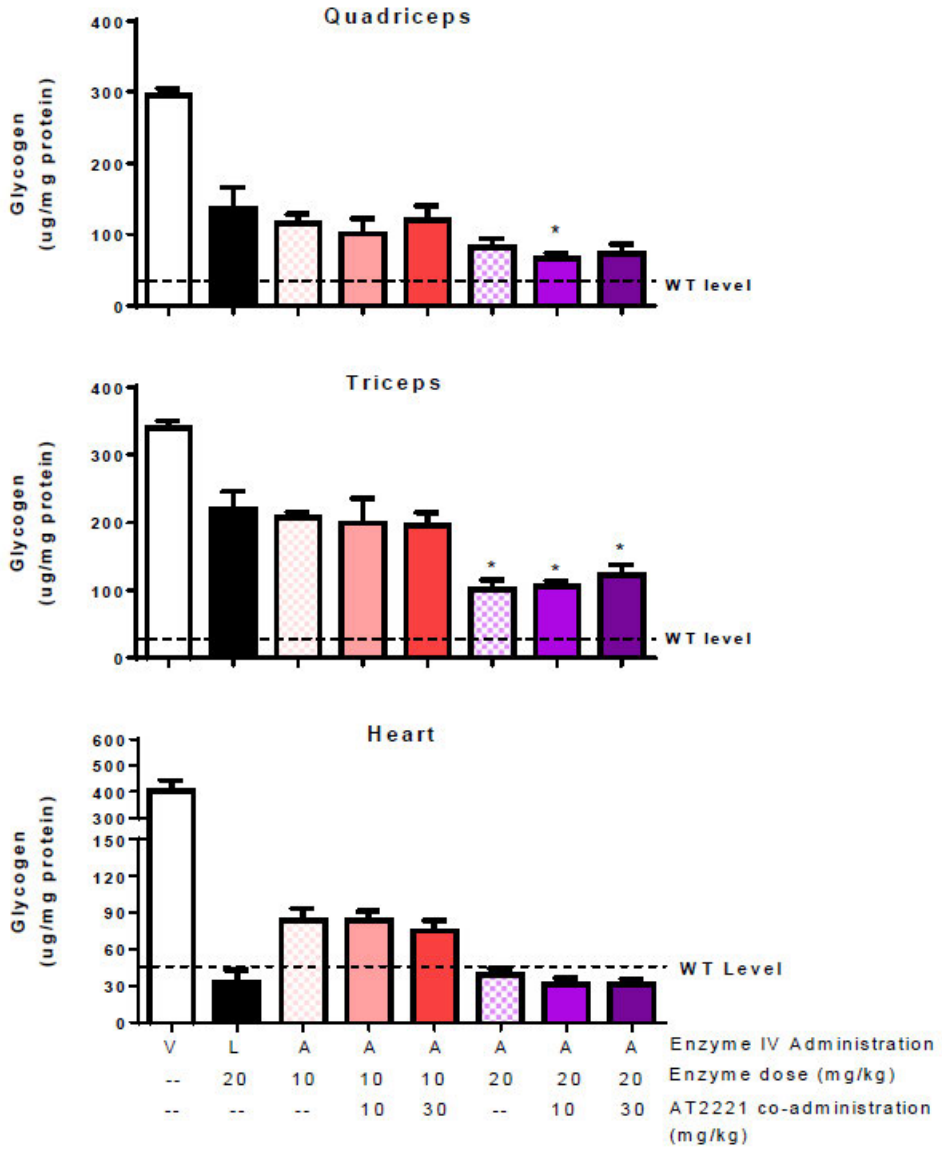
Methods

Ten-week-old male C57BL/6 wildtype mice (N=5) and 16-week-old male C57BL/6 *Gaa* KO mice (N=42, at 7 groups of 6 each) were administered biweekly IV bolus doses of either alglucosidase alfa (20 mg/kg) or ATB200 (10 or 20 mg/kg). In addition, some ATB200 groups received oral doses of 10 or 30 mg/kg of AT2221 30 minutes prior to ATB200 IV administration. Ten minutes prior to the second and successive IV bolus doses, mice received 10 mg/kg IP diphenhydramine injections to minimize anaphylaxis. The study was divided into two parts, with animals in study 294A receiving a total of 6 biweekly administrations, and animals in study 294B receiving a total of 4 biweekly administrations. Fourteen days after the last dose, animals were euthanized, and plasma and tissues (liver, kidney, heart, diaphragm, tongue, hind- and forelimbs) were collected for analysis. Measurements were done of *Gaa* activity in tissues; glycogen levels in tissues and glycogen accumulation in muscles; and measurement of anti-rhGaa IgG antibodies in plasma.

Results

Dose-dependent glycogen reduction with ATB200 administration alone, was observed in diseased tissues of the muscles (quadriceps, triceps) and heart of *Gaa* KO mice when measured biochemically by the amyloglucosidase method in both (294A/294B) studies (Figure 43 and Figure 44). ATB200 at 10 mg/kg showed improved glycogen reduction in skeletal muscles compared to 20 mg/kg alglucosidase alfa, and ATB200 at 20 mg/kg resulted in significantly greater glycogen reduction than that seen with 20 mg/kg alglucosidase alfa (Figure 43 and Figure 44) after the 4 or 6 biweekly administrations (Study 294A/B). A comparison of the percentage reduction in glycogen seen with 10 and 20 mg/kg ATB200 to that of 20 mg/kg alglucosidase alfa is shown in Table 63.

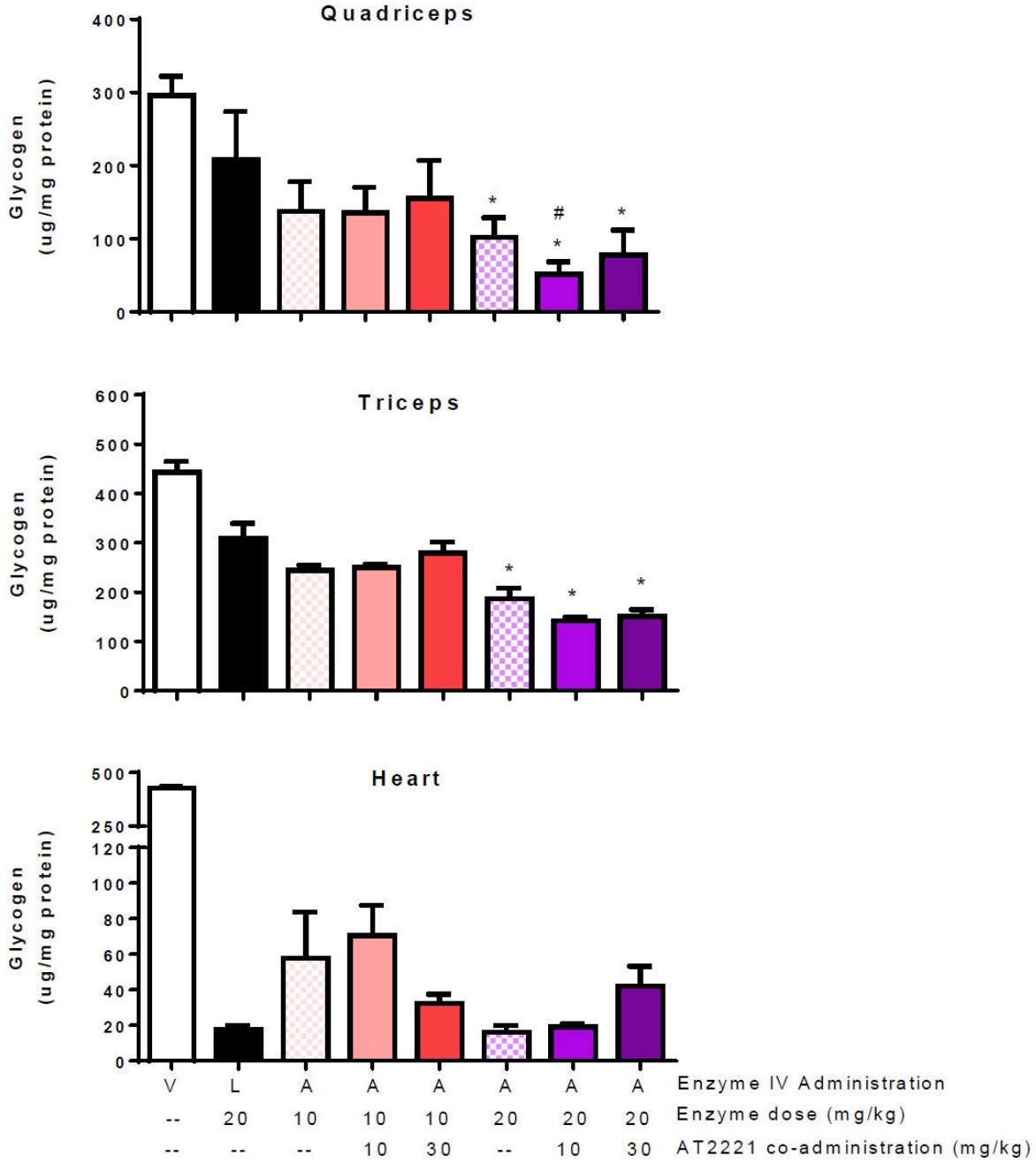
Figure 43. Glycogen Levels in Tissues of *Gaa* KO Mice Following 6 Biweekly IV Administrations of ATB200 With or Without AT2221 Coadministration (Study 294A)



Applicant's Figure from Pharmacology Study RRB200-004, Page 23.

Male *Gaa* KO mice (~16-weeks old) (n=6) were administered a total of 4 biweekly IV bolus injections of vehicle (V), 20 mg/kg alglucosidase alfa (L), or ATB200 (A) at 10 or 20 mg/kg. Some ATB200 groups were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 IV administration. Tissues were collected 14 days after the last injection (6th dose), and glycogen levels were measured. Each column represents mean ± SEM of the 4-6 animals in the group for which the samples were available. Statistical significance was determined using unpaired t-tests, where * represents $p<0.05$ versus alglucosidase alfa and # represents $p<0.05$ versus same-dose ATB200 alone.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout; SEM, standard error of means

Figure 44. Glycogen Levels in Tissues of *Gaa* KO Mice Following 4 Biweekly IV Administrations of ATB200 With or Without AT2221 Coadministration (Study 294B)



Source: Applicant's Figure from Pharmacology Study RRB200-004, Page 22.
Male *Gaa* KO mice (~16-weeks old) (n=6) were administered a total of 4 biweekly IV bolus injections of vehicle (V), 20 mg/kg alglucosidase alfa (L), or ATB200 (A) at 10 or 20 mg/kg. Some ATB200 groups were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 IV administration. Tissues were collected 14 days after the last injection (4th dose), and glycogen levels were measured. Each column represents mean ± SEM of the 4-6 animals in the group for which the samples were available. Statistical significance was determined using unpaired t-tests, where * represents $p<0.05$ versus alglucosidase alfa and # represents $p<0.05$ versus same-dose ATB200 alone.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout; SEM, standard error of means

With 10 mg/kg ATB200, AT2221 coadministration did not show any further improvement in glycogen reduction compared to the ATB200 enzyme alone; however, with 20 mg/kg ATB200, AT2221 coadministration at 10 mg/kg showed additional glycogen reduction, compared to same-dose 20 mg/kg enzyme alone (Table 63). AT2221 at 30 mg/kg however did not show any additional benefit, especially in the 6-dose 294A study.

Table 63. Glycogen Levels in Skeletal Muscles of *Gaa* KO Mice Following 4 Biweekly IV Administrations of ATB200 With or Without AT2221 Coadministration (Study 294B)

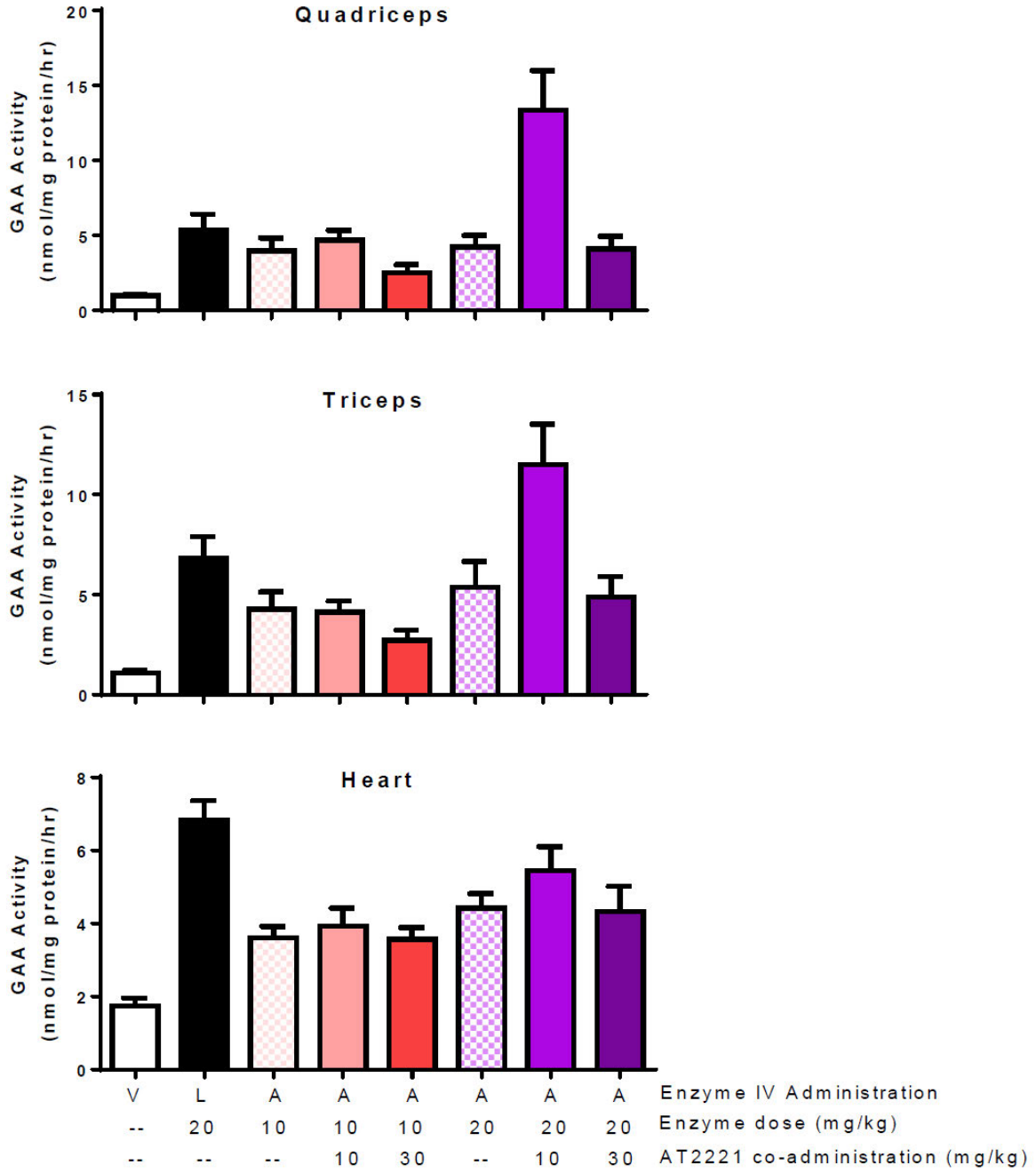
	Glycogen (% change from baseline)	
	Quadriceps	Triceps
alglucosidase alfa (20 mg/kg)	-33±10	-32±7
ATB200 (10 mg/kg)	-61±7	-48±3
ATB200 (10 mg/kg) + AT2221 (10 mg/kg)	-62±6	-46±2
ATB200 (20 mg/kg)	-74±4*	-62±5*
ATB200 (20 mg/kg) + AT2221 (10 mg/kg)	-94±3*#	-73±2*#

Source: Applicant's table from Pharmacology study RRB200-004.
Male *Gaa* KO mice (~16-weeks old) (n=6) were administered a total of 4 biweekly IV bolus injections of vehicle, alglucosidase alfa, or ATB200 at the indicated doses. Some ATB200 groups were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 IV administration. Tissues were collected 14 days after the last injection (4th dose), and glycogen levels were measured. Baseline glycogen levels in vehicle group *Gaa* KO mice were 296±12 and 443±22 µg/mg protein in the quadriceps and triceps, respectively, and in wild-type C57BL/6 mice were 35±5 and 28±6 µg/mg protein, respectively (mean ± SEM of 6 mice). The data shown represent the percent glycogen change from baseline in each tissue as normalized between wild-type (0%) and vehicle group *Gaa* KO (100%) levels. Each value represents the mean ± SEM of 4 to 6 mice. Statistical significance was determined using unpaired t-tests, where * represents $p<0.05$ versus alglucosidase alfa and # represents $p<0.05$ versus same-dose ATB200 alone.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout

The histological staining of muscle and heart tissues with periodic acid-Schiff (PAS) stain for glycogen levels show similar results as the biochemical measurements with improved glycogen reduction seen in smooth muscle cells (vSMCs) of the heart with ATB200, when compared to the alglucosidase alfa (Figure 43 and Figure 44). The uptake of ATB200 or alglucosidase in diseased muscle and heart tissues (indication of measured GAA activities) 14 days after the last administration showed an ATB200 dose-dependent increase in tissue GAA activity. Although the ATB200 treated group did not show a higher GAA activity than the alglucosidase alfa group, it was still associated with a greater reduction in glycogen levels in the muscles than the alglucosidase group (Figure 45). All animals receiving ATB200 or alglucosidase alfa yielded considerable levels of anti-rhGAA IgG antibodies. There was no obvious difference in antibody titers between the KO animals receiving either rhGAA enzymes (Figure 46 and Figure 47). The co administration of AT2221 did not change the antibody titers against ATB200 after either 4 or 6 biweekly dosing (Study 294A and 294B).

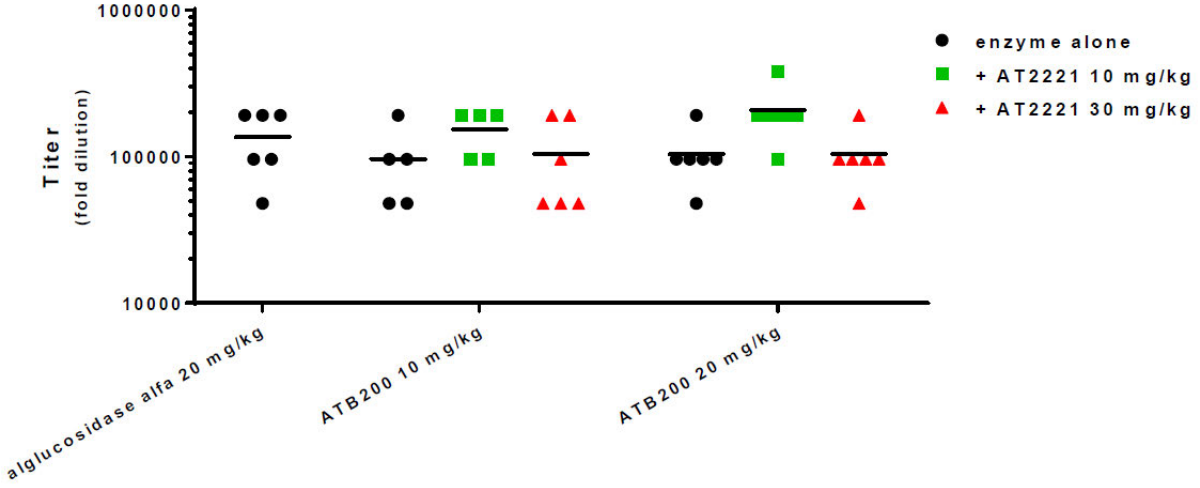
The results demonstrate that ATB200 is more effective in reducing glycogen accumulation in the disease-relevant skeletal muscles, in comparison to the current standard of care with alglucosidase alfa, in a mouse model of Pompe disease. Coadministration with AT2221 further facilitates glycogen reduction by ATB200 in this model.

Figure 45. GAA Activity in Tissues of *Gaa* KO Mice Following 4 Biweekly IV Administrations of ATB200 With or Without AT2221 Coadministration (Study 294B)



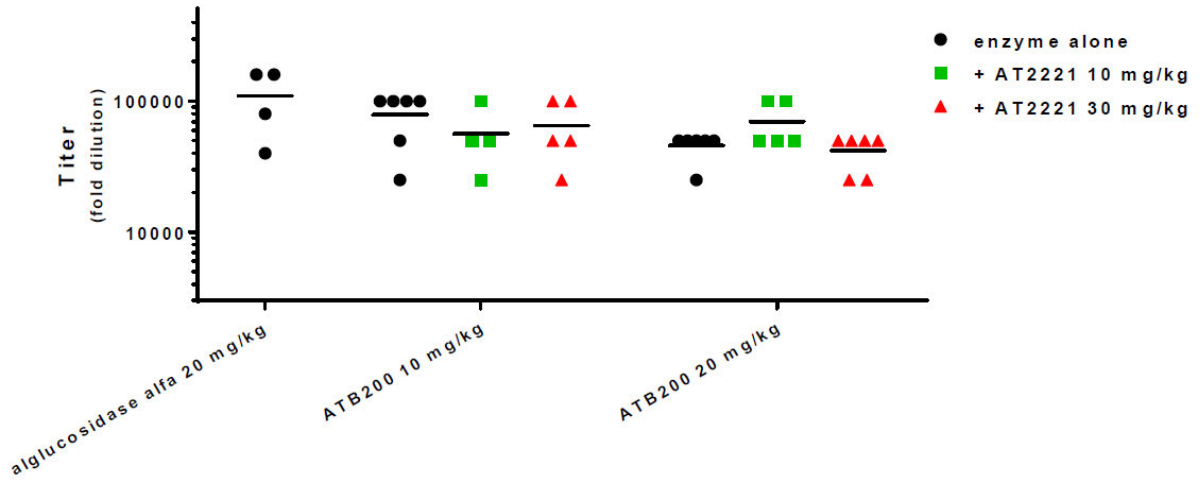
Source: Applicant's figure from pharmacology study RRB200-004.
Male *Gaa* KO mice (~16-weeks old) (n=6) were administered a total of 4 biweekly IV bolus injections of vehicle (V), 20 mg/kg alglucosidase alfa (L), or ATB200 (A) at 10 or 20 mg/kg. Some ATB200 groups were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 IV administration. Tissues were collected 14 days after the last injection (4th dose), and GAA activities were measured. Each column represents mean ± SEM of the 4-6 animals. The Gaa activity (nmol/mg protein/hr) in WT tissues is as follows: quadriceps-27.2; triceps-21.6; heart-18.9.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; GAA, acid alpha-glucosidase; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout; SEM, standard error of means

Figure 46. Anti-rhGAA IgG Titers Following 4 Biweekly IV Administrations of ATB200 With or Without AT2221 Coadministration (Study 294B)



Source: Applicant's figure from Pharmacology study RRB200-004, page 26.
Male *Gaa* KO mice (~16-weeks old) (n=6) were administered a total of 4 biweekly IV bolus injections of alglucosidase alfa 20 mg/kg, or ATB200 10 or 20 mg/kg. Some ATB200 groups were also orally administered the indicated doses of AT2221, 30 minutes prior to ATB200 IV administration. Plasma was collected 14 days after the last injection (4th dose), and anti-rhGAA IgG titers were measured.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IgG, immunoglobulin G; IV, intravenous; KO, knockout; SEM, standard error of means

Figure 47. Anti-rhGAA IgG Titers Following 6 Biweekly IV Administrations of ATB200 With or Without AT2221 Coadministration (Study 294A)



Source: Applicant's figure from Pharmacology study RRB200-004, page 26.
Male *Gaa* KO mice (~16-weeks old) (n=6) were administered a total of 6 biweekly IV bolus injections of alglucosidase alfa 20 mg/kg, or ATB200 10 or 20 mg/kg. Some ATB200 groups were also orally administered the indicated doses of AT2221, 30 minutes prior to ATB200 IV administration. Plasma was collected 14 days after the last injection (6th dose), and anti-rhGAA IgG titers were measured.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IgG, immunoglobulin G; IV, intravenous; KO, knockout; SEM, standard error of means

The enhanced lysosomal targeting of ATB200 in muscle tissue of KO mice show greater reduction of stored glycogen than in alglucosidase alfa treated mice and enhanced reduction with

the coadministration of miglustat (at -94% with 20 mg/kg ATB200 and 10 mg/kg miglustat), almost to the levels in wildtype mice.

In the cardiomyocytes and smooth muscle cells of the heart, the diaphragm and quadriceps, glycogen reduction was greater (and almost complete in the heart) than that seen with alglucosidase alfa, with even greater reduction with miglustat coadministration. The biochemical reduction seen was equally demonstrated with histological staining. Although the GAA enzyme activity for ATB200 group was not higher than the alglucosidase alfa group, the glycogen reduction effect for ATB200 in animal muscles was much higher than that of for alglucosidase alfa in animal muscles (triceps and quadriceps).

ATB200/AT2221: Efficacy of Two Biweekly Intravenous Administrations of ATB200 and Dose Selection of AT2221 Coadministration in *Gaa* KO Mice (Study # RRB200-005)

The study objectives were to determine the glycogen concentrations in *Gaa* KO mice muscles 14 days following two IV doses of ATB200 and/or AT2221, to determine the uptake of ATB200 in knockout mice muscles 14 days after 2 IV doses, to determine the optimal dose of AT2221 coadministration with ATB200 for maximal glycogen reduction in mice, and to determine if AT2221 alone has any effect on glycogen reduction.

Methods

In study # 296, 14 groups of 16-week-old male *Gaa* KO mice (N=7/group; 5 control) were administered two biweekly IV boluses of either vehicle, the standard drug alglucosidase alfa (20 mg/kg) or ATB200 (5, 10, or 20 mg/kg). The 5 and 10 mg/kg ATB20-0 dose groups were coadministered oral AT2221 at 0, 1, 3, or 10 mg/kg, and the 20 mg/kg dose group was coadministered oral AT2221 at 0, 1, 3, 10, or 30 mg/kg. On the 14^{th} day, after the second administered dose, the animals were euthanized and tissues from the liver, kidney, heart, diaphragm, tongue, hind limbs, and forelimbs were collected.

In the second part of the study (#320), nine groups of 16-week-old male *Gaa* KO mice (N=7/group, including control), were administered two biweekly IV bolus doses of either vehicle, alglucosidase alfa (20 mg/kg) or ATB200 at 5, 10, or 20 mg/kg. In addition, AT2221 at 0, 5, 10, 20, or 30 mg/kg doses was coadministered to the group receiving the 20 mg/kg dose of ATB200. Diphenhydramine (DPH) at an IP dose of 10 mg/kg was administered 10 minutes prior to the second IV bolus injections to reduce anaphylaxis. On Day 14, after the second administration, animals were euthanized and tissues from the liver, kidney, heart, diaphragm, tongue, hindlimbs, and forelimbs were collected.

In the third part of the study (#328), seven groups of 16-week-old male *Gaa* KO mice (N=7/group, including control) were administered two biweekly IV bolus of either vehicle, alglucosidase alfa (20 mg/kg) or ATB200 at 20 mg/kg. In addition, AT2221 at 0, 5, 10, 20, or 30 mg/kg doses was coadministered to the group receiving the 20 mg/kg dose of ATB200. DPH at an IP dose of 10 mg.kg was administered 10 minutes prior to the second IV bolus injections to reduce anaphylaxis. On Day 14, after the second administration, animals were euthanized and tissues from the liver, kidney, heart, diaphragm, tongue, hindlimbs, and forelimbs were collected for analysis.

In the fourth part of the study (#343), four groups of 16-week-old male *Gaa* KO mice (N=7/group, including control) were administered two biweekly IV bolus doses of either vehicle,

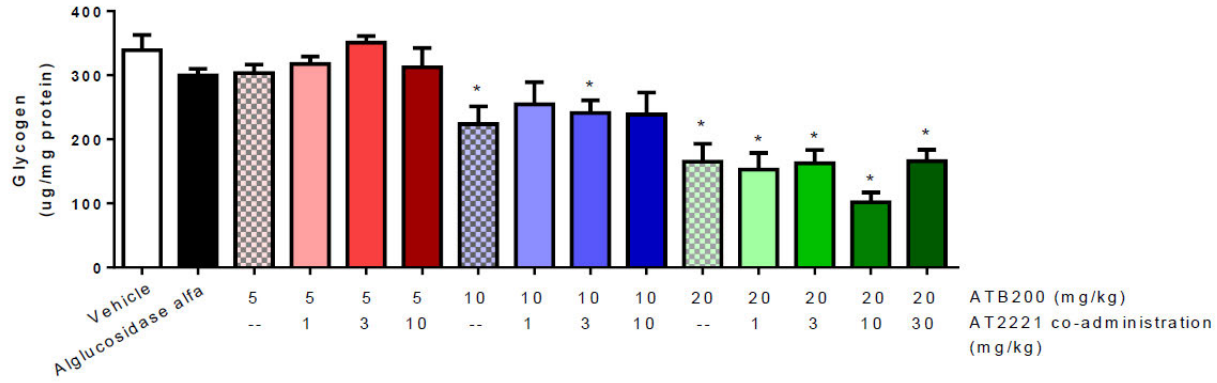
alglucosidase alfa (20 mg/kg), or ATB200 (20 mg/kg), oral AT2221 (10 mg/kg). IP DPH (10 mg/kg) was injected 10 minutes before the second IV injection of enzyme to reduce anaphylaxis. On Day 14 after the second dose, animals were euthanized and tissues from liver, kidney, heart, diaphragm, tongue, hindlimbs and forelimbs were collected for analysis.

Observations

In study #296, 5 animal mortalities occurred; one from (vehicle) control, one from Group 5 (5 mg/kg ATB200+3 mg/kg AT2221), one from Group 11 (20 mg/kg ATB200), one from group 14 (20 mg/kg ATB200+10 mg/kg AT2221), and one from group 15 (20 mg/kg ATB200+30 mg/kg AT2221). Two of the deaths occurred with anaphylaxis symptoms after the second dose, while the other three deaths were random and not treatment related. In the subsequent studies, the DPH predose 10 mins before the drug dose reduced anaphylaxis and prevented anaphylaxis-related deaths. In study #328, four animal mortalities occurred, all randomly: one from group 1 (vehicle), one from group 2 (20 mg/kg alglucosidase alfa), one from group 5 (20 mg/kg ATB200+10 mg/kg AT2221), and one from group 6 (20 mg/kg ATB200+20 mg/kg AT2221). There were no animal deaths from studies #320 or #343. At the time of necropsy all the animals looked healthy, and plasma and tissues were collected for analysis. Tissue lysates were collected, total protein concentrations determined, and absolute *Gaa* activities were determined after normalization to protein concentrations. The absolute glycogen concentration in tissue lysates were also determined after normalization to protein concentrations. Histological assessment of glycogen levels in tissues was also determined by PAS staining.

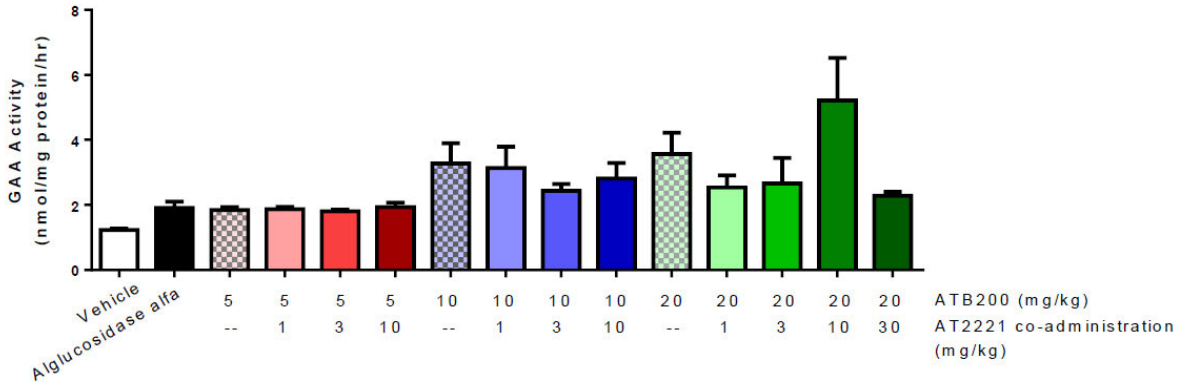
Doses (Study 296)

Figure 48. Glycogen Levels in Quadriceps of *Gaa* KO Mice Following Two Biweekly IV Administrations of ATB200 With AT2221 Oral Coadministration at Various Doses (Study 296)



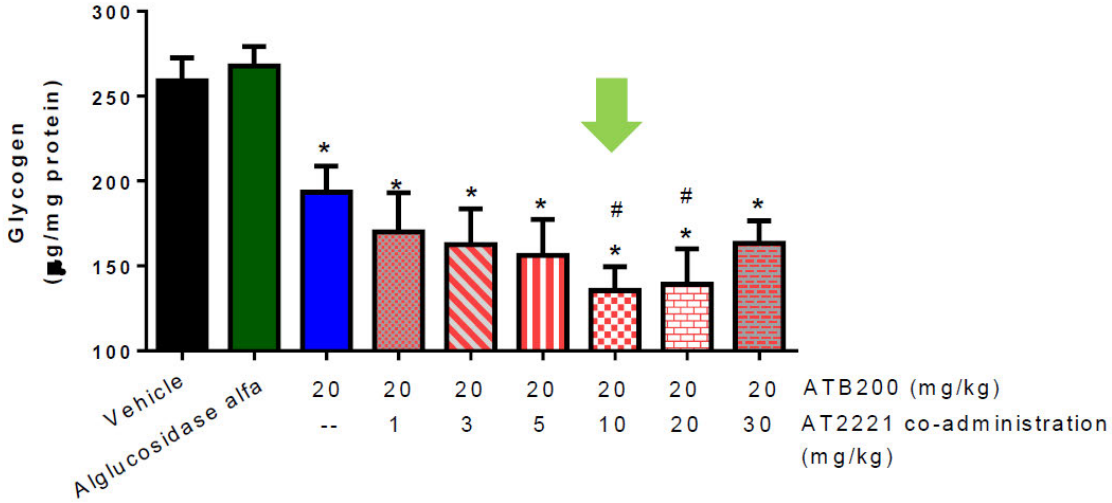
Source: Applicant's figure from Pharmacology study RRB200-005, page 21.
Male Gaa KO mice (~16 weeks old) (n=7) were administered two biweekly IV bolus tail vein injections of vehicle, 20 mg/kg alglucosidase alfa, or ATB200 at 5, 10, or 20 mg/kg. ATB200 groups of mice were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 IV administration. Tissues were collected 14 days after the last injection (2nd dose), and glycogen levels were measured. Each bar represents the mean ± SEM. Statistical significance was determined using unpaired t-tests, where * represents $p<0.05$ versus alglucosidase alfa, and # represents $p<0.05$ versus same-dose ATB200 alone.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout; SEM, standard error of means

Figure 49. GAA Activity in Quadriceps of *Gaa* KO Mice Following Two Biweekly IV Administrations of ATB200 With AT2221 Oral Coadministration at Various Doses (Study 296)



Source: Applicant's figure from Pharmacology study RRB200-005, page 21.
Male Gaa KO mice (~16 weeks old) (n=7 except for vehicle group where n=5) were administered two biweekly IV bolus tail vein injections of vehicle, 20 mg/kg alglucosidase alfa, or ATB200 at 5, 10, or 20 mg/kg. ATB200 groups of mice were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 IV administration. Tissues were collected 14 days after the last injection (2nd dose), and GAA activity in quadriceps were measured. Each bar represents the mean ± SEM. Statistical comparison was not performed on these activity data.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout; SEM, standard error of means

Figure 50. Glycogen Levels in *Gaa* KO Mouse Quadriceps Following Two Biweekly IV Administrations of 20 mg/kg ATB200 With or Without AT2221 Oral Coadministration at Various Doses (Studies 296, 320, and 328)



Source: Applicant's figure from Pharmacology study RRB200-005, page 23.
Male Gaa KO mice (~16 weeks old) were administered two biweekly IV bolus tail vein injections of vehicle, 20 mg/kg alglucosidase alfa, or 20 mg/kg ATB200 alone. Some ATB200 groups of mice were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 administration. Tissues were collected 14 days after the last injection (2nd dose), and glycogen levels were measured. The data shown represent pooling of several studies, with the 'Vehicle', 'Alglucosidase alfa', 'ATB200 (20 mg/kg)','ATB200 (20 mg/kg) + AT2221 (10 mg/kg)', and 'ATB200 (20 mg/kg) + AT2221 (30 mg/kg)' groups representing the mean ± SEM of 17-21 mice; the 'ATB200 (20 mg/kg) + AT2221 (5 mg/kg)' and 'ATB200 (20 mg/kg) + AT2221 (20 mg/kg)' groups representing the mean ± SEM of 13-14 mice; and the 'ATB200 (20 mg/kg) + AT2221 (1 mg/kg)' and 'ATB200 (20 mg/kg + AT2221 (3 mg/kg)' groups representing the mean ± SEM of 4-7 mice. Statistical significance was determined using unpaired t-tests, where # represents $p<0.05$ versus ATB200 alone; * represents $p<0.05$ versus alglucosidase alfa alone. The green arrow indicates the optimal dose coadministration of 10 mg/kg AT2221 with 20 mg/kg ATB200 with respect to glycogen reduction.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout; SEM, standard error of means

Table 64. Glycogen Levels in *Gaa* KO Mouse Quadriceps Following Two Biweekly IV Administrations of 20 mg/kg ATB200 With or Without AT2221 Oral Coadministration at Various Doses (Studies 296, 320, and 328)

Treatment Group		Glycogen (µg/mg protein) (mean ± SEM)	Glycogen (% of Vehicle) (mean ± SEM)	N (actually analyzed)
vehicle		259.1 ± 13.5	100.0 ± 5.3	17
alglucosidase alfa 20 mg/kg		267.8 ± 11.3	103.4 ± 4.4	20
ATB200 20 mg/kg	+ 0 mg/kg AT2221	193.4 ± 15.5	74.6 ± 6.0	20
	+ 1 mg/kg AT2221	153.0 ± 25.9	59.0 ± 10.0	6
	+ 3 mg/kg AT2221	162.7 ± 20.8	62.8 ± 8.0	7
	+ 5 mg/kg AT2221	156.3 ± 21.2	60.3 ± 8.2	14
	+ 10 mg/kg AT2221	135.5 ± 14.0	52.3 ± 5.4	19
	+ 20 mg/kg AT2221	139.3 ± 20.8	53.8 ± 8.2	13
	+ 30 mg/kg AT2221	163.4 ± 13.2	63.1 ± 5.1	20

Source: Applicant's table from Pharmacology study RRB200-005, page 24.
Male Gaa KO mice (~16 weeks old) were administered two biweekly IV bolus tail vein injections of vehicle, 20 mg/kg alglucosidase alfa, or 20 mg/kg ATB200 alone. Some ATB200 groups of mice were also orally coadministered the indicated doses of AT2221 30 minutes prior to ATB200 administration. Tissues were collected 14 days after the last injection (2nd dose), and glycogen levels were measured. The data from several studies were pooled, and the "N (actually analyzed)" column shows the actual number of mice for each treatment group that was analyzed for glycogen. The "Glycogen (% of Vehicle)" was calculated for each individual animal from all 3 studies, using the overall averaged value of glycogen levels of animals in the vehicle groups from all studies.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; IV, intravenous; KO, knockout; N, number of mice for each treatment group that were analyzed for glycogen; SEM, standard error of means

Results

In study #296, glycogen reduction in the KO diseased quadricep muscle in mice was dose-dependently reduced with ATB200 doses of 5, 10 and 20 mg/kg, following measurement 14 days after the last (second) biweekly administration. Alglucosidase alfa administration at 20 mg/kg dose showed similar glycogen reduction as 5 mg/kg ATB200 dose. The coadministration of AT2221 did not show any additive effect at doses of 1, 3, or 10 mg/kg on ATB200 doses of 5 or 10 mg/kg. AT2221 co- administration at 10 mg/kg to the 20 mg/kg ATB200 dosed mice was however optimally effective in further improving the reduction in muscle glycogen reduction in the KO mice.

GAA activity was also commensurate to the glycogen data, with increased activity at ATB200 doses of 10 and 20 mg/kg, and optimal additive effects only seen with the coadministration of 10 mg/kg AT2221. ATB200 dosing showed a greater reduction of muscle glycogen and greater GAA activity with 10 and 20 mg/kg IV dose and optimal additive effect with the coadministration of 10 mg/kg oral AT2221 than 20 mg/kg alglucosidase alfa. Histological PAS staining of the mice muscle tissue show commensurate effect with the biochemical measurements.

ATB200/AT2221: Effect of Long-Term Administration of ATB200 Alone or Coadministered with AT2221 on Muscle Biochemistry and Function in Gaa KO Mice (Study #RRB200-017)

The objective of this study was to investigate the effects of three or six-month administrations of ATB200 with or without oral coadministration of AT2221, compared to alglucosidase alfa, on glycogen levels, histological markers, and muscle function in *Gaa* KO mice.

Methods

Male *Gaa* KO mice were administered up to 12 biweekly (i.e., every other week) IV bolus injections of vehicle, 20 mg/kg ATB200 alone, 20 mg/kg alglucosidase alfa alone, or 20 mg/kg ATB200 coadministered with 10 mg/kg AT2221 (oral gavage 30 minutes before IV ATB200). Muscle function was assessed once per month. The wire-hang assay was conducted once on two consecutive days, while the grip-strength assay was repeated three times on the same day. Glycogen was measured using an amyloglucosidase-based biochemical method and a high-pH anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD). GAA activity was measured as digestion of 4-MU-α-Glc 4-methylumbeliferrone (4-MU) compared to a standard curve of 4-MU. The absolute GAA activity in each lysate was normalized by its protein concentration, and the final specific activity was expressed as nanomoles of released 4-MU per milligram of total protein per hour (nmol/mg protein/hr).

The results were reviewed for statistical significance by the CDER nonclinical statistical team.

Results

Over a period of 6 months, treatment of *Gaa* KO mice with ATB200/AT2221 showed a trend for increased hang time in the wire-hang assay compared to those treated with alglucosidase alfa; however, the pairwise comparisons showed no statistical difference between ATB200/ AT2221 and alglucosidase alfa. In the grip-strength assay, the pairwise comparisons showed statistically significant differences for the coadministration of ATB200/AT2221 when compared to alglucosidase alfa. For the wire hang assay, the trend reflects an apparent decrease in function in the alglucosidase animals while ATB200/AT2221 treated animals maintain function. In the grip strength assay, animals treated with ATB200/AT2221 show a significant increase in function compared to those treated with alglucosidase.

Table 65 was constructed from glycogen levels in muscles of *Gaa* KO mice following biweekly treatments for 1, 2, 3 or 6 months. The coadministration of ATB200/AT2221 significantly reduced glycogen levels in quadriceps for up to 3 months, in triceps and gastrocnemius at 3 months, and in heart at 3 and 6 months, compared to alglucosidase alfa. Standard deviations increased at the 6-month time point, potentially obscuring a treatment effect.

Table 65. Glycogen Levels (ug/g) in KO Mice Following 1, 2, 3, or 6 Months of Treatment With ABT200 (20 mg)/AT2221 (10 mg) or Alglucosidase (20 mg) (RRB200-017)

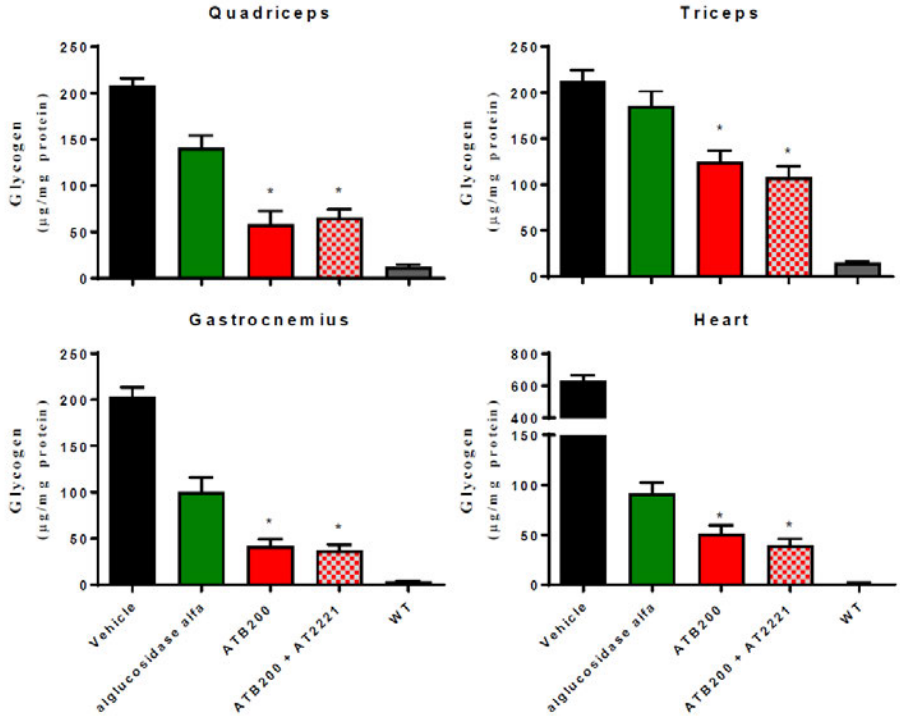
	1 Month			2 Months	3 Months		6 Months
Biweekly	**b 296**	**b 320**	**b 328**	**a 294B**	**a 294A**	**c**	**c**
Treatments	**2**			**4**	**6**		**12**
Muscle Type							
Quadriceps							
ABT200/AT2221	101.8*	112.4*	196.3	51.2*	66.5	65.4*	141.0
alglucosidase alfa	299.5	207.5	301.2	208.9	135.2	140.8	209.5

	1 Month			2 Months	3 Months		6 Months
Biweekly	**b 296**	**b 320**	**b 328**	**a 294B**	**a 294A**	**c**	**c**
Treatments	**2**			**4**	**6**		**12**
Muscle Type							
Triceps							
ABT200/AT2221				142.1	106.1	107.7*	136.8
alglucosidase alfa				308.4	220.8	185.4	238.8
Heart							
ABT200/AT2221				19.3	31.5	39.5*	95.1*
alglucosidase alfa				17.6	32.4	91.5	288.8
Gastrocnemius							
ABT200/AT2221						37.2*	61.4
alglucosidase alfa						100.6	178.5

Source: a from Study # RRB200-004 studies 294A and 294B, p.30; b from Study # RRB200-005 studies 296, 320 and 328, p.32; c from Study # RRB200-017, p.52.
a, c An amyloglucosidase-based biochemical method and a high-pH anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) chromatography method were used.
a Glycogen was digested and read with a glucose assay.
* CDER statistical analysis: statistical significance was determined using the 2-sided t-test, where * represents $p<0.05$ versus alglucosidase alfa
Abbreviations: ATB200, cipaglucosidase alfa; AT221, miglustat; HPAEC-PAD, high-pH anion exchange chromatography with pulsed amperometric detection; KO, knockout; pH, potential of hydrogen

Table depicts glycogen levels in quadriceps, triceps, heart and gastrocnemius of *Gaa* KO mice at the maximum treatment effect level at 3 months (ABT200 (20 mg/kg)/AT221 (10 mg/kg), Alglucosidase alfa (20 mg/kg).

Figure 51. Glycogen Levels in Tissues of *Gaa* KO Mice After 3 Months Treatment



Source: Applicant's figure from Pharmacology Study # RRB200-017, p.23.
Glycogen levels were measured 14 days after the 6th administration. About half of the animals in each group were sacrificed with tissues collected. Each column represents mean ± SEM of the 6-7 animals. Statistical significance was determined using Dunnett's multiple comparison under one-way ANOVA, where * represents p<0.05 versus alglucosidase alfa.
Abbreviations: ANOVA, analysis of variance; ATB200, cipaglucosidase alfa; AT2221, miglustat; KO, knockout; GAA, human acid α-glucosidase; SEM, standard error of means

ATB200 alone decreased glycogen in the quadriceps, triceps, gastrocnemius and heart relative to alglucosidase alfa at both 3 and 6 months. Coadministration of with AT2221 did not further enhance glycogen reduction.

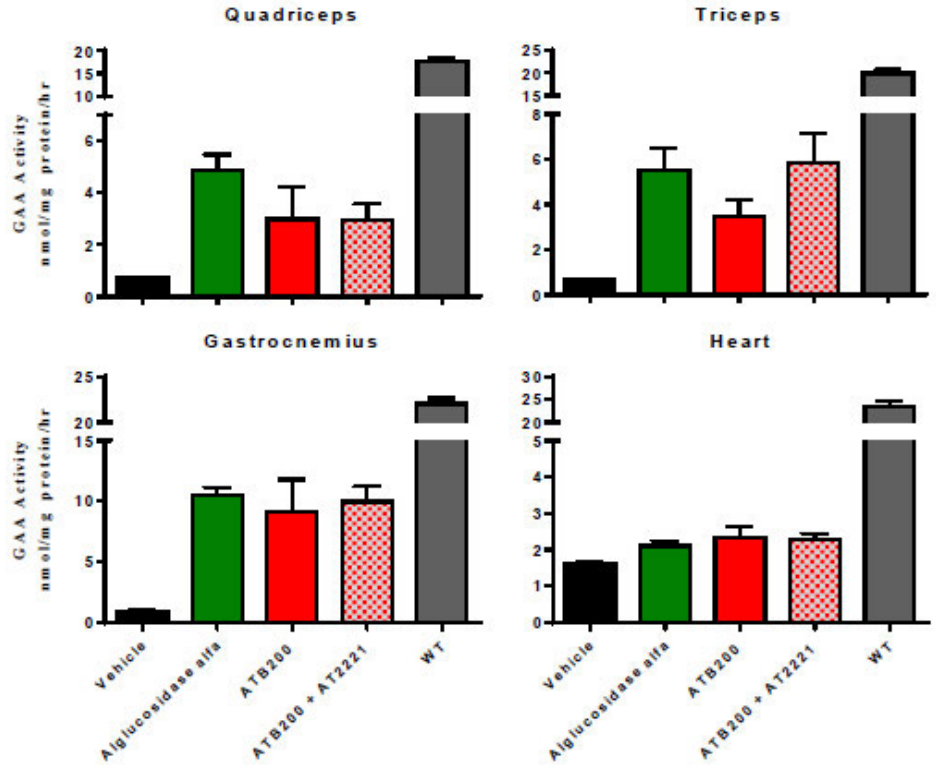
Table 66 and Figure 52 were constructed from GAA enzyme activity levels in muscles of *Gaa* KO mice following biweekly treatments for 3 or 6 months. The coadministration of ATB200/AT2221 did not increase enzyme activity levels in quadriceps, triceps, gastrocnemius or heart at 3 or 6 months, compared to alglucosidase alfa.

Table 66. GAA Enzyme Activity (nmol/mg protein/hour) Following 3 Months of Treatment

Muscle Type	Vehicle	Alglucosidase Alfa 20 mg/kg	ATB200 20 mg/kg	ATB200 20 mg/kg AT2221 10 mg/kg	Wild Type
Quadriceps	0.70	4.87	2.97	2.96*	17.6
Triceps	0.69	5.50	3.45	5.86	19.9
Heart	1.60	2.10	2.33	2.27	23.3
Gastrocnemius	0.95	10.5	9.17	9.97	22.0

Source: Study No. RRB200-017, pages 54-55.
GAA activity was measured as digestion of 4-MU-α-Glc 4-methylumbeliferrone (4-MU) compared to a standard curve of 4-MU. The absolute GAA activity in each lysate was normalized by its protein concentration, and the final specific activity was expressed as nanomoles of released 4-MU per milligram of total protein per hour (nmol/mg protein/hour).
* CDER statistical analysis: Statistical significance was determined using the 2-sided t-test, where * represents p<0.05 versus alglucosidase alfa.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; GAA, human acid α-glucosidase; 4-MU, 4-MU-α-Glc 4-methylumbeliferrone

Figure 52. GAA Enzyme Activity in Tissues After 3 Months of Treatment



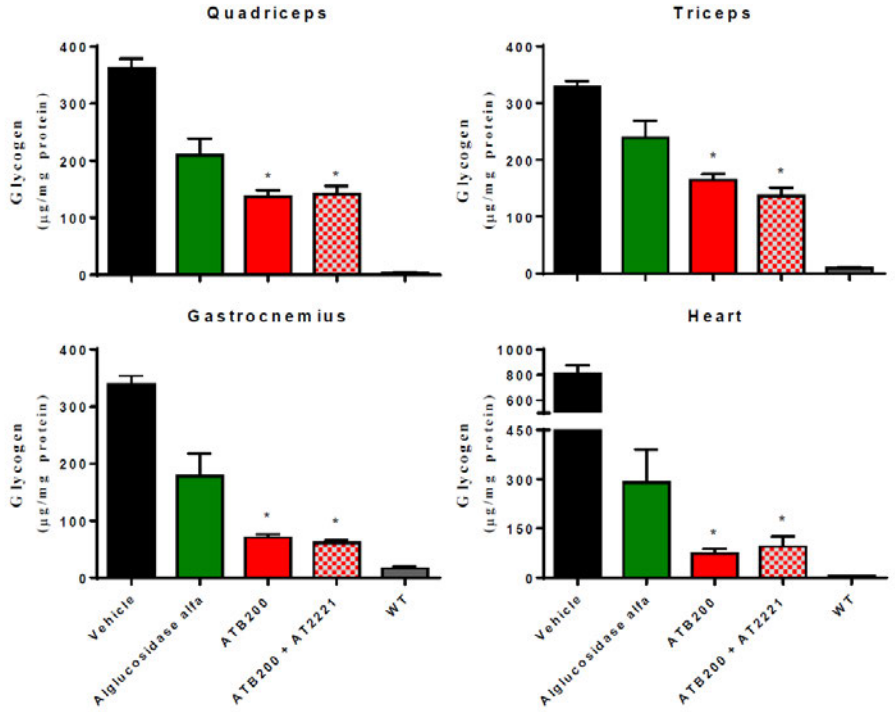
Source: Applicant's figure from Pharmacology Study # RRB200-017, p.24.
GAA enzyme activities were measured 14 days after the 6th administration in mice. Each column represents mean ± SEM of 6-7 animals. There were no differences in measured GAA activities between treatment groups in knockout (KO) mice.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; GAA, human acid α-glucosidase; KO, knockout; 4-MU, 4-MU-α-Glc 4-methylumbeliferrone; SEM, standard error of means

Table 67. GAA Enzyme Activity (nmol/mg protein/hour) Following 6 Months of Treatment

Muscle Type	Vehicle	Alglucosidase Alfa 20 mg/kg	ATB200 20 mg/kg	ATB200 20 mg/kg AT2221 10 mg/kg	Wild Type
Quadriceps	0.81	2.74	2.04	2.13	18.9
Triceps	0.67	3.64	5.02	3.56	16.6
Heart	1.52	3.03	3.27	2.65	19.0
Gastrocnemius	0.70	10.1	11.3	10.6	17.1

Source: Pharmacology Study No. RRB200-017, pages 58-59.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; GAA, human acid α-glucosidase

Figure 53. Glycogen Levels in Tissues of *Gaa* KO Mice After 6 Months of Treatment



Source: Applicant's figure from Pharmacology Study # RRB200-017, p.24.
Glycogen levels were measured 14 days after the 12th administration from remaining animals in each group. Each column represents mean ± SEM of the 5-8 animals. Statistical significance was determined using Dunnett's multiple comparison under one-way ANOVA, where * represents p<0.05 versus alglucosidase alfa.
Abbreviations: ANOVA, analysis of variance; ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; KO, knockout; SEM, standard error of means

Table 68. Grip-Strength (g) in *Gaa* KO Mice

Treatment	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Alglucosidase	112.2	99.5	103.8	102.5	104.5	102.8	126.2
ATB200/AT2221	103.9	111.4	117.7*	121.3*	138.6*	139.08*	151.5*
ATB200	106.9	109.3	123.1	118.8	128.0	122.0	152.3
Wild type	152.5	162	158	141.3	157	143	160.9
Vehicle	110.1	91.5	95.9	93.1	95.6	85.0	94.4

Source: Pharmacology Study No. RRB200-017, appendix C, pages 40-45.
Muscle function was assessed once per month. The wire-hang assay was conducted once on two consecutive days, with the data shown being the average of two assessments, while the grip-strength assay was repeated thrice on the same day, with the data shown being the average of those three assessments. Each point represents the mean ± SEM of 15 animals/group up to 3 months, and 8 animals/group for the remaining 3 months (7 animals sacrificed after 3 months). CDER statistical analysis was determined using the 2-sided t-test, where * represents p<0.05 versus alglucosidase alfa
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene; SEM, standard error of means

Over a period of 6 months, treatment of *Gaa* KO mice with ATB200/AT2221 showed a trend for increased hang time (wire hang latency) in the wire-hang assay compared to those treated with alglucosidase alfa; however, the pairwise comparisons showed no statistical difference between ATB200/ AT2221 and alglucosidase alfa. In this assay, the trend reflects an apparent decrease in function in the alglucosidase treated animals, particularly at month 1, while ATB200/AT2221-treated animals maintain function.

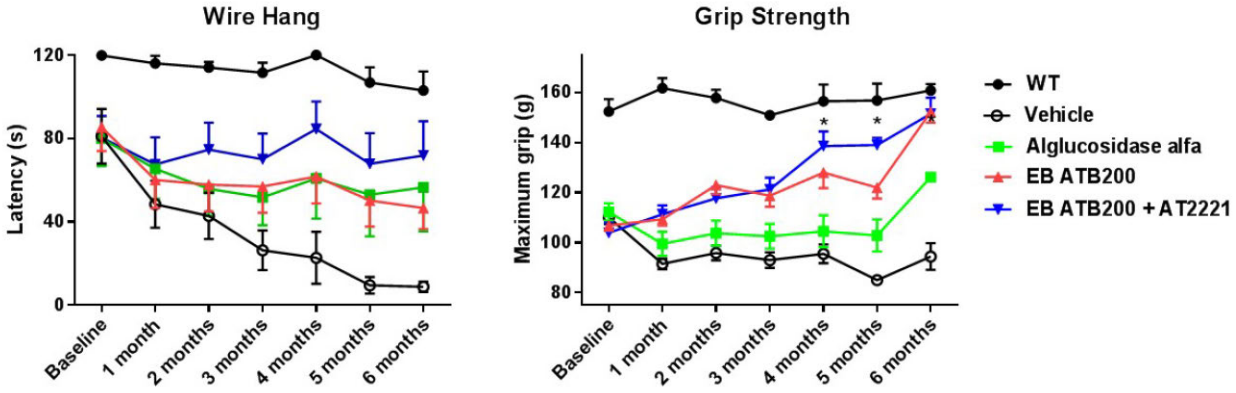
Table 69. Wire Hang Latency (secs) in *Gaa* KO Mice

Treatment	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Alglucosidase	79.9	65.4	55.6	51.8	60.8	53.1	56.6
ATB200/AT2221	80.4	67.4	74.6	70.1	84.5	67.8	71.8
ATB200	85.4	60.0	57.7	57.0	61.8	50.3	46.7
Wild type	119.9	116.1	114.1	115.5	105.8	94.8	103
Vehicle	81.0	48.4	42.8	26.4	22.7	9.6	8.9

Source: Pharmacology Study No. RRB200-017, appendix C, pages 46-51.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; Gaa, acid alpha-glucosidase gene

Figure 54 graphically depicts the results of the Wire Hang and Grip Strength assays in *Gaa* KO mice.

Figure 54. Muscle Function Assessments Using Wire Hang and Grip Strength Assays (RRB200-017)



Source: Pharmacology Study No. RRB200-017, p. 62.
The wire-hang assay was conducted once on 2-consecutive days, with the data shown being the average of 2 assessments, while the grip-strength assay was repeated (3 times) on the same day, with the data shown being the average of those three assessments (the Applicant considered the possibility of a systematic error during the 6th assessment for grip-strength). Each point represents the mean ± SEM of 15 animals/group up to 3 months, and 8 animals/group for the remaining 3 months (7 animals sacrificed after 3 months). Statistical significance was determined using the 2-sided t-test, where * represents p<0.05 versus alglucosidase alfa.
Abbreviations: ATB200, cipaglucosidase alfa; AT2221, miglustat; IV, intravenous; QOW, every other week; SEM, standard error of means; WT, wild type

Table 70 was constructed from glycogen levels in muscles of KO mice following biweekly treatments for 1, 2, 3 or 6 months. The coadministration of ATB200/AT2221 significantly reduced glycogen levels in quadriceps for up to 2 months, compared to ABT200 alone. There were no differences in glycogen level for the heart or skeletal muscles following coadministration of ATB200/AT222 or ABT200 alone at 3 or 6 months.

Table 70. Glycogen Levels (ug/g) in KO Mice Following 1, 2, 3, or 6 Months of Treatment With ABT200 (20 mg)/AT2221 (10 mg) or ABT200 (20 mg) Alone (RRB200-017)

	1 month			2 months	3 months		6 months
Number of Biweekly Treatments	**b 296**	**b 320**	**b 328**	**a 294B**	**a 294A**	**C**	**c**
		2		**4**	**6**		**12**
Muscle Type							
Quadriceps							
ABT200/AT2221	101.8*	112.4*	196.3	51.2*	66.5	65.4	141.0
ABT200 alone	165.2	186.2	224.7	101.9	81.9	58.3	136.4
Triceps							
ABT200/AT2221				142.1	106.1	107.7	136.8
ABT200 alone				187.0	100.7	124.9	164.6

Number of Biweekly Treatments	1 month b 296	b 320 2	b 328	2 months a 294B 4	3 months a 294A 6	C	6 months c 12
Muscle Type							
Heart							
ABT200/AT2221				19.3	31.5	39.5	95.1
ABT200 alone				16.2	39.2	50.6	74.9
Gastrocnemius							
ABT200/AT2221						37.2	61.4
ABT200 alone						42.1	70.4

Source: a from Study # RRB200-004 studies 294A and 294B, p.30; b from Study # RRB200-005 studies 296, 320 and 328, p.32; c from Study # RRB200-017, p.52.
a, c An amyloglucosidase-based biochemical method and a high-pH anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) chromatography method were used.
a Glycogen was digested and read with a glucose assay.
* CDER statistical analysis was determined using the 2-sided t-test, where * represents p<0.05 versus ABT200 alone.
Abbreviations: ATB200, cipaglucosidase alfa; AT221, miglustat; HPAEC-PAD, high-pH anion exchange chromatography with pulsed amperometric detection; KO, knockout; pH, potential of hydrogen

Table 71 was constructed from GAA enzyme activity levels in muscles of KO mice following biweekly treatments for 1, 2, 3, or 6 months. The coadministration of ATB200/AT2221 did not increase GAA enzyme activity levels in quadriceps, triceps, gastrocnemius or heart compared to ABT200 treatment alone.

Table 71. GAA Enzyme Activity (nmol/mg protein/hour) in KO Mice Following 1, 2, 3, or 6 Months of Treatment With ABT200 (20 mg)/AT2221 (10 mg) or ABT200 (20 mg) Alone (RRB200-017)

Number of Biweekly Treatments	1 Month C 2	b	2 Months b 4	3 Months a 6	d	6 Months d 12
Muscle Type						
Quadriceps						
ABT200/AT2221	8.35	5.22	13.3	2.90	2.96	2.13
ABT200 alone	4.68	3.56	4.21	1.68	2.97	2.04
Triceps						
ABT200/AT2221	4.35		11.5	3.90	5.86	3.56
ABT200 alone	4.89		5.35	2.95	3.45	5.02
Heart						
ABT200/AT2221	3.80		5.45	3.01	2.27	2.65
ABT200 alone	3.62		4.42	5.99	2.33	3.27
Gastrocnemius						
ABT200/AT2221					9.97	10.6
ABT200 alone					9.17	11.3

Source: a: From study report RRB200-004; b: From study report rrb200-005; c: From study report rrb200-014; d: From study report RRB200-017.
*CDER statistical analysis was determined using the 2-sided t-test, where * represents p<0.05 versus ABT200 alone.
Abbreviations: ATB200, cipaglucosidase alfa; AT221, miglustat; GAA, human acid α-glucosidase; KO, knockout

Table 72 and Table 73 were constructed from muscle function tests in *Gaa* KO mice following biweekly treatments for 1 to 6 months. In the grip-strength assay, the pairwise comparisons showed no differences for the coadministration of ATB200/AT2221, when compared to ABT200 treatment, for grip strength, except in month 5.

Table 72. Grip-Strength (g) in *Gaa* KO Mice

Treatment	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
ATB200/AT2221	103.9	111.4	117.7	121.3	138.6	139.0*	151.5
ATB200	106.9	109.3	123.1	118.8	128.0	122.0	152.3

Source: Pharmacology Study No. RRB200-017, appendix C, pages 40-45.
Muscle function was assessed once per month. The wire-hang assay was conducted once on two consecutive days, with the data shown being the average of two assessments, while the grip-strength assay was repeated thrice on the same day, with the data shown being the average of those three assessments. Each point represents the mean ± SEM of 15 animals/group up to 3 months, and 8 animals/group for the remaining 3 months (7 animals sacrificed after 3 months). Statistical significance was determined using the 2-sided t-test, where * represents $p<0.05$ versus ABT200 alone.
Abbreviations: ATB200, cipaglucosidase alfa; AT221, miglustat; Gaa, acid alpha-glucosidase gene; SEM, standard error of means

Over a period of 6 months, treatment of *Gaa* KO mice with ATB200/AT2221 did not increase wire hang time compared to those treated with ABT200 alone.

Table 73. Wire Hang Latency (secs) in *Gaa* KO Mice

Treatment	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
ATB200/AT2221	80.4	67.4	74.6	70.1	84.5	67.8	71.8
ATB200	85.4	60.0	57.7	57.0	61.8	50.3	46.7

Source: Pharmacology Study No. RRB200-017, appendix C, pages 46-51.
Abbreviations: ATB200, cipaglucosidase alfa; AT221, miglustat; Gaa, acid alpha-glucosidase gene

In in vivo PK studies to assess $t_{1/2}$ and AUC of IV cipaglucosidase alfa (5, 10, 20, or 100 mg/kg) or alglucosidase alfa (20 mg/kg), and the effects of oral coadministration of miglustat (10 or 30 mg/kg) in the plasma of *Gaa* KO mice, it was shown that the half-life of cipaglucosidase alfa was modestly increased by miglustat from 0.73 to 0.93 with 10 mg/kg miglustat and from 0.73 to 0.97 at 30 mg/kg. (Study no. RRB200-10).

Assessment of Study RRB200-017

The review team concluded from this study that cipaglucosidase alfa coadministered with miglustat treatment in male *Gaa* KO mice resulted in significant decreases in muscle tissue glycogen and significant increases in muscle function as measured by grip strength, compared to alglucosidase alfa treatment, the standard of care for Pompe disease. The effects on glycogen reduction in heart and on grip strength persisted for at least 6 months. The long-term contribution of miglustat to the efficacy of cipa-mig was not adequately demonstrated. Although cipa-mig treatment resulted in decreased glycogen levels in tissues compared to cipa alone up to 2 months of treatment, no improvement in glycogen levels was seen thereafter. No improvement of cipa-mig over cipa alone in GAA enzyme activity was observed at 3 or 6 months. Improvement in muscle function (grip strength) following cipa-mig treatment was observed at 5 months in KO mice, compared to cipa alone, but was not observed at 6 months. Over a period of 6 months, treatment of *Gaa* KO mice with ATB200/AT2221 did not increase wire hang time compared to those treated with ABT200 alone.

Pharmacokinetics

Comparison of Pharmacokinetics and Efficacy of ATB200 to AT2221 (Study # RRB200-066)

The objectives of this study were to determine the half-life and clearance of AT2221 and ATB200 in plasma and muscle tissues and to investigate the effects of AT2221 co-administration on ATB200 efficacy after two-bi-weekly dosing in male *Gaa* KO mice.

Methods

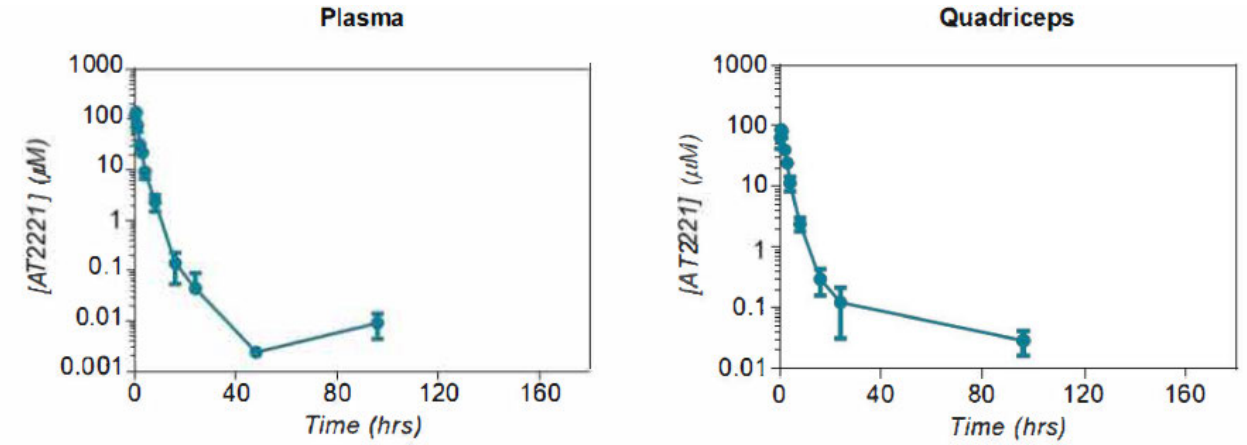
14-19 weeks old male C57BL6 or *Gaa* KO mice weighing 20-35 g were administered, either oral gavage doses of 100 mg/kg AT2221 for the wildtype mice (Study 169); or a single IV dose of 20 mg/kg ATB200 with or without oral co-administration of 10 and 30 mg/kg of AT2221, respectively for the KO mice (Study 338); or bi-weekly (i.e., every other week) IV administration of 20 mg/kg ATB200, in addition to some of the mice first receiving 10 mg/kg oral AT2221 30 minutes prior to the IV ATB200 for the wildtype (129/SvEv) and the KO mice (Study 359).

In Study 338, mice were sacrificed, and plasma and tissue samples were collected from 5 minutes to 7 days post-dose. In Study 359, following each IV administration, plasma was collected via submandibular bleeding, and 14-days after the dosing, animals were euthanized, and plasma and tissues (liver, kidney, heart, diaphragm, tongue, hind and fore limbs) were collected. Half-life and clearance of administered drugs were determined by LC-MS, along with measurements of substrate glycogen clearance, and *GAA enzyme* activity assay.

Results

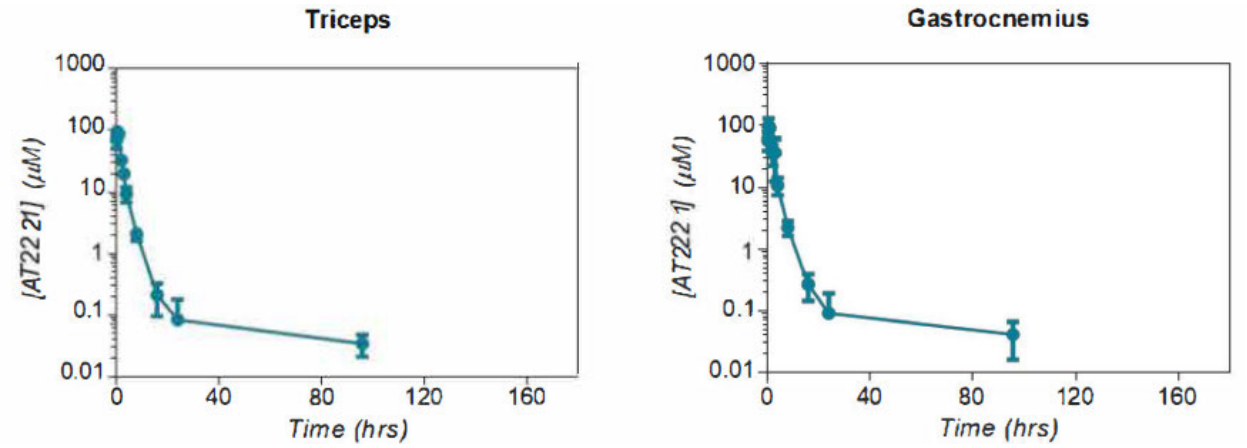
From data collected at up to 96 hours post AT2221 treatment, the half-life of Miglustat was determined to be 1.0 hour in plasma and 1.5 to 1.9 hours in muscle tissues. The half-life of ATB200 was also determined to be 0.6 hours in plasma and ranging from 58.1 – 87.3 hours in muscle tissues, as shown in the figure below.

Figure 55. Miglustat Half-life and Clearance



Source: Study number RRB200-066.

Figure 56. Miglustat Half-life and Clearance



Abbreviations: AT2221 = *N*-Butyldeoxynojirimycin, also known as miglustat
Note: Pharmacokinetics in plasma and tissues of mice treated with 100 mg/kg miglustat (AT2221). LC-MS was used to measure miglustat levels over time. Tissues were harvested at 0, 0.25, 0.5, 1, 2,3, 4,8, 16, 24 and 96 hours post-AT2221 administration. Datapoints were fitted to the One Phase Decay equation on Prism to estimate the half-life of miglustat (see Table 3).
Source: Pompe - Study 169 - NS - 001 (study 169)

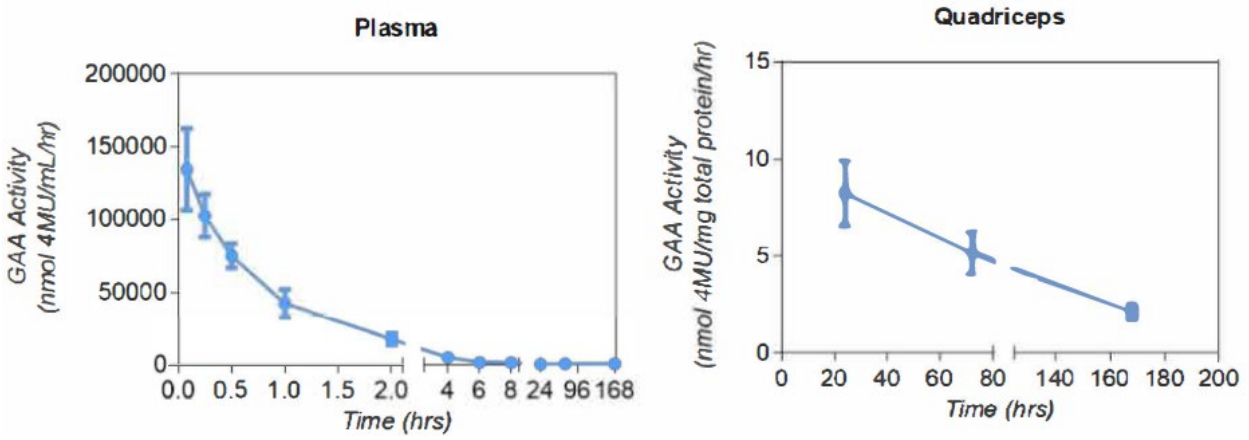
Table 74. Miglustat Half-life

Tissue	AT2221 Half-life	
	AT2221 Half-life (hrs)	AT2221 95% CI (hrs)
Plasma	1.0	0.8 to 1.0
Quad	1.8	1.4 to 2.6
Triceps	1.5	1.1 to 2.1
Gastroc	1.9	1.3 to 3.0

Abbreviations: AT2221 = *N*-Butyldeoxynojirimycin, also known as miglustat; Gastroc = gastrocnemius; Quad = quadriceps femoris
Source: Pompe - Study 169 - NS - 001 (study 169)

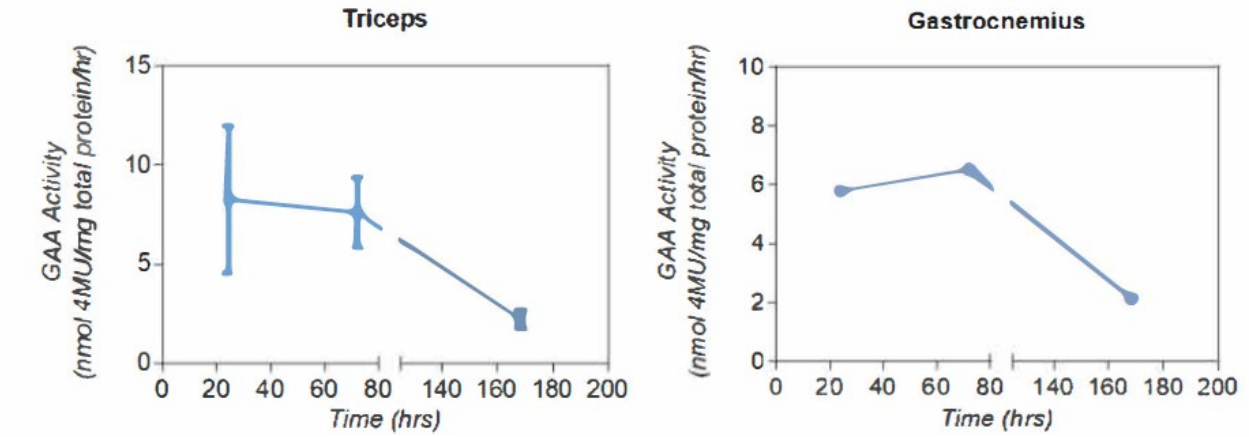
Figure 57. Cipaglucosidase Alfa Half-life and Clearance

:



Source: Study number RRB200-066.

Figure 58. Cipaglucosidase Alfa Half-life and Clearance



Abbreviations: 4MU = 4-methylumbelliferone; ATB200 Amicus's proprietary recombinant human α-glucosidase
Note: Pharmacokinetics of ATB200 in plasma and tissues of treated mice. Enzymatic activity was used as a readout for ATB200 levels over time. Plasma was collected at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 24, 72 and 168 hours, and tissues were harvested at 24, 72, and 168 hours post 20 mg/kg ATB200 administration. Datapoints were fitted to the One Phase Decay equation on Prism to estimate the half-life of ATB200 (see Table 4).
Source: Pompe combo - RS – 005 (study 359)

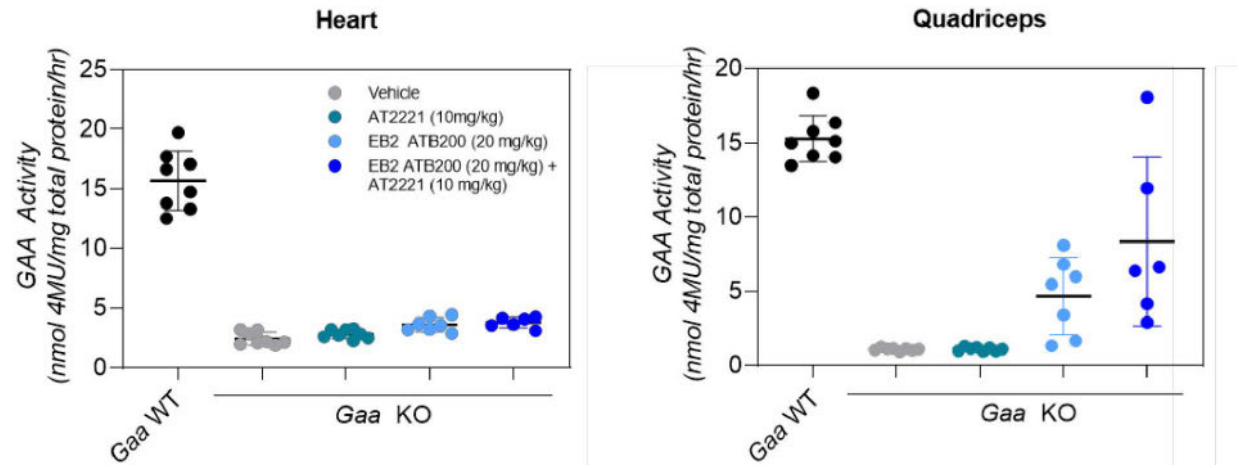
Table 75. Cipaglucosidase Alfa Half-life

Tissue	ATB200 Half-life	
	ATB200 Half-life (hrs)	ATB200 95% CI (hrs)
Plasma	0.6	0.5 to 0.7
Quad	58.1	39.1 to 90.0
Triceps	87.3	42.3 to 272.2
Gastroc	68.8	19.9 to 5288.0

Abbreviations: ATB200 Amicus's proprietary recombinant human α-glucosidase; gastroc = gastrocnemius; quad = quadriceps femoris
Source: Pompe combo - RS – 005 (study 359)

In studies 169, 338 and 359, comparable levels of GAA activity were observed with dual administration of AT2221 and ATB200 in the heart and triceps, with an overall trend toward increased GAA activity in the quadriceps and gastrocnemius, in comparison to individual treatments of AT2221 and ATB200. The dual administration of AT2221 and ATB200 resulted in similar levels of glycogen in all tissues, in comparison to ATB200 alone, with levels that were much lower than AT2221 alone. The study results are shown below.

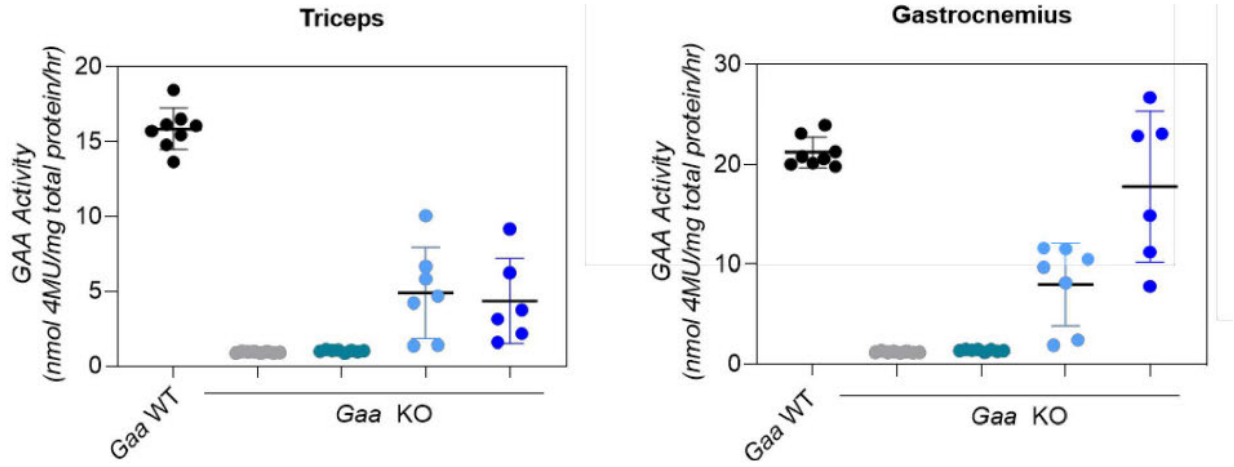
Figure 59. GAA Activity in Heart and Quadriceps Muscles



Abbreviations: 4MU = 4-methylumbelliferone; ATB200 Amicus's proprietary recombinant human α-glucosidase; AT2221 = N-Butyldeoxynojirimycin, also known as miglustat; GAA = α-glucosidase; KO = knockout
Note: GAA activity in the tissues of Gaa-KO mice treated with vehicle, AT2221 alone at 10 mg/kg, ATB200 alone at 20 mg/kg, or AT2221+ATB200 at 10 mg/kg and 20 mg/kg respectively. GAA activity in untreated WT animals is also shown. Co-administration with AT2221 at a 10 mg/kg dose 30 minutes prior to IV infusion of ATB200 does

Source: Study Number RRB200-066.

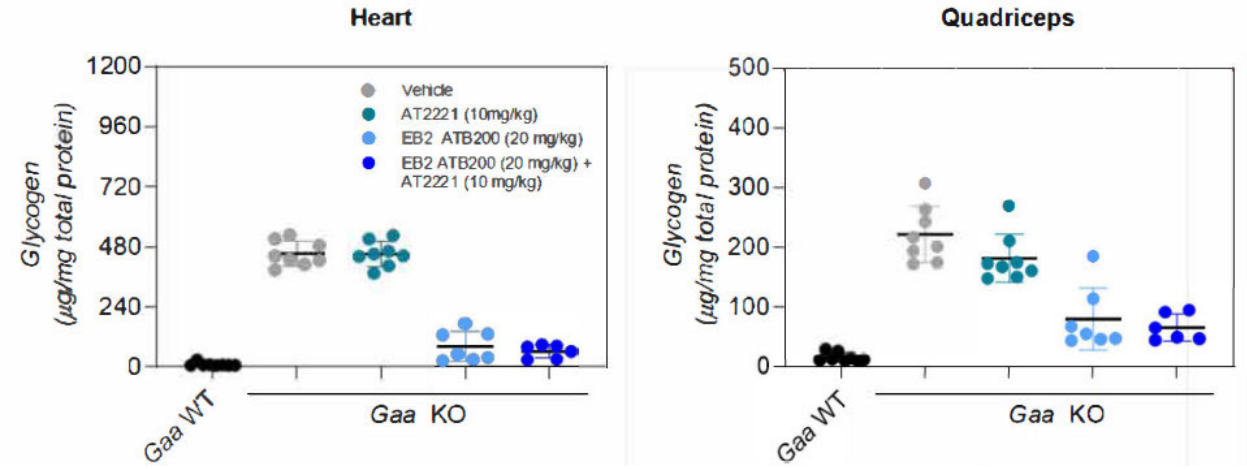
Figure 60. GAA Activity in Triceps, and Gastrocnemius Muscles



Abbreviations: 4MU = 4-methylumbelliferone; ATB200 Amicus's proprietary recombinant human α-glucosidase; AT2221 = N-Butyldeoxynojirimycin, also known as miglustat; GAA = α-glucosidase; KO = knockout
Note: GAA activity in the tissues of Gaa-KO mice treated with vehicle, AT2221 alone at 10 mg/kg, ATB200 alone at 20 mg/kg, or AT2221+ATB200 at 10 mg/kg and 20 mg/kg respectively. GAA activity in untreated WT animals is also shown. Co-administration with AT2221 at a 10 mg/kg dose 30 minutes prior to IV infusion of ATB200 does

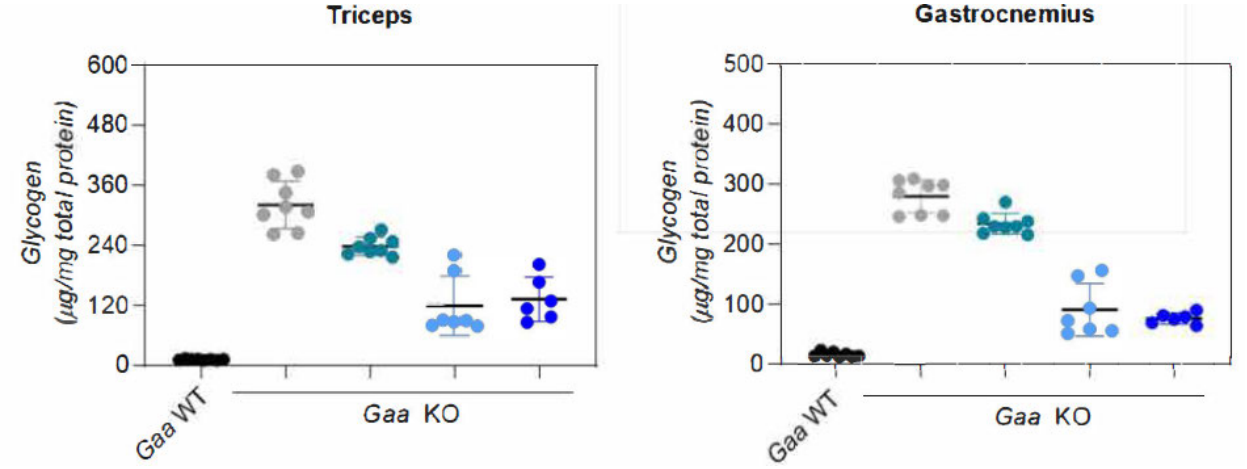
Source: Study number RRB200-066.

Figure 61. Glycogen Levels in Heart and Quadriceps Muscles



Abbreviations: ATB200 Amicus's proprietary recombinant human α-glucosidase; AT2221 = N-Butyldeoxynojirimycin, also known as miglustat; GAA = α-glucosidase; hrs = hours; KO = knockout
Note: Glycogen levels in quadriceps of Gaa-KO mice treated with a vehicle, AT2221 alone at 10 mg/kg, ATB200 alone at 20 mg/kg, or AT2221+ATB200 at 10 mg/kg and 20 mg/kg respectively. Glycogen levels in untreated WT animals are also shown. Glycogen reduction achieved in the tissues of animals treated with ATB200 alone is comparable to those to which ATB200 was co-administered with AT2221.
Source: Pompe-AG – 005 (study 338)

Figure 62. Glycogen Levels in Triceps and Gastrocnemius Muscles



Abbreviations: ATB200 Amicus's proprietary recombinant human α-glucosidase; AT2221 = N-Butyldeoxynojirimycin, also known as miglustat; GAA = α-glucosidase; hrs = hours; KO = knockout
Note: Glycogen levels in quadriceps of Gaa-KO mice treated with a vehicle, AT2221 alone at 10 mg/kg, ATB200 alone at 20 mg/kg, or AT2221+ATB200 at 10 mg/kg and 20 mg/kg respectively. Glycogen levels in untreated WT animals are also shown. Glycogen reduction achieved in the tissues of animals treated with ATB200 alone is comparable to those to which ATB200 was co-administered with AT2221.
Source: Pompe-AG – 005 (study 338)

In conclusion, the study results show that miglustat (AT2221) has a short half-life of less than 2 hours in plasma and muscles, even at an orally administered high dose of 100 mg/kg. In contrast, Cipaglucosidase alfa (ATB200) has a half-life of 2+ days following IV infusion, but is cleared from the plasma at a comparable rate to AT2221.

When miglustat is orally administered 30 minutes prior to ATB200 IV infusion, 10 mg/kg AT2221 does not cause prolonged inhibition of GAA activity since comparable activity was measured in muscle tissues, relative to animals dosed with ATB200 alone. Substrate glycogen reduction seen in tissues of mice treated with ATB200 and AT2221 co-administration was also comparable to, or superior to the reduction seen in treatment with ATB200 alone. The results show that the miglustat dose or co-administration dosing regimen does not interfere with or inhibit ATB200 activity in muscle tissues.

13.2. Individual Reviews of Studies Submitted to the BLA/NDA

General Toxicology

Study Number (b) (4).423.08 (A 26-Week Intravenous Repeat-Dose Toxicity and Toxicokinetic Study of ATB200 in Sprague-Dawley Rats Followed by a 4-Week Recovery)

Key Study Findings

In a 26-week GLP study in rats (biweekly, iv, N=10), no clinical signs, neurobehavioral effects (functional observation battery), effects on food consumption or body weights, ophthalmologic effects, clinical pathology (urinalysis, hematology, coagulation, and serum chemistry), organ weights, gross necropsy observations, organ weights or histopathology were observed at doses

up to 200 mg/kg/day (about 15.2 times the exposure at the MRHD of 20 mg/kg ABT200, via AUC).

Study Number (b) (4) 423.07 (A 26-Week Intravenous Repeat-Dose Toxicity and Toxicokinetic Study of ATB200 in Cynomolgus Monkeys by a 4-Week Recovery)

Key Study Findings

In a 26-week GLP study in monkeys (biweekly, IV, N=10), no clinical signs, effects on electrocardiography, effects on food consumption or body weights, ophthalmologic effects, clinical pathology (urinalysis, hematology, coagulation, and serum chemistry), organ weights, gross necropsy observations, organ weights or histopathology were observed at doses up to 200 mg/kg/day (about 18.1 times the exposure at the MRHD of 20 mg/kg ABT200, via AUC).

Study Number (b) (4) 423.10 (A 13-Week Repeat Dose Toxicity Study of ATB200 Coadministered with Miglustat in Cynomolgus Monkeys)

Key Study Findings

In a 13-week GLP study in monkeys (biweekly, IV, N=4), no clinical signs, effects on electrocardiography, effects on food consumption or body weights, ophthalmologic effects, clinical pathology (urinalysis, hematology, coagulation, and serum chemistry), organ weights, gross necropsy observations, organ weights or histopathology were observed at doses up to 100 mg/kg ABT200 (about 9.9 times the exposure at the MRHD of 20 mg/kg ABT200, via AUC) and 175 mg/kg miglustat (about 8.7 times the exposure at the MHRD of 260 mg miglustat for this indication).

General Toxicity of Miglustat

In a 13-week repeat dose toxicity study of ATB200 coadministered with miglustat in Cynomolgus monkeys (Study No. (b) (4) 423.10) (biweekly, IV, N=4), no clinical signs, effects on electrocardiography, effects on food consumption or body weights, ophthalmologic effects, clinical pathology (urinalysis, hematology, coagulation, and serum chemistry), organ weights, gross necropsy observations, organ weights or histopathology were observed at doses up to 100 mg/kg ABT200 (about 9.9 times the exposure at the MRHD of 20 mg/kg ABT200, via AUC) and 175 mg/kg miglustat (about 8.7 times the exposure at the MHRD of 260 mg miglustat for this indication).

However, in the Zavesca label, the following effects were noted at high doses of miglustat in animals:

Histopathology findings in the absence of clinical signs in the central nervous system of the monkey (brain, spine) that included vascular mineralization, in addition to mineralization and necrosis of white matter were observed at >750 mg/kg/day (4 times the human therapeutic systemic exposure based on area-under-the-plasma-concentration curve [AUC] comparisons) in a 52-week oral toxicity study using doses of 750 and 2000 mg/kg/d. Vacuolization of white matter was observed in rats dosed orally by gavage at ≥ 180 mg/kg/d (6 times the human therapeutic exposure based on surface area comparisons, mg/m2) in a 4-week study using doses of 180, 840, and 4200 mg/kg/d. Vacuolization can sometimes occur as an artifact of tissue processing. Findings in dogs included tremor and absent corneal reflexes at 105 mg/kg/day (10

times the human therapeutic systemic exposure, based on body surface area comparisons, mg/m2) after a 4-week oral gavage toxicity study using doses of 35, 70, 105, and 140 mg/kg/d. Ataxia, diminished/absent pupillary, palpebral, or patellar reflexes were observed in a dog at ≥495 mg/kg/day (50 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m2), in a 2-week oral gavage toxicity study using doses of 85, 165, 495, and 825 mg/kg/d.

Cataracts were observed in rats at ≥180 mg/kg/day (4 times the human therapeutic systemic exposure, based on AUC) in a 52-week oral gavage toxicity study using doses of 180, 420, 840, and 1680 mg/kg/d.

Gastrointestinal necrosis, inflammation, and hemorrhage were observed in dogs at ≥ 85 mg/kg/day (9 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m2) after a 2-week oral (capsule) toxicity study using doses of 85, 165, 495, and 825 mg/kg/d. Similar GI toxicity occurred in rats at 1200 mg/kg/day (7 times the human therapeutic systemic exposure, based on AUC) in a 26-week oral gavage toxicity study using doses of 300, 600, and 1200 mg/kg/d. In monkeys, similar GI toxicity occurred at ≥750 mg/kg/day (6 times the human therapeutic systemic exposure based on AUC) following a 52-week oral gavage toxicity study using doses of 750 and 2000 mg/kg/d.

Genotoxicity

No genotoxicity studies were conducted with cipaglucosidase alfa, consistent with ICH S6 (R1) *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*, June 2011; and, Guidance for Industry: *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment*, October, 2019, since cipaglucosidase alfa is a recombinant glycoprotein and a replacement enzyme, and is not expected to exhibit genotoxic potential.

The genotoxicity of miglustat was previously investigated as part of the Zavesca development program by Actelion Pharma LTD. From the Zavesca label: Miglustat was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including the bacterial reverse mutation (Ames), chromosomal aberration (in human lymphocytes), gene mutation in mammalian cells (Chinese hamster ovary), and mouse micronucleus assays.

Carcinogenicity

No carcinogenicity studies were conducted with cipaglucosidase alfa, consistent with ICH S6 (R1) *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*, June 2011 and, Guidance for Industry: *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment*, October 2019. No carcinogenicity studies were conducted with the coadministered products. Cipaglucosidase alfa is a recombinant glycoprotein and is not expected to exhibit carcinogenic potential.

The carcinogenicity of miglustat was previously investigated as part of the Zavesca development program by Actelion Pharma LTD. From the Zavesca label: Two-year carcinogenicity studies have been conducted with miglustat in CD-1 mice at oral doses up to 500 mg/kg/day and in Sprague Dawley rats at oral doses up to 180 mg/kg/day. Oral administration of miglustat for 104 weeks produced mucinous adenocarcinomas of the large intestine at 210, 420 and 500 mg/kg/day (about 3, 6 and 7 times the recommended human dose, respectively, based on the body surface area) in male mice and at 420 and 500 mg/kg/day (about 6 and 7 times the recommended human

dose, based on the body surface area) in female mice. The adenocarcinomas were considered rare in CD-1 mice and occurred in the presence of inflammatory and hyperplastic lesions in the large intestine of both males and females. In rats, oral administration of miglustat for 100 weeks produced increased incidences of interstitial cell adenomas of the testis at 30, 60 and 180 mg/kg/day (about 1, 2 and 5 times the recommended human dose, respectively, based on the body surface area).

Reproductive and Developmental Toxicity

Reviewer's Comment: All DART studies were of similar design, differing only in the windows of reproductive exposure. All doses were administered every other day, to assure that critical windows of development (prior to pregnancy, prior to implantation, organogenesis, the fetal period and lactation) were covered. This was unique in the toxicology assessment of cipaglucosidase alfa and miglustat; conventional single- and repeated-dose studies in rats and cynomolgus monkeys followed the clinical dosing paradigm, with dosing once every 14 days.

While the frequency of dosing in the DART studies addressed the importance of exposure during critical windows of development, it raised questions regarding the number of doses that produced developmental toxicity in three of four definitive studies. Briefly, a hallmark of DART study interpretation is the recognition that a single drug exposure during critical windows, however brief, may have lasting adverse effects on the conceptus. Existing DART study designs could not determine whether developmental toxicity was due to one or multiple gestational exposures in rats and rabbits.

As such, calculation of safety margins for the DART studies required careful consideration. The Applicants maintained that margins should be calculated based on cumulative gestational drug exposure, relative to every other week dosing in humans. This approach is problematic; as indicated, by virtue of the DART study designs, it is not possible to address whether single doses administered during critical windows are responsible for observed developmental toxicities. However, if single exposures are, in fact, responsible for findings, then margins calculated from cumulative gestational drug exposure will be inflated, with resultant faulty risk assessments for serious developmental toxicity.

The ORPURM Division of Pharmacology and Toxicology requested a consultation with the Pharmacokinetics Subcommittee (PKS) of the Pharmacology and Toxicology Coordinating Committee (PTCC) to request advice on this matter. Briefly, the PKS agreed that the most conservative approach to plasma exposure margin calculations is to proceed from the assumption that a single dose of cipaglucosidase alfa and miglustat could evoke the serious developmental toxicities reported. In this, they rejected margin calculations using cumulative gestational exposure.

In the following reviews, single-dose C_{max} and AUC values are presented for cipaglucosidase alfa and miglustat at NOAELs and LOAELs, to permit reader assessment of comparability to human exposure values. The assumption is that the comparator is the MRHD in humans cipaglucosidase alfa is 1200 mg (20 mg/kg x 60 kg), while the MHRD for miglustat is 260 mg. Clinical exposures for cipaglucosidase alfa and miglustat are assumed to be 1400 µg*h/mL and 20000 ng*h/mL, respectively.

Table 76. Fertility and Early Embryonic Development

Study title: Study of Fertility and Early Embryonic Development to Implantation, with Toxicokinetic Evaluation, in Rats with ATB200 Alone or Coadministered with AT2221	
Study no.:	8371927
Study report location:	0001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 12, 2018
GLP compliance:	Yes
QA statement:	Y
Drug, lot #, and % purity:	ATB200(WBP110), 2018-01-04, 96.4%

Source: Review team.
Abbreviations: GLP, good laboratory practices; QA, quality assurance

Key Study Findings

ATB200 was administered by infusion to male and female rats, at doses of 70, 150, or 400 mg/kg every other day. Dosing was initiated in males 28 days prior to cohabitation with untreated females; the total number of doses administered was unspecified. Dosing was initiated in females 14 days prior to cohabitation with untreated males, and continued through GD 7 among females with confirmed mating; or until 13 days beyond the end of mating, for females without confirmation of mating. DPH (10 mg/kg) was administered by intravenous push 90 min prior to the onset of the ATB200 infusion, beginning with the 2nd administered dose. One experimental group (Group 3) received oral AT2221 (60 mg/kg) alone, administered every other day. One experimental group (Group 7) received intravenous ATB200 with oral ATT2221 (60 mg/kg); the latter was administered 30 min prior to the onset of infusion, every other day.

Nine of 106 ATB200-treated females were found dead or euthanized (vs 1/72 control females); similarly, 7/106 ATB200-treated males were found dead (vs 1 among 72 control males). While the incidences of mortality were unrelated to nominal dose or length of dosing duration, animals treated with the highest dose of ATB200 and concomitant ATB2221 were represented more frequently than other treatment groups.

Increased incidence of preimplantation loss was noted among treated females in Groups 3 and 7 (> 21%), relative to concurrent control groups, as well as the upper range of historical control values (8.6%). Increased preimplantation loss was also noted among naïve females bred to treated males in Group 7 (25.9%) after the first cohabitation. Dosing of males was terminated, and the males were permitted a recovery period of unspecified duration, after which they were bred to a second group of naïve females. Following the second cohabitation, preimplantation loss in Group 7 (12%) still exceeded historical control values, although it was comparable to that in Group 3.

The maternal and paternal ATB200 NOAELs were 150 mg/kg. Toxicokinetic sampling was not conducted for either males or females in the present study at this dose level. ATB200 exposures are inferred from those of the same dose level in the Embryo-fetal Development (EFD) study in rats (noting that sex-based exposure differences have not been reported for either drug). The mean C_{max} associated with ATB200 at 150 mg/kg is 2715 mcg/mL; the mean AUC_{0-24} at this dose level is 6210 mcg*h/mL. The ATB200 safety margins (based on clinical C_{max} and AUC values of 280 µg/mL and 1400 µg*h/mL, respectively) at this dose level are 9.7 and 4.4, respectively.

There was no NOAEL for the coadministration of ATB200 with AT2221 in treated males or females. The Lowest adverse effect level (LOAEL) for AT2221 was 60 mg/kg. In treated males, the AT2221 C_{max} associated with this dose on Study Day 28 was 19900 ng/mL; the AUC was 96000. In treated males, the AT2221 safety margins (based on AT2221 clinical C_{max} of 2400 ng/mL and AUC value of 20000 ng*h/mL) were 8.3 and 4.8, respectively. In treated females, the AT2221 C_{max} associated with this dose on GD 7 is 16100 ng/mL; the AUC at this dose level is 87600 ng*h/mL. In treated females, the AT2221 safety margins are 6.7 and 4.4, respectively.

Table 77. Study 8371927 Methods

Doses:	ATB200 0, 70, 150, 400 mg/kg AT2221 60 mg/kg
Frequency of dosing:	Every other day from study initiation to necropsy (males) or GD 7 (females)
Dose volume:	ATB200 30 mL/kg, DPH 10 mL/kg, AT2221 10 mL/kg
Route of administration:	ATB 200 Intravenous infusion (over 10 min) AT2221 PO 30 min prior to onset of infusion
Formulation/Vehicle:	ATB200 0.9% NaCl
Species/Strain:	Rat
Number/Sex/Group:	22
Satellite groups:	Y (TK)
Study design:	See Table 78, Table 79, and Table 80.
Deviation from study protocol:	Y

Source: Review team.
Abbreviations: DPH, diphenhydramine; GD, gestation day; NaCL, sodium chloride; PO, by mouth; TK, toxicokinetic

Table 78. Group Designation and Dose Levels - Cohort A: Female Fertility

Cohort A	No. of Animals		ATB200 Dose Level	ATB200 Dose Concentration	Cumulative Dose VCA or ATB200
Group	Males[a]	Females	(mg/kg)	(mg/mL)	(No. of Days)[b]
(Group 1) Vehicle Control[c]	22	22	0	0	17
(Group 2) Vehicle Control (DPH)[d]	22	22	0	0	17
(Group 3) Vehicle Control (DPH + AT2221)[d,e]	22	22	0	0	17
(Group 4) Low ATB200 (DPH)[d]	22	22	70	3.5	17
(Group 5) Mid ATB200 (DPH)[d]	22	22	150	7.5	17
(Group 6) High ATB200 (DPH)[d]	22	22	400	20	17
(Group 7) High ATB200 (DPH + AT2221)[d,e]	22	22	400	20	17

VCA = vehicle control article.

a Male animals were treatment-naïve.

b See Protocol Deviations.

c Group 1 females: Administered 0.9% Sodium Chloride only via IV infusion every other day beginning at least 14 days prior to pairing and on GD 1, 3, 5, and 7.

d Groups 2 through 7 females: DPH oral antihistamine (10 mL/kg) administered at 90 minutes ± 15 minutes prior to IV infusion (0.9% Sodium Chloride or ATB200) beginning on the second dose administration and continuing every other day until the last dose administration.

e Groups 3 & 7 females: AT2221 oral drug chaperone (60 mg/kg) administered 30 minutes ± 5 minutes prior to IV infusion (0.9% Sodium Chloride or ATB200) every other day beginning at least 14 days prior to pairing until confirmation of mating and then on GD 1, 3, 5, and 7.

Source: BLA 761204, SDN0001, Study report number 8371927.
Abbreviations: DPH, diphenhydramine; GD, gestation day

Table 79. Group Designation and Dose Levels - Cohort B: Male Fertility

Cohort B	No. of Animals		ATB200 Dose Level	ATB200 Dose Concentration	Cumulative Dose VCA or ATB200
Group	Male	Female[a]	(mg/kg)	(mg/mL)	(No. of Days)[b]
(Group 1) Vehicle Control[c]	22	22	0	0	21
(Group 2) Vehicle Control (DPH)[d]	22	22	0	0	21
(Group 3) Vehicle Control (DPH + AT2221)[d,e]	22	22	0	0	21
(Group 4) Low ATB200 (DPH)[d]	22	22	70	3.5	21
(Group 5) Mid ATB200 (DPH)[d]	22	22	150	7.5	21
(Group 6) High ATB200 (DPH)[d]	22	22	400	20	21
(Group 7) High ATB200 (DPH + AT2221)[d,e]	22	22	400	20	21

VCA = vehicle control article.

a Female animals were treatment-naïve.

b See Protocol Deviations.

c Group 1 males: Administered 0.9% Sodium Chloride only via IV infusion beginning at least 28 days prior to pairing and continuing every other day through the day up to and including the day prior to termination.

d Groups 2 through 7 males: DPH oral antihistamine (10 mL/kg) administered at 90 minutes ± 15 minutes prior to IV infusion (0.9% Sodium Chloride or ATB200) beginning on the second dose administration and continuing every other day until the last dose administration.

e Groups 3 & 7 males: AT2221 oral drug chaperone (60 mg/kg) administered 30 minutes ± 5 minutes prior to IV infusion (0.9% Sodium Chloride or ATB200) beginning at least 28 days prior to pairing and continuing every other day for 6 weeks.

Source: BLA 761204, SDN0001, Study report number 8371927.
Abbreviations: DPH, diphenhydramine

Table 80. Group Designation and Dose Levels - Cohort C: Toxicokinetic Evaluation

Cohort C	No. of Animals		ATB200 Dose Level	ATB200 Drug Substance Dose Concentration	Cumulative Dose VCA or ATB200
Group	Males	Females	(mg/kg)	(mg/mL)[c]	(No. of Days)
(Group 8) Vehicle Control (DPH + AT2221)[a,b]	6	6	0	0	15
(Group 9) High ATB200 (DPH)[a]	6	6	400	13.34	15
(Group 10) High ATB200 (DPH + AT2221)[a,b]	12	12	400	13.34	15

a Groups 8 through 10: DPH oral antihistamine (10 mL/kg) administered 90 ± 15 minutes prior to IV infusion (0.9% Sodium Chloride or ATB200) beginning on the second dose administration and continuing every other day until the last dose administration.

b Groups 8 & 10: AT2221 oral drug chaperone (60 mg/kg,) administered 30 ± 5 minutes prior to IV infusion (0.9% Sodium Chloride or ATB200).

c Dose Volume for ATB200 Drug Substance is 30 mL/kg.

Source: BLA 761204, SDN0001, Study report number 8371927. Observations and Results.
Abbreviations: DPH, diphenhydramine; IV, intravenous

Mortality

Administration of ATB200 with or without AT2221 was associated with mortality exceeding that observed in vehicle-treated animals (9/10 females and 7/8 males) that was unrelated to nominal dose. To the extent that Group 7 and 10 females are represented more frequently (6/10), death in treated females may reflect cumulative drug exposure.

Frequently, there were no antecedent clinical signs. The cause(s) of mortality were not determined.

Reviewer's Comment: Deaths of animals with the observation "red, discolored lungs at necropsy" may be due to gavage errors, although the report comments that this is possibly an "adverse immunological response resulting from repeated administration of a human enzyme in an non-human species", citing a 2012 article.

ATB200-treated females and males that were found dead are listed below in Table 81.

Table 81. Premature Decedents Among Treated Females and Treated Males

Sex	Dose Group	Study Day (PM* or GD)	# of doses after which death occurred	Comment
Females	2	GD 1	>8	R0814: Died after dosing, no antecedent clinical signs
	4	PM 12	7	R1021: died after dosing, no antecedent clinical signs
		PM 12	7	R1022: died after dosing, no antecedent clinical signs
	5	GD 7	≥12	R1111: Died after dosing, no antecedent clinical signs
	7	PM 6	4	Red, discolored lungs at necropsy
		PM 8	5	Red, discolored lungs at necropsy
	10	PM 8	5	Died after dosing, no antecedent clinical signs
		PM 8	5	R1906: Red, discolored lungs at necropsy
		PM 8	5	R1907: Red, discolored lungs at necropsy
		PM 8	5	R1910: Red, discolored lungs at necropsy
Males	2	PM 8	5	R0103: found dead after dosing
	4	PM 2	2	R0302: found dead after dosing
		PM 4	3	R0303: found dead after dosing
		PM 6	4	R0311: found dead after dosing
		PM 8	5	R0322: found dead after dosing
	5	PM 4	3	R0422: found dead after dosing
	7	PM 0	1	R0607: found dead after dosing
		PM 6	4	R0608: found dead after dosing

Source: Review team.
Abbreviations: GD, gestation day; PM, premating phase
*PM indicates pre-mating phase
Clinical Signs

No treatment-related clinical signs were observed in treated females or treated males during the premating, cohabitation, or gestation phases of the study.

Body Weight

Body weights of treated females and treated males were comparable across all experimental groups. Body weight gain data are not reviewed here.

Food Consumption

There were no meaningful treatment-related effects on food consumption in treated females of treated males during any phase of the study.

Toxicokinetics

ATB200 and AT2221 toxicokinetic parameters were characterized on the first and last days of infusion (treated females PM 0 and GD 7; treated males, PM 0 and study day 28). ATB200 analyses were reported as 2 individual peptide fragments (TTPTFFPK and VTSEGAGLQLQK). Parameters for each peptide are reproduced below, in Table 82 and Table 83. AT2221 toxicokinetic parameters are reproduced in Table 84.

Table 82. Summary of the TTPTFFPK Toxicokinetic Parameters in Rat Plasma

Day	Dose Group	ATB200 Dose Level (mg/kg)	Sex	C_{max} (µg/mL)	T_{max} (h)	AUC_{0-24} (µg·h/mL)	$t_{1/2}$ (h)
1	9	400	M	9960	0.417	54400	5.54
			F	8770	0.417	38600	6.11
			MF	9360	0.417	46500	5.74
	10	400	M	8690	1.17	61600	5.19
			F	7840	1.17	48600	5.14
			MF	8260	1.17	55100	5.17
GD 7	9	400	F	9420	0.417	38700	5.01
	10	400	F	8100	0.417	37900	4.39
28	9	400	M	9320	0.417	55200	5.61
	10	400	M	10100	0.417	63000	5.03

GD Gestation day.
Note: Group 10 was co-administered with 60 mg/kg AT2221.

Source: BLA 761204, SDN0001, Study report number 8371927.
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life

Sex differences in TTPTFFPK C_{max} and AUC_{0-24} values were less than 2-fold after ATB200 administration on Day 1. No accumulation of TTPTFFPK was observed after multiple doses of ATB200 in pregnant rats on GD 7 or male rats on Day 28. The coadministration ratios (Group 9/Group 10) on Day 1 were 1.15 and 1.12 for C_{max} for males and females, respectively. The coadministration ratios for AUC_{0-24} for males and females, respectively, were 0.884 and 0.794. On GD 7, the coadministration (Group 9/Group 10) ratios for pregnant rats were 1.16 for C_{max} and 1.02 for AUC_{0-24}. On Day 28, the coadministration ratios (Group 9/Group 10) for male rats

were 0.921 for C_{max} and 0.876 for AUC_{0-24}. The coadministration of ATB200 with AT2221 did not have an impact on TTPTFFPK plasma exposure.

Table 83. Summary of the VTSEGAGLQLQK Toxicokinetic Parameters in Rat Plasma

Day	Dose Group	ATB200 Dose Level (mg/kg)	Sex	C_{max} (µg/mL)	T_{max} (h)	AUC_{0-24} (µg·h/mL)	$t_{1/2}$ (h)
1	9	400	M	9890	0.417	54600	4.86
			F	8940	0.417	38400	6.15
			MF	9420	0.417	46500	5.74
	10	400	M	8780	1.17	61100	5.18
			F	7820	1.17	49100	5.09
			MF	8300	1.17	55100	5.14
GD 7	9	400	F	9290	0.417	38100	5.03
	10	400	F	8270	0.417	38200	4.35
28	9	400	M	9440	0.417	55000	5.54
	10	400	M	10300	0.417	62900	4.92

GD Gestation day.
Note: Group 10 was co-administered with 60 mg/kg AT2221.

Source: BLA 761204, SDN0001, Study report number 8371927.
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life;

Sex differences in VTSEGAGLQLQK C_{max} and AUC_{0-24} values were less than 2-fold after ATB200 administration on Day 1. No accumulation of VTSEGAGLQLQK was observed after multiple doses of ATB200 in pregnant rats on GD 7 or male rats on Day 28. The coadministration ratios (Group 9 / Group 10) on Day 1 were 1.13 and 1.14 for C_{max} and 0.894 and 0.782 for AUC_{0-24} for males and females, respectively. On GD 7, the coadministration ratios (Group 9 / Group 10) for pregnant rats were 1.12 for C_{max} and 0.998 for AUC_{0-24}. On Day 28, the coadministration ratios (Group 9 / Group 10) for male rats were 0.917 for C_{max} and 0.875 for AUC_{0-24}. The coadministration of ATB200 with AT2221 did not have an impact on VTSEGAGLQLQK plasma exposure.

Table 84. Summary of the AT2221 Toxicokinetic Parameters in Rat Plasma

Day	Dose Group	AT2221 Dose Level (mg/kg)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
1	8	60	M	4510	1.00	34300	3.39
			F	3200	4.00	39600	NC
			MF	3910	1.00	36800	3.48
	10	60	M	20900	1.00	111000	2.61
			F	17000	1.00	103000	2.51
			MF	18900	1.00	107000	2.55
GD 7	8	60	F	6000	1.00	31400	4.74
	10	60	F	16100	1.00	87600	2.85
28	8	60	M	4530	2.00	27600	3.29
	10	60	M	19900	1.00	96000	3.20

GD Gestation day.
NC Not calculated due to lack of a distinct elimination phase
Note: Groups 10 was co-administered with 400 mg/kg ATB200.

Source: BLA 761204, SDN0001, Study report number 8371927.
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life;

Sex differences in AT2221 C_{max} and AUC_{0-24} values were less than 2-fold on Day 1. No accumulation of AT2221 was observed after multiple doses of AT2221 in pregnant rats on GD 7 or male rats on Day 28. The coadministration ratios (Group 8 / Group 10) on Day 1 were 0.216 and 0.189 for C_{max} and 0.310 and 0.383 for AUC_{0-24} for males and females, respectively. On GD 7, the coadministration ratios (Group 8 / Group 10) for pregnant rats were 0.372 for C_{max} and 0.358 for AUC_{0-24}. On Day 28, the coadministration ratios (Group 8 / Group 10) for male rats were 0.228 for C_{max} and 0.288 for AUC_{0-24}. The coadministration of AT2221 with ATB200 increased AT2221 plasma exposure in male and female rats.

Dosing Solution Analysis

Concentrations of the ATB200 dose formulations ranged from 90 to 102 of the theoretical concentrations, which met the SOP requirement of 90 to 110% of their theoretical concentrations. The ATB200 precision results (relative standard deviation) also met acceptance criteria, at less than 5%.

Concentrations of the AT2221 dose formulations ranged from 95 to 102% of the theoretical concentrations, which met the SOP requirement of 90 to 110% of their theoretical concentrations. The AT2221 precision results (relative standard deviation) also met acceptance criteria, at less than 5%.

ATB200 analyte was not detected in Group 1, 2, or 3 samples.

Necropsy

Beyond the comments noted in Table 81, there were no treatment-related macroscopic observations observed in males or females euthanized during any phase of the study.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, Etc.).

Treated females (Cohort A)

There were no meaningful differences among experimental groups of treated females, with respect to the number of estrous cycles over a 14-day window, nor in estrous cycle duration. Fertility and cesarean section parameters are reproduced in Table 85.

Table 85. Fertility and Cesarean Section Parameters in Treated Females

	1	2	3	4	5	6	7
Females in cohabitation	22	22	22	20	22	22	20
Females pregnant at C-section	20	18	19	17	18	19	18
Fertility Index	90.91	81.82	86.36	85.00	81.82	86.36	90.00
Corpora Lutea (N)	16	16	15	16	15	16	16
Implants (N)	15	15	12	16	14	15	13
Preimplantation Loss (N)	2	1	3	1	2	1	3
Preimplantation Loss (%)	9.6	8.5	21.6	4.2	11.8	8.5	21.4
Postimplantation Loss (%)	8.5	8.2	4.9	7.6	7	7.5	5.9
Live fetuses	13	14	12	14	13	14	12

Source: Review team.
*Fertility Index % = (number of pregnant females)/(number of females cohabited). N.B. Does not exclude females with undetermined pregnancy status at the end of cohabitation.
Abbreviations: N, number of subjects

Both the numbers of implantation sites and the incidence of preimplantation loss in group 7 differed significantly from control groups 1 and/or 2. Percent preimplantation loss in group 3 was equivalent to that in group 7, suggesting that it be attributed to AT2221.

Treated males (Cohort B)

Treated males were bred once, then permitted to "recover" due to questionable preimplantation loss in the first cohort of untreated females to which they were bred. Cesarean section parameters are reproduced below in Table 86 and Table 87.

Table 86. Fertility and Cesarean Section Parameters in Treated Males Bred to Naive Females (1st Breeding)

	1	2	3	4	5	6	7
Males in cohabitation	22	20	22	18	20	22	21
Males with at least 1 pregnancy	20	17	20	16	16	19	19
Fertility Index	90.91	85.00	90.91	88.89	80.00	86.36	90.48
Corpora Lutea (N)	17	17	16	17	17	17	17.00
Implantations (N)	15	14	14	14	14	14	13
Preimplantaton Loss (N)	2	3	2	3	3	2	
% Preimplantation Loss	13.3	18.7	14.8	17.8	19.5	10.5	25.9
Postimplantation (N)	1	1	1	1	1	1	1
Postimplantation Loss (%)	4.4	10.6	11.2	12.1	12.4	11.1	7.1
Live fetuses	14	13	13	13	13	14	12

Source: Review team.
*Fertility Index % = (number of males with at least 1 pregnant female)/(number of males cohabited). N.B. Does not exclude females with undetermined pregnancy status at the end of cohabitation.
Abbreviations: N, number of subjects

While the incidence of preimplantation loss in all experimental groups exceeded that of the highest value in the historical control database (8.6%), the value in group 7 (25.9%) is excessive, and represents a form of developmental mortality (notably, numbers of corpora lutea were unaffected). Males were permitted an unspecified period of recovery from dosing, then bred to a second group of naïve females.

Table 87. Fertility and Cesarean Section Parameters in Treated Males Bred to Naive Females (2nd Breeding)

	1	2	3	4	5	6	7
Males in cohabitation	22	20	22	18	20	22	21
Males with at least 1 pregnancy	20	17	20	16	16	19	20
Fertility Index	90.91	85.00	90.91	88.89	80.00	86.36	95.24
Corpora lutea	16	17	16	17	17	17	17
Implantations (N)	15	16	14	16	16	16	15
Preimplantaton Loss (N)	1	1	2	1	2	1	2
% Preimplantation Loss	8.7	5	12.4	6.3	8.9	6.4	12
Postimplantation (N)	1	1	1	1	1	1	1
Postimplantation Loss (%)	7.8	4.7	5.4	7.1	5.9	4.8	5.4
Live fetuses	14	15	14	14	15	15	14

Source: Review team.
*Fertility Index % = (number of males with at least 1 pregnant female)/(number of males cohabited). N.B. Does not exclude females with undetermined pregnancy status at the end of cohabitation.
Abbreviations: N, number of subjects

The comparability of preimplantation loss values in Groups 3 and 7 in the second cohabitation led the Applicant to conclude that residual effects were attributed to miglustat.

Sperm motility and concentration were analyzed after euthanasia. These were comparable across all experimental groups.

Embryo-Fetal Development

Rat EFD Study

Study title: Embryo-Fetal Development and Toxicokinetic Study for Effects with ATB200 Alone or Coadministered with AT2221 in Rats	
Study no.:	157387
Study report location:	0001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 23 2018
GLP compliance:	Y, with exceptions: 1). Characterization and stability of ATB200 were not performed in compliance with GLP or GMP regulations. 2). Characterization and stability of the commercially-available drug chaperone AT2221 was performed at a subcontractor's laboratory in compliance with GLP regulations. 3). Concentration and homogeneity analyses were not conducted on oral diphenhydramine (DPH) formulations. 4). Additional bioanalytical sample analyses conducted by the Applicant on samples collected after completion of the bioanalytical phase were not included in the Final Report.
QA statement:	Y
Drug, lot #, and % purity:	ATB200 (WBP110) for injection, lot 2018010081. Monomer (main peak) 96.4%

Source: Review Team. Enter source here
Abbreviations: DPH, diphenhydramine; GLP, good laboratory practices; GMP, good manufacturing practices

Key Study Findings

ATB200 was administered by infusion to pregnant rats, at doses of 70, 150, or 400 mg/kg every other day during organogenesis, beginning on GD 6 and ending on GD 18. DPH was administered by intravenous push 30 min prior to the onset of the ATB200 infusion, beginning GD 8. One experimental group (Group 7) received ATB200 with oral ATT2221 (60 mg/kg) every other day during organogenesis.

There were no adverse effects on any maternal in-life or caesarean section parameters. There was no developmental toxicity. Maternal and developmental No Observed Adverse Effect Levels (NOAELs) of ATB200 and AT2221 were 400 mg/kg and 60 mg/kg, respectively. Using Group 7 TK data from GD 18, the mean AUC_{0-24} of both peptide analytes of ATB200 was ~ 28,850 µg*h/mL, with a mean C_{max} of approximately 6790 µg /mL. The ATB200 safety margins (calculated from clinical AUC and C_{max} values of 1400 µg*h/mL and 280 µg /mL) are 20.6 and 24.2, respectively.

The AUC_{0-24} of coadministered AT2221 was 84,300 ng*h/mL; the C_{max} was ~13,200 ng/mL. The AT2221 safety margins (calculated from clinical AUC values of 20000 ng*h/mL and 2400 ng/mL, respectively) were 4.2 and 5.5.

Reviewer's Comment. The findings in this study are inconsistent with those described in the text of the Prescribing Information for Zavesca (a previously-approved miglustat product), although this may be attributed to the disparities in total dose administered between the 2 development

programs. Briefly, a study in the original program administered daily doses of 0, 20, 60 or 180 mg/kg/day to female rats for 15 days prior to cohabitation, throughout the duration of cohabitation, and for an additional 18 doses (GD 6 through GD 17); as such, the minimum number of doses a female received was 34, 18 of which were administered during gestation. Conversely, females in groups 3 and 7 of the present study received only 7 doses (60 mg QOD, from GD 6 through GD 18).

Table 88. Study 157387 Methods

Doses:	0, 70, 150, 400 mg/kg
Frequency of dosing:	Every other day, gestation days 6 through 18
Dose volume:	20 mL/kg
Route of administration:	Intravenous infusion
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	Rat, Sprague-Dawley
Number/Sex/Group:	22
Satellite groups:	Y
Study design:	See table below.
Deviation from study protocol:	Y

Source: Review team.
Abbreviations: GD, gestation days; NaCL, sodium chloride

Table 89. Rat EFD Study Groups Rat EFD Study Groups

Group	Number of Females	ATB dose (mg/kg/day)	ATB Dose Concentration (mg/mL)
Toxicity animals			
Group 1 Vehicle (V)[a]	22	0	0
Group 2 V+DPH[b]	22	0	0
Group 3 V+DPH+M[b,c]	22	0	0
Group 4 V+D+ATB200[b]	22	70	3.5
Group 5 V+D+ATB200[b]	22	150	7.5
Group 6 V+D+ATB200[b]	22	400	20
Group 7 V+D+ATB200+M[b,c]	22	400	20
Toxicokinetic animals			
Group 1 Vehicle (V)[a]	3	0	0
Group 2 V+DPH[b]	3	0	0
Group 3 V+DPH+M[b,c]	9	0	0
Group 4 V+D+ATB200[b]	9	70	3.5
Group 5 V+D+ATB200[b]	9	150	7.5
Group 6 V+D+ATB200[b]	9	400	20
Group 7 V+D+ATB200+M[b,c]	12	400	20

Source: Review team.
[a] Group 1: Administered 0.9% sodium chloride only via intravenous (IV) infusion beginning on GD 6 and continuing every other day through GD 18.
[b] Groups 2 to 7: DPH oral antihistamine (10 mg/kg) administered at 90±15 min prior to IV infusion (0.9% sodium chloride or ATB200) beginning on GD 8 and continuing every other day through GD 18.
[c] Groups 3 and 7: AT2221 oral drug chaperone (60 mg/kg, 6.0 mg/mL) administered 30±5 min prior to IV infusion (0.9% sodium chloride or ATB200) beginning on GD 6 and continuing every other day through GD 18.
Abbreviations: DPH, diphenhydramine, GD, gestation day

Cageside observations were conducted daily, while clinical observations were conducted 30-60 minutes after dosing. Body weights were collected prior to dosing. Food consumption was collected on cohoused rats (2 per cage) during the intervals of GD 4-6, 6-8, 8-10, 10-12, 12-14, 14-16, 16-18, and 18-21.

Blood samples for toxicokinetic analyses: approximately 0.4 mL blood was collected from 3 satellite dams per time point via jugular puncture. Plasma collected from Groups 1, 2, 4, 5, 6, and 7 post IV administration (vehicle control or ATB200) was harvested into two approximately 0.10-mL aliquots. One aliquot was designated for ATB200 analysis, and the other for analysis with the alpha-glucosidase activity assay (GAA).

Among ATB-treated groups (4-7), the following time points were chosen: predose, then following the end of the 10 min ATB200 infusion at 0.25, 1, 2, 4, 6, 24 hours. (N.B The C_{max} for an infusion of a large molecule is most likely to be at the infusion terminus; the election to delay sample collection until 15 min postinfusion likely resulted in an under -estimate of C_{max}.)

Samples were collected from Groups 1 and 2 predose and 2 hours post infusion for ATB200 analysis. Samples were collected from dams in Groups 3 and 7 for analysis of AT2221 at the following time points, relative to its oral administration at t-30 min ATB200 infusion: predose, then 0.25, 1, 2, 4, 6 and 24 h.

Caesarean sections were conducted on GD 21. Necropsy observations were reported, although few samples were collected (and none were examined microscopically). External examinations were conducted on all fetuses. Approximately half the fetuses were randomized for fresh visceral examinations; the heads of these were removed and cross-sectioned using Wilson's technique. Remaining fetuses were eviscerated and assigned for later skeletal evaluation, after processing and staining with Alizarin red.

Observations and Results

Mortality

Table 90. Unscheduled Mortality in Rat EFD Study

Dam	Group	Dose	GD	Comments
R0301	4	70	14	Found dead
R0401	5	150	8	Euthanized after administration of partial dose
R0528	6	400+D	6	Euthanized after administration of partial dose
R0613	7	400+D+M	8	Found dead after dosing
R0617	7	400+D+M	6	Found dead after dosing

Source: Review team.
Abbreviations: GD, gestation day

Dam R0301 (Group 4, 70 mg/kg) was found dead after dosing on GD 14. Dams R0401 (Group 5, 150 mg/kg) and R0528 (Group 6, 400 mg/kg) were sacrificed after administration of partial doses on GD 8 and GD6, respectively; neither dam had antecedent clinical observations, nor macroscopic notations at necropsy, and the reasons for their sacrifice were not explicitly stated. Dams R0613 and R0617 (Group 7, 400 mg/kg) were listed as unscheduled deaths on GD8 and GD6, respectively. The necropsy observations for both were "Lung, Discolored-lobes, all, dark red;" it is possible that these 2 deaths were gavage errors.

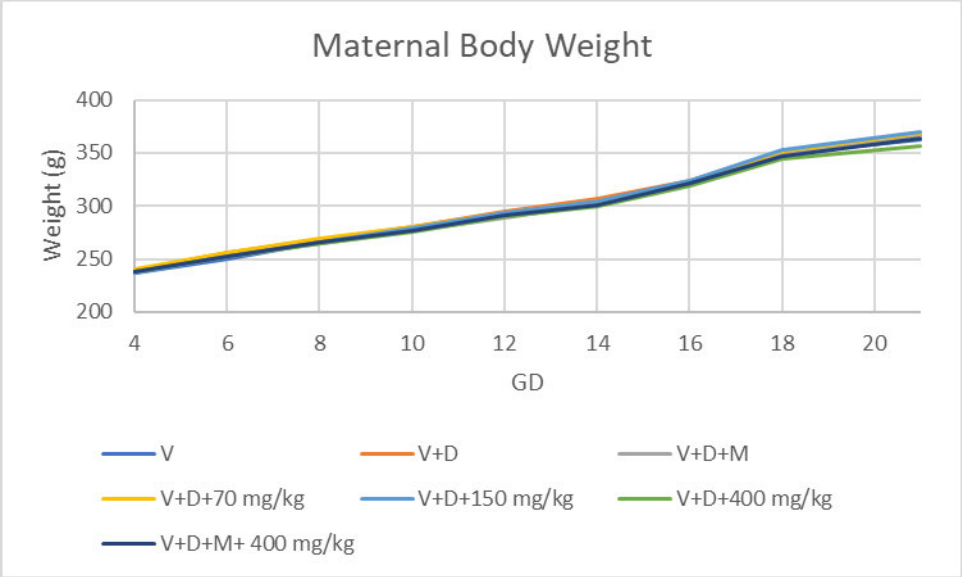
Clinical Signs

Observations made in groups 4-7, although not groups 1-3, included behavior: hypoactive, ataxic, vocalization; discharge: genital, red; appearance: hunched, limited use of limbs; respiration: irregular or labored.

Body Weight

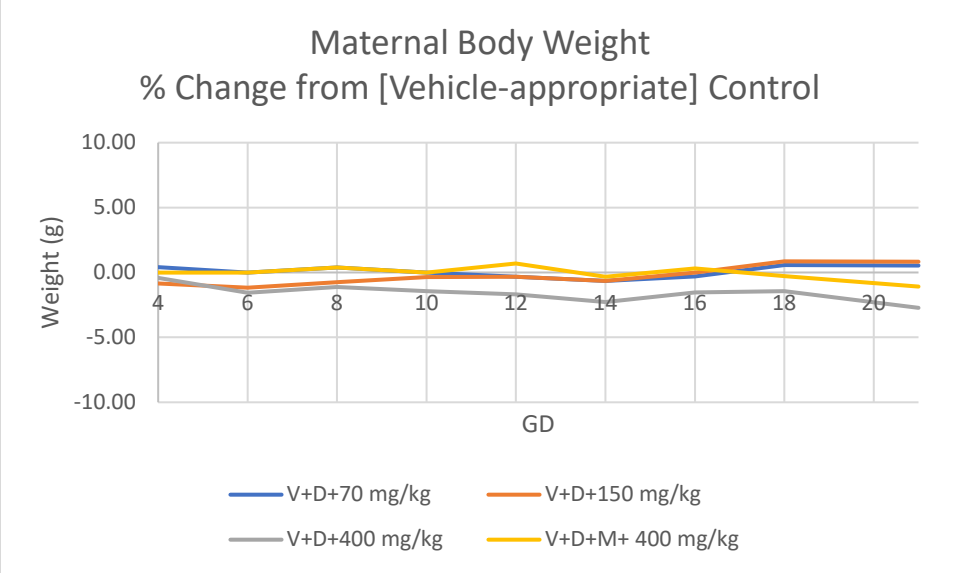
Group mean maternal body weights, absolute and expressed as the percent difference from vehicle-appropriate controls, are reproduced below in Figure 63 and Figure 64. There were no meaningful differences among vehicle and ATB-200-treated groups. Body weight gain data are not reported in this review.

Figure 63. Group Mean Maternal Body Weight in Rats



Source: Review team.

Figure 64. Group Mean Maternal Body Weight in Rats (% Change From Control)

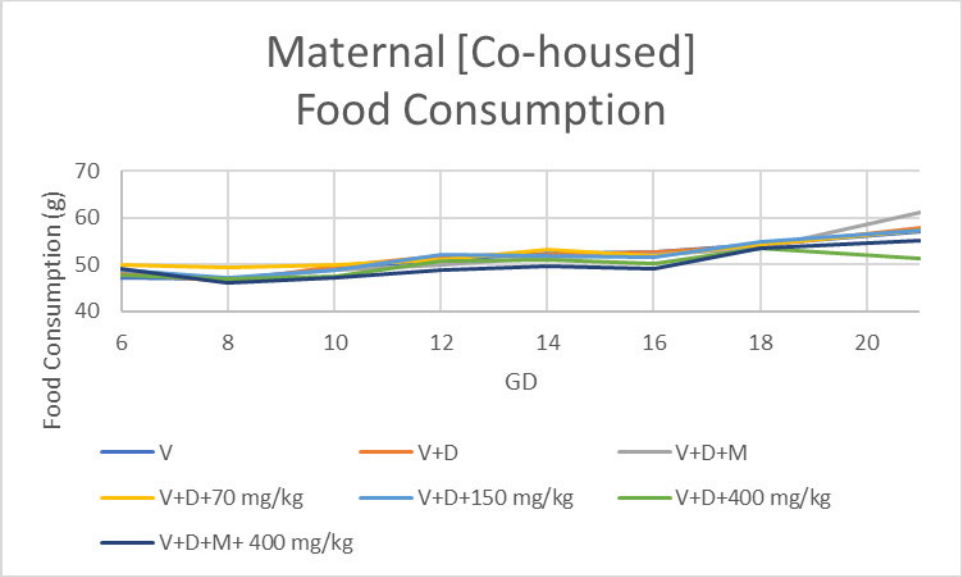


Source: Review team.

Food Consumption

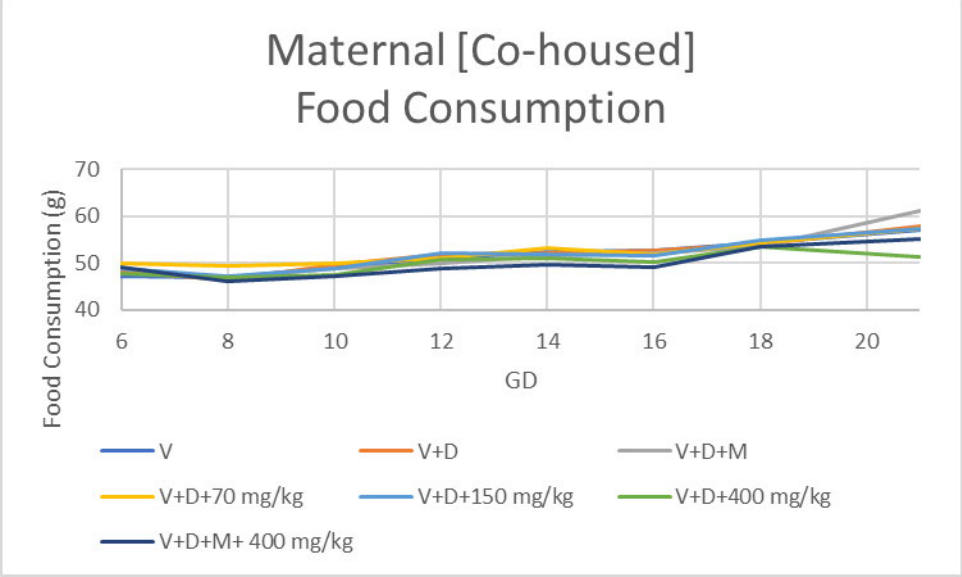
Group mean maternal food consumption data (per cage, both absolute and expressed as the percent difference from vehicle-appropriate controls), are reproduced below in Figure 65 and Figure 66. There were no meaningful differences among vehicle and drug-treated groups.

Figure 65. Group Mean Maternal Food Consumption



Source: Review team.

Figure 66. Group Mean Maternal Food Consumption in Rats (% Change From Control)



Source: Review team.
Abbreviations: AUC0-24, area under the concentration-time curve from time 0 to the last measurable concentration; Cmax, maximum concentration; h, hour; NC, Not calculated; Tmax, time to maximum concentration.

Toxicokinetics

Toxicokinetic parameters were characterized on the first and last days of infusion (GDs 6 and 18). ATB200 analyses were reported as 2 individual peptide fragments (TTPTFFPK and VTSEGAGLQLQK). Parameters for each peptide are reproduced below, in Table 91 and Table 92. Toxicokinetic parameters for AT2221 are reproduced in Table 93.

Exposure, as assessed by TTPTFFPK C_{max} and AUC_{0-24}, increased with the increase in ATB200 dose level from 70 to 400 mg/kg/day. The increases in C_{max} and AUC_{0-24} values were generally dose proportional on GD 6 and 18 (exception: AUC_{0-24} on GD 18 was greater than dose proportional). The coadministration ratios (Group 7 / Group 6) ranged from 0.902 to 1.08 for C_{max} and from 1.05 to 1.36 for AUC_{0-24}.

Exposure, as assessed by VTSEGAGLQLQK C_{max} and AUC_{0-24}, increased with the increase in ATB200 dose level from 70 to 400 mg/kg/day. The increases in C_{max} and AUC_{0-24} values were generally dose proportional on GD 6 and 18 (exception: AUC_{0-24} on GD 18 was greater than dose proportional). The coadministration ratios (Group 7 / Group 6) ranged from 0.929 to 1.09 for C_{max} and from 1.07 to 1.39 for AUC_{0-24}.

Table 91. Summary of TTPTFFPK Toxicokinetic Parameters in Pregnant Rat Plasma

Gestation Day	Dose Group	ATB200 dose (mg/kg)	C_{max} (mcg/mL)	T_{max} (h)	AUC_{0-24} (mcg*h/mL)	$t_{1/2}$
6	4	70	1240	0.417	2780	11.6
	5	150	3040	0.417	7750	10.1
	6	400	6130	0.417	21700	6.91
	7	400	6630	1.17	29500	5.37
18	4	70	1110	0.417	1850	7.63
	5	150	2600	0.417	6090	NC
	6	400	7500	0.417	27300	NC
	7	400	6760	0.417	28700	7.27

Source: Review team.
Abbreviations: AUC0-24, area under the concentration-time curve from time 0 to the last measurable concentration; Cmax, maximum concentration; h, hour; NC, Not calculated; Tmax, time to maximum concentration; t1/2, elimination half-life

Table 92. Summary of VTSEGAGLQLQK Toxicokinetic Parameters in Pregnant Rat Plasma

Gestation Day	Dose Group	ATB200 dose (mg/kg)	C_{max} (mcg/mL)	T_{max} (h)	AUC_{0-24} (mcg*h/mL)	$t_{1/2}$
6	4	70	1340	0.417	2850	11.4
	5	150	3130	0.417	7940	9.84
	6	400	6110	0.417	21700	6.72
	7	400	6670	1.17	30200	5.24
18	4	70	1170	0.417	1910	7.51
	5	150	2830	0.417	6330	NC
	6	400	7340	0.417	26900	NC
	7	400	6820	0.417	29000	7.09

Source: Review team.
Abbreviations: AUC0-24, area under the concentration-time curve from time 0 to the last measurable concentration; Cmax, maximum concentration; h, hour; NC, Not calculated; Tmax, time to maximum concentration; t1/2, elimination half-life

Table 93. Summary of AT2221 Toxicokinetic Parameters in Pregnant Rat Plasma

Gestation Day	Dose Group	AT2221 (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng*h/mL)	$t_{1/2}$
6	3	60	3980	1	29700	3.39
	7	60	15900	1	75200	3.09
18	3	60	6160	1	41100	5.02
	7	60	13200	1	84300	4.88

Source: Review team.

The coadministration ratios (Group 7/Group 3) were 4.00 and 2.14 for C_{max} and 2.53 and 2.05 for AUC_{0-24} on GD 6 and 18, respectively. The reason that AT2221 AUC and C_{max} parameters differed markedly between Groups 3 and 7 on both GDs 6 and 18 was not addressed. GAA results were reported for individual animals, but not summarized.

Dosing Solution Analysis

Concentrations of ATB200 dose formulations ranged from 91.6 to 101.6% of the theoretical concentrations, which met the SOP requirement of 90 to 110% of their theoretical concentrations. The ATB200 precision results (relative standard deviation) also met acceptance criteria at less than 5%.

Concentrations of AT2221 dose formulations ranged from 94.3 to 99.7% of the theoretical concentrations, which met the SOP requirement of 90 to 110% of their theoretical concentrations. The AT2221 precision results (relative standard deviation) also met acceptance criteria at less than 5%.

No detection of ATB200 analyte in samples from Groups 1, 2, and 3 was noted.

Necropsy

There were no findings associated with treatment at gross necropsy.

Cesarean Section Data

Cesarean section parameters are reproduced below in Table 94. There were no drug-related effects on any of the parameters examined.

Table 94. Rat Cesarean Section Data

Parameter	Group	1	2	3	4	5	6	7
Number of females pregnant at c-section	**N**	**21**	**22**	**21**	**21**	**22**	**21**	**21**
Corpora lutea	Mean	14	14	14	14	14	14	14
	SD	1.7	2.6	1.9	1.7	2.2	3.1	1.9
Implantation sites	Mean	13	13	12	13	13	13	13
	SD	1.6	1.8	1.4	1.3	2.2	1.9	1.5
Preimplantation loss	Mean	1	1	1	1	1	1	1
	SD	1.4	1.4	1.4	1.2	1.4	2.1	1.4
Preimplantation loss (%)	Mean	5.1	8.6	7.1	4.7	6.7	6.0	8.3
	SD	8.73	8.42	8.35	7.64	8.81	9.88	8.54
Early resorptions	Mean	1	0	0	0	0	0	0
	SD	1.0	0.8	0.4	0.2	0.5	0.7	0.7
Late resorptions	Mean	0	0	0	0	0	0	0
	SD	0	0.2	0.2	0	0	0	0
Total resorptions	Mean	1	0	0	0	0	0	0
	SD	1.0	0.8	0.4	0.2	0.5	0.7	0.7
Dead fetuses	Mean	0	0	0	0	0	0	0
	SD	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Postimplantation loss	Mean	1	0	0	0	0	0	0
	SD	1	0.8	0.4	0.2	0.5	0.7	0.7
Postimplantation loss (%)	Mean	4.2	3.3	1.8	0.4	1.7	1.5	3.0
	SD	8.13	5.59	3.24	1.82	3.91	5.56	4.74
Live fetuses	Mean	12	12	12	13	13	13	13
	SD	2.0	1.6	1.3	1.4	2.2, 2.0	2.0	1.4
Gravid uterine weight	Mean	93.3	93.5	96.6	97.6	97.9	94.2	100
	SD	11.26	14.05	12.56	10.35	13.86	9.94	8.4
Corrected body (carcass) weight	Mean	268.2	273.0	270.9	271.1	272.1	263.1	263.8
	SD	18.45	23.76	21.65	16.31	20.72	23.65	24.94
Corrected weight change	Mean	31.3	33.8	33.0	30.7	34.4	23.9	24.6
	SD	15.60	24.73	16.77	16.85	16.13	19.04	19.72
Total weight change	Mean	124.4	127.3	129.7	128.3	132.3	118.1	124.6
	SD	13.83	23.30	22.76	21.43	19.33	18.61	17.26
Mean number of male fetuses per litter	Mean	6	6	5	7	6	6	7
	SD	7.9	2.3	2.1	2.1	2.5	2.1	1.7

Parameter	Group	1	2	3	4	5	6	7
Number of females pregnant at c-section	**N**	**21**	**22**	**21**	**21**	**22**	**21**	**21**
Mean number of female fetuses per litter	Mean	7	6	7	6	7	7	6
	SD	2.2	1.9	2.1	2.1	2.5	2.1	1.9
Percentage male fetuses	Mean	46	52	44	52	48	48	54
	SD	14.8	15.6	15.8	16.1	18.0	13.0	12.6
Mean fetal weight	Mean*	5.51	5.61	5.64	5.61	5.60	5.41	5.63
	SD	0.345	0.354	0.406	0.366	0.366	0.363	0.399
Mean weight, male fetuses	Mean*	5.68	5.77	5.81	5.76	5.78	5.58	5.75
	SD	0.409	0.377	0.433	0.374	0.452	0.419	0.400
Mean weight, female fetuses	Mean*	5.38	5.45	5.50	5.46	5.46	5.25	5.48
	SD	0.318	0.368	0.375	0.376	0.376	0.351	0.452

Source: Review team.
* Listed as “adjusted” mean
Abbreviations: N, number of females pregnant at c-section; SD, standard deviation

Offspring (Malformations, Variations, etc.)

There were no drug-related effects on malformations or variations. The total numbers of affected litters and fetuses were unrelated to dose, and within the range of historical control data.

Table 95. EFD Study in Rabbits

Study title: Embryo-Fetal Development and Toxicokinetic Study for Effects with ATB200 Alone or Coadministered with AT2221 in Rabbits	
Study no.:	8371931
Study report location:	0001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 23, 2018
GLP compliance:	Yes Bioanalytical for ATB200 protein phase conducted in (b) (4) under OECD auspices. Bioanalytical for GAA analysis conducted (b) (4) under OECD auspices
QA statement:	QA Statement is included, without signatory.
Drug, lot #, and % purity:	ATB200 (WPB110), DEMO-WBP110-201704001-1KEB2-DP1, stated purity 97.9% (although this is not listed in CoA)

Source: Review Team.
Abbreviations: AT2221, miglustat; EFD, embryo-fetal development; GAA, human acid α-glucosidase; GLP, good laboratory practices; OECD, Organisation for Economic Co-operation and Development; QA, quality assurance

Key Study Findings

ATB200 was administered by infusion to pregnant rabbits, at doses of 30, 70, or 175 mg/kg every other day during organogenesis, beginning on GD 7 and ending on GD 19. DPH (10 mg/kg) was administered by intravenous push 90 min prior to the onset of the ATB200 infusion, beginning GD 9. One experimental group (Group 3) received only oral AT2221 (25 mg/kg). Another (Group 7) received ATB200 (175 mg/kg) with oral ATT2221 (25 mg/kg); the latter was administered 30 min prior to infusion every other day beginning on GD 7 and ending on GD 19.

One doe in Group 7 aborted on GD 21. Food consumption was reduced in groups 3 and 7; the effects were more profound in the latter. There were no adverse effects on any caesarean section parameters.

Clusters of treatment-related cardiac and great vessel malformations were observed in 1 fetus of a rabbit treated with ATB200 alone (175 mg/kg), and 1 fetus of a rabbit treated with ATT2221 alone. When the 2 drugs were co-administered (Group 7), 15 fetuses from 6/18 evaluable litters were noted with clusters of cardiac and great vessel malformations. There were no treatment-related external or skeletal malformations. The maternal No Observed Adverse Effect Level ($NOAEL_{maternal}$) of ATB200 was 70 mg/kg. Using Group 7 TK data from GD 19, the AUC_{0-24} of ATB200 at this dose was ~ 3665 µg *h/mL, with a C_{max} of approximately 1435 µg /mL. The safety margins (relative to clinical AUC of 1400 µg*h/mL and C_{max} of 280 µg/mL) are 2.6 and 5.1, respectively.

There was no developmental NOAEL for the coadministration of ATB200 with AT2221 (175 mg/kg and 25 mg/kg, respectively). AT2221 values for AUC_{0-24} and C_{max} at the Lowest-Observed Adverse Effect Level ($LOAEL_{developmental}$) were 66100 ng*h/mL and 13100 ng/mL,

respectively. The safety margins of AT2221 at the LOAEL (relative to clinical AUC and C_{max} values of 20000 ng*h/mL and 2400 ng/mL, respectively) are 3.3 and 5.4.

Reviewer's Comment: The findings in this study do not reflect those described in the text of the Prescribing Information for Miglustat, in which rabbit maternal mortality was reported (N.B. it was not dose-related). That said, the original review indicates a dose-related and statistically significant increase in the numbers of fetuses for which "additional blood vessel" emanating from the aortic arch was reported; notably, this information is not included in the present-day prescribing information. While the great vessel malformations in the current study do not include a finding that can be characterized as aortic arch with "additional blood vessel", it is interesting that aortic arch perturbations were described in the original rabbit study.

Notably, the original study was dosed daily from GD 6 through GD 18, at doses of 15, 30 and 45 mg/kg/day. The total body burden of AT2221 in the present study (175 mg/kg, administered as 7x25 mg/kg doses) is lower than that of any dose administered in the original study (15, 30 and 45 mg/kg daily for 13 doses). There were no toxicokinetic data in the original study.

Table 96. Study 8371931 Methods

Doses:	0, 30, 70, 175 mg/kg
Frequency of dosing:	Every other day, GDs 7 through 19
Dose volume:	10 mL/kg
Route of administration:	Intravenous infusion, marginal ear vein
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	Rabbit, New Zealand White
Number/Sex/Group:	20
Satellite groups:	N
Study design:	See table below.
Deviation from study protocol:	Y

Source: Review team.
Abbreviations: GD, gestation day, NaCL, sodium chloride

Table 97. Rabbit Embryo-fetal Development Study Groups

Group	Number of Females	ATB Dose (mg/kg/day)	ATB Dose Concentration (mg/mL)
Toxicity/toxicokinetic animals			
Group 1 Vehicle (V)[a]	20	0	0
Group 2 V+DPH[b]	20	0	0
Group 3 V+DPH+M[b,c]	20	0	0
Group 4 V+D+ATB200[b]	20	30	3
Group 5 V+D+ATB200[b]	20	70	7
Group 6 V+D+ATB200[b]	20	175	17.5
Group 7 V+D+ATB200+M[b,c]	20	175	17.5

Source: Review team. [a] Group 1: Administered 0.9% sodium chloride only via intravenous (IV) infusion beginning on GD 7 and continuing every other day through GD 19.
[b] Groups 2 to 7: DPH oral antihistamine (10 mg/kg) administered at 90±15 min prior to IV infusion (0.9% sodium chloride or ATB200) beginning on GD 9 and continuing every other day through GD 19.
[c] Groups 3 and 7: AT2221 oral drug chaperone (60 mg/kg, 6.0 mg/mL) administered 30±5 min prior to IV infusion (0.9% sodium chloride or ATB200) beginning on GD 7 and continuing every other day through GD 19.
Abbreviations: DPH, diphenhydramine; GD, gestation day; IV, intravenous

Cageside observations were conducted daily, while clinical observations were conducted 30 to 60 min postdose. Body weights were recorded prior to dosing. Food consumption data were recorded daily from GD5 through GD 29.

Blood samples for toxicokinetic analyses. On GD 7 and GD 19, approximately 1 mL of blood was collected (median auricular artery or another vessel) from 3 animals/group according to the Applicant-provided schedule in Table 98. ATB200 samples were centrifuged to plasma, and stored in 0.1 mL aliquots. Two aliquots (primary and backup) were designated for ATB200 analysis, while 2 (primary and backup) were designated for alpha glucosidase activity assay (GAA) analysis. Samples collected post AT2221 administration for each collection day were each harvested into aliquots designated for AT2221 concentration analysis.

Table 98. Rabbit EFD Toxicokinetic Blood Collections

Group	Set	GD 7 Time Point[a,b]	GD 19 Time Point[a,b]	GD 7& 19 Time Point Post Oral AT2221 Dose[a]
(Group 1) Vehicle Control	Three animals/ group	Predose and 0.25 and 2 hours postdose IV vehicle control	0.25 and 2 hours postdose IV vehicle control	NA
(Group 2) Vehicle Control (DPH)	Three animals/ group	Predose and 0.25 and 2 hours postdose IV vehicle control	0.25 and 2 hours postdose IV vehicle control	NA
(Group 3) Vehicle Control (DPH+AT2221)	Three animals/ group	Predose and 0.25 and 2 hours postdose IV vehicle control	0.25 and 2 hours postdose IV vehicle control	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose oral AT2221
(Group 4) Low ATB200 (DPH)	Three animals/ group	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	NA
(Group 5) Mid ATB200 (DPH)	Three animals/ group	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	NA
(Group 6) High ATB200 (DPH)	Three animals/ group	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	NA
(Group 7) High ATB200 (DPH+AT2221)	Three animals/ group	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose IV ATB200	Predose and 0.25, 1, 2, 4, 6, and 24 hours postdose oral AT2221

DPH = Diphenhydramine HCl; GD = Gestation day; IV = Intravenous; NA = Not applicable.
a Blood collection times are approximate, actual collection times were recorded in the raw data.
b Collection time points after the last dose administered/animal.

Source: BLA 761204, SDN0001, Study report number 8371931.

Cesarean sections were conducted on GD 29. All fetuses were examined for external, visceral, and skeletal malformations.

Observations and Results

Mortality

There was no drug-related mortality. A single doe (Group 7, B0618) was euthanized on GD 21 after abortion of her litter. The Applicant noted that this doe was inappetant, a frequent cause of abortion in pregnant rabbits; that said, food consumption was <100 g in many does that did not abort.

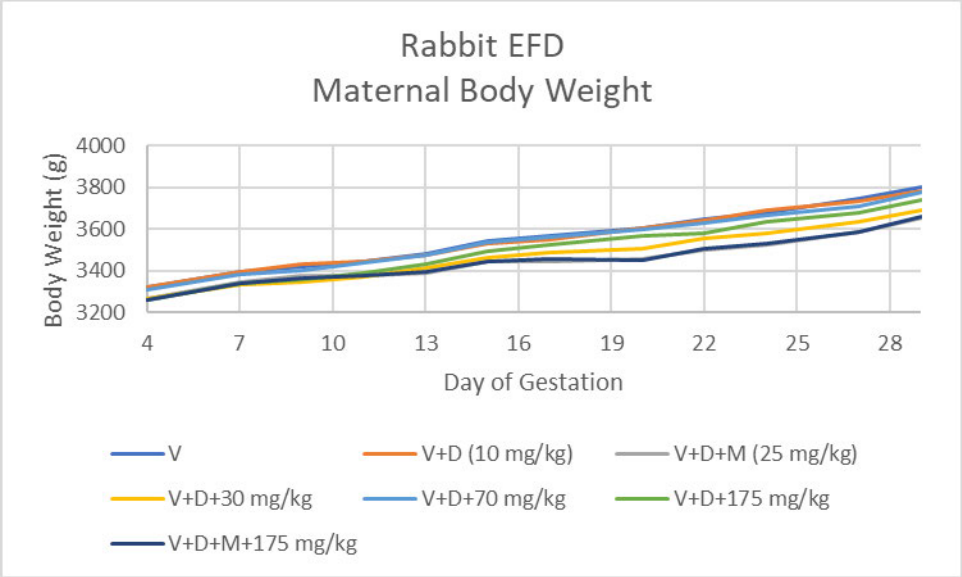
Clinical Signs

Clinical signs were generally nonspecific; they related to sparsity of coat, skin discoloration, and skin temperature.

Body Weight

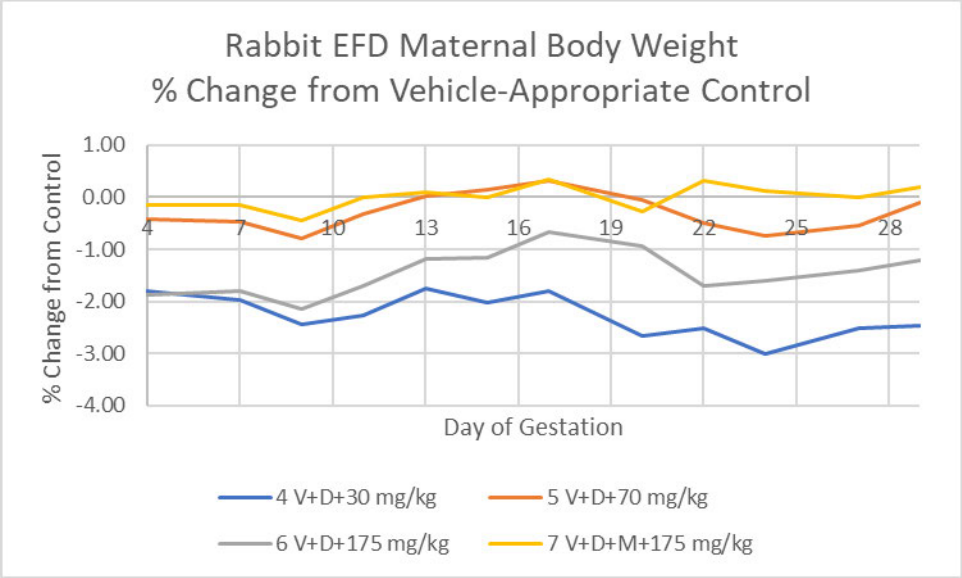
Group mean maternal body weight data are presented below (both absolute and % change from control) are reproduced below in Figure 67 and Figure 68. These did not differ meaningfully among treatment groups. Body weight gain data are not reported in this review.

Figure 67. Group Mean Maternal Body Weight in Rabbits



Source: Review team.

Figure 68. Group Mean Maternal Body Weight in Rabbits (Percentage Change From Control)

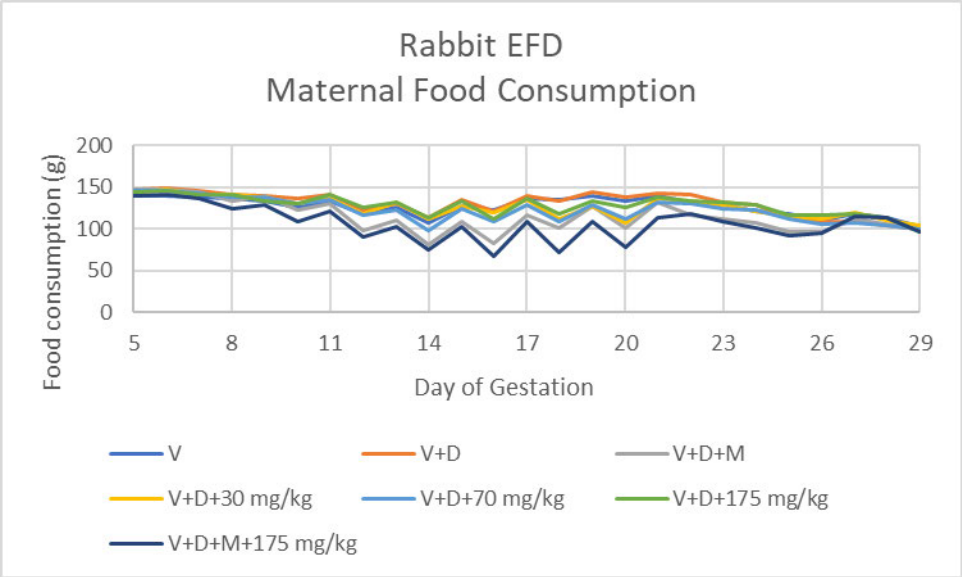


Source: Review team.

Food Consumption

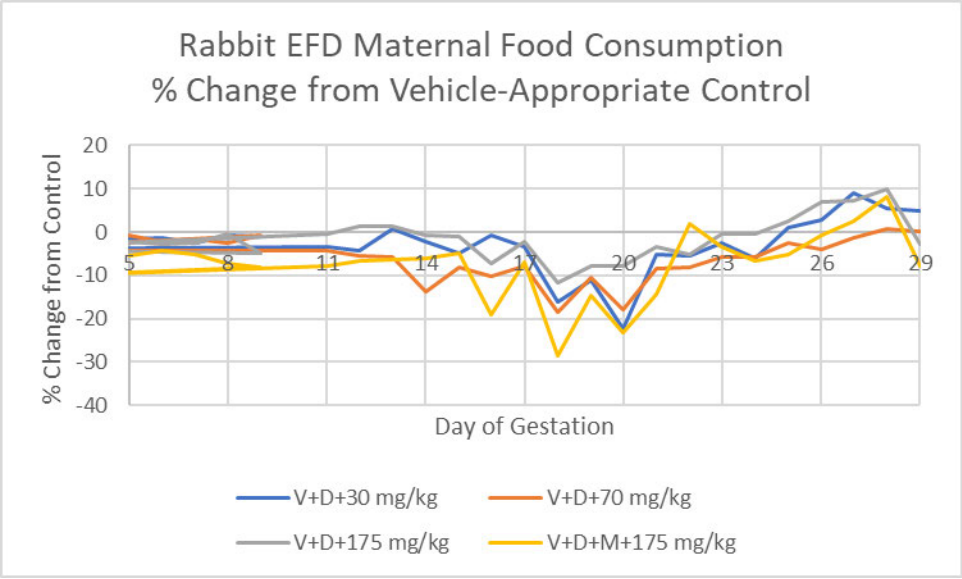
Group mean maternal food consumption (both absolute and percentage change from control) are reproduced below in Figure 69 and Figure 70. Food consumption was significantly decreased for Groups 3 and 7 from GD 11 to 25. Over the interval from GD 16 through GD 21, the difference between these 2 groups varied from 7-28%, with Group 7 mean values always reduced relative to those in group 3.

Figure 69. Group Mean Maternal Food Consumption in Rabbits



Source: Review team.

Figure 70. Group Mean Maternal Food Consumption in Rabbits (Percentage Change From Control)



Source: Review team.

Toxicokinetics

Exposure tables are reproduced below, in Table 99, Table 100, and Table 101. Briefly, as assessed by TTPTFFPK and VTSEGAGLQLQK peptides, mean C_{max} and AUC_{0-24} values increased with the increase in ATB200 dose level from 30 (Group 4) to175 (Group 6) mg/kg/day. The increases in mean C_{max} and AUC_{0-24} values were generally dose proportional, with the exception that AUC_{0-24} values from 70 (Group 5) to 175 (Group 6) mg/kg/day was greater than dose proportional. No accumulation of TTPTFFPK and VTSEGAGLQLQK was observed after multiple doses of ATB200 in pregnant rabbits. The mean C_{max} and AUC_{0-24} values for TTPTFFPK and VTSEGAGLQLQK were higher in Group 7 (175 mg/kg/day ATB200+25 mg/kg AT2221) when compared with Group 6 (175 mg/kg/day ATB200), although differences were <2-fold.

No accumulation of AT2221 was observed after multiple doses of AT2221 in pregnant rabbits. The mean C_{max} and AUC_{0-24} values for AT2221 were slightly higher in Group 7 (25 mg/kg AT2221+175 mg/kg/day ATB200) when compared with those of Group 3 (25 mg/kg AT2221), although differences were <2-fold.

GAA results were reported for individual animals, but not summarized.

Table 99. Summary of TTPTFFPK Toxicokinetic Parameters in Pregnant Rabbit Plasma

Gestation Day	Dose Group	ATB200 Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (h)	AUC_{0-24h} (µg·h/mL)	$t_{1/2}$
7	4	30	1640	0.459	1630	NC
	5	70	1740	0.417	4640	NC
	6	175	4200	0.434	19,900	3.78
	7	175	4900	0.417	27,300	3.43
19	4	30	648	0.442	1290	4.72
	5	70	1430	0.417	3640	5.08
	6	175	3500	0.417	11,500	4.44
	7	175	3820	0.428	22,700	3.17

Source: Review team.
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; NC, Not calculated; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life

Table 100. Summary of VTSEGAGLQLQK Toxicokinetic Parameters in Pregnant Rabbit Plasma

Gestation Day	Dose Group	ATB200 Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (h)	AUC_{0-24h} (µg·h/mL)	$t_{1/2}$
7	4	30	690	0.459	1640	NC
	5	70	1780	0.417	4730	NC
	6	175	4190	0.434	20,000	3.79
	7	175	4780	0.417	26,900	3.50
19	4	30	661	0.442	1300	4.63
	5	70	1440	0.417	3690	5.00
	6	175	3510	0.417	11,600	4.51
	7	175	3730	0.428	22,400	3.18

Source: Review team.
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; NC, Not calculated; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life

Table 101. Summary of AT2221 Toxicokinetic Parameters in Pregnant Rabbit Plasma

Gestation Day	Dose Group	AT2221 (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng·h/mL)	$t_{1/2}$
7	3	25	10,100	1.00	34,700	7.82
	7	25	14,500	1.00	58,400	5.50
19	3	25	9740	1.00	39,100	6.48
	7	25	13,100	1.03	66,100	4.94

Source: Review team.
Abbreviations: AT2221, miglustat; AUC_{0-24}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life

Dosing Solution Analysis

Concentrations of the AT2221 dose formulations ranged from 92.8 to 103.3% of the theoretical concentrations. The AT2221 precision results (relative standard deviation) were <5%. Concentrations of the ATB200 dose formulations ranged from 91.5 to 97.8% of the theoretical concentrations. The AT2221 precision results (relative standard deviation) were <5%. There was no detection of the ATB200 analyte in the Group 1, 2, and 3 samples.

Necropsy

There were no treatment-related macroscopic observations. Liver lobe depressions, discoloration, and rough surface were observed in Groups 4, 5, and 6 at incidences unrelated to dose (eight, nine and three, respectively).

Cesarean Section Data

Cesarean section parameters are reproduced below in Table 102. There were no treatment-related findings in any experimental group.

Offspring (Malformations, Variations, Etc.)

Treatment-related increases in great vessel and cardiac malformations were observed. These findings are summarized below in Table 103. The numbers of affected fetuses, as well as the total numbers of malformations reported, were increased in Group 7; however, one fetus in both groups 3 and group 6 were likewise affected.

Statistical analyses were conducted on individual malformations; however, many fetuses had multiple, related observations. Only dilated aortic arch, atretic pulmonary trunk and ventricular septal defects were flagged as both statistically significant and exceeding historical control values; however, this approach does not reflect the constellations of findings observed. Importantly, these malformations, as well as a variation never previously reported (pulmonary trunk narrowed), are known to proceed from aberrant migration and morphogenesis of cardiac neural crest. Individual fetal findings are summarized in Table 104. There were no treatment-related external or skeletal malformations.

Table 102. Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Parameter	Group	1	2	3	4	5	6	7
Number of females pregnant at c-section	**N**	**18**	**20**	**19**	**15**	**20**	**17**	**18**
Corpora lutea (n)	Mean	10	10	10	10	10	9	10
	SD	2.4	1.7	1.8	1.5	2.0	1.7	1.8
Implantation sites (n)	Mean	9	9	9	9	9	8	9
	SD	2.4	1.9	1.7	2.5	1.8	1.7	1.5
Preimplantation loss (n)	Mean	1	1	1	1	0	1	1
	SD	1.3	0.9	1.2	1.9	0.4	1.3	0.8
Preimplantation loss (%)	Mean	10.0	8.2	9.7	11.1	2.2	8.9	6.2
	SD	13.19	9.43	11.50	18.90	3.92	12.81	6.98
Early resorptions (n)	Mean	0	0	0	0	0	0	0
	SD	0.4	0.7	0.8	1.0	0.3	0.4	0.4
Late resorptions (n)	Mean	0	0	0	0	0	0	0
	SD	0.2	0.3	0.3	0.8	0.2	0	0.5
Total resorptions	Mean	0	0	0	1	0	0	0
	SD	0.4	0.7	0.8	1.0	0.3	0.4	0.5
Dead fetuses (n)	Mean	0	0	0	0	0	0	0
	SD	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Postimplantation loss (n)	Mean	0	0	0	1	0	0	1
	SD	0.4	0.7	0.8	1.0	0.3	0.4	0.5
Postimplantation loss (%)	Mean	2.5	4.7	7.0	8.5	1.0	2.7	5.6
	SD	4.85	7.38	14.90	10.85	3.03	6.16	5.93
Live fetuses (n)	Mean	9	9	8	8	9	8	9
	SD	2.5	1.7	2.2	2.3	1.7	1.9	1.6
Gravid uterine weight	Mean	522.0	508.7	487.7	477.1	531.7	484.7	525.5
	SD	108.11	77.64	100.74	124.4	82.34	74.52	87.08
Corrected body (carcass) weight (g)	Mean	3279.2	3274.1	3165.9	3212.4	3246.8	3252.2	3135.2
	SD	227.32	245.04	266.59	220.37	261.36	311.90	289.5
Corrected weight change (g)	Mean	-40.7	-49.0	-100	-50.3	-62.5	-8.3	-126.2
	SD	131.72	85.22	147.34	148.49	87.09	145.38	126.17
Total weight change (g)	Mean	481.3	459.7	387.6	426.8	469.3	476.4	399.3
	SD	131.35	83.01	141.84	121.74	117.81	123.72	115.85
Mean number of male fetuses per litter	Mean	5	5	4	4	4	4	4
	SD	2.1	2.3	1.4	1.5	1.7	1.9	1.6
Mean number of female fetuses per litter	Mean	4	4	5	4	5	4	5
	SD	1.6	1.4	2.0	1.8	2.0	1.3	1.2
% Male fetuses	Mean	53	56	45	50	48	50	43

Parameter	Group	1	2	3	4	5	6	7
Number of females pregnant at c-section	**N**	**18**	**20**	**19**	**15**	**20**	**17**	**18**
	SD	15.7	20.4	14.4	13.9	17.6	14.6	13.1
Mean fetal weight (g)	Mean*	41.5	41.2	41.9	39.2	39.3	40.9	39.4
	SD	4.01	3.54	5.56	3.44	2.95	5.11	5.19
Mean weight, male fetuses (g)	Mean	42.4	42.3	42.1	40.2	40.3	41.7	40.1
	SD	3.87	3.83	5.29	3.92	3.16	5.87	5.82
Mean weight, female fetuses	Mean	41.0	39.6	42.1	38.3	38.7	40.1	39.0
	SD	4.99	4.35	5.84	4.30	2.90	5.49	5.14

Source: Review team.
Abbreviations: N, number of females pregnant at c-section; SD, standard deviation

Table 103. Great Vessel and Cardiac Malformations

Affected Structure	Study Group	1	2	3	4	5	6	7
		18/160	**20/171**	**19/157**	**15/122**	**20/186**	**17/141**	**18/159**
Aorta, malpositioned	Fetuses/litters							1/1
	% Affected litters							5.56
	% Affected fetuses							0.63
Aortic arch, absent	Fetuses/litters							1/1
	% Affected litters							5.56
	% Affected fetuses							0.63
Aortic arch, dilated	Fetuses/litters			1/1			1/1	13/5
	% Affected litters			5.26			5.88	27.78
	% Affected fetuses			0.64			0.71	8.18
Aortic arch, retroesophageal	Fetuses/litters					1/1		
	% Affected litters					5.00		
	% Affected fetuses					0.54		
Carotid trunk, malpositioned	Fetuses/litters			1/1				1/1
	% Affected litters			5.26				5.56
	% Affected fetuses			0.64				0.63
DA, absent	Fetuses/litters							1/1
	% Affected litters							5.56
	% Affected fetuses							0.63
DA, atretic	Fetuses/Litters							2/2
	% Affected litters							11.11
	% Affected fetuses							1.26

Affected Structure	Study Group	1	2	3	4	5	6	7
		18/160	20/171	19/157	15/122	20/186	17/141	18/159
Pulmonary trunk, atretic or narrow	Fetuses/litters			1/1			1/1	11/5
	% Affected litters			5.26			5.88	27.78
	% Affected fetuses			0.64			0.71	6.92
Pulmonary trunk, narrow	Fetuses/litters							5/2
	% Affected litters							11.11
	% Affected fetuses							3.14
Subclavian, malpositioned	Fetuses/litters							1/1
	% Affected litters							5.56
	% Affected fetuses							0.63
Subclavian, retroesophageal	Fetuses/litters							1/1
	% Affected litters							5.56
	% Affected fetuses							0.63
Situs inversus, abdominal	Fetuses/litters							1/1
	% Affected litters							5.56
	% Affected fetuses							0.63
Dextrocardia	Fetuses/litters							2/2
	% Affected litters							11.11
	% Affected fetuses							1.26
AVSD	Fetuses/litters							3/3
	% Affected litters							16.67
	% Affected fetuses							1.89
Atrium, malpositioned	Fetuses/litters							2/1
	% Affected litters							5.56
	% Affected fetuses							1.26
Heart, three-chambered	Fetuses/litters							3/2
	% Affected litters							11.11
	% Affected fetuses							1.89
Heart, ventricle enlarged	Fetuses/litters							3/2
	% Affected litters							11.11
	% Affected fetuses							1.89
Heart, ventricle small	Fetuses/litters							1/1
	% Affected litters							5.56
	% Affected fetuses							0.63
Ventricle, thin	Fetuses/litters							2/1
	% Affected litters							5.56
	% Affected fetuses							1.26

Affected Structure	Study Group	1	2	3	4	5	6	7
		18/160	20/171	19/157	15/122	20/186	17/141	18/159
VSD	Fetuses/litters							7/5
	% Affected litters							27.78
	% Affected fetuses							4.40

Source: Review team.
Abbreviations: AVSD, atrioventricular septal defect; N, number of females pregnant at c-section; VSD, ventricular septal defect

Table 104. Clusters of Cardiac and Great Vessel Malformations in Affected Fetuses

Treatment Group	No. of Affected Litters	No. of Affected Fetuses	Doe	Fetus	Findings
3	1	1	B0209	L4	Dilated aortic arch Pulmonary trunk atretic Enlarged left ventricle Small right ventricle Membranous VSD Common carotid trunk malpositioned
5	1	1	B0414	L1	Retroesophageal aortic arch
6	1	1	B0511	R10	Dilated aortic arch Pulmonary trunk atretic Enlarged left ventricle Small right ventricle
7	6	15	B0605	L1	Dilated aortic arch Ductus arteriosus atretic Muscular VSD
				L3	Dilated aortic arch
				L5	Dilated aortic arch Muscular VSD
				L6	Dilated aortic arch Pulmonary trunk atretic 3-chambered heart
				R7	Dilated aortic arch Pulmonary trunk atretic Three-chambered heart Membranous atrio-ventricular septal defect
			B0606	R1	Dilated aortic arch Pulmonary trunk atretic Enlarged left ventricle Small right ventricle Membranous VSD
				R4	Dilated aortic arch
				R5	Dilated aortic arch Pulmonary trunk atretic Muscular VSD Dextrocardia Situs inversus (abdominal cavity)
			B0609	R4	Absent aortic arch Malpositioned descending aorta Absent ductus arteriosus Muscular VSD Malpositioned common carotid trunk Malpositioned left subclavian artery
			B0612	R6	Dilated aortic arch Pulmonary trunk atretic Muscular VSD Atretic ductus arteriosus Atrioventricular septal defect Dextrocardia
			B0613	L2	Dilated aortic arch Three-chambered heart

Treatment Group	No. of Affected Litters	No. of Affected Fetuses	Doe	Fetus	Findings
				L3	Dilated aortic arch Malpositioned right atrium Enlarged left ventricle Small right ventricle
				R5	Dilated aortic arch Malpositioned right atrium Enlarged left ventricle Small right ventricle
			B0615	L3	Dilated aortic arch Pulmonary trunk atretic Muscular VSD Retroesophageal subclavian
				L5	Membranous VSD

Source: Review team.
Abbreviations: AVSD, atrio-ventricular septal defect; VSD, ventricular septal defect

Table 105. Prenatal and Postnatal Development

Study title: Prenatal and Postnatal Development, Including Maternal Function, with ATB200 Alone or Coadministered with AT2221 in Rats	
Study no.:	8371932
Study report location:	0001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 23, 2019
GLP compliance:	Y
QA statement:	Y, with the following exceptions: 1). Characterization and stability of ATB200 and AT2221 performed by Applicant or subcontractor under GMP regulations 2). TK analyses of ATB200 and AT2221 in milk performed to test site SOPS 3). Plasma protein analysis of ATB200 conducted as per OECD regulations 4). Concentration and homogeneity analyses not conducted for oral diphenhydramine suspension
Drug, lot #, and % purity:	WBPIIO (ATB200), 110170720, ≥90%

Source: Review team.
Abbreviations: GLP, good laboratory practices; GMP, good manufacturing practices; OECD, Organisation for Economic Co-operation and Development; QA, quality assurance; SOP, standard operating procedure

Key Study Findings

ATB200 was administered by infusion to pregnant rats, at doses of 70, 150, or 400 mg/kg every other day during pregnancy, beginning on GD 6 through GD 20, with a pause thereafter to permit parturition; then resuming on LD 1 and ending on LD 19. DPH (10 mg/kg) was administered by intravenous push 90 min prior to the onset of the ATB200 infusion, beginning GD 8. One experimental group (Group 7) received ATB200 with oral ATT2221 (60 mg/kg) every other day; the latter was administered 30 min prior to ATB200 infusion. See Table 107 for complete details of study design.

F0 mortality was excessive in Group 7, relative to vehicle and vehicle/AT2221-treated controls. Frequently, there were no antecedent clinical observations; the cause of this is impossible to determine from existing data.

F1 mortality was excessive in Groups 6 and 7: all-cause F1 mortality (stillborn, missing/presumed cannibalized) numbered 25 and 31 pups, respectively, compared to a range of 0-15 pups among the 3 control groups. Groups 6 and 7 had 2 and 3 total/near total litter losses, respectively; this is contrasted with a single incidence of total litter loss among 69 vehicle-treated dams distributed across 3 vehicle-treated groups. There was no evidence of dystocia or delayed parturition, which can account for excessive neonatal mortality.

Group 7 F1 male pup weights were reduced relative to vehicle controls from PND 14-PND28 (range -4.8 to -6.4 %). Group 7 female pup weights were generally reduced from PND 14 through PND 49 (~-6%).

There were no additional treatment-related effects noted on any maternal or developmental parameter.

Toxicokinetic parameters (AUC and C_{max}) were not calculated in this study for either ATB 200 or AT2221, although they may be inferred from signal peptide values reported in Table 91, Table 92, and Table 93 in the study of embryo-fetal development in rats. Single time-point plasma and milk levels of ATB200 and AT2221 were determined in lactating dams on LD 13 treated with ATB200 400 mg/kg and AT2221 60 mg/kg. Ratios of milk to plasma for ATB200 and AT2221 were 0.038 and 1.72, respectively, suggesting that AT2221 is excreted into milk.

Maternal and developmental NOAELs for ATB200 were 150 mg/kg. The mean AUC and C_{max} values for these were 6210 µg·h/mL and C_{max} = 2715 µg/mL, respectively. The safety margins at this dose (relatively to MRHD AUC of 1400 µg *h/mL and 280 µg /mL) for each of these parameters is 4.4 and 9.7, respectively. The maternal and developmental LOAEL was 400 mg/kg; as per data from the embryo-fetal development study in rats, the AUC and C_{max} at this dose were 28850 µg*h/mL and 6790 µg/mL, respectively. These provide safety margins for cipaglucosidase of 20.6 and 24.2, relative to clinical AUC and C_{max} values of 1400 µg*h/mL and 280 µg/mL, of 20.6 and 24.2.

There was no $NOAEL_{developmental}$ for co-administered AT2221. The $LOAEL_{developmental}$ is 60 mg/kg. As per values reported from the embryo-fetal developmental study in rats, the AUC_{0-24} is 84,300 ng*h/mL. The C_{max} is 13,200 ng/mL. The safety margins at this dose are 4.2 and 5.5, respectively.

Reviewer's Comment. The findings in the present study confirm and extend those reported in the original miglustat (AT2221) review. Briefly, F1 offspring survival was reduced at 60 mg/kg in both studies, even though dosing in the current study was every other day, while dosing in the original study was conducted daily. Maternal mortality was reported at 60 mg/kg in a single dam. That said, F1 mortality in the present study was also excessive in Group 6 (cipaglucosidase alone).

Body weights of F1 males and females on PND 21 were reduced by 5.6% and 4.9%, respectively. The decrements in F1 treated males, although not females, persisted though PND 70. The original miglustat NOAEL for the PPND study was 20 mg/kg/day.

Table 106. Study 8371932 Methods

Doses	0, 70, 150, 400 mg/kg
Frequency of dosing	Every other day, GD 6-LD 19
Dose volume	30 mL/kg
Route of administration	Intravenous infusion
Formulation/vehicle	0.9% NaCl solution
Species/strain	Rat/Crl:CD Sprague-Dawley
Number/sex/group	24-30
Satellite groups	2 (Groups 8 and 9, for Group 7 and Group 1, respectively) for single-time-point assessment of ATB200 and AT2221 concentrations on LD 13.
Study design	See below (Table 107)
Deviation from study protocol	Listed below are deviations which could have impacted study interpretation. These have been copied from a table within the study report. 1). AT2221 was not prepared under sterile conditions 2). Instances of partial dosing are as follows. GD 6 and 10, Animal R0601 (Group 7) ATB200 GD 8, Animal R0305 (Group 4) ATB200 LD 1, Animal R0617 (Group 1) ATB200 LD 13, Animal R0604 (Group 7) DPH, oral antihistamine LD 13, Animal R0406 (Group 5) DPH, oral antihistamine LD 17, Animal R0411 (Group 5) ATB200 LD 19, Animal R0202 (Group 3) DPH, oral antihistamine 3). On 11 March 2020 (LD 17), several Group 7 F0 females (Animals R0527, R0530, R0531, and R0532) were evaluated for postdose observations 6 h 20 min late. 4). Milk samples for ATB200 protein analysis were stored at -20°C instead of the phase plan instructed -70°C.

Source: Review team.
Abbreviations: AT2221, miglustat; C, Celsius; GD, gestation day; LD, lactation day; NaCL, sodium chloride

Viability was checked twice daily. Cageside postdose clinical observations were conducted 30-60 minutes after dosing. Body weights were collected prior to dosing. (Dosing was halted after GD 20, and resumed on LD 1.) Food consumption was collected on cohoused rats (2 per cage) during 2-day intervals beginning GD 4 and ending GD 20l; and resumed these 2-day intervals beginning LD 1.

Blood samples for toxicokinetic analyses: Single-time-point blood and milk samples were drawn at approximately 3 hours post oral administration of AT2221 / 2.5 hours post infusion of ATB200. (The dosing interval for these dams was LD 1 to LD 13.)

F0 females were allowed to deliver naturally. When delivery was completed (LD0 for F0 females; PND 0 for F1 offspring), the numbers of live, dead, cannibalized and stillborn pups were recorded. Necropsies were attempted for dead and cannibalized toxicity pups, although not toxicokinetic pups. On PND1/LD1, numbers of live, dead and cannibalized pups were again recorded, with necropsies again attempted for dead and cannibalized toxicity pups.

Table 107. Experimental Groups in Rat PPND

Group	Number of Mated Females (F_0)	ATB200 Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dosing Schedule	Dose Interval
Toxicity Animals					
1 (Vehicle Control)	24	0	0	q.o.d.	GD 6 - LD 19
2 (Vehicle Control + DPH[a])	24	0	0	q.o.d.	GD 6 - LD 19
3 (Vehicle Control + DPH[a] + AT2221[b])	24	0	0	q.o.d.	GD 6 - LD 19
4 ATB200 + DPH[a] (Low)	24	70	2.3	q.o.d.	GD 6 - LD 19
5 ATB200 + DPH[a] (Mid)	24	150	5.0	q.o.d.	GD 6 - LD 19
6 ATB200 + DPH[a] (High)	24	400	13.3	q.o.d.	GD 6 - LD 19
7 ATB200 + DPH[a] + AT2221[b] (High)	30[c]	400	13.3	q.o.d.	GD 6 - LD 19
Toxicokinetic Animals					
8 (High) ATB200 + DPH[a] + AT2221[b]	3	400	13.3	q.o.d.	LD 1 - LD 13
9 Non-treated (Naïve)	6	NA	NA	NA	NA

DPH = Diphenhydramine; q.o.d. = every other day
a DPH dose level was 10 mg/kg.
b AT2221 dose level was 60 mg/kg.
c Due to the increase in deaths in Group 7, six additional time-mated animals were added to the study.

Source: BLA 761204, SDN 0001, Study Report Number 8371932.
Abbreviations: GD, gestation day; LD, lactation day; NA, not applicable; PPND, pre- and postnatal development

Litters were observed daily, and daily records made of pup mortality. Litters of F0 females found dead prior to LD 18 were euthanized, but no F1 necropsies were conducted. On PND 4, litters were culled to 8 pups (4 males and 4 females, when possible). On PND 7, 14 and 21, pups were sexed and weighed; detailed clinical examinations were conducted on individual pups. Developmental landmark assessment was conducted daily until an entire litter had attained the landmark.

- Pinna folding (Postnatal Day [PND] 1)
- Surface righting reflex (postculling on PND 4)
- Hair growth (PND 7)
- Incisor eruption (PND 7)
- Eye opening (PND 11)

F1 pups were weaned (removed from the F0 cage) on PND/LD 21, and one pup/sex/litter was selected from the first 20 litters and identified to yield at least 20 animals/sex/group (when possible) for the F1 maturation phase. Any F1 pups not selected were sacrificed, and necropsies were not conducted. General daily observations and unscheduled observations were conducted as previously described for the F0 generation.

N.B. Thereafter, the designation “Maturation Phase” was used to denote weeks beginning on PND 28 and ending on PND 84; the numbering of weeks during this phase was reset to 0 on

PND 28. F1 body weights and food consumption were recorded weekly thereafter/until evidence of confirmed mating of F1 females. F1 pregnant female body weights and food consumption were recorded on GD 0, 3, 7, 10 and 13.

Attainment of vaginal opening was assessed beginning on PND 28, and cleavage of the balanopreputial gland was evaluated beginning on PND 38. Each animal was evaluated until the day the milestone was achieved, and on the day of achievement, a body weight was recorded.

Locomotor activity (LMA) was conducted beginning on PND 56 (±4 days). Acoustic Morris water maze (MWM) testing began on PND 63 (±4 days). For F1 females, estrous cycles were evaluated using daily vaginal lavage beginning 6 weeks postweaning (when animals were approximately 10 weeks of age). Estrous cycle evaluations continued for 2 weeks prior to cohabitation, throughout cohabitation; and until positive signs of mating were observed or the pairing phase ended. Estrous slides were read fresh and were not stained or retained.

Following 2 weeks of estrous cycle evaluations, F1 females were placed into cages for mating with F1 males of the same treatment group for a total of 14 days; pairing of siblings was avoided. Once mating occurred, females were removed from the male cage, and that day was considered GD 0. When mating did not occur during the first week of pairing, the female was moved to a cage containing a proven male for the second week.

During cohabitation, a daily inspection was made for the presence of a retained copulatory plug or vaginal sperm. The day sperm or a plug was observed was designated as GD 0. Females without confirmation of mating were removed from study and necropsies conducted approximately 7 days after the end of cohabitation (or earlier if the female was demonstrably pregnant). On GD 13, Cesarean sections were conducted for females with a confirmation of mating. F1 males were sacrificed, and necropsies conducted, within 2 days of confirmation of mating.

Observations and Results

Mortality

All-cause maternal mortality and total litter loss are reproduced in Table 108. Two dams (R0101 and R0520) were euthanized in moribund condition on GD 6, and immediately replaced.

There was excessive mortality – both F0 and F1 - in Group 7. Six F0 animals were added to the original 24 enrolled on study to replace dams that died, were sacrificed in moribund condition, or were euthanized after total litter loss. Data from these additional dams diluted the impact of maternal and pup mortality on group statistics.

Individual F0 mortality is reproduced below in Table 109; frequently, there were no antecedent clinical observations. The Applicant cites clinical observations associated with the animals that died (e.g., struggling during dosing, cool to touch) that are likewise observed in animals that were not unscheduled decedents. Restraint needed for dosing, coupled with every-other-day infusions, did not materially increase the number of deaths in the vehicle-infused groups. The Applicant will need to furnish information on the causes of deaths in Group 7. Total F1 litter losses are reproduced in Table 110. Notably, these losses were all early in lactation, when most neonatal mortality occurs.

Table 108. All-Cause F0 and F1 (Total Litter Loss) Mortality

Group	ATB Dose (mg/kg)	AT2221 Dose (mg/kg)	Number of Dams Initially on Study	Number of Dams That Died on Study	Number of Dams With Total Litter Loss	Number of Dead Dams Replaced	Number of Litters Available for Examination
1	0	0	24	1	0	0	23
2	0	0	24	1	1	1	23
3	0	60	24	1	0	1	23
4	70	0	24	3	0	1	22
5	150	0	24	1	1	1	23
6	400	0	24	1	1	1	23
7	400	60	24	4	3	6	23

Source: Review team.
Abbreviations: AT2221, miglustat

Table 109. Unscheduled Mortality in PPND in F0 Rats

Rat	Group	ATB Dose (mg/kg)	AT2221 Dose (mg/kg)	Study Day	Comments
R0011	1	0	0	GD10	Found dead after dosing. No antecedent clinical observations.
R0101	2	0	0	GD6	Euthanized moribund after administration of partial dose.
R0213	3	0	60	GD8	Struggled during dosing, red discharge from nose and mouth, lateral recumbent posture. Sacrificed moribund
R0303	4	70	0	LD15	Found dead, no antecedent clinical observations
R0319	4	70	0	LD1	Dam not attending to litter, not producing milk. Sacrificed moribund.
R0325	4	70	0	GD8	Found dead after dosing. No antecedent clinical observations
R0419	5	150	0	GD6	Found dead. No antecedent clinical observations.
R0519	6	400	0	GD20	Found dead “following restraint”
R0520	6	400	0	GD6	Euthanized moribund after administration of partial dose
R0603	7	400	60	LD11	Found dead after dosing. No antecedent clinical observations.
R0609	7	400	60	GD22	Unspecified “severity of clinical observations.” Sacrificed moribund
R0612	7	400	60	LD7	Found dead after dosing. No antecedent clinical observations.
R0624	7	400	60	GD10	Found dead after dosing. No antecedent clinical observations.

Source: Review team.
Abbreviations: GD, gestation day; LD, lactation day

Table 110. Unscheduled Mortality in PPND in F1 Rats: Near/Total Litter Loss

Rat	Group	ATB Dose (mg/kg)	AT2221 Dose (mg/kg)	Study Day	Comments
R0115	2	0	0	LD2	
R0415	5	150	0	LD1	
R0521	6	400	0	LD0	
R0522	6	400	0		13 of 15 pups listed as missing/presumed cannibalized
R0528	7	400	60	LD0	Single stillborn pup
R0529	7	400	60	LD1	
R0608	7	400	60	LD3	

Source: Review team.
Abbreviations: LD, lactation day

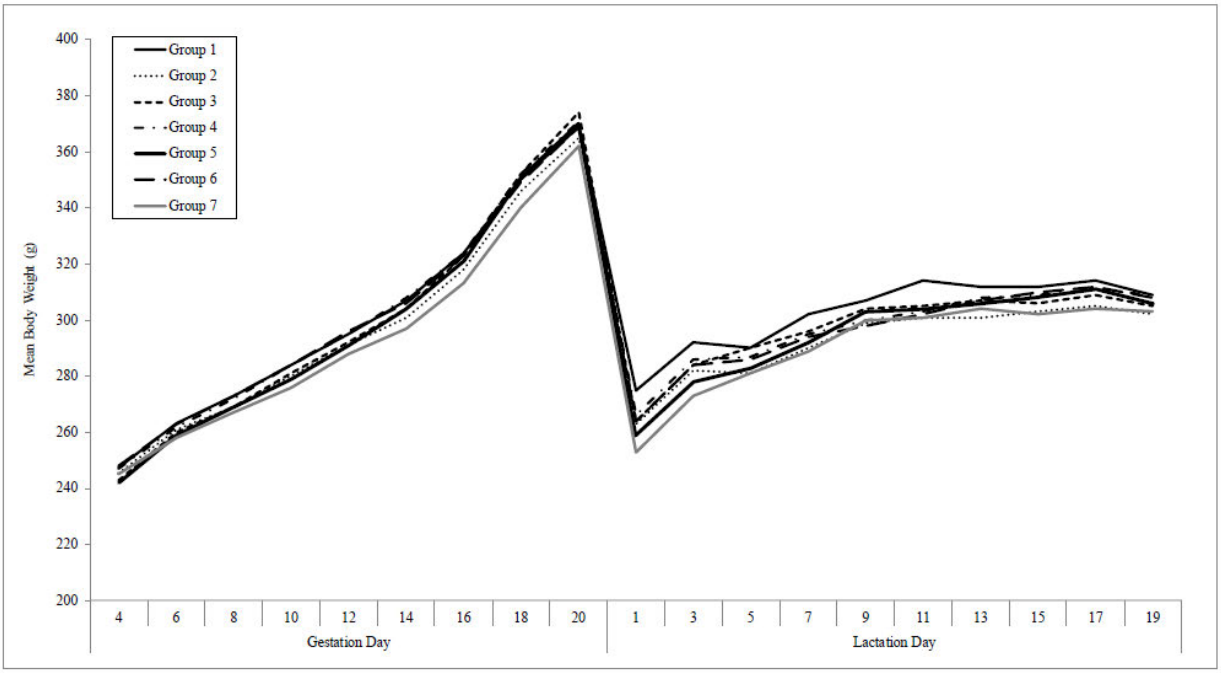
The number of dead/euthanized/missing/cannibalized pups (Days 0 to 4) were 5, 15, 0, 15, 5, 25, and 31 in Groups 1 through 7, respectively. There was an apparent non-statistically significant increase in the numbers of pups categorized as dead for any reason (i.e., found dead, sacrificed in a moribund condition, missing, or cannibalized) during Days 0 to 4 in Group 7 when compared to the control Group 3 (31 versus 0, respectively). The necropsy observation “no milk in stomach” was reported for 14 pups found dead in group 7 (relative to ≤3 in all other experimental groups).

Table 111. Study 8371932 Observations by Generation

F_0 Dams	
Survival:	See Table 109
Clinical signs:	Abnormal gait, reduced activity (Group 7)
Body weight:	See Figure 71. There were no statistically significant differences among experimental groups during gestation or lactation. Body weight gain data are not reviewed.
Food consumption:	See Figure 72. There were no statistically significant differences among experimental groups during gestation. Small, statistically significant changes in treatment groups during 2-day intervals were not biologically meaningful.
Necropsy observation:	There were no treatment-related necropsy observations in F0 dams.
Toxicokinetics:	See Table 91, Table 92, and Table 93
Dosing Solution Analysis	ATB200 solutions were all 94.9 - 99% of specified. AT2221 solutions were 99-102.6% of specified.
F_1 Generation	
Survival:	See Table 110 and accompanying text.
Clinical signs:	Pre-weaning: no treatment-related clinical signs.
Body weight:	Birth weights were not provided; instead, weights on PND 1 were reported. Weights of F1 males (and % change from appropriate vehicle) are reproduced in Figure 73 and Figure 74. Reductions were observed in Group 7 males on PND 14, when compared to Group 3 weights, persisting through PND 28 (range -4.8 to -6.5). These differences resolved by PND 50. Weights of F1 females (and % change from appropriate vehicle) are reproduced in Figure 75 and Figure 76. Weights of F1 females in Group 7 were generally reduced by ~6%, relative to those in Group 3, from PND 14 through PND 49 (-6%). Thereafter, these differences gradually declined. Body weight gain data were not reviewed.
Food consumption:	There were no adverse, treatment-related differences in food consumption among F1 males or females.
Physical development:	The mean days to achieve criteria for pinna unfolding, incisor eruption, hair growth, eye opening, and surface righting were similar to the control groups. No test article-related effects on sexual maturation were noted. The mean days to achieve balanopreputial separation ranged from 45.5 to 46.9, and the mean days to achieve vaginal opening ranged from 32.2 to 32.8 for all groups.
Neurological assessment:	Locomotor activity and latency to acoustic startle were highly variable across treatment groups, with no dose-related trends observed. Likewise, there were no differences among treatment groups in learning to swim the Morris Water Maze.
Reproduction:	The mean numbers of estrous cycles observed over the 14-day interval ranged from 2.1 to 2.4. Mean cycle duration ranged from 4.01 days (Group 1) to 4.61 days (Group 6). These differences are not considered biologically meaningful. Group mean days to mate ranged from 2.2 (Group 7) to 3.6 (group 6), were unrelated to dose. Pregnancy rates ranged from 77.8-100%, and were unrelated to dose.
F_2 Generation	
Survival:	Group mean numbers of life F2 fetuses ranged from 13.9 to 15.1, and were unrelated to dose.
Body weight:	Not assessed
External evaluation:	Not assessed
Male/Female ratio:	Not assessed

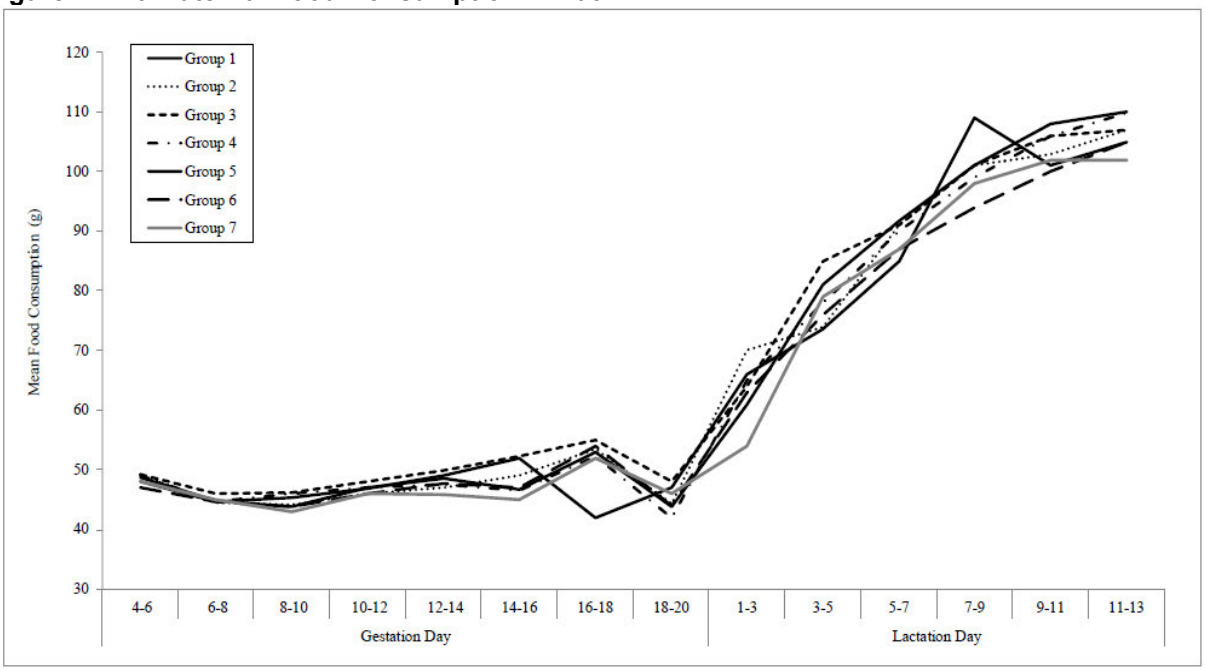
Source: Study report number 8371932.
Abbreviations: AT2221, miglustat; PND, postnatal day

Figure 71. F0 Maternal Body Weights in Rat PPND



Source: BLA 761204, SDN 0001, Study Report number 8371932.

Figure 72. F0 Maternal Food Consumption in Rat PPND



Source: BLA 761204, SDN 0001, Study Report number 8371932.

Table 112. F0 ATB200 Concentrations in Maternal Plasma and Milk on LD 13

	ATB200 mg/kg	Concentration in Plasma (mcg/mL)	Concentration in Milk (mcg/mL)	Milk: Plasma Ratio
Dose	400	4795	181	0.038

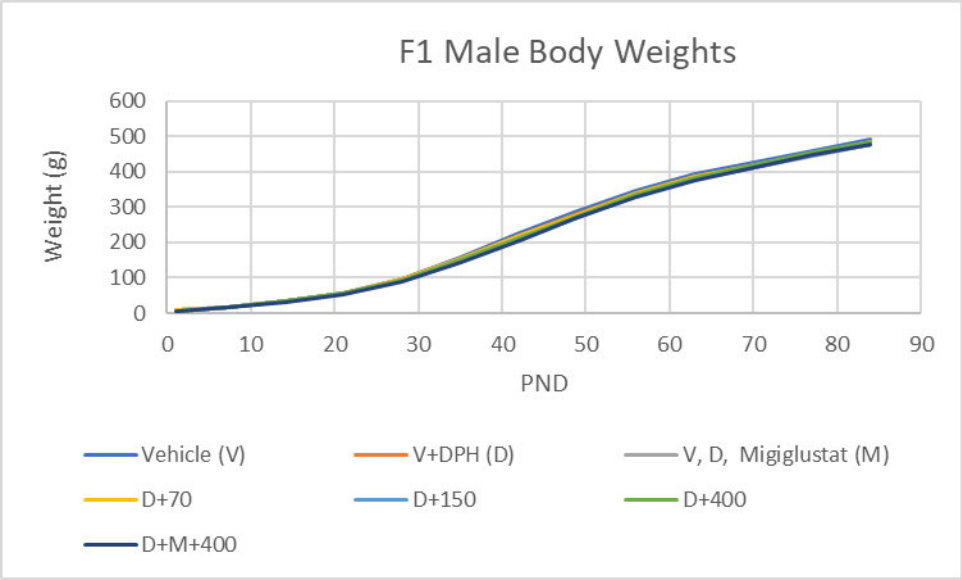
Source: Review team.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; LD, lactation day

Table 113. F0 AT2221 Concentrations in Plasma and Milk on LD 13

	AT2221	Concentration in Plasma (ng/mL)	Concentration in Milk (ng/mL)	Milk: Plasma Ratio
Dose	60	8960	15400	1.719

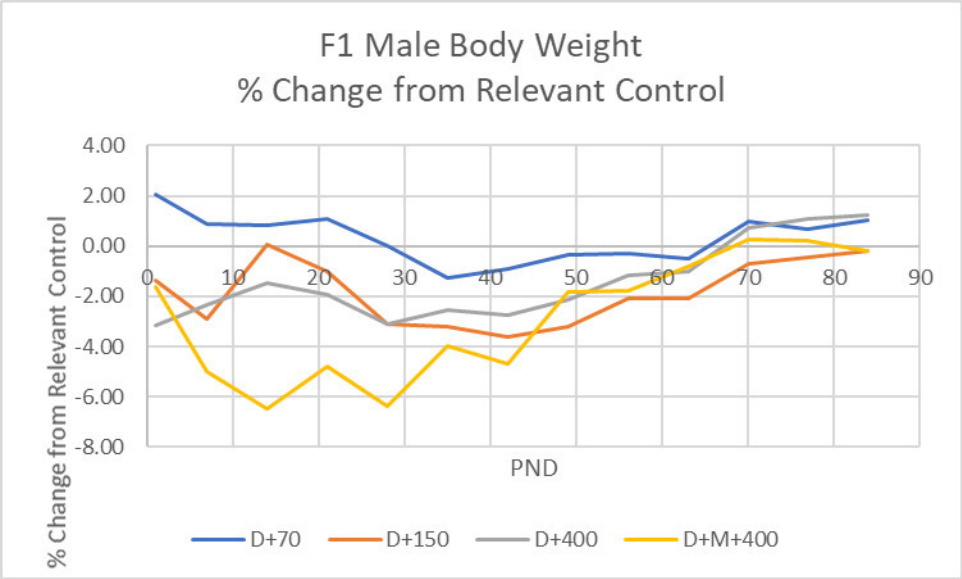
Source: Review team.
Abbreviations: AT2221, miglustat; LD, lactation day

Figure 73. Body Weights of F1 Male Rats



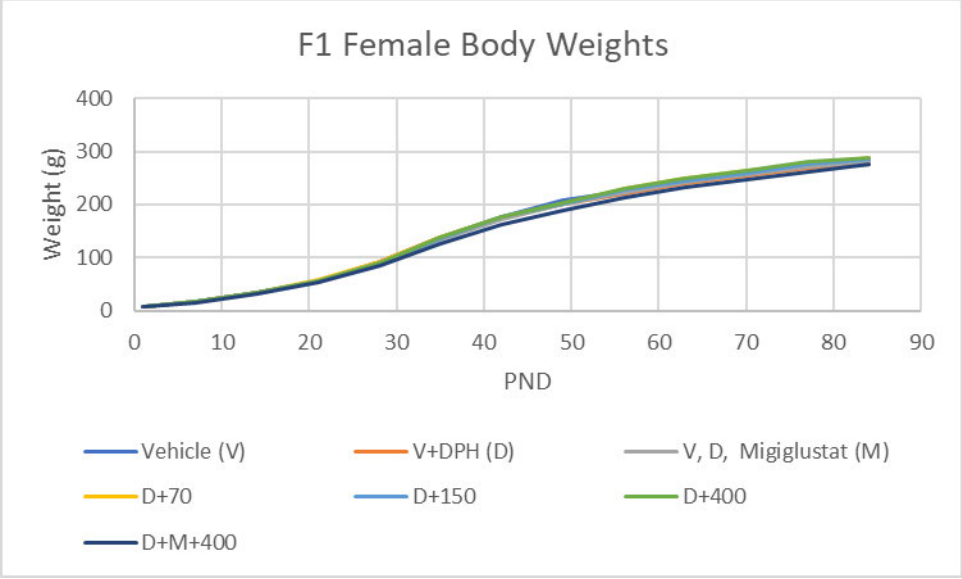
Source: Review team.
Abbreviations: DPH, diphenhydramine; M, miglustat; PND, postnatal day; V, vehicle

Figure 74. F1 Male Body Weights (Percentage Change From Vehicle)



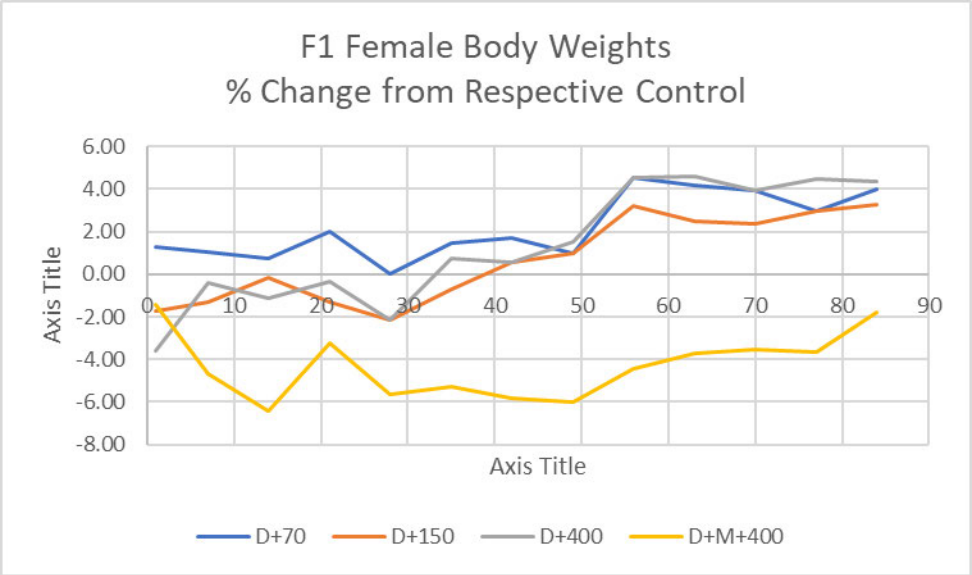
Source: Review team.
Abbreviations: DPH, diphenhydramine; M, miglustat; PND, postnatal day

Figure 75. F1 Female Body Weights



Source: Review team.
Abbreviations: DPH, diphenhydramine; M, miglustat; PND, postnatal day; V, vehicle

Figure 76. F1 Female Body Weights (Percentage Change From Vehicle Control)



Source: Review team.
Abbreviations: DPH, diphenhydramine; M, miglustat; PND, postnatal day

Toxicokinetics

Study 302

Male *Gaa* KO mice (n=5/group) were administered ATB200 5, 10, or 20 mg/kg, or alglucosidase alfa 20 mg/kg, as a 30-minute IV infusion. In a separate group, AT2221 at 10 mg/kg was orally administered 30 min prior to the start of the 20 mg/kg ATB200 IV infusion. In a final group, animals were untreated, but plasma and tissues were collected similarly to the dosed groups to serve as baseline values. Blood samples were collected at 30 min, 45 min, and 1, 1.5, 2, 3, and 24 h postdose. Tissues (liver, kidney, heart, diaphragm, tongue, hind and forelimbs) were collected after the last blood sample was collected. ATB200 was cleared faster from plasma than alglucosidase alfa, with a half-life of 47 min versus 78 min, correlating to an approximately 50% lower AUC for ATB200 (215,000 versus 480,000nM·h). Plasma GAA activity increased with increasing doses of ATB200, peaking at 30 min postdosing, similar to alglucosidase alfa. Plasma GAA activity was lower with ATB200 treatment compared to alglucosidase alfa at the same dose, correlating to the decreased plasma AUC observed in ATB200-treated animals compared to alglucosidase alfa. However, tissue activity of GAA was similar between the two treatments.

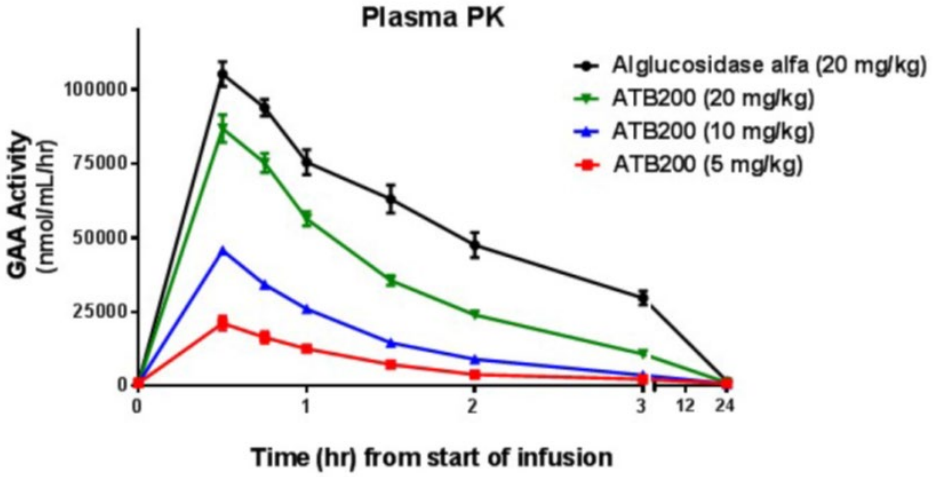
Oral coadministration of AT2221 (10 mg/kg) with ATB200 (20 mg/kg) did not increase AUC, C_{max}, or the half-life of ATB200 compared to ATB200 administration alone. Further, while oral coadministration with AT2221 only slightly increased GAA activity in quadriceps, it significantly increased GAA activity in triceps, and decreased GAA activity in heart tissue compared to ATB200 or alglucosidase alfa administered alone.

Table 114. PK Parameters of ATB200 After IV Infusion in *Gaa* KO Mice

AT2221 PO (mg/kg)*	Alglucosidase alfa (mg/kg)	ATB200 (mg/kg)	$AUC_{0\text{-}24h}$ (nmol/mL/hr * hr)	C_{max} (nmol/mL/hr)	t_{max} (h)	$t_{½}$ (h)
	20		480552	105543	0.5	1.32
		5	34145	21165	0.5	0.62
		10	74880	45721	0.5	0.61
		20	215238	86805	0.5	0.79
10		20	208866	74108	0.5	0.81

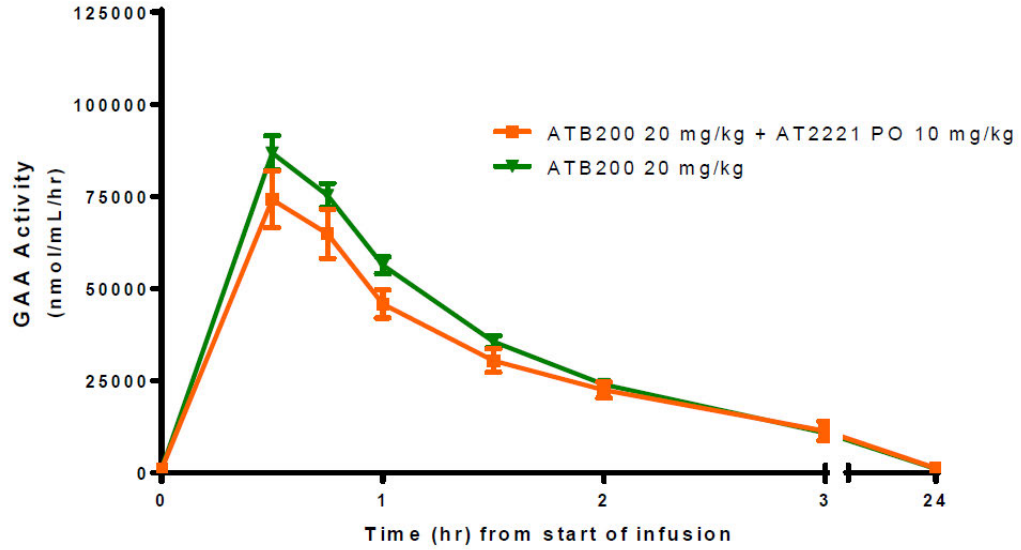
Source: Applicant's table from Pharmacokinetics study RRB200-03, page 27.
Abbreviations: AT2221, miglustat; ATB200, recombinant human acid alpha-glucosidase; $AUC_{0\text{-}24}$, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; PO, by mouth; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life

Figure 77. Plasma GAA Activity of ATB200 in *Gaa* KO Mice



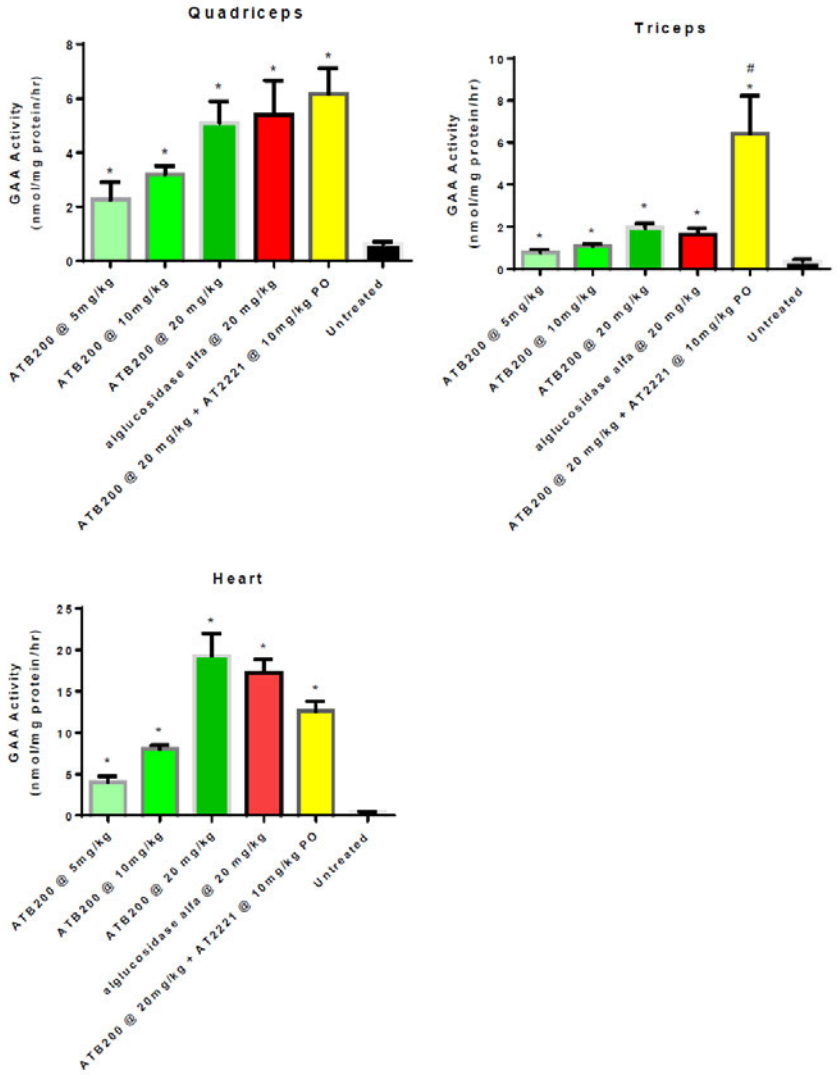
Source: Applicant's figure from Pharmacokinetics study rrb200-03, page 18.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; GAA, human acid α-glucosidase; KO, knockout; PK, pharmacokinetics

Figure 78. Plasma GAA Activity of ATB200 +/- Coadministration with AT2221



Source: Applicant's figure from Pharmacokinetics study rrb200-03, page 19.
Twenty-four-week-old male *Gaa* KO mice were administered 20 mg/kg ATB200 via a 30 min intravenous infusion. In addition, in one group AT2221 at 10 mg/kg via oral coadministration was administered 30 min prior to the IV administration of 20 mg/kg ATB200.
GAA activity in plasma at various time points following the start of infusion was measured by 4MU-Glc enzyme assay.
Abbreviations: AT2221, miglustat; ATB200, recombinant human acid alpha-glucosidase; GAA, human acid α-glucosidase

Figure 79. Tissue Activity of GAA After IV Infusion of ATB200 in *Gaa* KO Mice



Source: Applicant's figure from Pharmacokinetics study rrb200-03, page 21.
Twenty-four-week-old male *Gaa* KO mice were administered alglucosidase alfa (20 mg/kg) or ATB200 (5, 10, or 20 mg/kg) via a 30 min intravenous infusion. In addition, in one group AT2221 at 10 mg/kg via oral coadministration was administered 30 min prior to the IV administration of 20 mg/kg ATB200. The GAA activity in tissues 24 h after the start of infusion was measured by 4MU-Glc enzyme assay. Statistical comparisons are made against the untreated control (black bar) and the alglucosidase alfa group (red bar) using two-sided t-tests, and significance is indicated atop bars (* $p<0.05$ against untreated; # $p<0.05$ against alglucosidase alfa).
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; GAA, human acid α-glucosidase; IV, intravenous; KO, knockout; PO, by mouth

Study 297

Male *Gaa* KO mice (n=5/group) were administered ATB200 5, 10, or 20 mg/kg, or alglucosidase alfa 20 mg/kg, as a bolus IV injection. In a separate group, animals were untreated, but plasma and tissues were collected similarly to the dosed groups to serve as baseline controls. Oral coadministration with AT2221 was not conducted in this study. Blood samples were collected prior to dosing and at 5 min, 15 min, 30 min, and 1, 1.5, 2.5, and 24 h postdosing. Tissues were collected after the last blood sample was collected. ATB200 was cleared faster from plasma than alglucosidase alfa, with a half-life of 42 min versus 84 min, correlating to an approximately 50% lower AUC for ATB200 (268,000 versus 524,000nM·h). Plasma GAA activity increased with

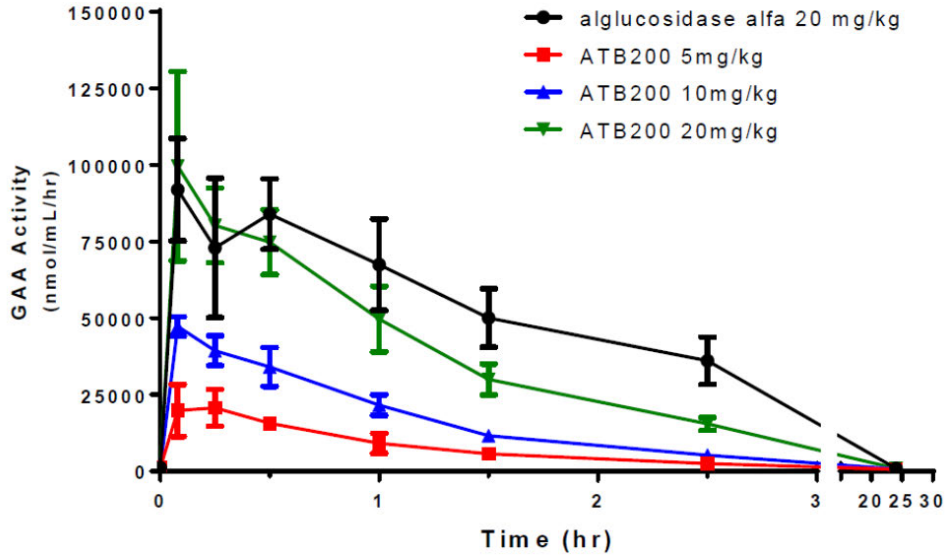
increasing doses of ATB200, peaking at 5-15 min postdosing, similar to alglucosidase alfa. Despite 50% lower plasma AUC of ATB200 compared to alglucosidase alfa at the same dose, plasma GAA activity was similar between the two treatments. Tissue activity of GAA was not recorded.

Table 115. PK Parameters of ATB200 After Bolus IV Injection in *Gaa* KO mice

Alglucosidase alfa (mg/kg)	ATB200 (mg/kg)	$AUC_{0\text{-}24h}$ (nmol/mL/hr * hr)	C_0 (nmol/mL/hr)	$t_{½}$ (h)
20		524219	112389	1.42
	5	35150	27333	0.67
	10	92535	55752	0.66
	20	268276	124171	0.79

Source: Applicant's table from Pharmacokinetics study rrb200-03, page 23.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; C_0, minimum concentration; GAA, human acid α-glucosidase; IV, intravenous; KO, knockout; PK, pharmacokinetics

Figure 80. Plasma GAA Activity of ATB200 After Bolus IV Injection in *Gaa* KO Mice



Source: Applicant's figure from Pharmacokinetics study rrb200-03, page 22.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; GAA, human acid α-glucosidase; IV, intravenous; KO, knockout

Study 304

Male Sprague-Dawley rats (n=3-4/group) were administered ATB200 at 5, 10, or 20 mg/kg, or vehicle (deionized water) as a bolus IV injection. In a separate group, AT2221 at 10 mg/kg was administered orally 30 min prior to the start of the 20 mg/kg ATB200 IV infusion. Alglucosidase alfa was not evaluated in this study. Blood samples were collected prior to dosing and at 15 min, 30 min, and 1, 1.5, 2, 3, 4, 8, and 24 h postdosing. ATB200 coadministered with AT2221 was cleared slightly slower from plasma compared to ATB200 alone, with a half-life of 52 min versus 46-minute, respectively, correlating to an approximately 19% higher AUC for ATB200 coadministered with AT2221 (184,000 versus 149,000nM·h). Oral coadministration of AT2221 (10 mg/kg) with ATB200 (20 mg/kg) increased plasma GAA activity from 15-30 min postdosing

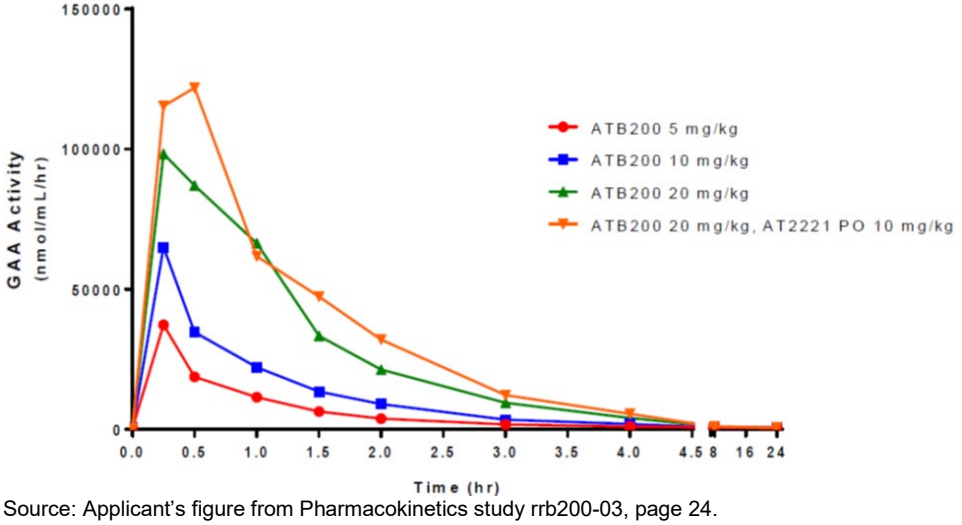
compared to ATB200 (20 mg/kg) alone, but plasma GAA activity was relatively similar for the remainder of the time points. Tissue activity of GAA was not evaluated.

Table 116. PK Parameters of ATB200 After Bolus IV Injection in Rats

ATB200 (mg/kg)	AT2221 PO (mg/kg)*	$AUC_{0\text{-}24h}$ (nmol/mL/hr * hr)	C_{max} (nmol/mL/hr)	$t_{½}$ (h)
5		32900	37249	0.64
10		64638	65056	0.52
20		148589	98341	0.77
20	10	184453	121932	0.87

Source: Applicant's table from Pharmacokinetics study rrb200-03, page 24.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; $AUC_{0\text{-}24}$, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; h, hour; PO, by mouth; T_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life

Figure 81. Plasma PK of ATB200 After Bolus IV Injection in Rats



Source: Applicant's figure from Pharmacokinetics study rrb200-03, page 24.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; GAA, human acid α-glucosidase; IV, intravenous; PK, pharmacokinetics

Study 338

Male *Gaa* KO mice (n=4/group/timepoint) were administered a single dose of ATB200 at 20 mg/kg via IV bolus injection, with or without oral coadministration of AT2221 HCl at 11.7 or 35.1 mg/kg (equivalent to 10 or 30 mg/kg AT2221; 30 min prior to IV injection). Blood samples were collected at 5 min, 0.25, 0.5, 1, 2, 4, 6, and 8 h, and 7 days postdosing. Plasma PK data from this study (ATB200 + AT2221; *Gaa* KO mice) were compared to plasma PK data collected in study 300 (AT2221 alone; WT mice). Plasma $AUC_{0\text{-}t}$ of AT2221 increased proportionally to dose between 10 and 30 mg/kg. Plasma $AUC_{0\text{-}t}$ of AT2221 was decreased when coadministered with ATB200 compared to administration alone, reflecting less circulating free drug likely due to binding with ATB200.

Table 117. Plasma PK of AT2221 Alone (Study 300) or When Coadministered With ATB200 (Study 338)

Treatment	Dose (mg/kg)	AUC_{0-t} (ng·h/mL)	$t_{1/2}$ (h)
AT2221	10	4700	0.4
AT2221 + ATB200		3518	0.5
AT2221	30	15095	0.5
AT2221 + ATB200		10938	0.6

Source: Generated by review team from Applicant's table from rrb200-007, page 18 and 19.
Abbreviations: AT2221, miglustat; ATB200, recombinant human acid alpha-glucosidase; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $t_{1/2}$, elimination half-life

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

No in vitro studies were conducted.

14.2. In Vivo Studies

14.2.1. ATB200-02

ATB200-02 was an open-label, fixed sequence, single- and multiple-ascending dose, first-in-human study to assess the safety, tolerability, PK, PD, and efficacy of IV infusions of cipaglucosidase alfa coadministered with oral miglustat (administered 1 hr before the start of cipaglucosidase infusion) in adult subjects with Pompe disease. Cipaglucosidase alfa and cipaglucosidase alfa coadministered with miglustat were evaluated in four stages as follows:

- Stage 1 was a 3-period, fixed-sequence, sequential, single ascending dose, of 5 mg/kg, 10 mg/kg, and 20 mg/kg of cipaglucosidase alfa alone administered intravenously 2 weeks apart in ERT treatment-experienced (on ERT for 2 to 6 years) ambulatory patients (Cohort 1; N=11).
- Stage 2 was a 2-period, fixed-sequence, single- and multiple-dose evaluation of 20 mg/kg cipaglucosidase alfa coadministered with multiple ascending doses of miglustat 130 mg administered orally every two weeks for 3 doses, followed by 20 mg/kg of IV-infused cipaglucosidase alfa coadministered with 260 mg of miglustat administered orally for 3 doses in patients who completed Stage 1 (Cohort 1; N=11).
- Stage 3 was 2-year treatment period of 20 mg/kg of IV-infused cipaglucosidase alfa coadministered with 260 mg of miglustat administered orally every 2 weeks in patients who completed Stages 1 and 2. Additional patients were enrolled in 3 additional cohorts (Cohort 2: treatment-experienced (on ERT for ≥2 years) non

ambulatory patients N=6; Cohort 3: treatment-naïve ambulatory patients N=6; Cohort 4: treatment-experienced (on ERT for >7 years) ambulatory patients N=6)

- Stage 4 was a long-term extension of patients who completed stage 3.

Blood samples were collected for single- and multiple-dose PK assessments for cipaglucosidase alfa (as GAA) and miglustat concentrations and GAA activity in cohort 1 and 3. Cipaglucosidase alfa concentrations were determined as total GAA protein using a signature peptide, T09, measurement. Total GAA protein PK parameters in patients in cohorts 1 and 3 are summarized in Table 118.

Table 118. Summary of Plasma Total GAA Protein by Signature Peptide T09 PK Parameters in ATB200-02

Parameter	C_{max} µg/mL	t_{max} h	AUC_{0-t} µg.h/mL	$AUC_{tmax-24h}$ µg.h/mL	$AUC_{0-\infty}$ µg.h/mL	$t_{1/2\alpha}$ h	CL_T L/h
Cohort 1							
Cipa 5 mg/kg (10)	58.4 (19.1)	3.95 (3.00 - 4.05)	208 (9.6)	107 (27.1)	209 (18.0)	1.1 (10.3)	2.17 (17.0)
Cipa 10 mg/kg (11)	135 (18.3)	4.00 (3.50 - 4.02)	533 (23.7)	454 (25.3)	537 (23.9)	1.3 (9.3)	1.66 (22.2)
Cipa 20 mg/kg (11)	325 (13.5)	4.00 (3.47 - 4.02)	1405 (16.2)	837 (19.4)	1410 (15.9)	1.5 (8.7)	1.26 (17.8)
Cipa 20 mg/kg + Mig 130 mg First dose (11)	329 (14.3)	3.95 (3.40 - 4.07)	1633 (17.3)	1069 (19.3)	1640 (16.9)	1.9 (10.6)	1.09 (18.7)
Cipa 20 mg/kg + Mig 130 mg Third dose (11)	335 (15.4)	3.97 (3.40 - 4.25)	1666 (19.1)	1080 (20.9)	1676 (18.6)	1.9 (22.4)	1.07 (18.5)
Cipa 20 mg/kg + Mig 260 mg First dose (10)	339 (12.9)	3.93 (3.47 - 4.00)	1778 (17.6)	1202 (18.5)	1778 (17.3)	2.2 (19.4)	0.99 (21.7)
Cipa 20 mg/kg + Mig 260 mg Third dose (11)	345 (18.5)	3.92 (3.37 - 4.00)	1801 (19.9)	1203 (23.4)	1812 (20.8)	2.1 (16.1)	0.99 (22.3)
Cohort 3							
Cipa 20 mg/kg + Mig 260 mg First dose (6)	342 (16.4)	4.00 (3.97 - 4.02)	1854 (18.2)	1235 (21.7)	1857 (18.3)	2.3 (14.5)	0.74 (24.9)
Cipa 20 mg/kg + Mig 260 mg Third dose (6)	323 (12.8)	4.03 (3.98 - 4.52)	1772 (17.3)	1153 (18.7)	1774 (17.4)	2.2 (9.1)	0.74 (25.5)

Source: ATB200-02 CSR Tables 13, 14.
Per the Applicant, PK sampling was not conducted for Cohort 2 due to sclerosis in peripheral veins of many nonambulatory patients precluding contralateral venous access and in Cohort 4 due to similarity with Cohort 1 in which PK was being characterized
C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{tmax-24h}$ are geometric mean (CV%), t_{max} expressed as median (minimum-maximum), $t_{½\alpha}$ and CL_T are arithmetic mean (CV%)
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time zero extrapolated to infinite time; $AUC_{tmax-24h}$, area under the plasma concentration-time curve from the time to reach maximum observed plasma concentration to 24 h after the start of infusion; CL_T, total clearance following intravenous administration; C_{max}, maximum observed plasma concentration; GAA, human acid α-glucosidase; PK, pharmacokinetics; $t_{½\alpha}$, alpha phase elimination half-life; t_{max}, time to reach the maximum observed concentration

Relative bioavailability of total GAA protein by signature peptide T09 PK parameter after single and multiple doses of cipaglucosidase alfa with and without miglustat administration is summarized in Table 119.

Table 119. ANOVA of PK Parameters Determined by Total GAA Protein in ATB200-02 Cohorts

Comparison of Interest	Signature Peptide PK Parameter Point Estimate (Lower 90% CI, Upper 90% CI)			
Test/Reference	C_{max} (µg/mL)	AUC_{0-t} (µg·h/mL)	$AUCt_{max}$-24h (µg·h/mL)	$AUC_{0-\infty}$ (µg·h/mL)
B / A	101.3 (96.9, 105.9)	116.2 (111.6, 121.1)	127.7 (120.6, 135.2)	116.3 (111.9, 120.9)
D / A	106.1 (101.4, 111.1)	128.9 (123.5, 134.5)	146.0 (137.6, 154.9)	129.1 (124.0, 134.4)
F / A	105.3 (91.0, 121.7)	132.0 (111.0, 156.9)	147.5 (120.0, 181.4)	131.7 (110.9, 156.3)
C / B	101.8 (96.6, 107.4)	102.0 (97.9, 106.4)	101.0 (97.7, 104.4)	102.2 (98.4, 106.2)
D / B	105.0 (100.7, 109.5)	110.8 (104.6, 117.3)	114.1 (107.5, 121.1)	110.9 (105.2, 116.9)
E / C	103.0 (97.9, 108.4)	108.0 (101.3, 115.3)	111.4 (103.2, 120.3)	108.1 (101.9, 114.7)
E / D	98.2 (95.3, 101.1)	97.7 (93.8, 101.7)	96.5 (92.3, 100.9)	97.8 (94.4, 101.3)
F / D	100.8 (88.6, 114.6)	104.3 (88.8, 122.5)	102.8 (85.9, 122.9)	103.9 (88.6, 121.8)
G / E	93.4 (80.8, 108.0)	98.4 (83.4, 116.2)	95.8 (79.4, 115.7)	97.9 (82.5, 116.1)
G / F	94.4 (87.7, 101.5)	95.5 (92.7, 98.4)	93.4 (90.7, 96.1)	95.5 (92.7, 98.5)

Source: ATB200-02 CSR.Table 91.
A =20 mg/kg cipaglucosidase alfa, signature peptide (SP) T09, Cohort 1
B =20 mg/kg cipaglucosidase alfa +130 mg miglustat, 1st Dose, SP T09, Cohort 1
C =20 mg/kg cipaglucosidase alfa +130 mg miglustat, 3rd Dose, SP T09, Cohort 1
D =20 mg/kg cipaglucosidase alfa +260 mg miglustat, 1st Dose, SP T09, Cohort 1
E =20 mg/kg cipaglucosidase alfa +260 mg miglustat, 3rd Dose, SP T09, Cohort 1
F =20 mg/kg cipaglucosidase alfa +260 mg miglustat, 1st Dose, SP T09, Cohort 3
G =20 mg/kg cipaglucosidase alfa +260 mg miglustat, 3rd Dose, SP T09, Cohort 3
Abbreviations: ANOVA, analysis of variance; ATB200, recombinant human acid alpha-glucosidase; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time zero extrapolated to infinite time; $AUC_{tmax-24h}$, area under the plasma concentration-time curve from the time to reach maximum observed plasma concentration to 24 h after the of infusion; CI, confidence interval; C_{max}, maximum observed plasma concentration; GAA, human acid α-glucosidase; PK, pharmacokinetic; SP, signature peptide

The plasma GAA enzyme activity assay measured the rate of artificial substrate turnover (4-methylumbelliferone-α-D-Glucopyranoside (4MU-Glc) to 4-methylumbelliferone (4MU) of cipaglucosidase alfa. Total GAA protein PK parameters in patients in cohorts 1 and 3 are summarized in Table 120.

Table 120. Summary of Plasma GAA Activity PD in ATB200-02

Parameters	C_{max} nmol/mL/h	t_{max} h	AUC_{0-t} nmol/mL/h/h	$AUC_{tmax-24h}$ nmol/mL/h/h	$AUC_{0-\infty}$ nmol/mL/h/h	$t_{1/2\alpha}$ h
Cohort 1						
Cipa 5 mg/kg (10)	25579 (15.2)	3.50 (3.00-3.98)	96811 (20.0)	56770 (27.8)	96823 (20.0)	1.1 (8.6)
Cipa 10 mg/kg (11)	54818 (22.2)	3.50 (2.97-4.00)	230925 (29.6)	142355 (31.3)	230928 (29.6)	1.3 (11.4)
Cipa 20 mg/kg (11)	131460 (21.3)	3.50 (3.47-4.00)	586201 (20.9)	363213 (20.4)	586230 (20.9)	1.4 (9.8)
Cipa 20 mg/kg + Mig 130 mg first dose (11)	109678 (23.5)	3.48 (2.97-4.00)	627892 (24.9)	450324 (25.6)	628151 (24.9)	1.8 (13.9)
Cipa 20 mg/kg + Mig 130 mg third dose (11)	110810 (17.2)	3.52 (3.20-4.00)	611982 (25.7)	429849 (30.7)	612274 (25.7)	1.8 (18.5)
Cipa 20 mg/kg + Mig 260 mg first dose (10)	108836 (20.5)	3.49 (3.47-4.00)	608180 (23.7)	440823 (25.3)	608985 (23.8)	2.0 (21.6)
Cipa 20 mg/kg + Mig 260 mg third dose (11)	119624 (25.7)	3.57 (3.35-4.00)	670754 (29.4)	472479 (30.3)	671575 (29.4)	2.1 (16.9)
Cohort 3						
Cipa 20 mg/kg + Mig 260 mg first dose (5)	132400 (14.3)	3.97 (3.47-4.00)	762484 (22.0)	547740 (24.6)	763146 (22.0)	2.0 (10.2)
Cipa 20 mg/kg + Mig 260 mg third dose (6)	105842 (15.4)	3.66 (3.50-3.98)	638984 (18.1)	467598 (21.8)	639644 (18.1)	2.1 (11.3)

Source: ATB200-02 CSR Table 19.
C_{max}, maximum observed GAA activity; t½α, alpha phase elimination half-life; t_{max}, time to reach the maximum observed GAA activity)
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; AUC_{0-t}, area under the GAA activity-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the GAA activity -time curve from time zero extrapolated to infinite time; $AUC_{tmax-24h}$, area under the GAA activity -time curve from the time to reach maximum observed GAA activity to 24 h after the start of infusion; CLT, total clearance following intravenous administration; GAA, human acid α-glucosidase; PD, pharmacodynamics

Plasma miglustat exposure (C_{max} and AUC) increased in a dose-dependent manner and PK parameters after the first and third doses of 130 mg and 260 mg miglustat were similar. The PK results are summarized in Table 121. The clearance of miglustat in ERT-naïve patients was lower than in ERT-experienced patients after the first and the 3rd doses. See Section 14.4.1 for impact of ERT-status on PK in population pk analysis.

Table 121. Summary of Miglustat PK Parameters in ATB200-02

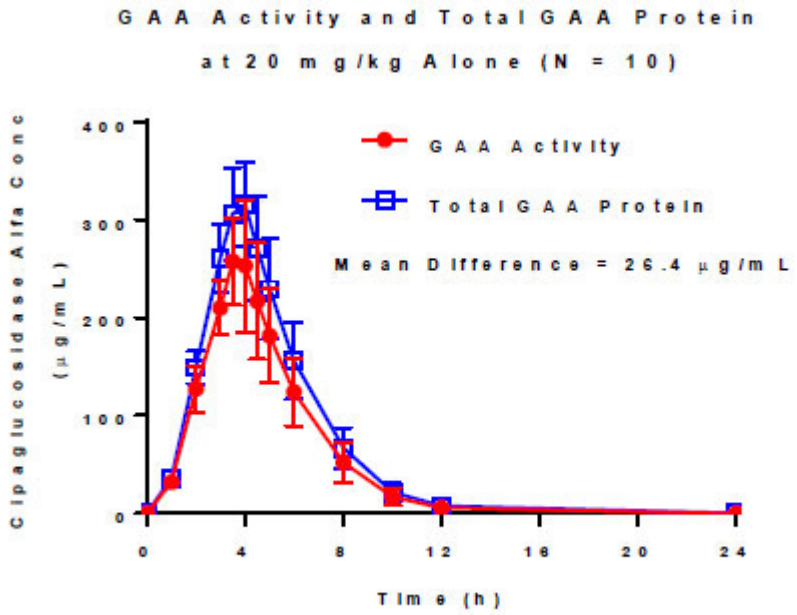
Parameters	C_{max} ng/mL	t_{max} h	AUC_{0-t} ng.h/mL	$AUC_{0-\infty}$ ng.h/mL	$t_{1/2\beta}$ h	CL/F L/h	V_z/F L
			Cohort 1				
Cipa 20 mg/kg + Mig 130 mg 1st Dose (11)	1527 (26.0)	3.47 (1.52 - 5.00)	11759 (29.9)	12611 (24.6)	6.13 (18.9)	10.5 (21.5)	93.4 (31.1)
Cipa 20 mg/kg + Mig 130 mg 3rd Dose (11)	1505 (23.9)	3.00 (1.50 - 4.00)	11946 (24.6	12880 (25.7)	6.41 (28.6)	10.3 (21.7)	96.3 (38.6)
Cipa 20 mg/kg + Mig 260 mg 1st Dose (10)	2665 (31.8)	3.99 (1.98 - 5.00)	22860 (33.4)	24695 (33.8)	6.51 (16.2)	10.9 (27.5)	103.3 (31.9)
Cipa 20 mg/kg + Mig 260 mg 3rd Dose (11)	3089 (28.8)	3.00 (0.92 - 4.05)	23492 (30.0)	24938 (30.6)	5.97 (18.1)	10.8 (18.1)	93.9 (35.2)
			Cohort 3				
Cipa 20 mg/kg + Mig 260 mg 1st Dose (6)	3632 (23.0)	2.01 (0.95 - 3.00)	25933 (11.6)	27203 (11.0)	5.61 (21.0)	9.61 (11.7)	78.1 (24.2)
Cipa 20 mg/kg + Mig 260 mg 3rd Dose (6)	3000 (17.5)	2.60 (2.00 - 3.00)	24413 (18.8)	25735 (16.5)	5.77 (17.8)	10.2 (15.1)	86.3 (28.4)

Source: ATB200-02 CSR Tables 17.
Per Applicant, PK sampling was not conducted for Cohort 2 due to sclerosis in peripheral veins of many non-ambulatory patients precluding contralateral venous access and in cohort 4 due to similarity with cohort 1 in which PK was being characterized.
C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, are geometric mean (CV%), t_{max} expressed as Median (Minimum-Maximum), t½β, Vz/F and CL/F are arithmetic mean (CV%)
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time zero extrapolated to infinite time; CL/F, apparent total clearance of the drug from plasma after oral administration; C_{max}, maximum observed plasma concentration' PK, pharmacokinetics; $t_{½\beta}$, terminal elimination half-life; t_{max}, time to reach the maximum observed concentration; Vz/F, terminal phase volume of distr bution following oral administration

GAA Activity and Total GAA Comparison in ATB200-02

In ATB200-02, the Applicant used two different bioanalytical assays to determine cipaglucosidase alfa concentrations: 1) cipaglucosidase alfa concentrations determined as total GAA protein using a signature peptide, T09, measurement; and 2) via an enzyme activity assay measuring total GAA activity in plasma. Total GAA protein measurement does not distinguish between active and inactive (e.g., unfolded protein) forms of GAA in plasma. To compare GAA activity levels to total GAA protein, the turnover rate (units: nmol/mL/h) was converted to concentration units (µg/mL) using the specific activity of cipaglucosidase alfa determined by the same GAA activity assay. In a response to a November 12, 2021 information request (IR), the Applicant noted that at the 20 mg/kg cipaglucosidase alfa dose, the mean difference between the concentration extrapolated from GAA activity (specific activity: 501.31 µmol/mg/hr applied to Table 120 data) and total GAA protein over all time points in the profile was 26.4 µg/mL (Figure 82), and this difference indicates a small amount of inactive enzyme was being measured by the total GAA protein assay.

Figure 82. Concentration Extrapolated From GAA Activity and Total GAA Protein – Time Profile



Source: ATB200-02 iCSR Table 14.4.1 and Table 14.4.2

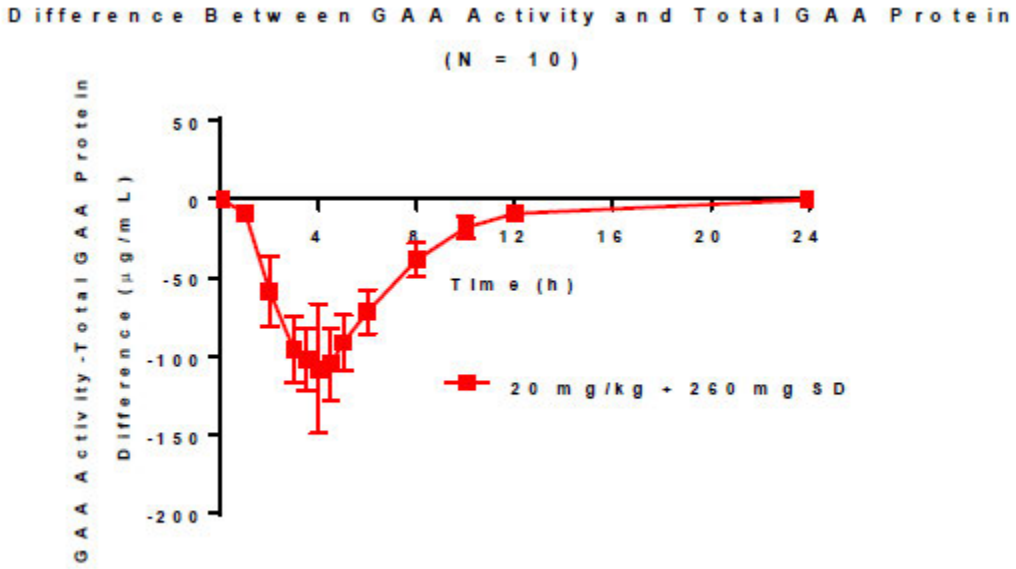
Source: Figure 1, Applicant's Response to November 12, 2021 Information Request.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; GAA, human acid α-glucosidase; N, number of subjects

The difference between exposure of plasma GAA activity and plasma total GAA protein after single doses of 5 mg /kg, 10 mg/ and 20 mg /kg cipaglucosidase alfa were 11.8%, 21.4% and 21.9% respectively. The Applicant did not deem these differences to be clinically meaningful. Regardless of the difference in the two assays, the trend of increasing total GAA protein with increasing doses of cipaglucosidase alfa is parallel to the observation of increasing GAA activity with increasing doses.

GAA Activity in the Context of Cipaglucosidase Alfa Administration with Miglustat.

While cipaglucosidase alfa C_{max} by total GAA protein demonstrated a dose-related increase (although not significant, Table 119) with increasing doses of miglustat, mean C_{max} extrapolated from GAA activity showed a dose-related decrease with increasing doses of miglustat indicating a dose-related decrease in GAA activity at and around cipaglucosidase alfa t_{max}. Figure 83 shows the mean difference between concentration extrapolated from GAA activity and total GAA protein over time after the 20 mg/kg cipaglucosidase alfa was coadministered with miglustat 260 mg.

Figure 83. Mean (SD) Difference Between GAA Activity and Total GAA Protein at the 20 mg/kg Cipaglucosidase Alfa With 260 mg Miglustat Dose Level



Source: ATB200-02 iCSR Table 14.4.2

Source: Figure 2, Applicant's Response to November 12, 2021 Information Request.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; GAA, human acid α-glucosidase; N, number of subjects; SD, standard deviation

The Applicant attributes this observation to residual miglustat binding to cipaglucosidase alfa, an interaction that confounds the ability to measure artificial substrate turnover when miglustat is bound to the active GAA site. The Applicant noted that interpreting measurements from the GAA activity assay in the context of miglustat and cipaglucosidase alfa measurement is likely an underestimation of actual GAA activity. The GAA activity assay was not used in the GAA estimation in the pivotal trial ATB200-03 and does not impact the conclusions of the E-R analysis (Section 14.4.2).

14.2.2. ATB200-03

ATB200-03 was a Phase 3, double-blind, randomized study to assess the efficacy and safety of 20 mg/kg cipaglucosidase alfa coadministered with 260 mg oral miglustat in adult subjects with late-onset Pompe disease compared with a non-U.S.-approved alglucosidase alfa product/placebo. Plasma total GAA protein measured by signature peptide T09 following serial blood sampling (on Day 1 in coordination with the first infusion of cipaglucosidase alfa or at the infusion visits for the second or third infusions of cipaglucosidase alfa) was performed for ERT treatment-naïve patients. Sparse PK sampling (on Day 1 and Week 52) was performed in ERT treatment-experienced patients for inclusion in population PK analysis. Of the ERT-naïve subjects (N=28), 16 had serial blood sampling (n=12 in Cipa-Mig arm; n=4 in comparator arm). The plasma total GAA parameters from the ERT treatment-naïve patients in summarized in Table 122.

In the ERT treatment-naïve patients in ATB200-03, plasma total GAA exposures were higher in patients in the comparator arm than in the cipa-mig arm despite similar mean body weight and

mean total dose in both arms (Table 122). In addition, the distribution half-life was 31% shorter and apparent total clearance was 32% faster for cipaglucosidase alfa.

Table 122. Summary of Plasma Total GAA PK Parameters in ERT Treatment-Naive Patients in ATB200-03

PK Parameter	Cipa-Mig (N=12)	Comparator (N=4)
C_{max} (µg/mL)	260 (18.4)	364 (66.7)
t_{max} (h)	3.99 (3.00 – 5.67)	3.00 (2.00 – 4.00)
AUC $_{tmax-24hr}$ (µg.h/mL)	1115 (28.0)	969 (25.4)
AUC_{0-t} (µg.h/mL)	1264 (28.9)	1656 (38.6)
$AUC_{0-\infty}$ (µg.h/mL)	1293 (26.8)	1661 (38.5)
$t_{1/2\alpha}$ (h)	1.9 (19.6)	2.5 (20.9)
CL (L/h)	1.08 (18.4)	0.82 (24.6)
Body weight (kg)	74.7 (24.2)	71.9 (31.3)
Total dose (mg)	1489 (24.6)	1437 (31.3)

Source: ATB200-03 CSR Tables 53.
C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, are geometric mean (CV%), t_{max} expressed as Median (Minimum-Maximum), t½ α is arithmetic mean (CV%)
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time zero extrapolated to infinite time; CL, total plasma clearance after IV administration; C_{max}, maximum observed plasma concentration; ERT, enzyme replacement therapy; GAA, human acid α-glucosidase; N, number of subjects; PK, pharmacokinetics; $t_{½\alpha}$, distr bution half-life; t_{max}, time to reach the maximum observed concentration

The PK parameters of miglustat from the ERT treatment-naïve patients are summarized in Table 123.

Table 123. Summary of Miglustat PK Parameters in ERT Treatment-Naive Patients in ATB200-03

PK Parameter	Cipa-Mig (N=12)
C_{max} (ng/mL)	2768 (30.8)
t_{max} (h)	3.04 (1.95- 6.58)
AUC_{0-t} (ng.h/mL)	20588 (36.8)
$AUC_{0-\infty}$ (ng.h/mL)	23031 (34.8)
$t_{1/2\beta}$ (h)	6.0 (23.7)
CL/F (L/h)	11.7 (25.9)
Vz/F (L)	101.3 (38.7)
Body weight (kg)	74.7 (24.2)

Source: ATB200-03 CSR Tables 54.
C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, are geometric mean (CV%), t_{max} expressed as Median (Minimum-Maximum), t½β, Vz/F and CL/F are arithmetic mean (CV%)
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time zero extrapolated to infinite time; CL/F, apparent total clearance of the drug from plasma after oral administration; C_{max}, maximum observed plasma concentration; ERT, enzyme replacement therapy; N, number of subjects; PK, pharmacokinetics; $t_{½\beta}$, terminal elimination half-life; t_{max}, time to reach the maximum observed concentration; Vz/F, terminal phase volume of distribution following oral administration

Data derived from sparse PK sampling in ERT treatment-experienced patients in ATB200-03 was included in the population PK analysis. See Section 14.4.1 for details.

14.2.3. AT2221-01

The proposed to-be-marketed product for miglustat is a 65 mg capsule which was used in the pivotal Phase 3 study (ATB200-03). The formulation used in the Phase 1/2 clinical studies was a miglustat 65 mg capsule containing only active pharmaceutical ingredient miglustat with no other excipients. The Applicant conducted a relative bioavailability (BA) study AT2221-01 comparing the PK between the Phase 1/2 formulation and the Phase 3 formulation.

AT2221-01 was a randomized, open-label, 3-way crossover study to evaluate the relative BA of miglustat orally administered as the Phase 3, 65 mg capsule swallowed whole (test) and a Phase 3, 65 mg capsule in solution (test) compared to the Phase 1/2, 65 mg powder in capsule (PIC) swallowed whole (reference) in healthy subjects.

Miglustat was absorbed with peak plasma concentrations achieved at approximately 2 hours postdose. Plasma and urine PK parameters were generally similar across treatment groups. A summary of PK parameters is presented in Table 124.

Table 124. Summary of Plasma and Urine Miglustat Pharmacokinetic Parameters by Treatment

Plasma PK Parameter	Treatment A (N=17)	Treatment B (N=18)	Treatment C (N=18)
C_{max} (ng/mL)	670.4 (28.8)	692.1 (26.5)	631.5 (36.1)
t_{max} (h)	2.0 (1.00- 4.00)	2.0 (1.00- 6.00)	2.0 (1.00- 4.10)
AUC_{0-t} (ng.h/mL)	5704.9 (18.8)	5853.6 (18.4)	5710.4 (22.6)
$AUC_{0-\infty}$ (ng.h/mL)	5738.3 (18.6)	5908.3 (17.8)	5741.3 (22.5)
$t_{1/2}$ (h)	9.7 (1.21)	9.5 (1.12)	9.7 (0.93)
CL/F (L/h)	11.51 (20.7)	11.16 (1.95)	11.60 (2.83)
Vz/F (L)	162.07 (41.96)	153.73 (39.01)	163.03 (49.02)
Urine PK Parameter	**Treatment A (N=17)**	**Treatment B (N=18)**	**Treatment C (N=18)**
Ae_{0-t} (mg)	42.47 (19.3)	42.80 (11.8)	40.45 (20.4)
% Fe (%)	66.38 (11.22)	66.27 (7.5)	63.34 (11.16)
CLr (L/h)	7.53 (1.15)	7.38 (1.24)	7.22 (1.34)

Source: Module 5.3.1.2, AT2221-01 CSR, Tables 6 and 7.
Treatment A = old Phase 1/2 65 mg miglustat capsule swallowed whole (reference)
Treatment B = new Phase 3 65 mg miglustat capsule swallowed whole (test)
Treatment C = new Phase 3 65 mg miglustat capsule reconstituted in water (test)
C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, Ae0-t are geometric mean (CV%), t_{max} expressed as Median (Minimum-Maximum), t½, Vz/F and CL/F are arithmetic mean (CV%)
Abbreviations: Ae_{0-t}, cumulative amount of unchanged drug excreted into urine from time zero to the end of the last urine collection time interval; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time zero extrapolated to infinite time; CL/F, apparent total clearance of the drug from plasma after oral administration; CLr, renal clearance; C_{max}, maximum observed plasma concentration; ERT, enzyme replacement therapy; % Fe, total urinary recovery after intravenous administration/fraction of drug excreted into urine in %; N, number of subjects; PK, pharmacokinetics; $t_{½}$, elimination half-life; t_{max}, time to reach the maximum observed concentration; Vz/F, terminal phase volume of distribution following oral administration

Statistical analyses of the relative BA among the three formulations showed that the 90% confidence interval of the geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are all within the bioequivalent range of [0.80, 1.25] (Table 125). The relative BA results also supported that the miglustat capsule can be reconstituted in water as an option for patients unable to swallow the capsule dosage form in whole.

Table 125. ANOVA of PK Parameters of Test and Reference Miglustat Formulations

	Treatment A		Treatment B		Ratio (B/A) (%)
Parameters	**N**	**Geom. LS Mean**	**N**	**Geom. LS Mean**	**(90% CI for Ratio)**
C_{max} (ng/mL)	17	664.79	17	691.88	104.1 (95.90, 112.95)
AUC_{0-t} (ng.h/mL)	17	5678.50	17	5906.41	104.0 (98.98, 109.30)
$AUC_{0-\infty}$ (ng.h/mL)	17	5711.22	17	5939.91	104.0 (99.02, 109.24)

	Treatment B		Treatment C		Ratio (B/C) (%)
Parameters	**N**	**Geom. LS Mean**	**N**	**Geom. LS Mean**	**(90% CI for Ratio)**
C_{max} (ng/mL)	18	692.06	18	634.50	109.1 (100.17, 118.76)
AUC_{0-t} (ng.h/mL)	18	5853.59	18	5710.36	102.5 (97.65, 107.61)
$AUC_{0-\infty}$ (ng.h/mL)	18	5908.33	18	5741.32	102.9 (97.96, 108.11)

	Treatment A		Treatment C		Ratio (C/A) (%)
Parameters	**N**	**Geom. LS Mean**	**N**	**Geom. LS Mean**	**(90% CI for Ratio)**
C_{max} (ng/mL)	17	664.79	17	652.31	98.1 (90.41, 106.49)
AUC_{0-t} (ng.h/mL)	17	5678.50	17	5815.23	102.4 (97.45, 107.61)
$AUC_{0-\infty}$ (ng.h/mL)	17	5711.22	17	5845.37	102.3 (97.44, 107.51)

Source: Compiled from AT2221-01 CSR, Tables 8, 9, 10.
Treatment A = old Phase 1/2 65 mg miglustat capsule swallowed whole (reference)
Treatment B = new Phase 3 65 mg miglustat capsule swallowed whole (test)
Treatment C = new Phase 3 65 mg miglustat capsule reconstituted in water (test)
The ANOVA model included treatment, sequence, and period as fixed effects and subjects nested within sequence as a random effect. A subject must have had a calculable PK parameter for both treatments in order to be included in the analysis for that parameter; Geom.LS Mean: Geometric LS means are the least squares means from the mixed model presented after back-transformation to the original scale; The 90% CIs are presented after back-transformation to the original scale
Abbreviations: ANOVA, analysis of variance; AUC_{0-t}, area under the plasma drug concentration-time curve from time zero to observed time (t); $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time zero extrapolated to infinite time; CI, confidence interval; C_{max}, maximum observed plasma concentration; geom. LS means, geometric least squares mean; N, number of subjects; PK, pharmacokinetics

14.3. Summary of Immunogenicity

Immunogenicity assessment was conducted in ERT treatment-experienced and ERT treatment-naïve patients with Pompe disease in Studies ATB200-02 (N=29) and ATB200-03 (N=123; cipa-mig arm [n =85], a non-U.S.-approved alglucosidase product-placebo arm [n =38]). Blood samples for immunogenicity assessment were collected at all visits before cipaglucosidase alfa infusion and before miglustat dosing. Bioanalytical strategy for the detection and characterization of antidrug antibodies (ADAs) followed a three-tiered, screening, confirmation, and titration approach. Further characterization of ADAs in confirmed positive samples included testing for cipaglucosidase alfa neutralizing antibodies (NAbs) in three different assays and for the potential of cipaglucosidase alfa antibodies to cross react with alglucosidase alfa (rhGAA cross reactivity). Bioanalytical assays were validated to determine the following:

- Total anti-rhGAA antibodies (total ADA).
- NAbs against cipaglucosidase alfa-mediated 4-methylumbelluferrone-α-D-glucopyranoside (4-MU-α-Glc) hydrolysis.
- NAbs against cipaglucosidase alfa-mediated glycogen hydrolysis.
- NAbs against cipaglucosidase alfa -mediated binding to cation-independent M6P receptor (CI-MPR).
- Anti-rhGAA IgE (at baseline and at the time of infusion-associated reactions [IAR]).

An assay, identical to the validated total ADA assay for cipaglucosidase alfa was qualified to detect antibody cross reactivity to alglucosidase alfa.

In the pivotal trial, blood samples for immunogenicity assessment were collected before cipaglucosidase alfa infusion and before miglustat dosing on Day 1 and Weeks 2, 4, 6, 12, 26, 38, and 52 and 30-day follow-up (if subjects discontinued the study). In Study ATB200-03, the majority of ERT treatment-experienced patients were positive for ADAs at baseline. Of the 65 ERT treatment-experienced subjects in the cipa-mig arm, 55 (84.6%) were positive for specific anti-rhGAA antibodies at baseline, 53% of whom had cross reactive antibodies to alglucosidase alfa, 46% with NAbs against CI-MPR and 15% had NAbs against 4-MU-α-Glc hydrolysis and glycogen hydrolysis. In comparison, 3 (15%) of the 20 ERT treatment-naïve patients in the cipa-mig arm were positive for anti-rhGAA antibodies at baseline, none of whom had cross-reactive antibodies to alglucosidase alfa or any of the NAbs assayed. A similar pattern, i.e., a high percentage of ERT treatment-experienced patients positive for ADAs at baseline (73%) and no ERT treatment-naïve patients positive for ADAs at baseline, is observed in patients in the alglucosidase alfa arm. Baseline anti-rhGAA IgE positivity was ≤10% across ERT treatment status across treatment arms. (Table 126).

Table 126. Characterization of Baseline ADAs in Patients in Study ATB200-03

	Cipa-Mig		Comparator	
Prevalence	**ERT treatment-experienced (N=65)**	**ERT treatment-naïve (N=20)**	**ERT treatment-experienced (N=30)**	**ERT treatment-naïve (N=8)**
Subjects Positive for Total ADA at Baseline N (%)	55 (84.6)	3 (15)	22 (73.3)	0 (0)
NAb positive: 4-MU-α-Glc	8 (14.5)	0 (0)	0 (0)	0 (0)
NAb positive: Glycogen	8 (14.5)	0 (0)	1 (0)	0 (0)
NAb positive: CI-MPR	25 (45.5)	0 (0)	N/A	N/A
Cross-reactivity to alglucosidase alfa	29 (52.7)	0 (0)	10 (45.5)	0 (0)
Baseline ADA positive with IgE	5 (7.7)	1 (5)	3 (10)	0 (0)

Source: Compiled from Applicant's Summary of Immunogenicity and its Relationship with Safety Report AMC0206-IMG-v1.0-Final, Tables 28, 31, and 32.
Total anti = recombinant human acid α-glucosidase rhGAA
CI-MPR binding NAb assay not validated for patients in comparator alglucosidase alfa/placebo arm due to the difference in cipaglucosidase alfa M6P compared to alglucosidase alfa
Abbreviations: ADA, antidrug antibody; ATB200, recombinant human acid alpha-glucosidase; CI-MPR, cation-independent M6P receptor; ERT, enzyme replacement therapy; 4-MU-α-Glc =4-methylumbelliferone-α-D-glucopyranoside; N, number of subjects; NAb, neutralizing antibody N/A, not applicable

In ATB200-03, ERT treatment-experienced subjects treated with cipa-mig, the incidence of treatment-emergent anti-rhGAA antibodies was 48%. The low incidence (5%) of treatment-induced ADA was due to the high rate of total ADA positivity at baseline. In ERT treatment-naïve patients, treatment-emergent ADA incidence was 95% and treatment-induced incidence was 85%. An assessment of ADA kinetics showed that 100% of treatment-induced and 64% of treatment-boosted ADA incidence were transient in ERT treatment-experienced patients, while in ERT treatment-naïve patients, 88% of treatment-induced and 100% of treatment-boosted ADA incidence were considered persistent. A similar pattern in kinetics of ADA by ERT treatment status was observed in the comparator arm (Table 127).

Table 127. Incidence of ADA Response and Kinetics of ADA in Study ATB200-03

	Cipa-Mig		Comparator	
Incidence	**ERT-experienced (N=65)**	**ERT-Naïve (N=20)**	**ERT-experienced (N=30)**	**ERT-Naïve (N=8)**
Treatment induced incidence (%)	3 (4.6)	17 (85)	3 (10)	8 (100)
*Transient (%)	3 (100)	2 (11.8)	3 (100)	2 (25)
** Persistent (%)	0 (0)	15 (88.2)	0 (0)	6 (75)
Treatment boosted incidence (%)	28 (43.1)	2 (10)	2 (6.7)	0 (0)
#Transient (%)	18 (64.3)	0 (0)	2 (100)	0 (0)
&Persistent (%)	10 (35.7)	2 (100)	0 (0)	2 (100)

	Cipa-Mig		Comparator	
Incidence	ERT-experienced (N=65)	ERT-Naïve (N=20)	ERT-experienced (N=30)	ERT-Naïve (N=8)
Treatment Emergent incidence (%)	31 (47.7)	19 (95.0)	5 (16.7)	8 (100)

Source: Compiled from Applicant's Summary of Immunogenicity and its Relationship with Safety Report AMC0206-IMG-v1.0-Final, Tables 82, 83, 84, 85.
Treatment induced = ADA incidence calculated as a percentage of the total number of evaluable subjects who were ADA negative at baseline; Treatment boosted = ADA incidence calculated as a percentage of the total number of evaluable subjects who were ADA positive at baseline, titer value that increased by >4× the baseline value was considered to be boosted; Treatment Emergent is sum of treatment-induced and treatment-boosted ADA-positive subjects as a proportion of the evaluable subject population
* Treatment-induced "persistent" if the Ab titer remains >4-fold above the assay minimum required dilution (MRD; 100) up to the last visit analyzed
** Treatment-induced "transient" if the Ab titer returns to ≤4-fold assay MRD (100) by last visit analyzed
# Treatment-boosted "persistent" if Ab titer remains >4-fold above baseline up to the last visit analyzed
& Treatment-boosted "transient" is "if the titer returns to ≤4-fold above baseline by last visit analyzed
Abbreviations: ADA, antidrug antibody; ATB200, recombinant human acid alpha-glucosidase; ERT, enzyme replacement therapy; MRD, minimal residual disease; N, number of subjects

In cipa-mig treated patients, the percentage of ERT treatment-experienced patients positive for anti-rhGAA antibodies was stable across study visits and ranged from 77.6% to 86.2% and the maximum median titer (102,400) was first observed on Day 182. In ERT treatment-naïve patients, the percentage positive for anti-rhGAA antibodies increased substantially from 15% at baseline to 93.8% at the end of treatment on day 364. In ERT treatment-naïve patients, the maximum median titer (51,200) was observed by Day 182 when 95% of patients were ADA positive although a majority >50% had seroconverted by Day 84 (Table 128).

Table 128. By Visit Summary of ADA-Positive Patients and Titers in Cipa-Mig Arm of ATB200-03

	ERT-Experienced			ERT-Naive		
Visit Number (Day)	N	N Positive (%)	Median Titer (Min; Max)	N	N Positive (%)	Median Titer (Min; Max)
3 (1)	65	55 (83.6)	12,800 (0.1; 52,428,800)	20	3 (15)	0.1 (0.1; 0.1)
4 (14)	64	53 (82.6)	12,800 (0.1; 26,214,400)	20	3 (15)	0.1 (0.1; 0.1)
5 (28)	65	56 (86.2)	12,800 (0.1; 13,107,200	20	3 (15)	100 (0.1; 100)
6 (42)	64	54 (84.4)	25,600 (0.1; 52,428,800)	20	8 (40)	600 (0.1; 12,800)
7 (84)	64	51 (79.7)	51,200 (100; 3,276,800)	19	16 (84.2)	9,600 (0.1; 102,400)
8 (182)	58	48 (82.8)	102,400 (0.1; 6,553,600)	19	18 (94.7)	51,200 (200; 409,600)
9 (288)	59	47 (79.7)	51,200 (0.1; 3,276,800)	20	18 (90)	38,400 (400; 204,800)
10 (364)	58	45 (77.6)	102,400 (0.1; 6,553,600)	16	15 (93.8)	12,800 (0.1; 204,800)

Source: Compiled from Applicant's Summary of Immunogenicity and its Relationship with Safety Report AMC0206-IMG-v1.0-Final, Tables 3, 6. Titer values that were below the assay minimum required dilution were imputed to a value of 0.1.
Abbreviations: ADA, antidrug antibody; ATB200, recombinant human acid alpha-glucosidase; ERT, enzyme replacement therapy; max, maximum; min, minimum; N, number of subjects

In ATB200-03, incidence of NAbs increased from baseline to after treatment in both ERT treatment-experienced and ERT treatment-naïve patients. Approximately 46% of ERT treatment-experienced patients were positive for at least one neutralizing antibody, 6% were positive for all three NAbs tested, and 54% of patients were not positive for any of the three NAbs tested. None of ERT treatment-naïve patient were positive for any of the three NAbs measured at baseline. At

the end of treatment, 81.5% of ERT treatment-experienced patients were positive for at least one NAb, 31% were positive for all three NAbs tested, and 19% of patients were not positive for any of the three NAbs tested. In ERT treatment-naive patients, 70% were positive for at least one of the three NAbs, 10% were positive for all three NAbs tested, and 19% of patients were not positive for any of the three NAbs. Amongst the NAbs measured, NAbs against CI-MPR was most commonly observed in ERT treatment-experienced patients before (at baseline) and after treatment. In ERT treatment-naïve patients, the rate of CI-MPR NAbs after treatment (40%) was similar to that observed in in ERT treatment-experienced patients (40%) (Table 129).

Table 129. Rate of NAb Positivity at Baseline and After Treatment With Cipa-Mig in Study ATB200-03

Antibody	At Baseline		After Treatment	
	ERT-Experienced (N=65)	ERT-Naïve (N=20)	ERT-Experienced (N=65)	ERT-Naïve (N=20)
4-MU-Glu NAb only	1 (1.5)	0 (0)	0 (0)	0 (0)
Glycogen NAb only	1 (1.5)	0 (0)	0 (0)	0 (0)
CI-MPR NAb only	21 (32.3)	0 (0)	26 (40)	8 (40)
At least one NAb	30 (46.2)	0 (0)	53 (81.5)	14 (70)
All 3 NAb	4 (6.2)	0 (0)	20 (30.8)	2 (10)
No NAb	35 (53.8)	20 (100)	12 (18.5)	6 (30)

Source: Applicant's Summary of Immunogenicity and its Relationship with Safety Report AMC0206-IMG-v1.0-Final, Tables 31, 33.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; CI-MPR, cation-independent M6P receptor; ERT, enzyme replacement therapy; 4-MU-α-Glc, 4-methylumbelliferone-α-D-glucopyranoside; N, number of subjects; NAb, neutralizing antibody

The descriptive comparisons and population PK analysis assessing the impact of immunogenicity markers (total ADA, neutralizing antibodies) on cipaglucosidase alfa PK, PD, and clinical endpoints included patients from Studies ATB200-02 and ATB200-03.

14.3.1. Impact of Immunogenicity on PK

The PK of cipaglucosidase alfa and results of statistical testing between subjects who were positive for ADA and negative for ADA at baseline are summarized in Table 130. The results indicated a slight trend of increased C_{max} and AUC in ADA+ subjects compared to ADA- subjects, however, the differences are not considered clinically meaningful.

Table 130. Between-Subject Comparison of PK Parameters by Baseline ADA Status in ATB200-02, ATB200-03 and Combined

Parameter in Study		Baseline ADA Negative		Baseline ADA Positive		P-value
ATB200-02						
N	Mean C_{max} (SD)	7	304.73 (33.33)	10	357.96 (61.61)	0.0702
N	Mean AUC (SD)	7	1647.01 (256.62)	10	1867.55 (414.86)	0.601
ATB200-03						
N	Mean C_{max} (SD)	24	264.55 (51.56)	55	279.56 (51.1)	0.174
N	Mean AUC (SD)	24	1328.58 (368.43)	55	1420.81 (327.25)	0.123
ATB200-02 and ATB200-03						
N	Mean C_{max} (SD)	31	273.62 (50.52)	65	291.62 (59.57)	0.185
N	Mean AUC (SD)	31	1489.54 (375.43)	65	1400.48 (368.18)	0.253

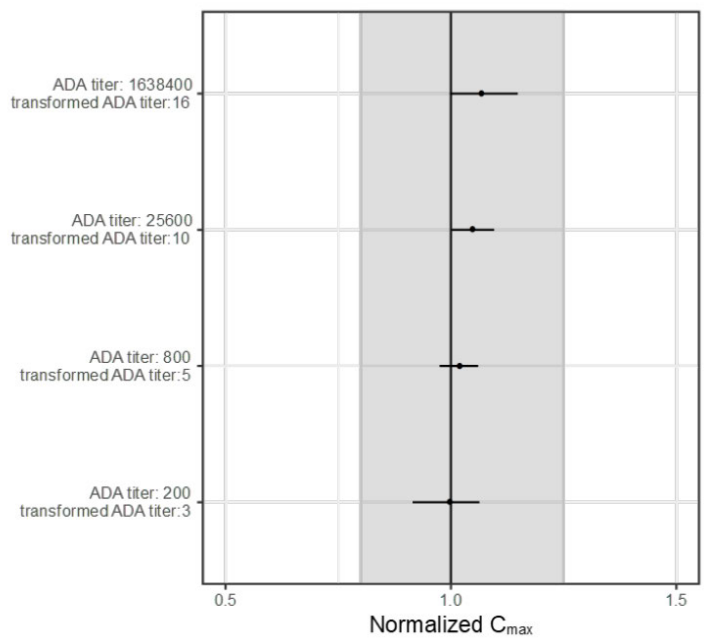
Source: Tables 5.1.1, 5.1.2, 5.1,3, 5.1.7, 5.1.8, 5.1.9 Descriptive Analysis Summaries of the Impact of Anti-Drug Antibodies on PK, PD, Efficacy, and Safety. Response to February 23, 2022 IR.
Abbreviations: ATB200, recombinant human acid alpha-glucosidase; ADA, antidrug antibody; AUC, area under the plasma drug concentration-time curve; C_{max}, maximum observed plasma concentration; N, number of subjects; SD, standard deviation

Similar observations indicating lack of clinically meaningful impact on cipaglucosidase alfa exposure were made when comparing subjects who were positive for NAbs at baseline to

subjects who were negative for NAbs at baseline in ATB200-02 and ATB200-03 and when data from both studies combined. Further comparison of subjects positive for ADAs and NAbs at any time point compared to negative subjects at all time points showed similar results. None of the between-subject comparisons of C_{max} and AUC reached a threshold for statistical significance.

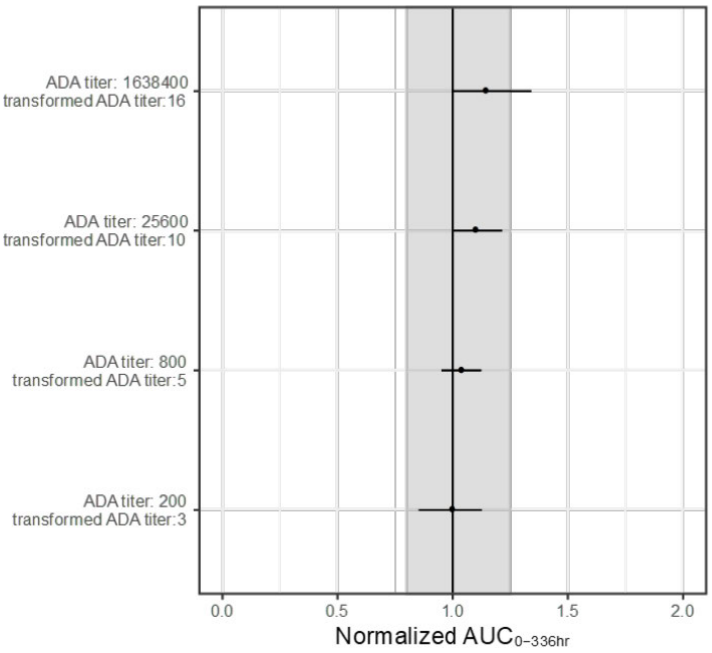
The Applicant also evaluated the potential effects of immunogenicity covariates on cipaglucosidase alfa PK via population PK approach. Models including the effect of (i) inhibition of rhGAA-mediated hydrolysis of glycogen, (ii) antibody cross-reactivity to alglucosidase alfa, (iii) confirmed positive specific anti-cipaglucosidase alfa antibodies, (iv) anti-rhGAA IgE, (v) inhibition of rhGAA binding to CI-MPR, (vi) ADA titer and (vii) rhGAA-mediated hydrolysis of 4-MU-glucoside on CL were evaluated. Only anti-rhGAA IgE and ADA titer showed significant effects on cipaglucosidase alfa CL. For anti-rhGAA IgE, the effect on CL was estimated to be approximately 73% of the reference CL without anti-rh GAA IgE, which was not considered clinically meaningful. For the effect of ADA titer on cipaglucosidase alfa CL, the typical clearance estimate for not detected or missing ADA was similar to the clearance estimate for detected ADA titer value of 800 (0.830 versus 0.784 L/h). There was a slight trend towards increasing normalized C_{max} and AUC with increasing ADA titers (Figure 84 and Figure 85).

Figure 84. Antibody Titer Versus Normalized C_{max}



Source: Figure 14 Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibody; C_{max}, maximum observed plasma concentration

Figure 85. Antibody Titer Versus Normalized AUC
Cipaglucosidase Alfa Final Model: Covariate Effect of ADA Titer on the Normalized Area Under the Curve (AUC)



Source: Figure 15 Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibody; AUC_{0-336h}, area under the plasma drug concentration-time curve from time zero to time 336h;

The AUC and C_{max} at different titer values (the 5th, 50th, and 95th percentiles of the observed values) were comparable to those with no detected or missing ADA, with 95% CIs for the covariate effect generally fell within 80% to 125% range. Thus, the effects of immunogenicity on cipaglucosidase alfa exposures are not considered clinically meaningful.

In addition to cipaglucosidase alfa, the Applicant also evaluated the potential effects of immunogenicity covariates on miglustat PK. Models including the effect of (i) inhibition of rhGAA-mediated hydrolysis of glycogen, (ii) antibody cross-reactivity to alglucosidase alfa, (iii) confirmed positive specific ADA, (iv) anti-rhGAA immunoglobin E (IgE), (v) inhibition of rhGAA binding to CI-MPR, (vi) ADA titer and (vii) rhGAA-mediated hydrolysis of 4-MU-glucoside on CL were evaluated. All models resulted in a small decrease in objective function value (OFV) that was not considered to be statistically significant. Thus, the Applicant concluded that none of the immunogenicity effects had a significant impact on miglustat PK. The impact of ADA titer on the normalized AUC and C_{max} generally fell within 80% to 125% range.

14.3.2. Impact of Immunogenicity on PD

Comparison of the mean change from baseline to week 52 in pharmacodynamic biomarkers (Hex4 and CK) between patients who were ADA positive at baseline and patients who were ADA negative at baseline did not indicate that presence of ADA at baseline had a significant impact on PD (Table 131). Similarly, presence of NAbs at baseline did not indicate a significant difference in mean change in Hex4 and CK from baseline to week 52 across trials.

Table 131. Between-Subject Comparison of PD Markers by ADA Status in ATB200-02, ATB200-03 and ATB200-02 and ATB200-03 Combined

PD Biomarker in Study		Baseline ADA Negative		Baseline ADA Positive		P-value
ATB200-02						
N	Mean Δ Hex4 (SD) BL to Wk 52	7	-5.3 (8.83)	21	-2.36 (4.33)	0.249
N	Mean Δ CK (SD) BL to Wk 52	7	-232.86 (269.6)	21	-94.14 (154.92)	0.111
ATB200-03						
N	Mean Δ Hex4 (SD) BL to Wk 52	22	-1.83 (2.5)	45	-2.11 (2.55)	0.382
N	Mean Δ CK (SD) BL to Wk 52	27	-152.11 (276.51)	58	-115 (200.51)	0.821
ATB200-02 and ATB200-03						
N	Mean Δ Hex4 (SD) BL to Wk 52	29	-2.66 (4.87)	66	-2.19 (3.19)	0.0894
N	Mean Δ CK (SD) BL to Wk 52	34	-168.74 (273.04)	79	-109.46 (188.73)	0.340

Source: Tables 5.1.4, 5.1.5, 5.1.6, 5.1.13, 5.1.14, 5.1.15, Descriptive Analysis Summaries of the Impact of Anti-Drug Antibodies on PK, PD, Efficacy, and Safety. Response to February 23, 2022 IR.
Abbreviations: ADA, antidrug antibody; ATB200, cipaglucosidase alfa; BL, Baseline; CK, creatinine phosphokinase; Hex4, hexose tetrasaccharide; N, number of subjects; PD, pharmacodynamics; Wk, Week

Within-subject comparisons in patients who were ADA negative at baseline and then developed ADA following treatment with cipa-mig demonstrated that these subjects had significant differences in the PD biomarkers, Hex4 and CK when mean baseline values are compared to Week 52 values across ATB200-02 and ATB200-03 and when both trials are combined (Hex 4: n=7 in ATB200-02, n=19 in ATB200-3; CK: n=7 in ATB200-02; ATB200-03 n=20). This trend was observed in within-patient comparison in patients who were negative for a NAb at baseline but later developed a NAb, indicating that statistically-significant reduction in PD biomarkers were observed Week 52 despite developing ADAs or NAbs later in the study. Furthermore, the majority of patients had developed ADAs by Week 12 of treatment (Table 128) and serum CK and urinary Hex4 reduction were sustained through Week 52 (Figure 2 and Figure 3). Therefore, there is no evidence showing that PD biomarkers are impacted by the development of ADAs as Hex4 and CK continue to decrease after Week 12.

The impact of immunogenicity on cipaglucosidase alfa effect on Hex4 and CK was also evaluated in the indirect PK-PD models as covariate effects on the drug effect (IMAX). Refer to section 14.5.2 for the details regarding the indirect PK-PD models. The covariates included the following: (i) inhibition of rhGAA-mediated hydrolysis of glycogen, (ii) antibody cross-reactivity to alglucosidase alfa, (iii) confirmed positive specific ADA, (iv) anti-rhGAA IgE, (v) inhibition of rhGAA binding to CI-MPR, (vi) ADA titer and (vii) rhGAA-mediated hydrolysis of 4-MU-glucoside.

For anti-rhGAA IgE, inhibition of rhGAA-mediated hydrolysis of glycogen, and rhGAA-mediated hydrolysis of 4-MU-glucoside, the number of subjects tested positive (n=10, 27 and 30, respectively) was very limited compared to over 100 negative subjects for each biomarkers. Thus, no definitive conclusion can be reached for these three covariate effects.

For antibody cross-reactivity to alglucosidase alfa and inhibition of rhGAA binding to CI-MPR, similar numbers of subjects tested positive and negative. The 95% CI of the estimates of these effects included the null, indicating that these immunogenicity effects were not meaningful.

There were 119 subjects with confirmed positive specific ADA and 47 without. The estimate for the effect was near zero, and the 95% CI included the null value. For total ADA, the point estimate of the coefficient for the effect was near zero with the 95% CI across the null value. Thus, these effects were not considered meaningful. In addition, lack of clinically meaningful effect of the ADA titer on IMAX for Hex4 and CK was also observed.

Thus, the immunogenicity markers did not have clinical meaningful impact on cipaglucosidase alfa effect on Hex4 and CK.

14.3.3. Impact of Immunogenicity on Efficacy

Comparison of patients who were ADA positive at baseline and patients who were ADA negative at baseline showed a difference in the mean FVC Week 52 change from baseline in ATB200-02, the comparison was not significant in ATB200-03 and when data from both studies were combined (Table 132).

Table 132. Between-Subject Comparison of Efficacy Endpoints by ADA Status in ATB200-02, ATB200-03 and ATB200-02 and ATB200-03 Combined

Parameter in Study			Baseline ADA Negative		Baseline ADA Positive	P-value
ATB200-02						
N	Mean Δ FVC (SD) BL to Wk 52	7	5.29 (7.2)	18	-1.39 (5.67)	0.0365
N	Mean Δ 6MWD (SD) BL to Wk 52	7	38.79 (35.91)	15	40.41 (50.77)	0.783
ATB200-03						
N	Mean Δ FVC (SD) BL to Wk 52	26	-2.73 (8.78)	58	-2.72(8.93)	0.858
N	Mean Δ 6MWD (SD) BL to Wk 52	27	20.68 (46.55)	58	15.24 (40.95)	0.581
ATB200-02 and ATB200-03						
N	Mean Δ FVC (SD) BL to Wk 52	33	-1.03(9)	76	-2.4 (8.26)	0.432
N	Mean Δ 6MWD (SD) BL to Wk 52	34	24.4 (44.68)	73	20.41 (43.97)	0.536

Source: Tables 5.1.10, 5.1.11, 5.1.12, 5.1.22, 5.1.23, 5.1.24, Descriptive Analysis Summaries of the Impact of Anti-Drug Antibodies on PK, PD, Efficacy, and Safety. Response to February 23, 2022 IR.
Abbreviations: ADA, antidrug antibody; ATB200, cipaglucosidase alfa; BL, Baseline; Δ FVC, change in forced vital capacity; Δ 6MWD, change in 6-minute walk distance; N, number of subjects; PD, pharmacodynamics; Wk, Week

The between-subject comparison of efficacy endpoints by NAb status in ATB200-02, ATB200-03 and ATB200-02 and ATB200-03 combined are summarized in Table 133. Differences in mean change in FVC from baseline to Week 52 were observed between patients who were glycogen hydrolysis NAb positive at baseline and glycogen hydrolysis NAb negative at baseline, and between patients who were 4-MU hydrolysis NAb positive at baseline and 4-MU hydrolysis NAb negative patients at baseline in ATB200-03 and in the combined studies. Patients with baseline NAbs against enzyme activity (4-MU hydrolysis or glycogen hydrolysis) appear to have higher decline in FVC from baseline than patients with no NAbs against enzyme activity at baseline. However, the reverse was observed in 6MWD where patients with baseline NAbs against enzyme activity had a higher mean change in 6MWD from baseline than patients who did not have NAbs against enzyme activity at baseline. These differences were not observed when baseline status of NAbs against CI-MPR was evaluated (Table 133).

Table 133. Between Subject Comparison of Efficacy Endpoints by NAb Status in ATB200-02, ATB200-03 and ATB200-02 and ATB200-03 Combined

Parameter in Study		Baseline Glycogen Hydrolysis NAb Negative		Baseline Glycogen Hydrolysis NAb Positive	P-value
ATB200-02					
N Mean Δ FVC (SD) BL to Wk 52	17	-1.47 (5.83)	1	N/A	N/A
N Mean Δ 6MWD (SD) BL to Wk 52	15	40.41 (50.77)	0	N/A	N/A
ATB200-03					
N Mean Δ FVC (SD) BL to Wk 52	50	-1.29 (7.69)	8	-11.62 (11.45)	0.0074
N Mean Δ 6MWD (SD) BL to Wk 52	50	13.94 (42.49)	8	23.36 (30.44)	0.279
ATB200-02 and ATB200-03					
N Mean Δ FVC (SD) BL to Wk 52	67	-1.4 (7.22)	9	-10.33 (11.39)	0.0109
N Mean Δ 6MWD (SD) BL to Wk 52	65	20.05 (45.53)	8	23.36 (30.44)	0.508
Parameter in Study		**Baseline 4-MU NAb Negative**		**Baseline 4-MU NAb Positive**	**P-value**
ATB200-02					
N Mean Δ FVC (SD) BL to Wk 52	15	-0.93 (5.5)	3	-3.67 (7.23)	0.812
N Mean Δ 6MWD (SD) BL to Wk 52	13	34.08 (48.5)	2	81.5 (625.93)	0.229
ATB200-03					
N Mean Δ FVC (SD) BL to Wk 52	50	-1.59(8.7)	8	-9.75 (7.4)	0.00818
N Mean Δ 6MWD (SD) BL to Wk 52	50	12.99 (42.88)	8	29.3 (22.77)	0.0805
ATB200-02 and ATB200-03					
N Mean Δ FVC (SD) BL to Wk 52	65	-1.44 (8.04)	11	-8.09 (7.54)	0.0107
N Mean Δ 6MWD (SD) BL to Wk 52	63	17.34 (44.53)	10	39.74 (36.44)	0.0484
Parameter in Study		**Baseline CI-MPR NAb Negative**		**Baseline CI-MPR NAb Positive**	**P-value**
ATB200-02					
N Mean Δ FVC (SD) BL to Wk 52	13	-1.38 (6.29)	4	-3 (2.58)	0.650
N Mean Δ 6MWD (SD) BL to Wk 52	12	42.59 (51.09)	2	25.56 (49.9)	1.00
ATB200-03					
N Mean Δ FVC (SD) BL to Wk 52	33	-2.89 (10.43)	25	-2.52 (6.66)	0.741
N Mean Δ 6MWD (SD) BL to Wk 52	32	19.37 (48.76)	29	9.79 (27.52)	0.530
ATB200-02 and ATB200-03					
N Mean Δ FVC (SD) BL to Wk 52	46	-2.45 (9.4)	29	-2.59 (6.23)	0.612
N Mean Δ 6MWD (SD) BL to Wk 52	45	25.56 (49.9)	27	13.1 (31.52)	0.257

Source: Tables 7.1.10, 7.1.11, 7.1.12, 7.1.22, 7.1.23, 7.1.24, 7.2.10, 7.2.11, 7.2.12, 7.2.22, 7.2.23, 7.2.24, 7.3.10, 7.3.11, 7.3.12, 7.3.22, 7.3.23, 7.3.24 Descriptive Analysis Summaries of the Impact of Anti-Drug Antibodies on PK, PD, Efficacy, and Safety. Response to February 23, 2022 FDA IR.
Abbreviations: ATB200, cipaglucosidase alfa; BL, Baseline; CI-MPR, cation-independent M6P receptor; Δ FVC, change in forced vital capacity; 4-MU, 4-methylumbelliferone-α-D-glucopyranoside; Δ 6MWD, change in 6-minute walk distance; N, number of subjects; NAb, neutralizing antibody; Wk, Week

In the comparison of patients who were NAb positive at any timepoint compared to patients who were NAb negative at all time points in the combined ATB200-02 and ATB200-03 analysis, patients positive for NAbs against enzyme activity (4-MU hydrolysis or glycogen hydrolysis) at any time point appear to have a higher decline in FVC from baseline than patients who were negative for NAbs against enzyme activity at all times whereas no differences were observed in 6MWD. These differences were not observed when positivity of CIMPR NAbs at any timepoint was evaluated in comparison to CIMPR NAb negative at all time points. Overall, the impact of ADAs and NAbs on efficacy is inconclusive given the large intersubject variability in the efficacy parameters and the different direction of association in 6MWD and FVC in ADA/NAb positive and ADA/NAb negative patient.

The impact of immunogenicity on cipaglucosidase alfa effect on 6MWD and FVC were also evaluated as covariate effects on the drug effect in the exposure-response analyses. Models

estimating multiplicative covariate effects of (i) inhibition of rhGAA-mediated hydrolysis of glycogen, (ii) antibody cross-reactivity to alglucosidase alfa, (iii) confirmed positive specific ADA, (iv) anti-rhGAA IgE, (v) inhibition of rhGAA binding to CI-MPR, and (vi) rhGAA-mediated hydrolysis of 4-MU-glucoside on the miglustat and alglucosidase alfa drug effects were evaluated, as well as (vii) a model to estimate the effect of ADA titer as an exponential covariate on the drug effects of cipaglucosidase alfa.

Because of the high variability and the low magnitude of the estimated effect in the FVC endpoint and the inability to characterize exposure-response (E-R) relationships from the data, analyses of immunogenicity effects on FVC were not performed.

In the E-R analyses for 6MWD, the numbers of subjects who tested positive for anti-rhGAA IgE, inhibition of rhGAA-mediated hydrolysis of glycogen, and rhGAA-mediated hydrolysis of 4-MU-glucoside were 10, 27 and 29, respectively, compared to 121, 102 and 96 tested negative subjects for each covariate. Thus, it is inconclusive whether these three immunogenicity covariates have an impact on cipaglucosidase alfa effect on 6-minute walk test (6MWT). For antibody cross-reactivity to alglucosidase alfa, confirmed positive specific ADA and inhibition of rhGAA binding to CI-MPR, good number of subjects were tested in both positive and negative categories. However, the 95% CI was large for the estimates for these 3 of the immunogenicity markers, and crossed the null value, indicating that the impact of these immunogenicity markers on the drug effect for the 6MWT was not conclusive. The effect of cipaglucosidase alfa on the 6MWD increased with increasing titer levels. However, the estimates were poorly estimated with wide 95% CI. Thus, it was not conclusive if the ADA titer had a clinical meaningful impact on 6MWD.

14.3.4. Impact of Immunogenicity on Safety

In cipa-mig treated patients who experienced IARs (ERT treatment-experienced patients N=25; ERT treatment-naïve patients, N=7) in ATB200-02 and ATB200-03, coincident ADA titer range at the time of IARs was wide ranging from 100 to 6,553,600 in ERT-experienced patients and from <100 to 16,348,400 in ERT-naïve patients. Although the titer ranges are wide, the maximum coincident titers are high relative to the median maximum titers in patients who did not experience IARs, particularly in ERT treatment-experience patients (Table 134).

Table 134. Antibody Titer Metrics in Patients With and Without Infusion Associated Reactions (IARs)

ERT-Experienced			ERT-Naïve		
Number of IARs	**Patients (N)**	**Median Maximum Post-treatment Titer (IQR)**	**Number of IARs**	**Patients (N)**	**Median Maximum Post-treatment Titer (IQR)**
0	56	102,400 (198,400)	0	19	76,800 (76,800)
Number of IARs	**Patients (N)**	***Coincident Titer Range**	**Number of IARs**	**Patients (N)**	***Coincident Titer Range**
1	7	800 to 3,276,800	1	3	<100 to 25,600
2	5	100 to 3,276,800	2	1	102,400, 102,400
3	4	12,800 to 6,553,600	3	1	3200 to 25,600
5	5	100 to 3,276,800	5	1	400 to 102,400
6	1	12,800 to 204,800	-	-	-
10	1	6400 to 204,800	-	-	-
12	1	819,200 to 3,276,800	12	1	400 to 16,348,400

Source: Summary of Immunogenicity and Its Relationship to Safety Report AMC0206-IMG-v1.0-Final, Table 48 and Integrated Summary of Immunogenicity.
* Titer value was assessed at the same visit as the IAR; or if not available at the same visit, then at either the visit prior or the visit after the IAR, usually within 1 month of the IAR, but maximally within 2 months.
Abbreviations: ERT, enzyme replacement therapy; IAR, infusion-associated reactions; IQR, interquartile range; N, number of subjects

14.4. Pharmacometrics Review

Two population pharmacokinetics (popPK) models were developed by the Applicant to characterize the PK of cipaglucosidase alfa and miglustat, respectively, in patients with late onset Pompe disease (LOPD). Subjects intrinsic and extrinsic factors which influence the PK and PK variability of cipaglucosidase alfa and miglustat were identified. Individual exposure metrics of the two drugs were derived from the popPK models for subsequent exposure-response (E-R) analyses for efficacy and safety.

14.4.1. Population PK Analyses

Two clinical studies (ATB200-02 and ATB200-03) were included in the popPK analysis. The Applicant developed popPK models for cipaglucosidase alfa, miglustat and alglucosidase alfa. This pharmacometrics review will focus on the popPK model development for cipaglucosidase alfa and miglustat. Covariates of interest for the analysis included time-independent baseline variables (age, weight, sex, race and ERT-history), and time-varying variables (weight and immunogenicity measures). Ninety-six subjects who received coadministration of cipaglucosidase alfa and miglustat were included. These subjects contributed 1606 observations (121 (7.5%) were BLQ) for cipaglucosidase and 1296 observations (16 (1.2%) were BLQ) for miglustat.

Subjects received cipaglucosidase alfa/miglustat were adults aged 19 to 74 years old (median 48 years) and weighing 40.1 to 116 kg (median 74 kg). Subjects were predominantly white (82.3%), five subjects were Asian (5.2%), and information was missing for 12 subjects (12.5%). All subjects had late onset Pompe disease (LOPD), 71 (74%) subjects were ERT-experienced and 25 (26%) were ERT-naive.

Cipaglucosidase Alfa

With the wide dosing range of cipaglucosidase alfa (5 mg/kg to 20 mg/kg), cipaglucosidase alfa PK was described by the two-compartment model with parallel linear and nonlinear clearances. The final model included estimated effects of body weight on CL and V1, fixed effects of body weight on Q, V2 and Vmax, and the estimated miglustat effect on linear CL. The effects of age, race (Asian versus non-Asian), sex (male versus female) and ERT-history (naive versus experienced) were estimated on drug linear CL. The final model parameters are summarized in Table 135. The goodness-of-fit plots of the final model are shown in Figure 86.

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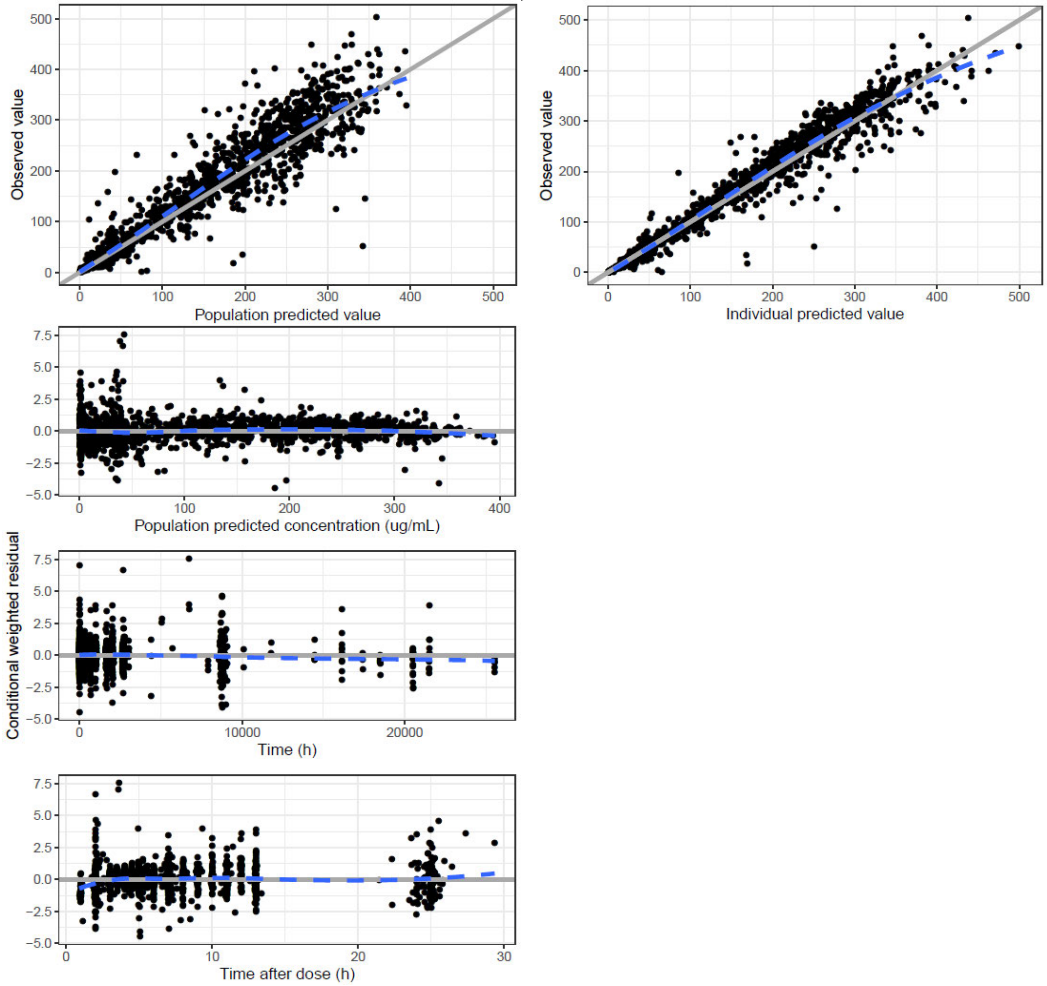
Table 135. Cipaglucosidase Alfa Final Model Parameter Estimates

			Estimate	95% CI
Structural model parameters				
CL (L/h)	$\exp(\theta_1)$	Clearance	0.880	0.716, 1.08
V1 (L)	$\exp(\theta_2)$	Central volume of distribution	3.19	3.04, 3.35
V2 (L)	$\exp(\theta_3)$	Peripheral volume of distribution	0.812	0.592, 1.11
Q (L/h)	$\exp(\theta_4)$	Intercompartmental clearance	0.130	0.0674, 0.252
Vmax (mg/hr)	$\exp(\theta_5)$	Maximum elimination rate	87.6	62.7, 122
Km (ug/mL)	$\exp(\theta_6)$	Concentration at half-maximum elimination rate	52.3	32.9, 83.1
Covariate effect parameters				
$AT2221_{130}$	$\exp(\theta_7)$	AT2221 dose of 130 mg on CL	0.740	0.702, 0.781
$AT2221_{gt130}$	$\exp(\theta_8)$	AT2221 dose of >130 mg on CL	0.628	0.588, 0.672
WT_{CL}	θ_9	Weight effect on CL	0.399	-0.0656, 0.863
WT_{V1}	θ_{10}	Weight effect on V1	0.580	0.371, 0.790
AGE_{CL}	θ_{11}	Age effect on CL	-0.458	-0.692, -0.224
$ASIAN_{CL}$	$\exp(\theta_{12})$	Race (Asian) effect on CL	1.03	0.756, 1.39
ERT_{CL}	$\exp(\theta_{13})$	Effect of ERT-history on CL	0.955	0.804, 1.13
SEX_{CL}	$\exp(\theta_{14})$	Gender (female) effect on CL	0.891	0.772, 1.03

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CL	$\Omega_{(1,1)}$	0.0543 [CV%=23.6]	0.0283, 0.0804	20.7
IIV-V1	$\Omega_{(2,2)}$	0.0301 [CV%=17.5]	0.0150, 0.0452	15.0
IIV-V2	$\Omega_{(3,3)}$	0.0756 [CV%=28.0]	0.0103, 0.141	33.0
IIV-Q	$\Omega_{(4,4)}$	0.158 [CV%=41.4]	-0.0651, 0.381	41.3
IIV-VMAX	$\Omega_{(5,5)}$	0.0409 [CV%=20.4]	-0.00613, 0.0879	34.8
Interindividual covariance parameters				
CL-V1	$\Omega_{(2,1)}$	0.0146 [Corr=0.361]	-0.00822, 0.0374	-
CL-V2	$\Omega_{(3,1)}$	0.00860 [Corr=0.134]	-0.0502, 0.0674	-
V1-V2	$\Omega_{(3,2)}$	0.0177 [Corr=0.372]	-0.0165, 0.0520	-
CL-Q	$\Omega_{(4,1)}$	0.0455 [Corr=0.491]	-0.0708, 0.162	-
V1-Q	$\Omega_{(4,2)}$	-0.000910 [Corr=-0.0132]	-0.0553, 0.0535	-
V2-Q	$\Omega_{(4,3)}$	0.0716 [Corr=0.655]	-0.0431, 0.186	-
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.0363 [CV%=19.1]	0.0280, 0.0446	-

Source: Applicant's population PK study report.
Abbreviations: AT2221, miglustat; CI, confidence interval; CL, clearance; corr, correlation; CV, coefficient of variation; ERT, enzyme replacement therapy; IIV, interindividual variance; Km, concentration at half-maximum elimination rate; Q, intercompartmental clearance; V1, central volume of distribution; V2, peripheral volume of distribution; Vmax, maximum elimination rate; WT, weight

Figure 86. Goodness-of-Fit Plots of Cipaglucosidase Alfa Final Population PK Model



Source: Applicant's population PK study report.
Abbreviations: PK, pharmacokinetics

The Applicant evaluated the potential effects of immunogenicity covariates on cipaglucosidase alfa PK via population PK approach. The details were discussed in section 14.3.1.

Miglustat

Miglustat popPK model was described by a two-compartment population PK model with sequential zero and first order absorption and linear clearance. Body weight, age and Asian race appeared to have meaningful impact on miglustat CL/F based on their estimates and 95% CI that did not include the null value. Asian subjects had 55% (95% CI: 16-107) higher CL/F than non-Asian subjects. Miglustat AUC and C_{max} increased with decreasing body weight and increasing age. Effects of ERT-history and sex on miglustat PK were minimal. Miglustat reduced cipaglucosidase alfa CL by approximately 26% for the 130-mg dose and by 37% for >130 dose (mainly 260 mg). Miglustat increased cipaglucosidase alfa AUC by approximately 22% (95% CI: 18, 26) for the 130-mg dose and by 35% (95% CI: 29, 41) for >130 dose (mainly 260 mg). Body weight, age, race, ERT-history and sex were not considered to have a clinically meaningful impact on cipaglucosidase alfa AUC and C_{max} based on their small effect sizes within 80% to 125% range when compared to the reference subject. The PK parameters of the final popPK model are shown in Table 136. The goodness-of-fit plots of the final model are shown in Figure 87.

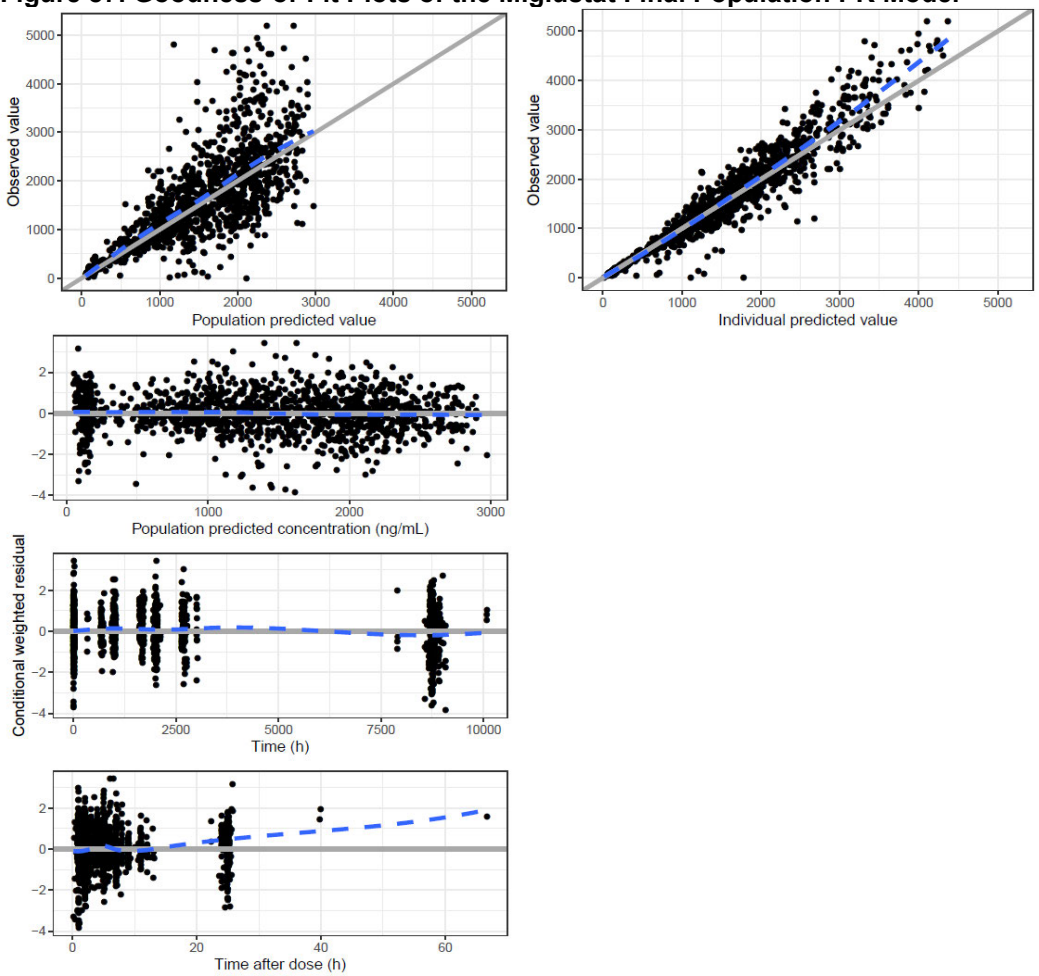
Table 136. Summary of the PK Parameters Estimated From the Final PopPK Model of Miglustat

			Estimate	95% CI
Structural model parameters				
CL/F (L/h)	$\exp(\theta_1)$	Apparent clearance	5.68	4.10, 7.87
V2/F (L)	$\exp(\theta_2)$	Apparent central volume	21.0	17.9, 24.7
V3/F (L)	$\exp(\theta_3)$	Apparent peripheral volume	535	289, 988
Q/F (L/h)	$\exp(\theta_4)$	Apparent intercompartmental clearance	6.65	5.04, 8.78
KA (/h)	$\exp(\theta_5)$	First-order absorption rate constant	0.219	0.199, 0.241
D1 (h)	$\exp(\theta_6)$	Duration of zero-order absorption	0.446	0.351, 0.567
Covariate effect parameters				
$WT_{CL/F}$	θ_7	Weight effect on CL/F and Q/F	0.727	0.485, 0.969
$WT_{V2/F}$	θ_8	Weight effect on V2/F and V3/F	0.475	0.132, 0.818
$AGE_{CL/F}$	θ_9	Age effect on CL/F	-0.613	-0.884, -0.342
$RACE_{CL/F}$	$\exp(\theta_{10})$	Race (Asian) effect on CL/F	1.55	1.16, 2.07
$ERT_{CL/F}$	$\exp(\theta_{11})$	ERT-history effect on CL/F	0.930	0.791, 1.09
$Sex_{CL/F}$	$\exp(\theta_{12})$	Gender (female) effect on CL/F	1.14	0.962, 1.36

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CL/F	$\Omega_{(1,1)}$	0.0948 [CV%=31.5]	0.0311, 0.159	19.4
IIV-V2/F	$\Omega_{(2,2)}$	0.128 [CV%=37.0]	0.0581, 0.199	31.2
IIV-KA	$\Omega_{(5,5)}$	0.0452 [CV%=21.5]	0.0194, 0.0710	29.9
IIV-D1	$\Omega_{(6,6)}$	0.448 [CV%=75.2]	0.252, 0.644	33.3
Interindividual covariance parameters				
CL/F-V2/F	$\Omega_{(2,1)}$	0.0183 [Corr=0.166]	-0.0199, 0.0565	-
Interoccasion variance parameters				
IOV-KA	$\Omega_{(7,7)}$	0.0235 [CV%=15.4]	0.0126, 0.0344	46.0
IOV-F1	$\Omega_{(11,11)}$	0.0240 [CV%=15.6]	0.0129, 0.0351	33.1
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.0409 [CV%=20.2]	0.0324, 0.0495	-

Source: Applicant's population PK study report.
Abbreviations: AT2221, miglustat; CI, confidence interval; CL, clearance; corr, correlation coefficient; CV, coefficient of variation; ERT, enzyme replacement therapy; IIV, interindividual variance; IOV, interoccasion variance; Km, concentration at half-maximum elimination rate; PK, pharmacokinetics; popPK, population pharmacokinetics; Q, intercompartmental clearance; V1, central volume of distribution; V2, peripheral volume of distribution; Vmax, maximum elimination rate; WT, weight

Figure 87. Goodness-of-Fit Plots of the Miglustat Final Population PK Model

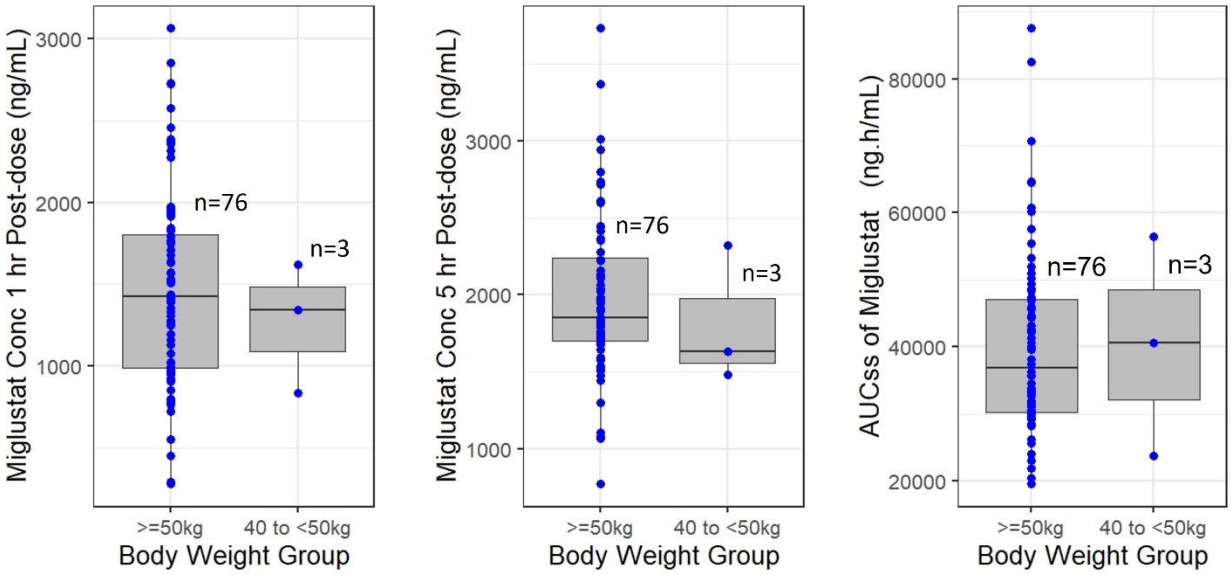


Source: Applicant's population PK study report.
Abbreviations: PK, pharmacokinetics

The Applicant also evaluated the potential effects of immunogenicity covariates on miglustat PK. The details were discussed in section 14.3.1.

The Applicant's population PK models were acceptable to describe the PK of cipaglucosidase alfa and miglustat, respectively, in LOPD patients. The Applicant proposed and evaluated miglustat dose levels in Study ATB200-03 were 260 mg for subjects weighing 50 kg and above, and 195 mg for subjects weighing 40 to less than 50 kg, followed approximately 1 hour later by cipaglucosidase alfa IV infusion every other week. The Applicant did not provide rationale or justification for the proposed dosing regimen by body weight. Thus, FDA review team conducted independent analysis to evaluate whether the proposed dosing regimen for miglustat is reasonable. Miglustat concentrations at 1-hour and 5-hour postdose were derived based on population PK model for each subject in Study ATB200-03. One-hour and 5-hour time points were selected because 1-hour postdose is the start of the infusion of cipaglucosidase alfa, and 5-hour postdose is the end of the infusion of cipaglucosidase alfa. The miglustat concentrations at 1-hour and 5-hour postdose, AUC at steady-state (AUCss) were compared between the body weight groups of 40 to <50 kg and ≥50 kg. Overall, the exposures in these two body weight groups were largely overlapped (Figure 88), supporting the proposed miglustat dosing adjustment for patients weighing 40 to <50 kg. However, it should be noted that there were only 3 subjects in the body weight group of 40 to <50 kg.

Figure 88. Comparison of Miglustat Exposure in Subjects Weighing ≥50 kg and 40 to <50 kg



Source: Review team.
Abbreviations: n, number of subjects

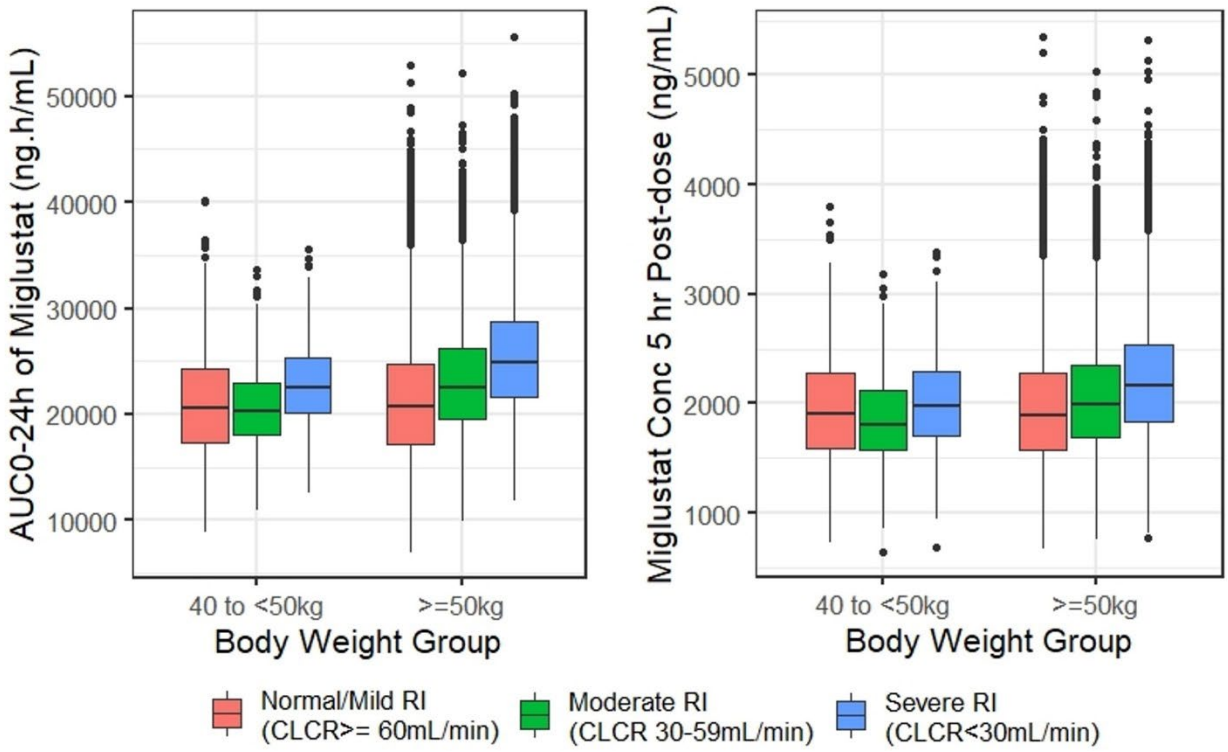
A dedicated renal impairment (RI) study for Zavesca NDA (section 8.1.2.2) indicated that subjects with moderate to severe RI had 60% to 70% decrease in miglustat CL/F, compared to subjects with normal renal function/mild RI. Based on the simulation in subjects with RI received 260 mg QOW miglustat, $AUC_{0\text{-}24hr}$ was estimated to increase by 26% and 31% for subjects with moderate and severe RI, respectively, compared to subjects with normal renal functions. In addition, the simulation results suggested that miglustat dosing regimen of 260 mg QOW will not have accumulation in patients with severe RI. To avoid potential risks associated with high miglustat exposure in subjects with moderate or severe RI, as well as to match the exposure in subjects with normal renal functions or mild RI, FDA review team recommends a lower dose level (Table 137) in these subgroup populations based on the availability of the miglustat capsule strength of 65 mg. As shown in Figure 89, following the FDA recommended dose adjustment of miglustat, $AUC_{0\text{-}24hr}$ and 5-hour post dose (the ending of the infusion of cipaglucosidase alfa) concentration of miglustat will be comparable in subjects with moderate or severe RI to subjects with normal renal functions/mild RI.

Table 137. FDA-Recommended Dose Adjustment for Subjects With Moderate or Severe Renal Impairment

Parameter	Moderate RI (CL_{CR} 30-59 mL/min)	Severe RI (CL_{CR} 15-29 mL/min)
Patients weighing ≥50 kg	195 mg	195 mg
Patients weighing 40 to <50 kg	130 mg	130 mg

Source: Review team.
Note: Renal function classified by creatinine clearance based on the Cockcroft-Gault equation.
Abbreviations: CLcr, creatine clearance; RI, renal impairment

Figure 89. Miglustat Exposure Comparison in Subjects With Normal Renal Functions/Mild Renal Impairment, Moderate and Severe Renal Impairment, Following the FDA-Recommended Dose Adjustment



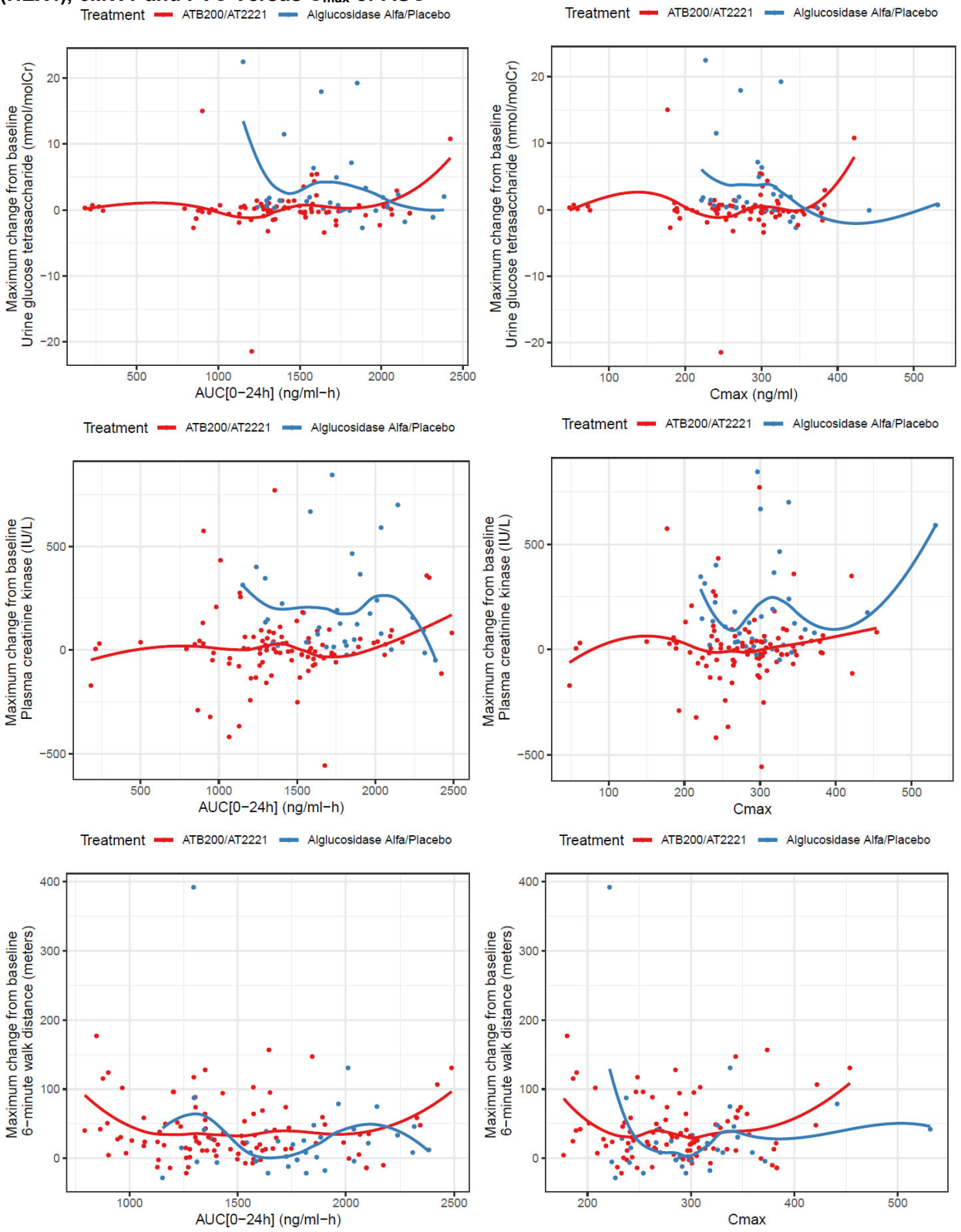
Source: Review team.
Abbreviations: AUC_{0-24}, area under the plasma drug concentration-time curve from time zero to time 24h; CLcr, creatine clearance; RI, renal impairment

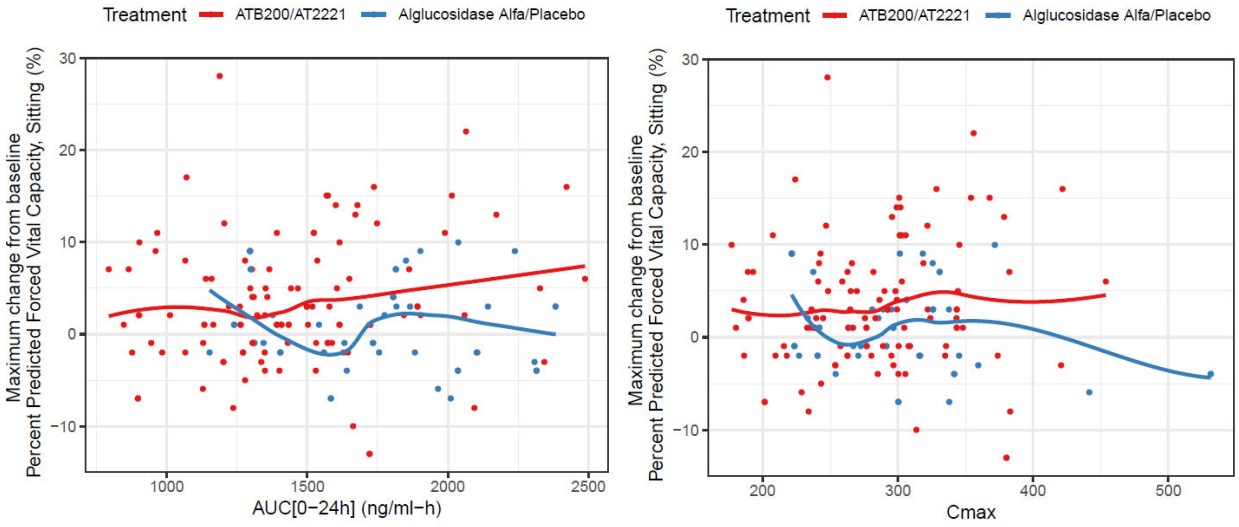
14.4.2. Exposure-Response Analyses

Exposure-Response Analyses for Efficacy

The Applicant conducted exposure-response (E-R) analyses for efficacy based on the data from all subjects with at least one observation and associated time-point available, or reliably assumed. Two biomarker endpoints (serum CK and urinary Hex4) and two functional endpoints (6MWT and FVC) were evaluated. Overall, no apparent E-R relationship was identified for both the biomarker endpoints and functional endpoints using AUC or C_{max} as the exposure metrics (Figure 90). Of note, because cipaglucosidase alfa exerts its pharmacological effect after being taken up into the cells, plasma concentration may not be the most relevant driver for efficacy.

Figure 90. Maximum Change From Baseline of Creatinine Kinase (CK), Urinary Tetrasaccharide (HEX4), 6MWT and FVC Versus C_{max} or AUC





Source: Applicant population PK and PK/PD study report.
Abbreviations: AT2221, miglustat; ATB220, cipaglucosidase alfa; AUC, area under the concentration-time curve; C_{max}, maximum concentration; PD, pharmacodynamic; PK, pharmacokinetic

Biomarker endpoints (Hex4 and CK)

The Applicant also developed Emax model to describe the E-R relationship for Hex4 and CK. The parameter estimates are shown in Table 138 and Table 139. For both biomarkers, a shared race effect was estimated on IMAX and different ERT-history effects on IMAX were estimated for cipaglucosidase alfa and alglucosidase alfa. The age effect on IMAX was estimated separately for cipaglucosidase alfa and alglucosidase alfa for the Hex4 biomarker and a shared age effect on IMAX was estimated for the CK biomarker. The diagnostic plots for the final models are acceptable.

The model estimates show that the baseline urine Hex4 decreased with increasing age and was higher in Asian subjects compared to non-Asian subjects. However, baseline urine Hex4 was comparable in ERT-experienced and ERT-naïve subjects, as well as in female and male subjects (95% CI included the null value). The age effect estimate indicated that IMAX decreased with increasing age. In addition, the effect of ERT-experience indicated that IMAX was slightly lower in ERT-experienced subject compared to ERT-naïve subjects. However, the 95%CI included the null value. Thus, the Applicant concluded that IMAX following cipaglucosidase alfa was comparable in ERT-experience and ERT-naïve subjects.

For plasma CK, the model estimates indicated that Asian subjects were likely to have a higher baseline plasma CK. The estimate of the effect of ERT-experience indicated that IMAX decreased in ERT-experienced subjects receiving cipaglucosidase alfa compared to ERT-naïve subjects.

For both urine Hex4 and plasma CK, given the flat E-R relationship in observed range, the model estimates for EC50 could be associated with high uncertainty and thus not reliable.

Table 138. Hex4 Final Model: Summary of Parameter Estimates

			Estimate	95% CI
Structural model parameters				
KIN (mmol/molCr/day)	$\exp(\theta_1)$	Zero-order production rate of urine HEX4	0.0639	0.0437, 0.0934
BASE (mmol/molCr)	$\exp(\theta_2)$	Baseline urine HEX4	3.08	2.21, 4.29
$IMAX_{ATB200}$	θ_3	Maximal treatment effect of ATB200 on urine HEX4	0.481	0.262, 0.701
$IMAX_{Lumizyme}$	θ_4	Maximal treatment effect of Lumizyme on urine HEX4	0.161	-0.0306, 0.354
IAUC50 (ug/ml*hr)	$\exp(\theta_5)$	AUC achieving half of inhibitory effect	223	12.2, 4.09e+03
Covariate effect parameters				
WT_{BASE}	θ_6	Weight effect on BASE	-0.105	-0.396, 0.187
AGE_{BASE}	θ_7	AGE effect on BASE	-0.874	-1.28, -0.468
$RACE_{BASE}$	$\exp(\theta_8)$	Race (Asian) effect on BASE	2.00	1.48, 2.71
ERT_{BASE}	$\exp(\theta_9)$	ERT-history effect on BASE	1.06	0.773, 1.45
Sex_{BASE}	$\exp(\theta_{10})$	Gender (female) effect on BASE	1.19	0.960, 1.47
$AGE_{IMAX_{ATB200}}$	θ_{11}	AGE effect on $IMAX_{ATB200}$	-0.0107	-0.0185, -0.00283
$AGE_{IMAX_{Lumizyme}}$	θ_{12}	AGE effect on $IMAX_{Lumizyme}$	0.00769	-0.00217, 0.0175
$RACE_{IMAX}$	θ_{13}	Race (Asian) effect on IMAX	-0.0202	-0.287, 0.246
$ERT_{IMAX_{ATB200}}$	θ_{14}	ERT-history effect on $IMAX_{ATB200}$	-0.133	-0.271, 0.00416
$ERT_{IMAX_{Lumizyme}}$	θ_{15}	ERT-history effect on $IMAX_{Lumizyme}$	-0.340	-0.591, -0.0890

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; HEX4 = glucose tetrasaccharide; SE = standard error
Confidence intervals = estimate ± 1.96 * SE
Source: Applicant's popPK and E-R study report.

Table 139. CK Final Model: Summary of Parameter Estimates

			Estimate	95% CI
Structural model parameters				
KIN (IU/L/day)	$\exp(\theta_1)$	Zero-order production rate of plasma CK	16.2	11.5, 22.8
BASE (IU/L)	$\exp(\theta_2)$	Baseline plasma CK	355	267, 472
$IMAX_{ATB200}$	θ_3	Maximal treatment effect of ATB200 on plasma CK	0.461	0.346, 0.576
$IMAX_{Lumizyme}$	θ_4	Maximal treatment effect of Lumizyme on plasma CK	0.00395	-0.136, 0.144
IAUC50 (ug/ml*hr)	$\exp(\theta_5)$	AUC achieving half of inhibitory effect	216	55.9, 836
Covariate effect parameters				
WT_{BASE}	θ_6	Weight effect on BASE	0.605	0.0695, 1.14
AGE_{BASE}	θ_7	AGE effect on BASE	-1.08	-1.49, -0.663
$RACE_{BASE}$	$\exp(\theta_8)$	Race (Asian) effect on BASE	1.99	1.28, 3.08
ERT_{BASE}	$\exp(\theta_9)$	ERT-history effect on BASE	0.801	0.621, 1.03
Sex_{BASE}	$\exp(\theta_{10})$	Gender (female) effect on BASE	0.887	0.694, 1.13
AGE_{IMAX}	θ_{11}	AGE effect on IMAX	-0.00373	-0.00791, 0.000461
$RACE_{IMAX}$	θ_{12}	Race (Asian) effect on IMAX	0.136	-0.00766, 0.279
$ERT_{IMAX_{ATB200}}$	θ_{13}	ERT-history effect on $IMAX_{ATB200}$	-0.209	-0.309, -0.109
$ERT_{IMAX_{Lumizyme}}$	θ_{14}	ERT-history effect on $IMAX_{Lumizyme}$	-0.150	-0.324, 0.0242

Abbreviations: CI = confidence intervals; CK = creatinine kinase; Corr = Correlation coefficient; SE = standard error
Confidence intervals = estimate ± 1.96 * SE
Source: Applicant's popPK and E-R study report.
Abbreviations: AUC, area under the concentration-time curve; ERT, enzyme replacement therapy

Functional Endpoints (6MWD and FVC)

The Applicant previously developed PK-PD models of 6MWD and FVC were refined with the addition of data from Study ATB200-03. The model included disease progression and drug effects as below:

$$S(t) = BASE + SLOPE \cdot t + E(t)$$

where:

- $S(t)$ is the disease progression at time t.
- $BASE$ is the baseline disease status.
- $SLOPE$ is the slope of natural disease progress.
- $E(t)$ is a function describing drug effect in response to exposure.

Given the slope of the natural disease progression (SLOPE) and the drug effect (E(t)) are confounded, the natural history models were developed first using predose and historical data.

Parameters from the final natural history model were fixed and used in the model to estimate the effect of exposure.

Natural History Models

The natural history models of 6MWD and FVC were best described with linear models. The effects of age, race (Asian versus non-Asian), ERT-history (naive versus experienced) and sex (male versus female) were included on the baseline disease status (BASE) parameter. The model estimates for 6MWD and FVC are shown in Table 140 and Table 141. For 6MWT, the model estimates indicated that baseline 6MWD was lower in Asian subjects compared to non-Asian subjects, lower in female subjects than male subjects, and 6MWD decrease with increasing age. For FVC, the model estimates indicated that the baseline percent predicted FVC (ppFVC) was lower in Asian subjects compared to non-Asian subjects, and lower in ERT-experienced subjects than ERT-naïve subjects, and decreased with increasing age.

Table 140. 6MWT Natural History Final Model Parameter Estimates

			Estimate	95% CI	Shrinkage (%)
Structural model parameters					
BASE (m)	θ_1	Baseline 6MWT	416	375, 456	-
SLOPE (m/day)	θ_2	Slope of natural disease progression	-0.0458	-0.0615, -0.0301	-
SHAPE	θ_7	Shape parameter	-2.31	-2.99, -1.64	-
Covariate effect parameters					
$RACE_{BASE}$	θ_3	Race (Asian) effect on BASE	0.812	0.714, 0.910	-
Sex_{BASE}	θ_4	Gender (female) effect on BASE	0.860	0.804, 0.916	-
ERT_{BASE}	θ_5	ERT-history effect on BASE	0.926	0.846, 1.01	-
AGE_{BASE}	θ_6	Age effect on BASE	-0.386	-0.474, -0.298	-
Interindividual variance parameters					
IIV-BASE	$\Omega_{(1,1)}$	Variance of BASE	0.0670 [CV%=26.3]	0.0437, 0.0903	4.35
IIV-SLOPE	$\Omega_{(2,2)}$	Variance of SLOPE	0.00172 [CV%=90.6]	0.000248, 0.00320	52.1
Residual variance					
Additive	$\Sigma_{(1,1)}$	Variance	923 [SD=30.4]	507, 1.34e+03	-

Abbreviations: 6MWT = Six minute walk test; CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error
Confidence intervals = estimate ± 1.96 * SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) * 100
CV% of additive omegas = (sqrt(estimate) / abs(mean)) * 100
Source: Applicant's popPK and E-R study report.
Abbreviations: ERT, enzyme replacement therapy

Table 141. FVC Natural History Final Model Parameter Estimates

			Estimate	95% CI	Shrinkage (%)
Structural model parameters					
BASE (%)	θ_1	Baseline FVC	68.6	62.1, 75.1	-
SLOPE (%/day)	θ_2	Slope of natural disease progression	-0.00388	-0.00542, -0.00234	-
SHAPE	θ_7	Shape parameter	-0.738	-1.27, -0.206	-
Covariate effect parameters					
$RACE_{BASE}$	θ_3	Race (Asian) effect on BASE	0.859	0.728, 0.990	-
Sex_{BASE}	θ_4	Gender (female) effect on BASE	1.09	0.997, 1.17	-
ERT_{BASE}	θ_5	ERT-history effect on BASE	0.891	0.806, 0.976	-
AGE_{BASE}	θ_6	Age effect on BASE	-0.292	-0.418, -0.167	-
Interindividual variance parameters					
IIV-BASE	$\Omega_{(1,1)}$	Variance of BASE	0.0799 [CV%=28.8]	0.0577, 0.102	1.84
IIV-SLOPE	$\Omega_{(2,2)}$	Variance of SLOPE	2.01e-05 [CV%=115]	3.92e-07, 3.97e-05	49.7
Residual variance					
Additive	$\Sigma_{(1,1)}$	Variance	31.1 [SD=5.57]	24.7, 37.4	-

Abbreviations: FVC = forced vital capacity; CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error
Confidence intervals = estimate ± 1.96 * SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) * 100
CV% of additive omegas = (sqrt(estimate) / abs(mean)) * 100
Source: Applicant's popPK and E-R study report.
Abbreviations: ERT, enzyme replacement therapy

Drug Effect Model for 6MWD

The final model estimated parameters are shown in Table 142. The model was acceptable based on the diagnostic plots. Based on the model estimates, regardless of cipaglucosidase alfa or alglucosidase alfa, drug effect was lower in ERT-experienced subjects compared to ERT-naïve subjects. Of note, in the PK/PD model, the ERT effect was assumed to be the same on the drug effect of cipaglucosidase alfa and alglucosidase alfa. We considered this assumption was reasonable. In addition, the drug effect decreased with increasing age. Cipaglucosidase alfa was estimated to have a higher drug effect compared to alglucosidase alfa for 6MWD.

Table 142. 6MWD Drug Effect Final Model Parameter Estimates

			Estimate	95% CI	Shrinkage (%)
Structural model parameters					
$DEFF_{ATB200}$ (m/ug/ml*hr)	θ_8	ATB200 drug effect	0.0277	0.0187, 0.0367	-
$DEFF_{Lumizyme}$ (m/ug/ml*hr)	θ_9	Lumizyme drug effect	0.0156	0.00181, 0.0293	-
Covariate effect parameters					
$RACE_{DEFF}$	θ_{10}	Race (Asian) effect on DEFF	1.73	0.294, 3.17	-
ERT_{DEFF}	θ_{11}	ERT-history effect on DEFF	0.535	0.281, 0.789	-
AGE_{DEFF}	θ_{12}	Age effect on DEFF	-0.633	-1.09, -0.172	-
Interindividual variance parameters					
IIV-DEFF	$\Omega_{(3,3)}$	Variance of DEFF	0.000186 [SD=0.0136]	-7.86e-06, 0.000380	34.3
Residual variance					
Additive	$\Sigma_{(1,1)}$	Variance	709 [SD=26.6]	389, 1.03e+03	-

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error
Confidence intervals = estimate ± 1.96 * SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) * 100
CV% of additive omegas = (sqrt(estimate) / abs(mean)) * 100
Source: Applicant popPK and E-R study report.

Drug Effect Model for FVC

The FVC data were not sufficient to support the development of an E-R model. A simplified PD model (Drug Effect = $\theta + \eta_i$) was therefore developed to include an additive drug effect. No covariates (outside of those included in the final natural history model) were estimated in the final PD model. The final model parameters are shown in Table 143. Based on the diagnostic plots, the model was acceptable.

Table 143. FVC Drug Effect Final Model Parameter Estimates

			Estimate	95% CI
Structural model parameters				
$DEFF_{ATB200}$ (%)	θ_8	ATB200 drug effect	0.0953	-0.865, 1.06
$DEFF_{Lumizyme}$(%)	θ_9	Lumizyme drug effect	-1.14	-2.66, 0.387
Residual variance				
Additive	$\Sigma_{(1,1)}$	Variance	29.7 [SD=5.45]	21.6, 37.8

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; SD = standard deviation; SE = standard error
Confidence intervals = estimate ± 1.96 * SE

Source: Applicant popPK and E-R study report.

Exposure-Response Analyses for Safety

Cipaglucosidase alfa

Upon FDA's request, the Applicant conducted multivariate E-R analysis for safety endpoints for cipaglucosidase alfa using the data from Studies ATB200-02 and ATB200-03. The analysis population were subjects who had cipaglucosidase alfa PK data following the treatment of 20 mg/kg cipaglucosidase alfa +260 mg miglustat. The most frequent treatment-emergent adverse events (TEAEs) (≥10%) included in the analyses were fall, headache, nasopharyngitis, arthralgia, back pain, myalgia, nausea, diarrhea, pain in extremity, urinary infection, fatigue, musculoskeletal pain, orthopharyngeal pain, and muscle spasms (Table 144). The covariates evaluated include age, race (Asian/non-Asian), gender and ERT status (treatment-experienced and treatment-naïve). The results of the analysis indicated positive E-R relationships for nasopharyngitis, pain in extremity, and muscle spasms (Figure 91).

Pain in extremity was addressed by the adverse drug reactions of pain, arthralgia, and myalgia. For nasopharyngitis, while the positive E-R relationship was observed, the number of subjects were limited. In addition, none of the reported TEAEs of nasopharyngitis was considered related to study drugs.

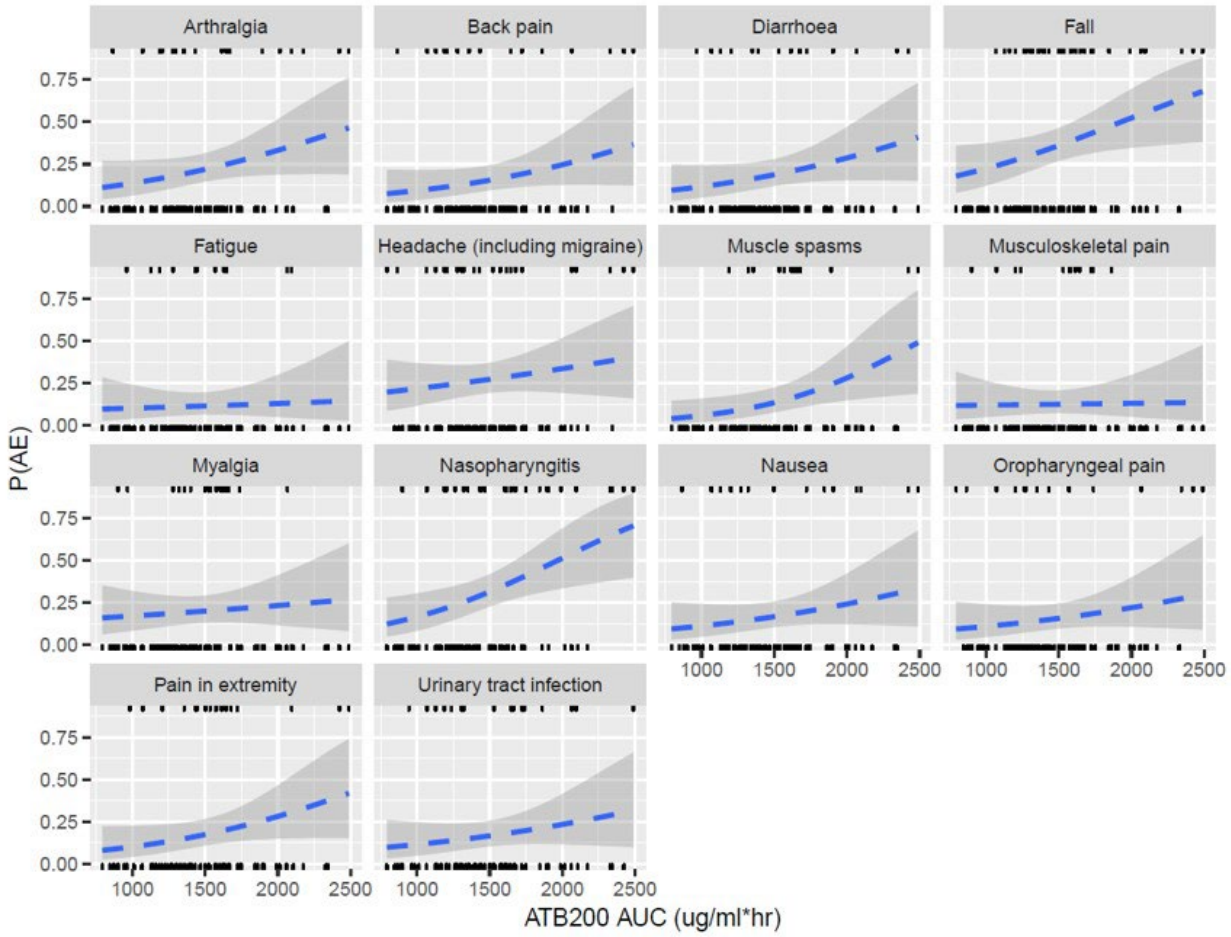
Table 144. Summary of Treatment-Emergent Adverse Event by Preferred Term

Preferred term	n/N (%)
Arthralgia	21/96 (21.9)
Back pain	15/96 (15.6)
Diarrhoea	18/96 (18.8)
Fall	34/96 (35.4)
Fatigue	11/96 (11.5)
Headache (including migraine)	26/96 (27.1)
Muscle spasms	14/96 (14.6)
Musculoskeletal pain	12/96 (12.5)
Myalgia	19/96 (19.8)
Nasopharyngitis	30/96 (31.2)
Nausea	16/96 (16.7)
Oropharyngeal pain	15/96 (15.6)
Pain in extremity	17/96 (17.7)
Urinary tract infection	16/96 (16.7)

N = number of subjects in the analysis. n = number of subjects who experinced at lease one adverse event.

Source: Applicant's response to 9 September 2021 Information Request.

Figure 91. Exposure-Response Analysis for Safety for Cipaglucosidase Alfa, ATB200-03 and ATB200-02 (Cohorts 1 and 3)

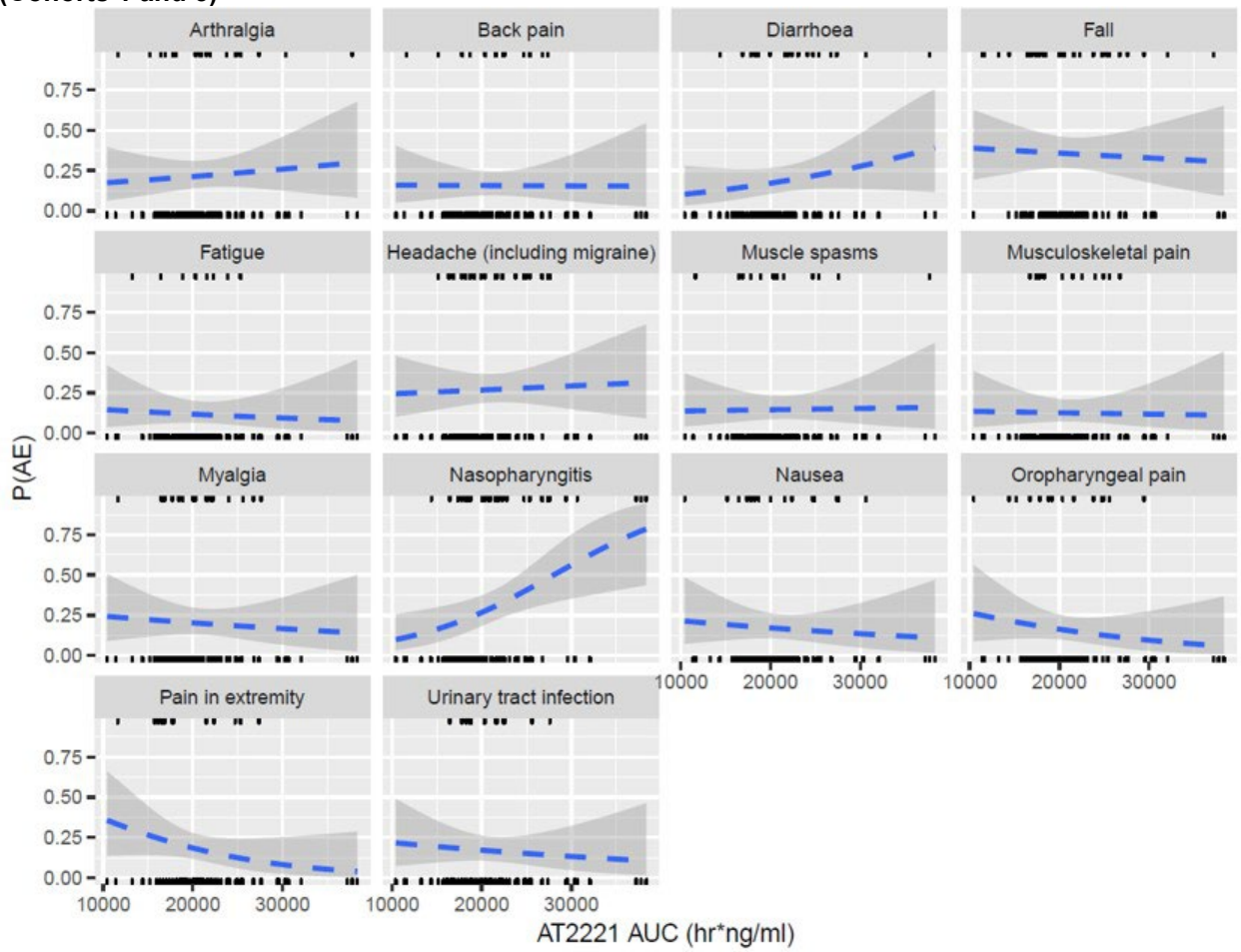


Source: Applicant's response to 9 September 2021 Information Request.
Abbreviations: AE, adverse event; ATB220, cipaglucosidase alfa; AUC, area under the concentration-time curve

Miglustat

Upon FDA's request, the Applicant conducted E-R analysis for safety endpoints (Figure 92) for miglustat. The most frequent TEAEs (≥10%) included in the analyses were fall, headache, nasopharyngitis, arthralgia, back pain, myalgia, nausea, diarrhea, pain in extremity, urinary infection, fatigue, musculoskeletal pain, orthopharyngeal pain, and muscle spasms (Table 144). As shown in Figure 92, overall, no significant E-R relationship was identified between the incident rate of adverse events versus AUC of miglustat based on the data from Study ATB200-03 and ATB200-02 (Cohorts 1 and 3), except for nasopharyngitis. Per the Applicant, none of the reported TEAEs of nasopharyngitis was considered related to miglustat. In addition, because no monotherapy arm of miglustat was included in the Study ATB200-03, the E-R analysis could be confounded by the effect of cipaglucosidase alfa. Based on currently available data analysis, the proposed body weight-tiered dosing regimen of miglustat appears appropriate.

Figure 92. Exposure-Response Analysis for Safety for Miglustat, ATB200-03 and ATB200-02 (Cohorts 1 and 3)



Source: Applicant's response to 1 October 2021 Information Request.
Abbreviations: AE, adverse event; AT2221, miglustat; AUC, area under the concentration-time curve

14.5. Summary of Bioanalytical Method Validation and Performance

14.5.1. Cipaglucosidase Alfa

Bioanalytical methods to determine cipaglucosidase alfa concentration in plasma (Total GAA protein) in Studies ATB200-02 and ATB-200-03 were validated [redacted] (b) (4) [redacted] (b) (4) The performance of the method and assay validation parameters are summarized in Table 145. The method validation was acceptable.

The bioanalytical method used to determine plasma GAA activity was validated [redacted] (b) (4) [redacted] (b) (4) and was used in Study ATB200-02. An exploratory concentration of active GAA can be extrapolated using the measured activity and the specific activity validated at CR-MTL. The assay validation parameters are acceptable.

Table 145. Summary of Method Performance and Assay Validation of the Bioanalytical Method for the Determination of ATB200 in Human Plasma

Method Parameter	Method Information	
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a method for the determination of ATB200 in human plasma samples Additional validation of a method for the determination of ATB200 in human EDTA plasma samples by LC-MS/MS (Triple Quad 6500) – stabilities from separate aliquots	
Method description	Plasma protein precipitation followed by pellet digestion and ultraperformance liquid chromatography with tandem mass spectrometric detection of GAA-specific signature peptide(s). Two ATB200 signature peptides were measured: (T50) VTSEGAGLQLQK and (T09) TTPTFFFPK. The validation results for both signature peptides were reported. The results for the T09 peptide were regarded as the validation results for the protein ATB200.	
Materials used for standard calibration curve and concentration	ATB200 Calibration curve concentrations: 0.500, 1.00, 2.50, 10.0, 25.0, 100, 250, 400, and 500 µg/mL	
Validated Assay Range	0.500 µg/mL to 500 µg/mL	
Material used for quality controls (QCs) and concentration	ATB200 QC concentrations: 1.50, 25.0, 400 µg/mL	
Minimum required dilutions (MRDs)	Not applicable	
Source and lot of reagents	Reference standard: ATB200 WuXi AppTec, Shanghai, China Batches 110150625, 110160724, 110171111, and 2S1902 Signature peptides: 2794-33 for VTSEGAGLQLQK and 2821-45 for TTPTFFPK Internal standard: VTSEGAGLQLQK-13C_6-15N_2 (Batch F1847); TTPTFFPK-13C_6-15N_2 (Batch 3094-35/37-2) (b) (4)	
Regression model and weighting	Linear, $1/x^2$	
Validation Parameters		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9
	Cumulative accuracy (%bias) from LLOQ to ULOQ	
	T09 (TTPTFFPK)	-3.8% to 2.0%
	T50 (VTSEGAGLQLQK)	-4.9% to 2.8%
	Cumulative precision (%CV) from LLOQ to ULOQ	
	T09 (TTPTFFPK)	≤4.8%
	T50 (VTSEGAGLQLQK)	≤4.3%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	
	T09 (TTPTFFPK)	-3.2% to 0.5%
	T50 (VTSEGAGLQLQK)	-3.2% to -0.1%
	Interbatch %CV	
	T09 (TTPTFFPK)	≤4.2%
	T50 (VTSEGAGLQLQK)	≤2.5%
	Total error (TE)	Not applicable

Method Parameter	Method Information
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a method for the determination of ATB200 in human plasma samples Additional validation of a method for the determination of ATB200 in human EDTA plasma samples by LC–MS/MS (Triple Quad 6500) – stabilities from separate aliquots
Selectivity and matrix effect	Selectivity: Six samples spiked at 0.500 µg/mL; response at the retention time of each signature peptide was acceptable (<25.0% of the mean response for each signature peptide) in the 6 samples. Matrix effect: Six relative matrix factors were calculated by dividing the signature peptide response (peak area ratio over internal standard) for plasma by the response for the corresponding test sample. Results were acceptable (CV of ≤20%), with mean %CV of ≤10.4 for T50 and ≤11.8 for T09 at both concentrations tested.
Interference and specificity	Effect of miglustat: Blank and human plasma samples spiked at 3 concentrations of ATB200 plus 200µM miglustat. Effect of anti-rhGAA antibodies: Blank and 3 concentrations of spiked human plasma samples tested with 0.500 and 50.0 µg/mL anti-rhGAA antibodies (tested both goat anti-rhGAA and rabbit anti- ATB200 antibodies). Both interference tests met acceptance criteria (absolute bias from the nominal concentration of ≤20% for at least 4 of 6 spiked samples and at least 1 spiked sample at each concentration).
Hemolysis effect	One source of human plasma at a concentration of 0.500 µg/mL was spiked with 2% (v/v) lysed human whole blood and tested in triplicate. Calculation was done in relation to a calibration curve in nonhemolytic plasma. Selectivity was found to be within the criteria (absolute bias of ≤25% from the nominal concentration for at least 2 out of 3 results).
Lipemic effect	Lipemic plasma at a concentration of 0.500 µg/mL was tested in triplicate. Calculation was done in relation to a calibration curve in nonlipemic plasma. Selectivity was found to be within the criteria (absolute bias of ≤25% from the nominal concentration for at least 2 out of 3 results).
Dilution linearity and hook effect	Spiked human plasma samples were tested at a concentration of 1500 µg/mL at 10-fold dilution. The range of observed bias was 0.7% to 1.8% for T09 and T50, respectively.
Bench-top/process stability	Autosampler stability was tested at 2 concentrations for 121 hours (mean bias of ≤18.4%). Bench-top stability was tested at 2 concentrations for 25 hours (mean bias of ≤4.5%). The results for both the stability assessments met the acceptance criteria (the absolute bias of the mean concentration in samples following storage of ≤20% of the nominal concentration; CV of the 3 results was ≤20%). Plasma stability of ATB200 from separate aliquots was tested up to 23 hours at RT at 2 concentrations. The results for both the stability assessments met the acceptance criteria (the absolute bias of the mean concentration in samples following storage of ≤20% of the nominal concentration; CV of the 3 results was ≤20%).
Freeze-thaw stability	Five cycles of freeze-thaw stability were tested at 2 concentrations of 1.5 and 400 µg/mL at -20°C and at -70°C. All measurement bias of ≤19.5%. The results met the acceptance criteria (the absolute bias of the mean concentration in samples following storage of ≤20% of the nominal concentration; CV of the 3 results was ≤20%). Plasma freeze-thaw stability from separate aliquots was tested at 2 concentrations up to 5 cycles in plasma at -20°C and at -70°C.
Long-term storage	Spiked human plasma sample stability was assessed at 2 concentrations. The results demonstrated that both signature peptides were stable up to 562 days at -20°C at 1.50 µg/mL and up to 552 days at -20°C at 400 µg/mL and at -70°C at both concentrations. Plasma long-term storage from separate aliquots was tested up to 560 days at -20°C and -70°C.
Parallelism	Not applicable

Method Parameter	Method Information
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a method for the determination of ATB200 in human plasma samples Additional validation of a method for the determination of ATB200 in human EDTA plasma samples by LC-MS/MS (Triple Quad 6500) – stabilities from separate aliquots
Carryover	Three blank plasma samples were analyzed directly following the sample at the highest calibration level and directly following the last validation sample at the highest level. All responses were ≤11.8%. All acceptance criteria were met (response of <25.0% of the mean analyte response found for the validation samples at the LLOQ level analyzed in the same run).
Method Performance in Study ATB200-02	
Assay passing rate	Thirty-three analytical runs passed acceptance criteria out of a total of 33 runs. Two qualification runs were performed.
Standard curve performance	Standard curve performance for VTSEGAGLQLQK: Cumulative bias range: -2.8% to 2.2% Cumulative precision: ≤4.6% CV Standard curve performance for TTPTFFPK: Cumulative bias range: -3.2% to 2.3% Cumulative precision: ≤4.9% CV
QC performance	QC performance for VTSEGAGLQLQK: Cumulative bias range: 3.0% to 5.3% Cumulative precision: ≤6.5% CV QC performance for TTPTFFPK: Cumulative bias range: 3.3% to 6.0% Cumulative precision: ≤6.3% CV
Method reproducibility	Incurred sample reproducibility was performed in 115/1251 (9.2%) of the study samples, and 100% of the samples met the pre-specified criteria for VTSEGAGLQLQK, and 100% of the samples met the pre-specified criteria for TTPTFFPK.
Study sample analysis/stability	1251 human plasma samples were analyzed for ATB200 (rhGAA) by ultra-performance LC-MS/MS detection within the validated stability period of 560 days at -70℃. The maximum frozen storage duration for study samples between collection and analysis was 182 days. Data on the performance of the method and stability indicate that the plasma concentration results of VTSEGAGLQLQK and TTPTFFPK as reported are reliable.
Standard calibration curve performance during accuracy and precision runs	33 standard calibration curves were run during sample analysis with 9 calibrators each. For VTSEGAGLQLQK, all calibrators from LLOQ to ULOQ met the acceptance criteria except for two analytical runs where individual calibrators failed to meet acceptance criteria and were rejected (two calibrators in total). These rejected calibrators are the 1 ng/mL calibrator in analytical run 29 and 0.5 ng/mL calibrator in analytical run 31. For TTPTFFPK, all calibrators from LLOQ to ULOQ met the acceptance criteria except for analytical run 29, where the 1 ng/mL calibrator failed to meet acceptance criteria and was rejected.
Method Performance in Study ATB200-03	
Assay passing rate	Eighteen analytical runs passed acceptance criteria out of a total of 18 runs. One qualification run was performed.
Standard curve performance	Standard curve performance for VTSEGAGLQLQK: Cumulative bias range: -1.2% to 1.2% Cumulative precision: ≤4.2% CV Standard curve performance for TTPTFFPK: Cumulative bias range: -0.9% to 1.2% Cumulative precision: ≤4.4% CV

Method Parameter	Method Information
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a method for the determination of ATB200 in human plasma samples Additional validation of a method for the determination of ATB200 in human EDTA plasma samples by LC-MS/MS (Triple Quad 6500) – stabilities from separate aliquots
QC performance	QC performance for VTSEGAGLQLQK: Cumulative bias range: 2.0% to 6.0% Cumulative precision: ≤6.2% CV QC performance for TTPTFFPK: Cumulative bias range: 2.3% to 6.0% Cumulative precision: ≤7.2% CV
Method reproducibility	No incurred sample reproducibility was assessed because this was previously done in samples from the same population in ATB200-02
Study sample analysis/stability	1101 human plasma samples were analyzed for ATB200 (rhGAA) by ultraperformance LC-MS/MS detection within the validated stability period of 560 days at -70℃. Data on the performance of the method and stability indicate that the plasma concentration results of VTSEGAGLQLQK and TTPTFFPK as reported are reliable.
Standard calibration curve performance during accuracy and precision runs	Eighteen standard calibration curves were run during sample analysis with 9 calibrators each. All calibrators from LLOQ to ULOQ met the acceptance criteria.

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods.
Abbreviations: %CV, percent of coefficient of variation; ATB200, cipaglucosidase alfa; CV, coefficient of variation; EDTA, ethylenediaminetetraacetic acid; GAA, human acid α-glucosidase; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; rhGAA, recombinant human acid α-glucosidase; QC, quality control; RT, room temperature; TTPTFFPK, threonine-threonine-proline-threonine-phenylalanine-phenylalanine-proline-lysine; ULOQ, upper limit of quantification; VTSEGAGLQLQK, valine-threonine-serine-glutamic acid-glycine-alanine-glycine-leucine-glutamine-leucine glutamine-lysine

Pharmacodynamic Biomarkers

Bioanalytical method to determine urinary hexose tetrasaccharide (Hex4) in Studies ATB200-02 and ATB200-03: The target Glc4 (Glcα1-6Glcα1-4Glcα1-4Glc), the predominant hex4 isomer in urine, was isolated via ultra-performance liquid chromatography and detected by electrospray ionization tandem mass spectrometry in an assay that was validated (b) (4) (b) (4) Assay validation parameters are summarized in Table 146. The Applicant reported that sample analysis was performed along with other samples unrelated to the Applicant's clinical studies therefore the method performance in ATB200-02 and ATB200-03 are not available.

Table 146: Summary of Method Performance and Assay Validation of the Bioanalytical Method for the Determination of Glucose Tetrasaccharide in Urine

Method Parameter	Method Information	
Bioanalytical method validation report name, amendments, and hyperlinks	Analytical determination of the glucose tetrasaccharide, Glcα1-6Glcα1-4Glcα1-4Glc, Glc4 in urine using UPLC-electrospray tandem mass spectrometry, V013-Glc4 Validation Report (LTR129990)	
Method description	Urinary neutral oligosaccharides were derivatized to butyl-p-aminobenzoic derivatives and the target biomarker Glc4 (Glcα1-6Glcα1-4Glcα1-4Glc) separated from other hexose tetrasaccharides by hydrophilic interaction ultra-performance liquid chromatography and detected by electrospray ionization tandem mass spectrometry. Additional selectivity is achieved by detection using selected reaction monitoring of 2 transitions each for Glc4 and the [13C6]-labeled internal standard. This methodology has sufficient sensitivity, with a high signal to noise ratio (≥ 1400 to 1) at the lower limit of quantification using a Xevo TQD or Xevo TQ MS mass spectrometer (b) (4) (b) (4)	
Materials used for standard calibration curve and concentration	Glcα1-6Glcα1-4Glcα1-4Glc (Glc4) Calibration curve concentrations: 1.9, 3.8, 7.7, 19.1, 38.3, 76.6, 153.1, 191.4, and 229.7 µM	
Validated Assay Range	Dynamic Range: 1.6 µM to 600 µM Analytical Measurement Range (AMR), (85% of the lowest calibrator and extended beyond the highest calibrator to 600 µM)	
Material used for quality controls (QCs) and concentration	Glcα1-6Glcα1-4Glcα1-4Glc (Glc4) QC concentrations: 8, 125, 540 µM (Intra-day QC; daily quality control samples) QC concentrations: 8.6, 117.6, 159.8 µM (Inter-day QC; prepared from patient samples within the AMR)	
Minimum required dilutions (MRDs)	Not applicable	
Source and lot of reagents	Reference standard: Glcα1-6Glcα1-4Glcα1-4Glc (Glc4) Cat No: G419100 Source: (b) (4) Internal standard: Glcα1-6Glcα1-4Glcα1-4-[13C6]-Glc ([13C6]-Glc4) Source: In house preparation by (b) (4)	
Regression model and weighting	Linear, no weighting factor applied	
Validation Parameters		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-8% to 4%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 17%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	Not reported
	Interbatch %CV	≤ 6%
	Total error (TE)	Not applicable
Selectivity and matrix effect	The selectivity of the assay, defined as the ability to detect specifically the target analyte and its added internal standard (IS), was assessed by the method of ion ratios. In this method, the glucose tetrasaccharide fraction and IS are detected using selected reaction monitoring (SRM) for the transitions m/z 844>358 for Glc4 and m/z 850>364 for the IS derivative. Secondary transitions m/z 844>520 for Glc4 and m/z 850>526 are monitored to detect interfering substances. The ratios of the intensities for the primary and secondary transitions (ion ratios) are calculated for each injection (sample or QC) and compared with pre-established means. The target ion ratio of the primary to secondary transition for 75 injections over 3 days showed an imprecision of 10.8% or less.	

Method Parameter	Method Information
Bioanalytical method validation report name, amendments, and hyperlinks	Analytical determination of the glucose tetrasaccharide, Glcα1-6Glcα1-4Glcα1-4Glc, Glc4 in urine using UPLC-electrospray tandem mass spectrometry, V013-Glc4 Validation Report (LTR129990)
Interference and specificity	Not applicable
Hemolysis effect	Not applicable
Lipemic effect	Not applicable
Dilution linearity and hook effect	Samples analyzed undiluted and diluted (maximum dilution factor of 20-fold) showed consistent results with percent differences of 11% or less. Analysis of a 20-fold dilution of a sample with a concentration significantly above the AMR showed good agreement (1.2%) with the measurement of the undiluted sample.
Bench-top/process stability	The stability of Hex4 concentrations in urine was assessed by analysis of patient samples at low and high concentrations after 2 weeks of storage at ambient temperature (22-25°C). The data show that instability was < ±15% and demonstrated stability for up to 13 days at ambient storage. The stability of samples stored in the refrigerator at 4°C was assessed using medium and high QC samples. The QCs (stored at -20°C) were removed from the freezer and relocated to a refrigerator maintained at 4°C once a day for up to 3 weeks. The results show that there was no significant change for the medium and high concentration samples after 20 days.
Freeze-thaw stability	Freeze-thaw stability for samples maintained at -20°C was assessed by analyzing low and high concentration patient samples. Samples were analyzed after each freeze-thaw cycle (up to the 7th cycle). The results show that samples were stable over 6 freeze-thaw cycles (instability ≤ ±10% for the low and high concentration samples).
Long-term storage	The -20°C storage stability was evaluated by reanalyzing patient samples and comparing to the original results. The results show that samples were stable for at least 2 years with a mean % difference of 12.
Parallelism	Not applicable
Carryover	Not applicable

Abbreviations: AMR = analytical measurement range; CV = coefficient of variation; LCMS/MS = liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantification; QC = quality control; RT = room temperature; ULOQ = upper limit of quantification

In response to a September 22, 2021 information request, the Applicant reported that serum creatine kinase (CK) was measured as part of standard serum chemistry across studies in the central lab used for Studies ATB200-03 and ATB200-07 and the lab used for Study ATB200-02. The Applicant reported serum CK was assayed using creatine kinase assays with 510(k) clearance in a CLIA-certified labs.

Refer to OBP review for assessment of bioanalytical method validation and performance of anti-rhGAA and neutralizing antibody assays.

14.5.2. Miglustat

PK Assays

The PK of miglustat was characterized in clinical studies ATB200-02 and ATB200-03. The concentration of miglustat in human plasma was measured using a liquid chromatography with tandem mass spectrometry method (Validation report RPT03721). The life cycle of the

bioanalytical method is summarized in Table 147 and the performance of the method and assay validation parameters are summarized in Table 148.

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Table 147. Bioanalytical Method Life Cycle Information: AT2221 in Plasma

Parameter	Method Validation Number 1	Clinical Study AT2221-01	Clinical Study ATB200-02	Clinical Study ATB200-03
Analyte	AT2221 (miglustat hydrochloride; N-butyl- deoxynojirimycin hydrochloride)	AT2221 (miglustat hydrochloride; N-butyl-deoxynojirimycin hydrochloride)	AT2221 (miglustat hydrochloride; N-butyl-deoxynojirimycin hydrochloride)	AT2221 (miglustat hydrochloride; N-butyl-deoxynojirimycin hydrochloride)
Validation type	Full	In-study	In-study	In-study
eCTD reference number	BLA 761204, sequence no. 0003	BLA 761204, sequence no. 0003	BLA 761204, sequence no. 0003	BLA 761204, sequence no. 0003
Method identification	(b) (4) 15075-M01 (b) (4) 15075-M02 (minor changes)	(b) (4) 15075-M01	(b) (4) 15075-M01	(b) (4) 15075-M01 (b) (4) 15075-M02 (minor changes)
Duration of time method was in use	August 2015 to March 2020 (method 01) March 2020 to present (method 02)	April 2018 to May 2018 (method 01)	May 2016 to September 2019 (method 01)	June 2019 to March 2020 (method 01) March 2020 to January 2021 (method 02)
Bioanalytical site	(b) (4)			
Matrix	Human plasma (K_2EDTA)			
Platform	Liquid chromatography with tandem mass spectrometry (LC-MS/MS)			
Format	A validated multiple reaction monitoring (MRM) format for quantitative determination of AT2221 that is captured by a solid phase extraction and HPLC purification			

Parameter	Method Validation Number 1	Clinical Study AT2221-01	Clinical Study ATB200-02	Clinical Study ATB200-03
Stock reference, lot number, expiration date	Analyte: AT2221 Lot number: 5-AQL-169-4 Expiration date: 11 February 2022 Recertification: 10 February 2022 Internal standard: AT2221-d9 (miglustat hydrochloride-d9; N-butyl- deoxynojirimycin hydrochloride-d9 Lot number: 2-GAB-185-1 Expiration date: 23 July 2021	Analyte: AT2221 Lot number: 5-AQL-169-4 Expiration date: 11 February 2022 Recertification: 10 February 2022 Internal standard: AT2221-d9 (miglustat hydrochloride-d9; N-butyl-deoxynojirimycin hydrochloride-d9 Lot number: 2-GAB-185-1 Expiration date: 23 July 2021	Analyte: AT2221a Lot number: 5-AQL-169-4 Expiration date: Feb 11, 2022 Recertification: Feb 11, 2022 Lot number: 4237.G.16.1 Expiration date: Nov 1, 2019 Recertification: Nov 1, 2019 Internal standard: AT2221-d9 (miglustat hydrochloride-d9; N-butyldeoxynojirim ycin hydrochloride- d9 Lot no.: 2-GAB-185-1 Expiration date: 23 July 2021	Analyte: AT2221a Lot number: 4237.G.16.1 Expiration date: Nov 1, 2019 Recertification: Nov 1, 2019 Internal standard: AT2221-d9 (miglustat hydrochloride-d9; N-butyl- deoxynojirimycin hydrochloride-d9 Lot number: 2-GAB-185-1 Expiration date: Jul 23, 2021
Calibration range from the LLOQ to the ULOQ	0.500 ng/mL to 250 ng/mL	0.500 ng/mL to 250 ng/mL	0.500 ng/mL to 250 ng/mL	0.500 ng/mL to 250 ng/mL
Matrix study population	Normal	Normal	Diseased	Diseased
Synopsis of amendment history	Amendment 1: Personnel changes, new lots of AT2221 and AT2221-d9, changes to the analysis period, additional experiments (long-term storage stability, hemolysis, hyperlipidemia, extraction recovery at 3 levels for analyte and IS, processed sample stability at ambient and refrigerated conditions, and whole blood stability), changes in tables for standards and QCs for noncore runs	Not applicable	Not applicable	Sample analysis alteration: Study monitor update due to change in Amicus personnel

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods.
[a] This lot is the non-HCl form of miglustat. It was used for the last run of study ATB200-02. The HCl and non-HCl forms of miglustat were found equivalent in the assay during method development. On the expiration date, all compounds were retested and recertified for continual use without changes in lot numbers.
Abbreviations: BLA, Biologic License Application; eCTD, electronic Common Technical Document; HCl, hydrochloride; HPLC, high-performance liquid chromatography; IS, Internal Standard; K_2EDTA, ethylenediaminetetraacetic acid; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Table 148. Summary Method Performance – Determination of AT2221 (Miglustat) in Plasma

Method Parameter	Method Information
Method description	An LC-MS/MS method for the determination of AT2221 in K_2EDTA human plasma
Materials used for standard calibration curve and concentration	AT2221 (miglustat hydrochloride; N-butyl-deoxynojirimycin hydrochloride) Standard calibration curve concentrations: 0.500, 1.00, 4.00, 10.0, 50.0, 100, 225, and 250 ng/mL
Validated assay range	0.500 ng/mL to 250 ng/mL
Material used for quality controls (QCs) and concentration	AT2221(miglustat hydrochloride; N-butyl-deoxynojirimycin hydrochloride) QC concentrations: 1.50 (QCL), 20.0 (QCM), and 200 (QCH) ng/mL
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Analyte: AT2221 (miglustat hydrochloride; N-butyl-deoxynojirimycin hydrochloride) Batch no.: 5-AQL-169-4 Source: (b) (4) Internal standard: AT2221-d9 (miglustat hydrochloride-d9; N-butyldeoxynojirimycin hydrochloride-d9) Batch no.: 2-GAB-185-1 Source: (b) (4)
Regression model and weighting	Linear, 1/x2
Validation Parameters	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 8 Cumulative accuracy (%bias) from LLOQ to ULOQ: -2.00% to 2.00% Cumulative precision (%CV) from LLOQ to ULOQ: ≤4.44%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs: -2.67% to 2.50% Interbatch %CV: ≤8.02% Total error (TE): Not applicable
Selectivity and matrix effect	6 lots of matrix blanks: The response at the retention time of the analyte in 5 out of 6 matrix blanks must be ≤20% of the mean analyte peak response of the LLOQ. The response at the retention time of the IS in 5 out of 6 matrix blanks must be ≤5% of the mean peak response of the IS of the LLOQ. 6 lots of matrix blanks with IS: The response at the retention time of the analyte in 5 out of 6 matrix blanks with IS must be ≤20% of the mean analyte response of the LLOQ. Pooled matrix blanks with IS: If there is a peak area response at the analyte retention time, the peak area ratio must be ≤20% of the peak area ratio of the LLOQ. ULOQ pooled matrix with analyte only: The response at the retention time of the IS must be ≤5% of the mean IS peak area of the LLOQ. There was no interference observed at the retention time of the analyte.
Interference and specificity	Analytical performance of AT2221 low quality control (1.50 ng/mL) was tested in human plasma spiked with ATB200 (1500 µg/mL). Overall %RE was -12.67%. No interference was observed at the retention time of the analyte with coadministered drug ATB200.
Hemolysis effect	Two concentrations of QCs (QCL: 1.50 ng/mL and QCH: 200 ng/mL) were tested at 2% hemolysis. The cumulative %RE was 0.67% (for QCL), and -4.00% (for QCH) of nominal in the samples tested, which met the acceptance criteria (%RE within ±15% of nominal).
Lipemic effect	Hyperlipidemia was tested in 2 concentrations of QCs (QCL: 1.50 ng/mL; QCH: 200 ng/mL). The cumulative %RE was 5.33% (for QCL) and -2.00% (for QCH) of nominal in the samples tested, which met the acceptance criteria (%RE within ±15% of nominal).

Method Parameter	Method Information
Dilution linearity and hook effect	Dilution integrity of AT2221 in human plasma quality control samples (1,000 ng/mL) was tested at 10-fold and 100-fold dilutions. %RE ranged from -9.60% to -2.80% at 10-fold dilution and -15.50% to -7.70% at 100-fold dilution.
Bench-top/process stability	Stored at 4°C: 104 h Stored at room temperature: 64 h
Freeze-thaw stability	Six cycles of freeze (-70ºC)-thaw stability were tested at 2 concentrations (QCL and QCH) (mean RE% was 6.00% for QCL and -4.5% for QCH). The results for both the stability assessments met the acceptance criteria (the %RE of the QC samples should be ±15% of nominal; %CV of the QC samples should be ≤15%)
Long-term storage	1641 days at -70ºC 1626 days at -20ºC
Parallelism	Not applicable
Carryover	0% carry over Blank samples had peak area of 0 in all injections.
Method Performance in Study AT2221-01	
Assay Passing Rate	100%
Standard curve performance	Cumulative bias range: -3.60% to 4.75% Cumulative precision: ≤9.08%
QC performance	Cumulative bias range: -4.00% to 8.67% Cumulative precision: ≤37.79% CV (1 outlier in the QCL run); all other (QCM and QCH) %CV ≤2.16
Method reproducibility	Incurred sample re-analysis was performed in 10% of study samples, and 93.51% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples were analyzed within sample storage stability. The earliest sample collection date occurred on 24 April 2018. The sample storage time from this date to completion of plasma sample analysis on 17 May 2018 is 23 days.
Standard calibration curve performance during accuracy and precision runs	Fifteen standard calibration curves were run with 8 calibration standards each. Only 2 calibrators were rejected among the total of 120 from LLOQ to ULOQ.
Method Performance in Study ATB200-02	
Assay passing rate	96.2%
Standard curve performance	Cumulative bias range: -2.75% to 2.00% Cumulative precision: ≤4.51%
QC performance	Cumulative bias range: 0.67% to 8.00% Cumulative precision: ≤4.72%
Method reproducibility	Incurred sample re-analysis was performed in 11% of study samples, and 98.75% of the samples met the prespecified criteria.
Study sample analysis/stability	AT2221 in human plasma is stable for 1641 days in a freezer set to -70°C. All samples were analyzed within sample storage stability. The longest storage time from sample collection to extraction is 431 days for 1 subject sample that was collected on 26 May 2016 and extracted to run on 31 July 2017.
Standard calibration curve performance during accuracy and precision runs	Twenty-three standard calibration curves were run with 8 calibration standards each. Only 2 were rejected among the total of 184 calibrators from LLOQ to ULOQ.
Method Performance in Study ATB200-03	
Assay Passing Rate	93.75%
Standard curve performance	Cumulative bias range: -0.90% to 2.00% Cumulative precision: ≤8.25% CV

Method Parameter	Method Information
QC performance	Cumulative bias range: -0.50% to 7.00% Cumulative precision: ≤39.81% CV (QCM precision is 39.81%, all other (QCM and QCH) %CV ≤7.43%)
Method reproducibility	Incurred sample re-analysis was performed in 105 samples (11% of study samples), and 95 out of 105 samples (90.48%) met the acceptance criteria.
Study sample analysis/stability	AT2221 in human plasma is stable for 1641 days in a freezer set to -70°C. All samples were analyzed within sample storage stability. The longest actual sample storage time prior to analysis is 546 days for a subject sample which was collected on 09 May 2019 and extracted on 05 November 2020 in Run 19.
Standard calibration curve performance during accuracy and precision runs	Thirty standard calibration curves were run with 8 calibration standards each. Ten calibrators were rejected among the total of 240 from LLOQ to ULOQ.

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods.
Abbreviations: %CV, percent coefficient of variation; %RE, percent of relative error; ATB200, cipaglucosidase alfa; IS, internal standard; K_2EDTA, ethylenediaminetetraacetic acid; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; QCH, high quality control sample; QCL, quality control low; QCM, middle quality control sample; ULOQ, upper limit of quantification

15. Trial Design: Additional Information and Assessment

Not applicable.

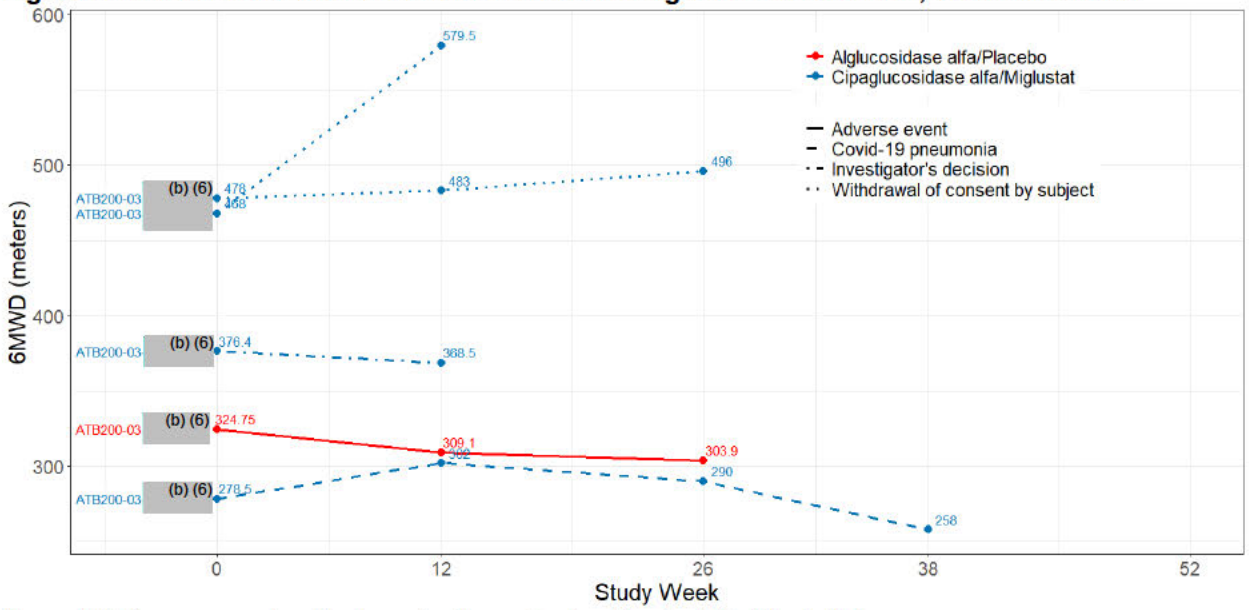
16. Efficacy: Additional Information and Assessment

6MWD for Patients Missing Values at Week 52

A total of five patients (4%) were missing an observation of the change from baseline of 6MWD at week 52. There were four patients receiving cipa-mig and one on the comparator arm. Figure 93 presents the observations over time for the five patients missing the primary endpoint. The reasons for missing the 52-week observation were as follows:

- Patients [redacted] (b) (6) withdrew consent. Patient [redacted] (b) (6) withdrew due to "SAE of IAR/anaphylactic event" and patient [redacted] (b) (6) withdrew due to "not wanting to travel to the site."
- Patient [redacted] (b) (6) withdrew upon investigator's decision due to IAR.
- Patient [redacted] (b) (6) discontinued due to an SAE of COVID-19 related pneumonia.
- Patient [redacted] (b) (6) discontinued due to a cerebrovascular accident AE.

Figure 93. 6MWD Over Time for Patients With Missing Values at Week 52, Trial ATB200-03

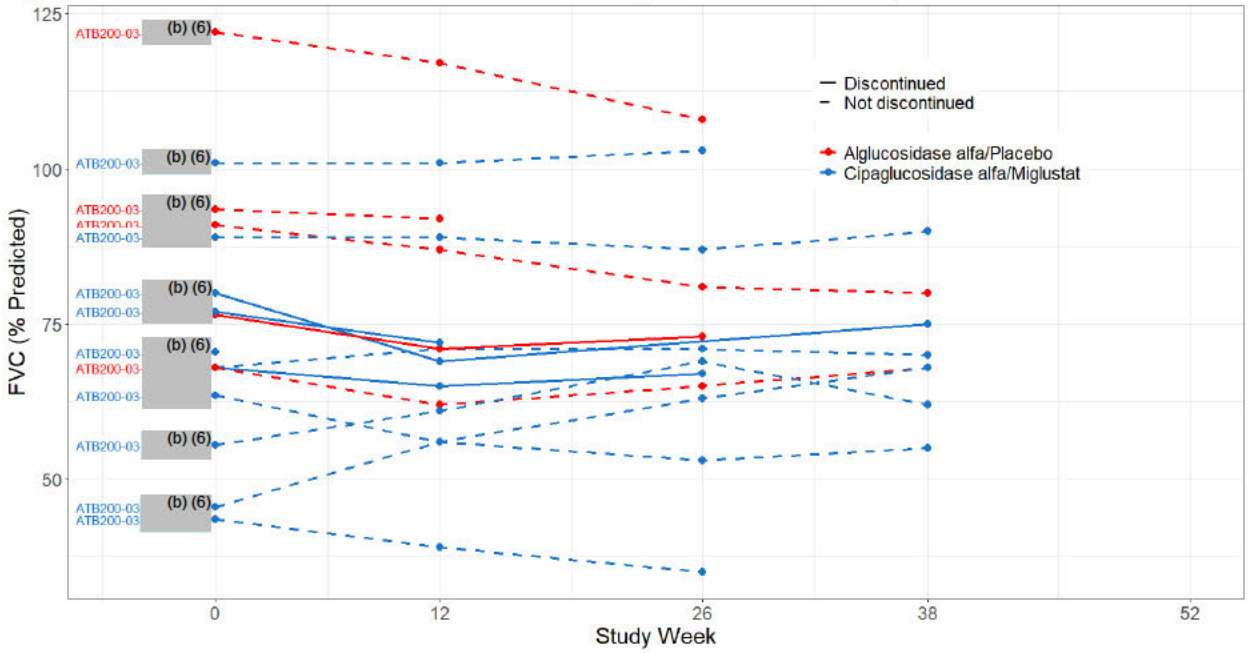


Source: This figure was produced by the review team using the dataset adeff.xpt located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
Abbreviations: 6MWD, six-minute wa k distance

Patients with Missing FVC Values at Week 52

A total of 16 patients (13% in each treatment group) were missing the FVC measure at Week 52. Fifteen of these patients have a postbaseline measure and 1 patient only has a baseline FVC measure. Five of the 16 patients were receiving the comparator and 11 were receiving cipa-mig. Figure 94 presents the FVC observations for these 16 patients. Solid lines in the plot indicate patients who discontinued the trial and dashed lines indicate those who did not discontinue. When the LOCF approach is used to impute missing values, only the postbaseline values are used to impute, meaning that Subjec (b) (6) is excluded from analysis of FVC.

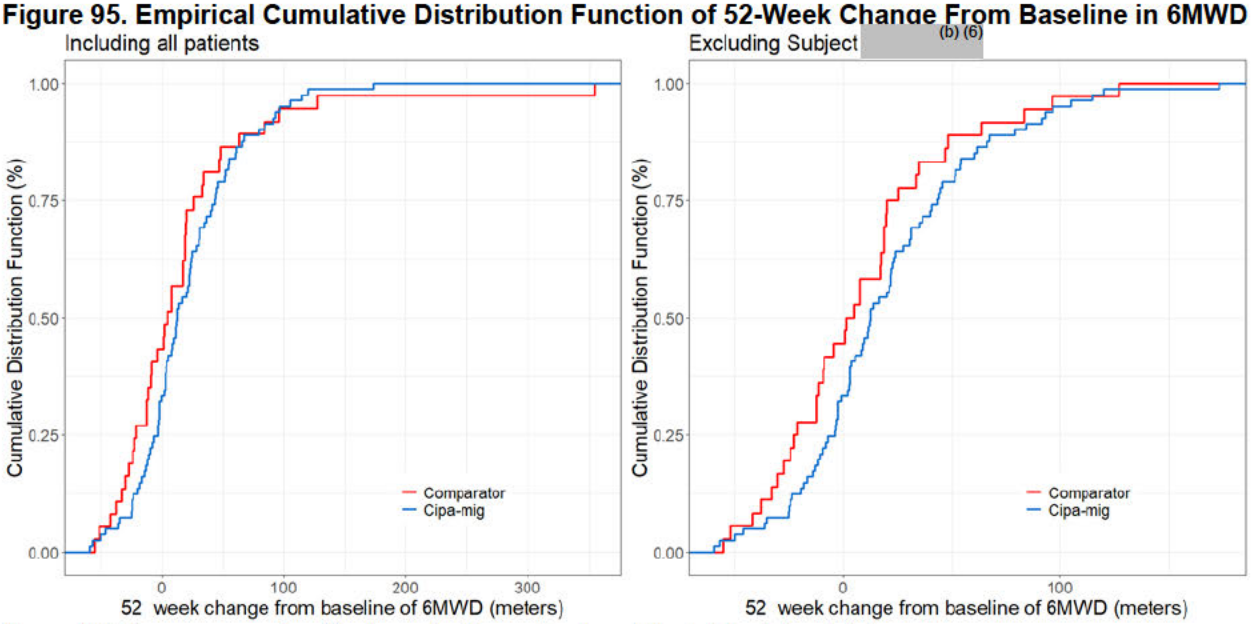
Figure 94. FVC Over Time for Patients With Missing Values at Week 52, Trial ATB200-03



Source: This figure was produced by the review team using the dataset adeff.xpt located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
Abbreviations: FVC, forced vital capacity

Figure 95 shows the impact of Subject (b) (6) on the cumulative distribution function. There is some separation between the two curves along the full range of observed change from baseline in 6MWD when the outlier is removed (right panel of Figure 95).

Figure 95. Empirical Cumulative Distribution Function of 52-Week Change From Baseline in 6MWD

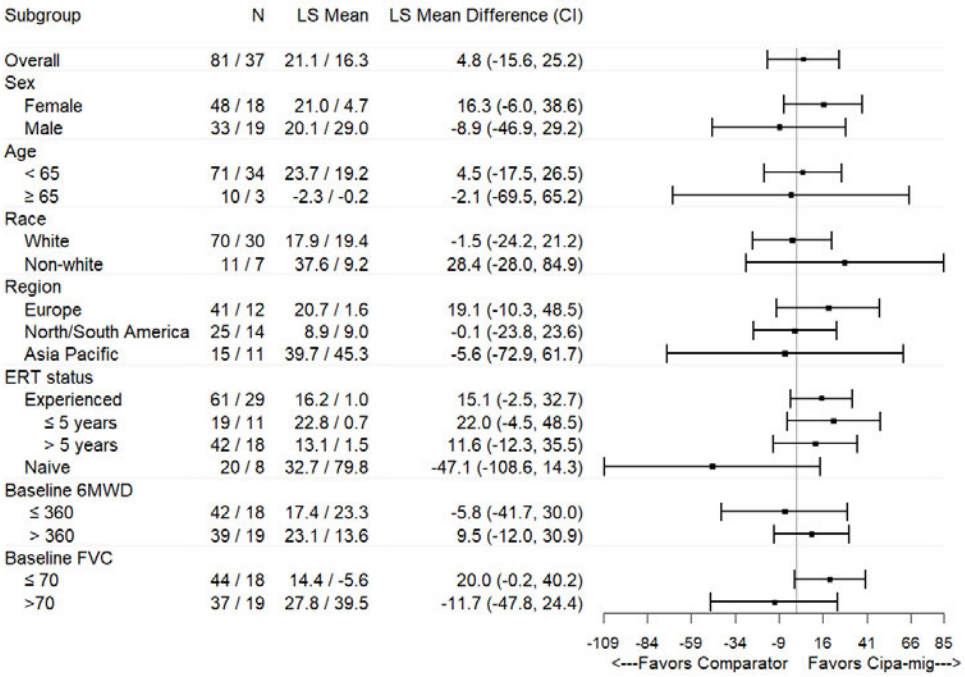


Source: This figures was produced by the review team using the adeff.xpt dataset, located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
Abbreviations: 6MWD, 6-minute walk distance

Results of the subgroup analyses for all patients (ITT, including the outlier) for 6MWD are presented in Figure 96. Note that the outlier subject was a white male, aged 34, ERT naïve, with

baseline 6MWD ≤360 meters, and baseline FVC >70%, from the Asia Pacific region and would thus impact the results of those subgroups.

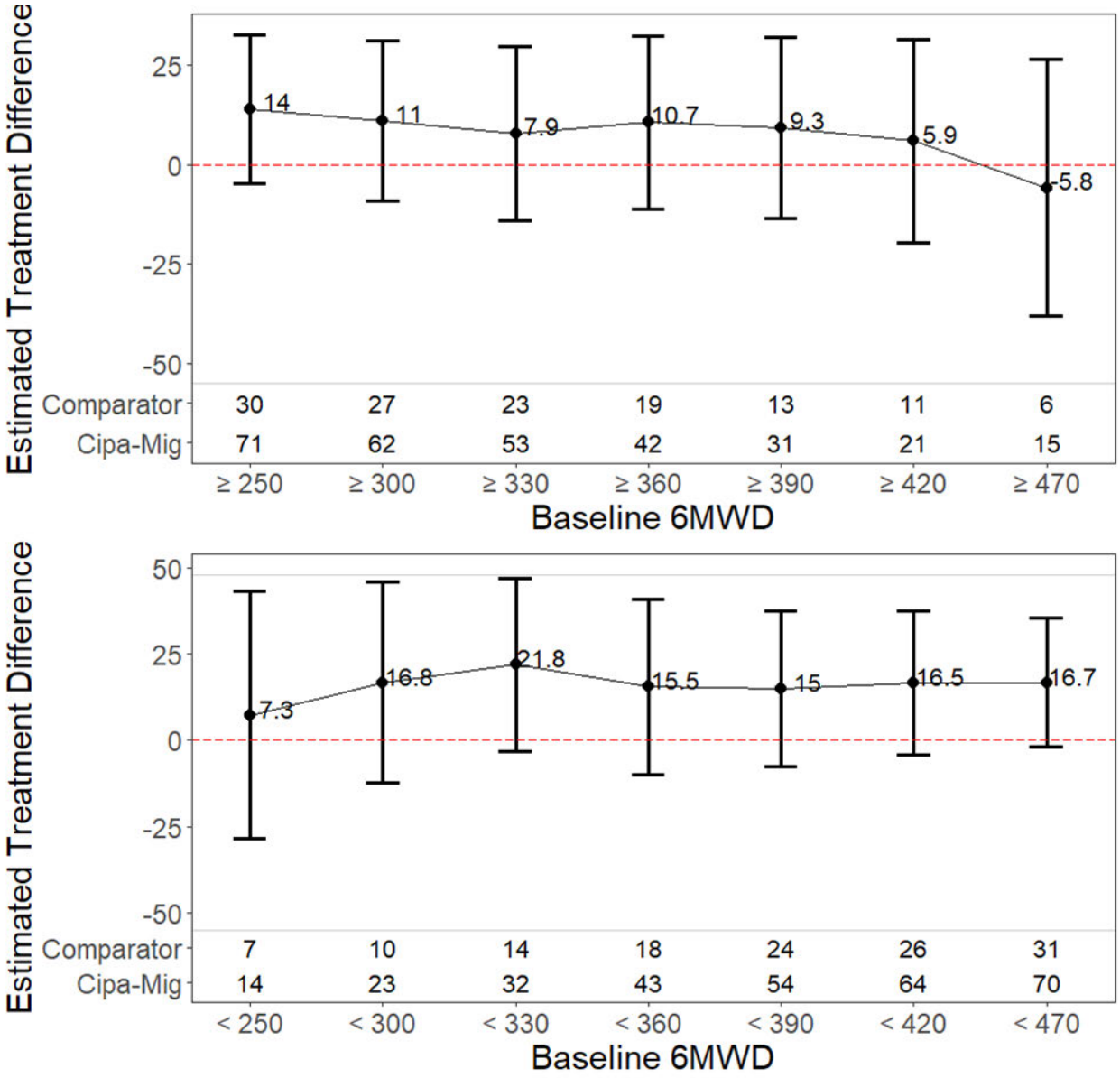
Figure 96. Estimated Mean Treatment Difference for 6MWD Across Subgroups (All ITT Patients)



Source: This figure was produced by review team based on the adeff.xpt dataset, located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets. The estimates corresponding to 'Overall' come from a model including: treatment, baseline 6MWD, ERT status, sex, age, baseline weight, and baseline height and the other models include only treatment and baseline 6MWD. LOCF was used to impute missing values at week 52.
Abbreviations: AT2221, miglustat; ATB200, cipaglucosidase; CI, confidence interval; FVC, forced vital capacity; LS, least squares; 6MWD, 6-minute wa k distance

Figure 97 presents the estimated treatment difference for subgroups determined by different baseline 6MWD values. The plots show that the estimated treatment difference is fairly consistent across subgroups regardless of the baseline 6MWD value.

Figure 97. Estimated Treatment Difference for Subgroups Based on Baseline 6MWD (Excluding the Outlier)



Source: This figure was produced by review team based on the adeff.xpt dataset, located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets. The estimates come from a model including: treatment group and baseline 6MWD. LOCF was used to impute missing values at week 52.

Analysis of Percent Change from Baseline of 6MWD and FVC

Analysis of the percent change from baseline of 6MWD was performed in addition to the primary analysis of the absolute change in 6MWD. Table 149 presents the results for the percent change from baseline of 6MWD at week 52. The estimated treatment difference was 2.8% improvement from baseline in favor of cipa-mig. When the outlier is excluded the estimated treatment difference is 5.3% of baseline (Table 150).

Table 149. Baseline and Percent Change in 6MWD to Week 52, ITT Population (All Subjects), ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=85	N=38		
Mean (SD)	357.9 (111.8)	350.1 (119.8)		
Median (min, max)	359.5 (79.0, 575.0)	358.4 (112.5, 623.0)		
Week 52	N=81	N=37		
Mean (SD)	376.4 (122.9)	368.2 (145.0)		
Median (min, max)	380.5 (79.6, 601.5)	373.5 (67.0, 675.4)		
Percent change from baseline to Week 52				
Mean (SD)	5.8 (13.1)	4.1 (23.9)		
Median (min, max)	4.1 (-24.2, 45.1)	1.3 (-45.3, 110.9)		
Estimated change from baseline to Week 52				
ANCOVA[2]	6.05 (1.79)	3.26 (2.72)	2.79 (-3.75, 9.34)	0.3996
Wilcoxon Rank-Sum				0.1207

Source: This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig – comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (LOCF).
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; LS, least squares; max, maximum; min, minimum; 6MWD, 6-minute walk distance; 6MWT, 6-minute wa k test; SD, standard deviation

Table 150. Baseline and Percent Change in 6MWD to Week 52, ITT Population (Excluding Outlier), ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=85	N=37		
Mean (SD)	357.9 (111.8)	351.0 (121.3)		
Median (min, max)	359.5 (79.0, 575.0)	365.5 (112.5, 623.0)		
Week 52	N=81	N=36		
Mean (SD)	376.4 (122.9)	359.7 (137.4)		
Median (min, max)	380.5 (79.6, 601.5)	371.8 (67.0, 648.5)		
Percent change from baseline to Week 52				
Mean (SD)	5.8 (13.1)	1.2 (16.0)		
Median (min, max)	4.1 (-24.2, 45.1)	0.9 (-45.3, 41.5)		
Estimated change from baseline to Week 52				
ANCOVA[2]	5.94 (1.50)	0.61 (2.30)	5.33 (-0.20, 10.85)	0.0585
Wilcoxon Rank-Sum				0.0694

Source: This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig – comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (LOCF).
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; LS, least squares; max, maximum; min, minimum; 6MWD, 6-minute walk distance; 6MWT, 6-minute wa k test; SD, standard deviation

Analysis of the percent change from baseline of FVC (% predicted) was also performed and is presented in Table 151. The estimated treatment difference for the 52-week percent change from baseline of FVC was 4% (95% CI: 0.36, 7.73).

Table 151. Baseline and Percent Change in FVC to Week 52, ITT Population (All Subjects), ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=85	N=38		
Mean (SD)	70.7 (19.6)	70.0 (21.3)		
Median (min, max)	70.0 (30.5, 132.5)	71.2 (31.5, 122.0)		
Week 52	N=74	N=33		
Mean (SD)	69.8 (20.2)	63.7 (20.8)		
Median (min, max)	69.0 (30.0, 137.0)	56.0 (28.0, 96.0)		
Change from baseline to Week 52				
Mean (SD)	-1.4 (9.8)	-5.5 (8.0)		
Median (min, max)	-1.6 (-25.0, 24.1)	-3.1 (-27.3, 9.0)		
Estimated change from baseline to Week 52				
ANCOVA[2]	-1.19 (1.02)	-5.24 (1.53)	4.04 (0.36, 7.73)	0.0319
Wilcoxon Rank-Sum				0.0201

Source: This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig – comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (LOCF).
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; Cipa-Mig, cipaglucosidase alfa coadministered with miglustat; ERT, enzyme replacement therapy; LS, least squares; max, maximum; min, minimum; 6MWD, 6-minute walk distance; 6MWT, 6-minute wa k test; SD, standard deviation

Sensitivity Analysis of FVC Observations with Unacceptable Grade

An information request (IR023) was sent to the Applicant on January 4, 2022 requesting clarification on inclusion of 13 FVC observations from forced spirometries that had an unacceptable grade assessed by [redacted] (b) (4) The Applicant explained that these data were included in the derived analysis datasets because they were graded as acceptable or borderline acceptable by a second consulting company. The review team performed a sensitivity analysis by excluding these 13 FVC observations. This impacted 6 subjects in total: 2 subjects [redacted] (b) (6) were excluded due to both screening measures having an unacceptable [redacted] (b) (4) grade, 4 subjects [redacted] (b) (6) had adjusted baseline values due to one screening measurement having an unacceptable [redacted] (b) (4) grade, and 2 of those subjects had measures omitted at Week 12 (Subject [redacted] (b) (6)), Week 26 (Subject [redacted] (b) (6)), and Week 52 (Subject [redacted] (b) (6)) due to an unacceptable [redacted] (b) (4) grade.

Table 152 presents the results of this sensitivity analysis. The estimated treatment difference was 2.38 (95% CI: 0.04, 4.71; p=0.0460), slightly larger than 2.32 (95% CI: 0.02, 4.62; p=0.0484) obtained based on the datasets that included these 13 observations.

Table 152. Baseline and Change in FVC to Week 52, Excluding Observations With Unacceptable (b) (4) Grade, ATB200-03

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95% CI)	P-Value
Baseline	N=84	N=37		
Mean (SD)	70.8 (19.7)	70.0 (21.6)		
Median (min, max)	70.0 (30.5, 132.5)	71.0 (31.5, 122.0)		
Week 52	N=74	N=31		
Mean (SD)	69.8 (20.2)	62.5 (20.8)		
Median (min, max)	69.0 (30.0, 137.0)	55.0 (28.0, 96.0)		
Change from baseline to Week 52				
Mean (SD)	-1.3 (6.2)	-3.6 (5.0)		
Median (min, max)	-1.0 (-17.0, 14.0)	-3.0 (-19.5, 7.5)		
Estimated change from baseline to Week 52				
ANCOVA[2]	-1.25 (0.63)	-3.63 (0.97)	2.38 (0.04, 4.71)	0.0460
Wilcoxon Rank-Sum				0.0236

Source: This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig – comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, (b) (4) status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (LOCF).

Sensitivity Analysis of 6MWT with Deviations

Table 153 presents the 15 patients who had at least one 6MWT with a deviation at the screening or week 52/EOS timepoints. The sensitivity analysis was limited to ERT-experienced patients, and 13 of the 15 affected patients were ERT-experienced. Patients who had all their week 52 observations impacted were removed from the sensitivity analysis. Patients who did not have observations at week 52 and their EOS observation had a deviation were removed from the sensitivity analysis. For patients who had only one of two screening observations impacted or only one of two week 52 observations impacted, their observation without a deviation was used instead of the average of the two measures. This resulted in 8 patients being removed from the sensitivity analysis, 2 patients with adjusted screening values, and 3 patients with adjusted week 52 values.

Table 153. Subjects With Major or Minor Deviations in 6MWT

Subject ID	Deviation Type	Remove Patient	Affected Timepoint	Reviewer Note on Handling Deviation(s)
ERT-experienced				
(b) (6) (A)	Major	Yes	EOS	Removed patient due to lack of week 52 observation and deviation at EOS 6MWT
(P)	Minor	No	52	Removed one week 52 observation
(A)	Major	No	0	Removed one screening observation
(A)	Major	Yes	52	Removed patient due to having only one week 52 observation
(P)	Major	No	52	Removed only one week 52 observation
(A)	Major	Yes	52	Removed patient due to having only one week 52 observation
(A)	Major	Yes	EOS	Removed patient due to lack of week 52 observation and deviation at EOS 6MWT
(P)	Major	Yes	52	Removed patient due to deviation on date of both week 52 measures
(A)	Minor	No	52	Removed one week 52 observation
(P)	Minor	Yes	52	Removed patient due to both week 52 measures having a deviation
(A)	Major	Yes	52	Removed patient due to both week 52 measures having a deviation
(P)	Minor	Yes	52	Removed patient due to both week 52 measures having a deviation
(A)	Minor	No	0	Removed one screening observation
ERT-naïve				
(b) (6) (A)	Major	Yes	52	Removed patient due to both week 52 measures having a deviation
(P)	Major	Yes	52	Removed patient due to deviation on date of both week 52 measures

Source: Review team.
Abbreviations: A, cipa-mig; P, comparator.

Table 154 presents the results of the sensitivity analysis. The estimated treatment difference is 11 meters in favor of cipa-mig.

Table 154. ERT-experience patients (ATB200-03): Baseline and Change in 6MWD to Week 52, Excluding 6MWT With Major and Minor Deviations

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95%CI)	P-Value
Baseline	N=60	N=27		
Mean (SD)	349.1 (112.0)	333.9 (119.7)		
Median (min, max)	359.5 (79.0, 557.5)	345.5 (112.5, 532.2)		
Week 52	N=58	N=26		
Mean (SD)	362.0 (125.3)	338.3 (138.1)		
Median (min, max)	370.5 (79.6, 601.5)	360.8 (67.0, 576.0)		
Change from Baseline to Week 52				
Mean (SD)	15.3 (39.0)	3.8 (40.5)		
Median (min, max)	9.4 (-57.0, 173.5)	1.0 (-55.5, 127.0)		
Estimated Change from Baseline to Week 52				
ANCOVA[2]	14.68 (4.96)	3.58 (7.40)	11.10 (-6.64, 28.84)	0.2169
Wilcoxon Rank-Sum				0.0721

Source: This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig – comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (LOCF).

If we remove only observations with a major deviation, this results in 6 patients being removed, 1 with adjusted screening values, and 1 with adjusted week 52 values. Table 155 presents the results of the sensitivity analysis excluding only major deviations. The estimated treatment difference is 13 meters in favor of cipa-mig.

Table 155. ERT-experience patients (ATB200-03): Baseline and Change in 6MWD to Week 52, Excluding 6MWT With Major Deviations

Time Point Parameter	Cipa-Mig	Comparator	Difference[1] (95%CI)	P-Value
Baseline	N=60	N=29		
Mean (SD)	349.1 (112.0)	335.7 (115.9)		
Median (min, max)	359.5 (79.0, 557.5)	345.5 (112.5, 532.2)		
Week 52	N=58	N=28		
Mean (SD)	362.0 (125.3)	338.7 (133.0)		
Median (min, max)	370.5 (79.6, 601.5)	357.5 (67.0, 576.0)		
Change from Baseline to Week 52				
Mean (SD)	15.5 (39.1)	2.4 (39.4)		
Median (min, max)	9.4 (-57.0, 173.5)	-4.0 (-55.5, 127.0)		
Estimated Change from Baseline to Week 52				
ANCOVA[2]	14.89 (4.93)	2.17 (7.10)	12.72 (-4.49, 29.92)	0.1453
Wilcoxon Rank-Sum				0.0405

Source: This table was produced by review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.
[1] Estimated difference (cipa-mig – comparator) and 95% confidence interval
[2] LS mean change from baseline to Week 52 was estimated by analysis of covariance (ANCOVA) including treatment, visit, treatment-by-visit interaction, ERT status, gender, baseline 6MWT, age (continuous), weight, and height. Imputation of Week 52 values was done using last observation carried forward (LOCF).

Summary of Study Sites

There was a total of 49 sites in the study. Table 91 presents the number of patients per site by treatment group. The average number of patients per site was 2.08 (sd =1.58) and the median

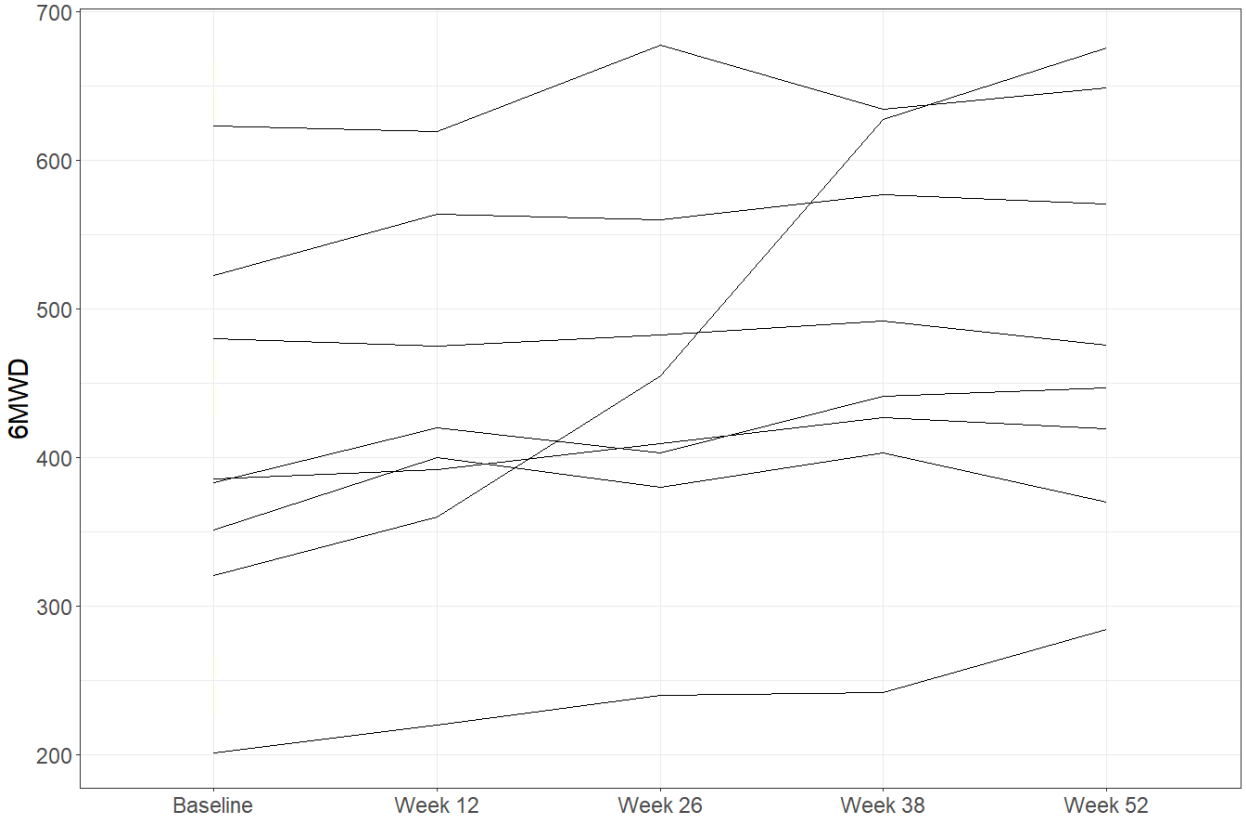
number of subjects per site was 2 (min =1, max =11). The largest site was site 4002 which had 11 patients and belonged to the Asia Pacific region.

Table 156: Number of Subjects in Each Treatment Group Per Site

Site ID	Treatment group	Total N	ERT Experienced	ERT Naïve	Site ID	Treatment group	Total N	ERT Experienced	ERT Naïve
1105	Cipa-Mig	2	1	1	2058	Cipa-Mig	1	1	0
	Comparator	1	1	0	2062	Cipa-Mig	2	1	1
1106	Cipa-Mig	2	2	0	2063	Cipa-Mig	3	1	2
1107	Cipa-Mig	2	2	0	2068	Comparator	1	0	1
1108	Cipa-Mig	2	1	1	2103	Cipa-Mig	3	3	0
	Comparator	1	0	1	2151	Cipa-Mig	1	1	0
1125	Comparator	1	1	0	2186	Cipa-Mig	1	1	0
1204	Cipa-Mig	2	1	1	2191	Cipa-Mig	1	0	1
	Comparator	1	1	0		Comparator	1	0	1
1205	Comparator	1	1	0	2301	Cipa-Mig	3	2	1
1208	Cipa-Mig	1	1	0	2304	Cipa-Mig	2	0	2
1402	Cipa-Mig	4	2	2		Comparator	1	0	1
1405	Cipa-Mig	1	1	0	2306	Comparator	1	1	0
1406	Cipa-Mig	2	2	0	2307	Cipa-Mig	1	1	0
1605	Cipa-Mig	1	1	0		Comparator	1	1	0
1606	Cipa-Mig	1	1	0	2402	Cipa-Mig	1	1	0
1703	Cipa-Mig	1	1	0	2602	Cipa-Mig	1	1	0
1803	Cipa-Mig	1	1	0		Comparator	2	1	1
1906	Cipa-Mig	1	1	0	3002	Cipa-Mig	1	1	0
	Comparator	1	1	0	4002	Cipa-Mig	8	6	2
2001	Cipa-Mig	1	1	0		Comparator	3	3	0
	Comparator	1	1	0	4005	Cipa-Mig	1	0	1
2003	Comparator	3	3	0		Comparator	2	1	1
2010	Cipa-Mig	2	2	0	4006	Cipa-Mig	1	1	0
2017	Cipa-Mig	1	1	0		Comparator	1	1	0
2024	Cipa-Mig	3	3	0	4007	Cipa-Mig	2	2	0
2027	Cipa-Mig	1	1	0	4107	Comparator	1	1	0
	Comparator	1	1	0	4109	Comparator	1	1	0
2029	Cipa-Mig	1	0	1	4110	Cipa-Mig	1	1	0
	Comparator	3	3	0		Comparator	1	1	0
2030	Cipa-Mig	1	1	0	4111	Comparator	1	1	0
	Comparator	2	0	2	4113	Cipa-Mig	1	1	0
2036	Cipa-Mig	3	2	1	4202	Cipa-Mig	1	1	0
2037	Comparator	1	1	0	4303	Cipa-Mig	1	1	0
2046	Cipa-Mig	1	0	1		Comparator	1	1	0
2049	Cipa-Mig	1	0	1	6003	Comparator	1	1	0
2050	Cipa-Mig	2	2	0	6004	Cipa-Mig	1	0	1
	Comparator	1	1	0		Comparator	1	1	0
2052	Cipa-Mig	1	1	0	9004	Cipa-Mig	6	6	0

Source: Review team based on the adeff.xpt dataset located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets. Site IDs 1XXX, 21XX, 23XX, 24XX, 26XX, and 90XX belong to the European region. Site IDs 20XX, 30XX, and 60XX belong to the North/South American region. Site IDs 4XXX belong to the Asia Pacific region.

Figure 98. 6MWD over Time for ERT Naïve Patients who Received the Comparator, ATB200-03



Source: Review team based on the adeff.xpt dataset, located at \\CDSESUB1\evsprod\BLA761204\0003\m5\datasets\atb200-03\analysis\adam\datasets.

17. Clinical Safety: Additional Information and Assessment

Not applicable.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

As part of its quality module, Amicus submitted a comparative analytical assessment to support a scientific bridge between the non-U.S.-approved alglucosidase alfa product used in trial ATB200-03 and a U.S.-approved alglucosidase alfa product (Lumizyme). The Agency reviewed this submission and found that Amicus did not provide adequate data or information to establish an acceptable scientific bridge, including because the assessment did not include analysis of some highly critical quality attributes. In addition, the review team consulted with CDER's Office of Regulatory Policy because Amicus's assessment included various types of information that the Agency would not rely upon in determining whether an adequate scientific bridge was established. The Agency believed that the inadequacy of Amicus's comparative analytical assessment could be addressed by the addition of a labeling statement rather than the submission of additional analytical data and, to that end, recommended the following statement (which reflects regulatory policy input) in cipa-mig labeling to clarify that the clinical trial data from ATB200-03 is adequate to support the safety, purity, and potency, i.e., effectiveness of cipa-mig for use as a second-line therapy according to recommendations in the approved labeling but that no conclusions can be drawn from the clinical trial regarding comparative effectiveness:

> *A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and POMBILITI in combination with Opfolda for the treatment of adult patients with LOPD weighing ≥ 40 kg and who are not improving on their current ERT.*

In the absence of an adequate scientific bridge, Amicus is unable to make comparative claims of effectiveness between a U.S.-approved alglucosidase alfa product and cipa-mig. In addition, aspects of the design and results of trial ATB200-03 create additional complexities related to comparative claims even if Amicus established an acceptable scientific bridge between the non-U.S.-approved alglucosidase alfa product used in the trial and U.S.-licensed Lumizyme.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

ATB200-03 was the single pivotal trial, with no single site enrolling more than 11 subjects. Selection of clinical sites for inspection was based on the number of subjects enrolled, outliers for efficacy endpoints, inspection history, and geographic location. Site 2063 (United States) was inspected, and sites 4002 (Australia) and 4005 (Australia) participated in a Remote Regulatory Assessment (RRA). Due to travel restrictions from the COVID-19 pandemic, the inspection planned for site 9004 (Denmark) could not be conducted. The inspection and RRAs verified results of the 6MWT, the primary efficacy endpoint, and FVC (% predicted), the key secondary efficacy endpoint.

Inspection of site 4005 was planned, in part, to obtain more information for subject (b) (6) who was randomized to a non-U.S.-approved alglucosidase alfa product coadministered with placebo and who the Applicant identified as a statistical outlier for the 6MWT and sitting FVC (see Section 6.2.1.3.1). Based on information obtained during the RRA, there was insufficient evidence to support exclusion of this subject from the primary analysis population.

The review team identified 27 patients with a protocol deviation for the 6MWT described by the Applicant as "6MWT not done or not completed correctly as described in the functional assessment manual." For 15 of those patients, this deviation occurred in either both or only one of the two assessments performed at screening or Week 52, the timepoints used for the efficacy analyses; the Applicant included this data in the analysis for efficacy. In the Applicant's response to an information request (received on January 13, 2022) regarding error codes in the spirometry reports, the Applicant clarified that 13 sitting FVC (% predicted) spirometry values for 6 patients received a Quality Control (QC) grade of unacceptable. The QC grade for the spirometry was assigned centrally, before the database lock and unblinding, by a consultant. For those 6 patients, the unacceptable QC grade was for 8 spirometry tests performed at screening and one spirometry test at Week 52. The data from these spirometry tests were included in the data analyses after a reassessment based in the 2005 ATS/ERS Standardization of Spirometry guidelines(Graham et al. 2019). The review team performed sensitivity analyses to assess the robustness of the results in relation to the data from patients with 6MWT protocol deviations and FVC (% predicted) QC grades rated as unacceptable (see Section 16).

The review team concluded that inspection of one site in the United States and the RRA at the two sites in Australia was sufficient to assess the data quality and integrity. The Office of Scientific Investigations concluded that, other than the issues described above, the clinical data collected at the three sites appeared reliable. No significant trial conduct issues or regulatory violations were identified at any of the three sites. Overall, the improvement in motor and pulmonary function is minimally affected by the identified discrepancies and would not change our regulatory decision.

See the Clinical Inspection Summary dated April 5, 2021 for additional details.

21. Labeling Summary of Considerations and Key Additional Information

21.1. Cipaglucosidase Alfa Label

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved). The finalized PI was compared to the Applicant's draft PI (see the table below). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Full Prescribing Information Sections[1]	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)[2]
All Sections	Distinguished the term "alglucosidase alfa" with adding the phrase "a non-U.S.-approved" or "U.S.-approved" before "alglucosidase alfa product" in appropriate areas of the PI.
BOXED WARNING	Updated Applicant's proposed boxed warning to be consistent with other similar enzyme replacement therapies (e.g., Nexviazyme).
1 INDICATIONS AND USAGE	• Narrowed the Applicant's proposed indication (b) (4) to adult patients with LOPD weighing ≥40 kg who are not improving on their current enzyme replacement therapy. (b) (4)
2 DOSAGE AND ADMINISTRATION	(b) (4) Recommended Dosage and Administration • Revised text recommending starting the POMBILITI infusion (b) (4) (b) (4) after oral Opfolda administration to initiating Pombiliti infusion "approximately 1 hour" after oral administration of Opfolda. • Moved Figure on (b) (4) Timeline (b) (4) to this sub-section. • Added instructions for healthcare provider to follow should Pombiliti not be started within 3 hours of Opfolda administration. (b) (4) Dosage and Administration Modifications Due to Hypersensitivity Reactions and/or Infusion-Associated Reactions • Moved information pertaining to dosage and administration modifications due to hypersensitivity and/or infusion-associated reactions under separate subsection (b) (4) • Included specific recommendations for persistent and subsiding symptoms of HSRs and IARs. (b) (4) Reconstitution & Dilution Instructions • Removed Applicant's proposed (b) (4) Re-organized information and text for clarity on reconstitution and dilution instructions for Pombiliti. • Moved storage information of reconstituted solution (b) (4) to this sub-section and revised information to show Pombiliti is stable for up to 24 hours (b) (4) as the Applicant proposed due to microbial and stability data submitted for reconstituted drug product. • Moved storage information of diluted solution (b) (4) to this sub-

	section and revised information to show Pombiliti is stable for up to 16 hours [redacted] as the Applicant proposed due to microbial and stability data submitted for diluted drug product. [redacted] Administration Instructions • Revised Table 1 on recommended Pombiliti infusion volumes and rates using 140 kg as upper end of body weight based on clinical trial data. Information supporting [redacted] was not submitted to BLA.
4 CONTRAINDICATIONS	• Removed Applicant's proposal [redacted] • Added pregnancy as CI because based on findings from animal studies, Pombiliti in combination with Opfolda may cause fetal harm (See 7.7.2).
5 WARNINGS AND PRECAUTIONS	• Created separate sub-sections for Hypersensitivity Reactions Including Anaphylaxis (5.1) and Infusion-Associated Reactions (5.2) consistent with other similar ERT's (e.g., Nexviazyme). • Removed [redacted] • Created separate sub-section for risk of acute cardiorespiratory failure consistent with other similar ERT's. • Added W&P for embryo-fetal toxicity risk based on animal studies. Risk evident with use of combination Opfolda and Pombiliti. • Added W&P to refer healthcare provider to Opfolda Prescribing Information for risks related to Opfolda use that are not discussed in labeling.
6 ADVERSE REACTIONS	• The review team based the safety evaluation on 151 adult patients with LOPD and includes patients enrolled in studies ATB200-02, ATB200-03, ATB200-07 (See 7.4). • Adverse reactions reported in these patients were infusion-associated in nature. • Revised Table 2 to include events with ≥2% frequency arranged in decreasing order of frequency and percentages rounded to nearest integer. Removed [redacted] • Moved [redacted] • Included adverse reactions associated with anti-drug antibodies under a separate heading.
7 DRUG INTERACTIONS	• N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy • Revised Applicant proposed language to align with Pregnancy and Lactation Labeling Rule 8.2 Lactation • Revised Applicant proposed language to align with Pregnancy and Lactation Labeling Rule 8.3 Females and Males of Reproductive Potential <u>Pregnancy Testing</u> Added heading to verify pregnancy status for females of reproductive potential prior to initiating Pombiliti. <u>Contraception</u> Applicant's proposed heading was not agreed upon. Instead, information was added that females of reproductive potential should use effective contraception during treatment with POMBILITI in combination with Opfolda and for at least 60 days after the last dose. <u>Infertility</u> Revised Applicant proposed language to include infertility data for males and females. 8.4 Pediatric Use

	• No pediatric data were included in the application. Pompe disease is an orphan designation and exempt from PREA. Included a standard statement that safety and effectiveness in pediatric patients have not been established. 8.5 Geriatric Use • Revised Applicant proposed language to align with the *Guidance for Industry-Content and Format for Geriatric Labeling*.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	N/A
12 CLINICAL PHARMACOLOGY	12.1 Mechanism of Action • Removed information (b) (4) as this information doesn't belong in this subsection. 12.2 Pharmacodynamics • Modified language to summarize the PD biomarker data for Glc4. Removed (b) (4) • Removed (b) (4) • Removed (b) (4) 12.3 Pharmacokinetics. • Modified Table 3 to focus on exposure parameters AUC and C_{max} (b) (4) 12.6 Immunogenicity • Created subsection as recommended in Guidance for Industry-*Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling* to contain immunogenicity information • Removed (b) (4)
13 NONCLINICAL TOXICOLOGY	Moved animal toxicology findings for miglustat to Opfolda Prescribing Information.
14 CLINICAL STUDIES	• Added the following footnote to the figures and tables: *A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and POMBILITI in combination with Opfolda for the treatment of adult patients with LOPD weighing ≥ 40 kg and who are not improving on their current ERT.* • Added additional details such as demographic data of the study population. • Added percentage of patients in each racial and ethnic group per guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016). • Removed (b) (4) as this information was considered not necessary to support efficacy. • Updated Table 5 & 6 to present results by ERT subgroup/status (b) (4) (b) (4)
17 PATIENT COUNSELING INFORMATION	Revised for consistency with the revisions to the Full Prescribing Information focusing on major risks of the drug (e.g., W&P), and when appropriate, how the patient may mitigate or manage these risks.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	11 Description • Revised inactive ingredients to compendial names which required recalculation of quantitative amount based on USP monograph definition. • Added pH of reconstituted solution.

	• Revised to include molecular weight. 16 How Supplied/Storage and Handling • Revised to include proper name and dosage form as required.

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the Applicant's draft PI.

21.2. Miglustat Label

Full Prescribing Information Sections[1]	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)[2]
All Sections	Distinguished the term "alglucosidase alfa" with adding the phrase "a non-U.S.-approved" or "U.S.-approved" before "alglucosidase alfa product" in appropriate areas of the PI.
BOXED WARNING	(b) (4)
1 INDICATIONS AND USAGE	• Narrowed the Applicant's proposed indication for the treatment of adults aged 18 years and older with a confirmed diagnosis of Pompe disease to adult patients with LOPD weighing ≥40 kg who are not improving on their current enzyme replacement therapy. (b) (4)
2 DOSAGE AND ADMINISTRATION	2.1 Recommended Dosage and Administration • Moved Figure 1 on OPFOLDA and Pombiliti dosage timeline (b) (4) (b) (4) to section 2. • Added instructions on what healthcare provider should do if Opfolda dosage is missed and what to do with Opfolda dosage if Pombiliti is not administered (b) (4) 2.2 Recommended Dosage in Patients with Renal Impairment • Added sub-section based on subsection 8.6 titled "Renal Impairment" that was added under Use in Specific Populations section.
4 CONTRAINDICATIONS	• Removed Applicant's proposal (b) (4) • Added Pregnancy as CI because based on findings from animal studies, Pombiliti in combination with Opfolda may cause fetal harm (See 7.7.2).
5 WARNINGS AND PRECAUTIONS	• Removed (b) (4) • Added W&P for embryo-fetal toxicity risk based on animal studies. Risk evident with use of combination Opfolda and Pombiliti. • Added W&P to refer healthcare provider to Pombiliti Prescribing Information for risks related to Pombiliti use that are not discussed in labeling.
6 ADVERSE REACTIONS	• Updated Section to be consistent with subsection 6.1 of the Pombiliti labeling with the exception of including IARs and anaphylaxis information as those AR's relevant to Pombiliti use. • Deleted (b) (4)
7 DRUG INTERACTIONS	• (b) (4)

	(b) (4)
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy • Revised Applicant proposed language to align with Pregnancy and Lactation Labeling Rule (See 8.4): 8.2 Lactation • Revised Applicant proposed language to align with Pregnancy and Lactation Labeling Rule (See 8.4): 8.3 Females and Males of Reproductive Potential <u>Pregnancy Testing</u> Added heading to verify pregnancy status for females of reproductive potential prior to initiating Pombiliti. <u>Contraception</u> Applicant's proposed heading was not agreed upon. Instead, information was added that females of reproductive potential should use effective contraception during treatment with OPFOLDA in combination with Pombiliti and for at least 60 days after the last dose. <u>Infertility</u> Revised Applicant proposed language to include infertility data for males and females. 8.4 Pediatric Use • No pediatric data were included in the application. Pompe disease is an orphan designation and exempt from PREA. Included a standard statement that safety and effectiveness in pediatric patients have not been established. 8.5 Geriatric Use • Revised Applicant proposed language to align with the *Guidance for Industry-Content and Format for Geriatric Labeling*. 8.6 Renal Impairment • Added subsection based on population PK analysis results. Dosage adjustments are recommended accordingly with consideration of currently available dosage strengths and the dosage adjustment recommended in Zavesca.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	This section omitted as no specific overdosage data available that would be useful to health care practitioner.
12 CLINICAL PHARMACOLOGY	12.1 Mechanism of Action • Removed (b) (4) 12.2 Pharmacodynamics • Removed Applicant's proposed language (b) (4) 12.3 Pharmacokinetics • Deleted Applicant's proposed (b) (4) • Deleted (b) (4) (b) (4) • Modified language under Renal Impairment subheading based on population PK analysis results. • Included relevant information from Zavesca under Drug Interaction Studies heading as Applicant has not conducted additional DDI studies.

13 NONCLINICAL TOXICOLOGY	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility • Added "linkage" statements to clearly note when data are from "another miglustat product" (i.e., Zavesca). • Included findings from the carcinogenicity and fertility studies with the other miglustat product (i.e., Zavesca). 13.2 Animal Toxicology and/or Pharmacology • Included animal toxicology findings from studies with another miglustat product (i.e., Zavesca).
14 CLINICAL STUDIES	• Updated to be consistent with Section 14 Clinical Studies of the Pombiliti labeling.
17 PATIENT COUNSELING INFORMATION	Revised for consistency with the revisions to the Full Prescribing Information focusing on major risks of the drug (e.g., W&P), and when appropriate, how the patient may mitigate or manage these risks.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	16 How Supplied/Storage and Handling • Statement (b) (4) was removed as these statements are not applicable to special handling and storage conditions for the healthcare provider.

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the Applicant's draft PI.

22. Postmarketing Requirements and Commitments

The following PMRs and PMCs were agreed upon with the Applicant and will be issued in the action letter, if approval is recommended following completion of the pending facility inspection for cipaglucosidase alfa.

22.1. Risk of Electrocardiogram Changes and Potential for Cardiac Arrhythmias (QTc Study for Miglustat)

PMR 4234-1

An evaluation of the effects of miglustat on the QTc interval designed according to ICH E14 guidances for industry Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (October 2015) and (b) (4)

PMR Schedule Milestones

- Draft Protocol Submission: 01/2023
- Final Protocol Submission: 04/2023
- Study Completion: 03/2024
- Interim/Other: None
- Final Report Submission: 09/2024

22.2. Risk of CYP Enzyme- and Transporter-Mediated Drug-Drug Interaction Potential (DDI Study for Miglustat).

PMR 4234-2

In vitro studies to evaluate whether miglustat is a substrate, inhibitor, or inducer of metabolizing enzymes and transporters as outlined in the FDA guidance for industry In Vitro Drug Interaction Studies -Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020). If in vitro studies suggest a potential for drug interaction, additional in vivo studies may be required.

PMR Schedule Milestones

- Study Completion: 03/2023
- Final Report Submission: 09/2023

22.3. Chemistry, Manufacturing, and Controls

The chemistry, manufacturing, and controls postmarketing commitments between OPQ and the Applicant listed below will be included in the action letter if approval is recommended:

Table 157. Chemistry, Manufacturing, and Controls Postmarketing Commitments

Postmarketing Commitments	Milestones
(b) (4)	
3. To develop an endotoxin method for the drug product which mitigates the low endotoxin recovery (LER) effect, to submit method qualification results with three lots of drug product and provide results of an LER study performed with the updated method with three batches of drug product.	Final report submission: July, 2023

Postmarketing Commitments	Milestones
4. To perform extractables/leachables studies and risk assessments to evaluate leachables from the container closure system(s) and manufacturing product conduct surfaces of cipaglucosidase alfa drug substance and drug product and assess the potential impact of leachables on product quality at the end of drug product shelf-life. The analyses will be performed using drug substance and drug product lot(s) and/or representative samples (e.g., (b) (4) if justified) analyzed at appropriate time points, including at the end of drug product shelf life. Appropriate methods will be used to detect, identify, and quantify organic nonvolatile, volatile and semivolatile species, and metals. Characterization of the potential impact of leachables on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be provided in the final study report per 21 CFR 601.12.	Final report submission: March, 2023
5. To develop, validate, and implement a test method with justified numerical acceptance criteria for control of cipaglucosidase alfa kinetic parameters during drug product release and stability testing. Critical kinetic parameters (e.g., Km, Kcat, etc.,) will be determined, justified, and included in the control strategy. If applicable, justification and data supporting (b) (4) will be provided. The method validation report for the enzyme kinetic assay, the revised drug product release and stability specifications, and all supporting studies and data will be provided in a final study report per 21 CFR 601.12.	Final report submission: March, 2024

Source: Review team.
Abbreviations: CFR, Code of Federal Regulations; LER, low endotoxin recovery

23. Financial Disclosure

Table 158. Covered Clinical Studies: ATB200-02, ATB200-03, and ATB200-07

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 307		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

24. References

du Bois, RM, D Weycker, C Albera, WZ Bradford, U Costabel, A Kartashov, TE King, Jr., L Lancaster, PW Noble, SA Sahn, M Thomeer, D Valeyre, and AU Wells, 2011, Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference, Am J Respir Crit Care Med, 184(12):1382-1389.

FDA, 2013, Guidance for Industry; Financial Disclosure by Clinical Investigators, accessed August 27, 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/financial-disclosure-clinical-investigators.

FDA, 2019, Guidance for Industry; Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, accessed August 27, 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products.

FDA, 2020, Guidance for Industry; In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.

Graham, BL, I Steenbruggen, MR Miller, IZ Barjaktarevic, BG Cooper, GL Hall, TS Hallstrand, DA Kaminsky, K McCarthy, MC McCormack, CE Oropez, M Rosenfeld, S Stanojevic, MP Swanney, and BR Thompson, 2019, Standardization of Spirometry 2019 Update. An Official

American Thoracic Society and European Respiratory Society Technical Statement, Am J Respir Crit Care Med, 200(8):e70-e88.

Gupta, N, ZB Kazi, S Nampoothiri, S Jagdeesh, M Kabra, RD Puri, M Muranjan, M Kalaivani, C Rehder, D Bali, IC Verma, and PS Kishnani, 2020, Clinical and Molecular Disease Spectrum and Outcomes in Patients with Infantile-Onset Pompe Disease, J Pediatr, 216:44-50 e45.

Harlaar, L, JY Hogrel, B Perniconi, ME Kruijshaar, D Rizopoulos, N Taouagh, A Canal, E Brusse, PA van Doorn, AT van der Ploeg, P Laforêt, and N van der Beek, 2019, Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease, Neurology, 93(19):e1756-e1767.

Janssen, 2020, Zavesca Prescribing Information, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021348s016lbl.pdf.

Kishnani, PS, RD Steiner, D Bali, K Berger, BJ Byrne, LE Case, JF Crowley, S Downs, RR Howell, RM Kravitz, J Mackey, D Marsden, AM Martins, DS Millington, M Nicolino, G O'Grady, MC Patterson, DM Rapoport, A Slonim, CT Spencer, CJ Tifft, and MS Watson, 2006, Pompe disease diagnosis and management guideline, Genet Med, 8(5):267-288.

Kuperus, E, ME Kruijshaar, SCA Wens, JM de Vries, MM Favejee, JC van der Meijden, D Rizopoulos, E Brusse, PA van Doorn, AT van der Ploeg, and N van der Beek, 2017, Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study, Neurology, 89(23):2365-2373.

Leslie, N and L Bailey, 1993, Pompe Disease, GeneReviews(®), Adam, M. P., H. H. Ardinger, R. A. Pagon et al., Seattle (WA): University of Washington, Seattle Copyright © 1993-2021, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

Muscular Dystrophy Association, AMDA, United Pompe Foundation, 2022, The Voice of the Patient Report: Pompe Disease. Pompe disease Patient-Focused drug development meeting (2022, May 18), accessed May 24, 2022, https://cqrcengage.com/mda/pfddmeeting2020?0.

O'Brien, PC, 1984, Procedures for comparing samples with multiple endpoints, Biometrics, 40(4):1079-1087.

Raben, N, T Fukuda, AL Gilbert, D de Jong, BL Thurberg, RJ Mattaliano, P Meikle, JJ Hopwood, K Nagashima, K Nagaraju, and PH Plotz, 2005, Replacing acid alpha-glucosidase in Pompe disease: recombinant and transgenic enzymes are equipotent, but neither completely clears glycogen from type II muscle fibers, Mol Ther, 11(1):48-56.

Sampson, HA, A Muñoz-Furlong, RL Campbell, NF Adkinson, Jr., SA Bock, A Branum, SG Brown, CA Camargo, Jr., R Cydulka, SJ Galli, J Gidudu, RS Gruchalla, AD Harlor, Jr., DL Hepner, LM Lewis, PL Lieberman, DD Metcalfe, R O'Connor, A Muraro, A Rudman, C Schmitt, D Scherrer, FE Simons, S Thomas, JP Wood, and WW Decker, 2006, Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, J Allergy Clin Immunol, 117(2):391-397.

Schoser, B, A Stewart, S Kanters, A Hamed, J Jansen, K Chan, M Karamouzian, and A Toscano, 2017, Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis, J Neurol, 264(4):621-630.

25. Review Team

Table 159. Reviewers of Integrated Assessment

Role	Names
Regulatory Project Manager	Jenny Doan, MSN, BSN
Chief Project Management Staff	Michael G. White, PhD
Nonclinical Reviewer	B. Emmanuel Akinshola, PhD Mary Ellen McNerney, PhD
Nonclinical Team Leader	Laurie McLeod-Flynn, PhD
Office of Clinical Pharmacology Reviewers	Oluseyi Adeniyi, PharmD, PhD Travis Ready, PharmD, Ruojing Li, PhD, Pharmacometrics Reviewer
Office of Clinical Pharmacology Team Leaders	Jie (Jack) Wang, PhD, Clinical Pharmacology Team Leader Lian Ma, PhD, Pharmacometrics Team Leader
Clinical Reviewer	Daniela Varela Luquetti, MD, PhD
Clinical Team Leader (acting)	Linda Jeng, MD, PhD
Statistical Reviewer	Emily Morris, PhD
Statistical Team Leader	Yan Wang, PhD
Cross-Disciplinary Team Leader	Linda Jeng, MD, PhD
Division Director (Nonclinical)	Mukesh Summan, PhD, DABT
Division Director (OCP)	Michael Pacanowski, PharmD, MPH
Deputy Division Director (OB)	Lei Nie, PhD
Division Director (ORO)	Pamela Lucarelli
Division Director (clinical)	Kathleen M. Donohue, MD, MSc
Office Director	Janet Maynard, MD, MHS

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; ORO, Office of Regulatory

Table 160. Additional Reviewers of Application

Office or Discipline	Names
Biomedical Informatics	Veronica Yang Pei, Associate Director for Biomedical Informatics
Division of Cardiology and Nephrology/ Interdisciplinary Review Team (IRT) for Cardiac Safety Studies	Lars Johannesen, PharmD, Clinical Analyst Christine Garnett, PharmD, Clinical Analyst Devi Kozeli, MSc, Senior Regulatory Project Manager
Division of Pediatric and Maternal Health (DPMH) Team Leaders	Tamara Johnson, MD, Maternal Health Team Leader Shetarra Walker, MD, Pediatrics Team Leader
DPMH/Maternal Health Reviewer	Jeannie Limpert, MD
DPMH/Pediatrics Reviewer	Ethan Hausman, MD
DPMH/Regulatory Project Manager	Meshaun Payne, PharmD
DPMH/Chief Project Management Staff	Rosemary Addy, PharmD
Division of Rare Diseases and Medical Genetics (DRDMG)	Mona Patel, Associate Director Labeling Yuliya Yasinskaya, MD, Deputy Director for Safety (Acting) Cheronda Cherry-France, RN, MHA, BSN, Safety Regulatory Project Manager

Office or Discipline	Names
New Drug Transition Team	Florence Moore, MS, PhD Rhonda Hearns-Stewart, MD Anh Thu Lam, Clinical Data Scientist James Ebersole, PhD, Medical Editor Megan Young, PhD, Medical Editor Graeme O'May, PhD, Medical Editor
Office of Medical Policy Initiatives/Division of Medical Policy Programs	Jessica Chung, PharmD, Patient Labeling Reviewer Barbara Fuller, RN, MSN, Patient Labeling Team Leader
Office of New Drugs Policy	Julieann DuBeau, MSN, RN, Regulatory Policy Advisor Debra Beitzell, BSN, Clinical Advisor for Labeling Eric Brodsky, MD, Associate Director, Labeling Policy Team
Office of Orphan Products Development	Henry Startzman III, MD, Director, ODD Program Roberta Szydlo, RPh, MBA
Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products	Frances Namuswe, PhD, Application Team Leader Davinna Ligons, PhD, CMC and Immunogenicity Reviewer CAPTAIN Vicky Borders-Hemphill, PharmD, Labeling Assessor
OPQ/Office of New Drug Products (ONDP)	Hamid Shafiei, PhD, Application Team Leader Jeffery Medwid, PhD, ONDP DS Assessor Donna Christner, PhD, ONDP DS Team Leader Zhengfang Ge, PhD, ONDP DP Assessor and Labeling Reviewer Hong Cai, PhD, ONDP DP Team Leader Kamrun Nahar, PhD, Biopharmaceutics Reviewer Vidula Kolhatkar, PhD, Biopharmaceutics Team Leader
OPQ/Office of Pharmaceutical Manufacturing Assessment	Richard Ledwidge, PhD, Microbiologist and Facilities Reviewer Virginia Carroll, PhD, Microbiologist and Facilities Team Leader Mesfin Abdi, PhD, Microbiologist Reviewer Vaikunth Prabhu, PhD, Microbiologist Team Leader
OPQ/ Office of Program and Regulatory Operations	Kelly Ballard, PharmD, Regulatory Business Project Manager
Office of Regulatory Affairs	Caryn McNab
Office of Regulatory Policy	Daniel Ritterbeck, JD, Regulatory Counsel Janice Weiner, JD, Regulatory Counsel
Office of Prescription Drug Promotion	Carrie Newcomer, PharmD, Regulatory Reviewer James S. Dvorsky, PharmD, Team Leader
Office of Scientific Investigations	Cara Alfaro, PharmD, Clinical Analyst Phillip Kronstein, MD, Team Leader
Office of Surveillance & Epidemiology (OSE)/ Division of Epidemiology (DEPI)	Sally Peprah, PharmD, Reviewer Benjamin Booth, PhD, Team Leader
OSE/ Division of Medication Error Prevention and Analysis (DMEPA 2)	Sali Mahmoud, PharmD, BCPS, Safety Evaluator Janine Stewart, PharmD, Team Leader

Office or Discipline	Names
OSE/Division of Pharmacovigilance (DPV)	Mohamed A. Mohamoud, PharmD, MPH, BCPS, Safety Evaluator Ivone Kim, MD, Medical Reviewer Carmen Cheng, PharmD, Team Leader
OSE/Division of Risk Management (DRM)	Yasmeen Abou-Sayed, PharmD, Team Leader Courtney Cunningham, PharmD, Reviewer
OSE/ Safety Regulatory Project Manager (SRPM)	Aleksander Winiarski, PharmD, RPh, Team Leader Su-Lin Sun, RPh, PharmD, GWCPM, SRPM
Office of Therapeutic Biologics and Biosimilars	Sarah Yim, MD, Director Emanuela Lacana, PhD, Deputy Director

Table 161. Signatures of Reviewers

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Tertiary Reviewer	**Signature:** Kathleen Donohue -S Digitally signed by Kathleen Donohue -S Date: 2022.10.14 08:36:33 -04'00'		
Clinical	Kathleen M. Donohue, MD, MSc Director	OND/Division of Rare Diseases and Medical Genetics (DRDMG)	All ☐ Authored ☒ Contributed ☒ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Linda Jeng, MD, PhD	OND/DRDMG	All ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Linda Jeng -S Digitally signed by Linda Jeng -S Date: 2022.10.12 15:56:49 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Daniela Varela Luquetti, MD, PhD	OND/DRDMG	1,2,3,4,6,7,10,11,20, 21,23,24 ☒ Authored ☒ Contributed ☐ Approved
Primary Reviewer	**Signature:** Daniela Varela-luquetti -S Digitally signed by Daniela Varela-luquetti -S Date: 2022.10.04 10:47:50 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Mona Patel, PharmD, RAC	OND/DRDMG	21 ☒ Authored ☐ Contributed ☒ Approved
Associate Director for Labeling	**Signature:** Mona Patel -S Digitally signed by Mona Patel -S Date: 2022.08.22 14:28:40 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Michael G. White, PhD Chief Program Management Staff	OND/DRO-RPURM	12, 25 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Michael White -S Digitally signed by Michael White -S Date: 2022.08.23 18:52:36 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Jenny Doan, MSN, BSN	OND/DRO-RPURM	12, 25 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** Jenny Doan -S Digitally signed by Jenny Doan -S Date: 2022.10.04 10:55:56 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Mukesh Summan, PhD Director	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine/Specialty Medicine (DPT-ORPURM/SM)	5.1, 7.1, 7.7, 8.4, 13 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Mukesh Summan -S Digitally signed by Mukesh Summan -S Date: 2022.10.14 13:59:42 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Laurie McLeod-Flynn, PhD Team Leader	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine/Specialty Medicine (DPT-ORPURM/SM)	5.1, 7.1, 7.7, 8.4, 13 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Laurie L. Mcleod-flynn -S Digitally signed by Laurie L. Mcleod-flynn -S Date: 2022.08.24 10:04:54 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	B. Emmanuel Akinshola, PhD	OB/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine (DPT-ORPURM)	5.1, 7.1, 7.7, 8.4, 13 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Babatunde Akinshola -S Digitally signed by Babatunde Akinshola -S Date: 2022.10.04 11:25:30 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Mary Ellen McNerney, PhD	OB/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine (DPT-ORPURM)	5.1, 7.1, 7.7, 8.4, 13 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Mary Ellen Mcnerney -S Digitally signed by Mary Ellen Mcnerney -S Date: 2022.08.24 09:11:29 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Michael Pacanowski, PharmD, MPH Director	OTS/OCP/ Division of Translational and Precision Medicine (DTPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Michael Pacanowski -S Digitally signed by Michael Pacanowski -S Date: 2022.08.24 15:17:10 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jie (Jack) Wang, PhD Team Leader	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22.1, 22.2, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Jie Wang -S Digitally signed by Jie Wang -S Date: 2022.08.23 12:52:46 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Oluseyi Adeniyi, PharmD, PhD	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22.1, 22.2, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Oluseyi Adeniyi -S Digitally signed by Oluseyi Adeniyi -S Date: 2022.08.23 10:23:18 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Travis Ready, PharmD	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22.1, 22.2, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Travis W. Ready -S5 Digitally signed by Travis W. Ready -S5 Date: 2022.08.17 08:53:58 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jiang Liu, PhD Team Leader	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.08.28 22:10:13 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Ruojing Li, PhD	OTS/OCP/DPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Ruojing Li -S Digitally signed by Ruojing Li -S Date: 2022.08.25 17:23:23 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Lei Nie, PhD Director	OB/Division of Biometrics IV (DBIV)	6.2, 6.3, and 16 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Lei Nie -S Digitally signed by Lei Nie -S Date: 2022.08.28 10:09:21 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Yan Wang, PhD Team Leader	OB/DBIV	6.2, 6.3, and 16 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Yan Wang -S Digitally signed by Yan Wang -S Date: 2022.08.23 12:06:17 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Emily Morris, PhD	OB/DBIV	6.2, 6.3, and 16 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Emily L. Morris -S Digitally signed by Emily L. Morris -S Date: 2022.08.31 12:15:30 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Frances Namuswe, PhD Application Team Leader	OPQ/Office of Biotechnology	9, 22.3 ☒ Authored ☐ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Frances Namuswe -S Digitally signed by Frances Namuswe -S Date: 2022.10.12 15:17:45 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Hamid Shafiei, PhD Application Team Leader	OPQ/ Office of New Drug Product	9 ☒ Authored ☐ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Hamid Shafiei -S Digitally signed by Hamid Shafiei -S Date: 2022.08.24 14:36:06 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Tertiary Reviewer	**Signature:** Kathleen Donohue -S Digitally signed by Kathleen Donohue -S Date: 2022.10.14 08:36:33 -04'00'		
Clinical	Kathleen M. Donohue, MD, MSc Director	OND/Division of Rare Diseases and Medical Genetics (DRDMG)	All ☐ Authored ☒ Contributed ☒ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Linda Jeng, MD, PhD	OND/DRDMG	All ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Linda Jeng -S Digitally signed by Linda Jeng -S Date: 2022.10.12 15:56:49 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Daniela Varela Luquetti, MD, PhD	OND/DRDMG	1,2,3,4,6,7,10,11,20, 21,23,24 ☒ Authored ☒ Contributed ☐ Approved
Primary Reviewer	**Signature:** Daniela Varela-luquetti -S Digitally signed by Daniela Varela-luquetti -S Date: 2022.10.04 10:47:50 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Mona Patel, PharmD, RAC	OND/DRDMG	21 ☒ Authored ☐ Contributed ☒ Approved
Associate Director for Labeling	**Signature:** Mona Patel -S Digitally signed by Mona Patel -S Date: 2022.08.22 14:28:40 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Michael G. White, PhD Chief Program Management Staff	OND/DRO-RPURM	12, 25 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Michael White -S Digitally signed by Michael White -S Date: 2022.08.23 18:52:36 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Jenny Doan, MSN, BSN	OND/DRO-RPURM	12, 25 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** Jenny Doan -S Digitally signed by Jenny Doan -S Date: 2022.10.04 10:55:56 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Mukesh Summan, PhD Director	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine/Specialty Medicine (DPT-ORPURM/SM)	5.1, 7.1, 7.7, 8.4, 13 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Mukesh Summan -S Digitally signed by Mukesh Summan -S Date: 2022.10.14 13:59:42 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Laurie McLeod-Flynn, PhD Team Leader	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine/Specialty Medicine (DPT-ORPURM/SM)	5.1, 7.1, 7.7, 8.4, 13 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Laurie L. Mcleod-flynn -S Digitally signed by Laurie L. Mcleod-flynn -S Date: 2022.08.24 10:04:54 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	B. Emmanuel Akinshola, PhD	OB/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine (DPT-ORPURM)	5.1, 7.1, 7.7, 8.4, 13 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Babatunde Akinshola -S Digitally signed by Babatunde Akinshola -S Date: 2022.10.04 11:25:30 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Mary Ellen McNerney, PhD	OB/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine (DPT-ORPURM)	5.1, 7.1, 7.7, 8.4, 13 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Mary Ellen Mcnerney -S Digitally signed by Mary Ellen Mcnerney -S Date: 2022.08.24 09:11:29 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Michael Pacanowski, PharmD, MPH Director	OTS/OCP/ Division of Translational and Precision Medicine (DTPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Michael Pacanowski -S Digitally signed by Michael Pacanowski -S Date: 2022.08.24 15:17:10 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jie (Jack) Wang, PhD Team Leader	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22.1, 22.2, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Jie Wang -S Digitally signed by Jie Wang -S Date: 2022.08.23 12:52:46 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Oluseyi Adeniyi, PharmD, PhD	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22.1, 22.2, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Oluseyi Adeniyi -S Digitally signed by Oluseyi Adeniyi -S Date: 2022.08.23 10:23:18 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Travis Ready, PharmD	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22.1, 22.2, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Travis W. Ready -S5 Digitally signed by Travis W. Ready -S5 Date: 2022.08.17 08:53:58 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jiang Liu, PhD Team Leader	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.08.28 22:10:13 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Ruojing Li, PhD	OTS/OCP/DPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Ruojing Li -S Digitally signed by Ruojing Li -S Date: 2022.08.25 17:23:23 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Lei Nie, PhD Director	OB/Division of Biometrics IV (DBIV)	6.2, 6.3, and 16 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Lei Nie -S Digitally signed by Lei Nie -S Date: 2022.08.28 10:09:21 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Yan Wang, PhD Team Leader	OB/DBIV	6.2, 6.3, and 16 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Yan Wang -S Digitally signed by Yan Wang -S Date: 2022.08.23 12:06:17 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Emily Morris, PhD	OB/DBIV	6.2, 6.3, and 16 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Emily L. Morris -S Digitally signed by Emily L. Morris -S Date: 2022.08.31 12:15:30 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Frances Namuswe, PhD Application Team Leader	OPQ/Office of Biotechnology	9, 22.3 ☒ Authored ☐ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Frances Namuswe -S Digitally signed by Frances Namuswe -S Date: 2022.10.12 15:17:45 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Hamid Shafiei, PhD Application Team Leader	OPQ/ Office of New Drug Product	9 ☒ Authored ☐ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Hamid Shafiei -S Digitally signed by Hamid Shafiei -S Date: 2022.08.24 14:36:06 -04'00'		

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/s/

JANET W MAYNARD
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