

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761204Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: 7/27/22

To: Jenny Doan, Regulatory Project Manager, (DRDMG)

From: James Dvorsky, Team Lead
Office of Prescription Drug Promotion (OPDP)

CC: Carrie Newcomer, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for:

- Pombiliti (cipaglucosidase alfa-atga)
- Opfolda (miglustat)

NDA/BLA: BLA 761204 and NDA 215211

In response to DRDMG's consult request dated July 30, 2021, OPDP has reviewed the proposed product labeling (PI), for the original BLA and NDA submissions for Pombiliti and Opfolda.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRDMG on July 25, 2022 and are provided below.

OPDP comments on the proposed Opfolda PPI will be sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP) review.

Thank you for your consult. If you have any questions, please contact James Dvorsky at james.dvorsky@fda.hhs.gov.

41 Pages of Draft Labeling have been
Withheld in Full as B4(CCI/TS) Immediately
Following this Page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES S DVORSKY
07/27/2022 11:07:09 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Division of Pediatrics and Maternal Health Review

Date: March 23, 2022 **Date consulted:** July 30, 2021

From: Jean Limpert, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Rare Diseases and Medical Genetics (DRDMG)

Drugs: POMBILITI (cipaglucosidase alfa) and OPFOLDA (miglustat)

BLA/NDA: BLA 761204 and NDA 215211

Applicant: Amicus Therapeutics

Subject: Proposed labeling for the Pregnancy and Lactation Subsections

**Proposed
Indication:**

[REDACTED] (b) (4)

**Materials
Reviewed:**

- DPMH consult request dated July 30, 2021, DARRTS Reference ID 4834518
- Applicant's submitted background package and proposed labeling for NDA 215211, BLA 761204

- DPMH Pregnancy and Lactation Labeling Rule (PLLR) review for Zavesca (miglustat), NDA 021348, October 12, 2020, Jean Limpert, MD, DARRTS Reference ID 4692242¹
- DPMH PLLR Review of Lumizyme (alglucosidase alfa) BLA 125291 and Myozyme (alglucosidase alfa) BLA 125141, May 10, 2019, Miriam Dinatale, MD, DARRTS Reference ID 4431988²
- DPMH PLLR Review of Nexviazyme (avalglucosidase alfa) for injection, BLA 761194, February 18, 2021, Kristie Baisden, DO, February 18, 2021, DARRTS Reference ID 4748711³

Consult Question: “DRDMG would like input from DPMH MHT on the labeling and potential post-marketing studies required for these applications.”

INTRODUCTION AND BACKGROUND

On July 29, 2021, Amicus Therapeutics submitted an original 351(a) BLA for cipaglucosidase alfa and a 505(b)(1) NDA for miglustat for treatment of PD. DRDMG is planning concurrent reviews and actions for both NDA 215211 and BLA 761204. On July 30, 2021, DRDMG consulted DPMH to assist with the PLLR subsections of labeling.

Regulatory History

- Cipaglucosidase alfa, a new biological product, is a modified recombinant enzyme replacement therapy (ERT) that provides an exogenous source of acid α -glucosidase (GAA). Cipaglucosidase alfa is not approved in the United States or internationally.
- Miglustat is a small molecule pharmacological chaperone that is intended to stabilize cipaglucosidase alfa and increase uptake in tissues. Miglustat has been approved for use in the United States since July 31, 2003 (under NDA 021348), for the treatment of Type 1 Gaucher disease in patients for whom ERT is not a therapeutic option. Miglustat is also approved for use outside of the United States for the treatment of Type 1 Gaucher disease and Niemann-Pick type-C disease.
- FDA granted Orphan Drug Designation (September 2017) and Breakthrough Therapy Designation (February 2019) for cipaglucosidase alfa co-administered with miglustat for the treatment of PD
- November 9, 2020: FDA issued an Advice letter for cipaglucosidase alfa and miglustat to be co-labeled (b) (4)

DPMH has provided PLLR input for other ERTs for PD (i.e., alglucosidase alfa (US-licensed Lumizyme and US-licensed Myozyme) and avalglucosidase alfa-ngpt (US-licensed Nexviazyme) as well as miglustat. The referenced reviews are noted above.

¹ The Zavesca review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

² The Lumizyme and Myozyme review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

³ The Nexviazyme review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

Drug Characteristics for cipaglucosidase alfa⁴

- Drug class: ERT
- Mechanism of action: cipaglucosidase alfa is a recombinant human GAA (rhGAA)
- Molecular weight: not stated
- Plasma half-life: 1.5 hours when administered as cipaglucosidase alfa alone; 2.2 hours when administered with miglustat.
- Tissue half-life: 7 to 10 days.
- Plasma protein binding: not characterized
- Bioavailability: 100%
- Dose and administration: 20 mg/kg administered every other week as an intravenous infusion one hour after oral administration of miglustat.

Reviewer comment: DPMH discussed the tissue half-life with the Clinical Pharmacology team. Miglustat acts as a pharmacokinetic enhancer by binding to cipaglucosidase alfa to stabilize and protect it from denaturation in the systemic circulation. The tissue half-life of 7-10 days was based on animal studies that assessed other sources of alglucosidase alfa but did not assess cipaglucosidase alfa co-administered with miglustat. It is not known whether miglustat impacts the tissue half-life of cipaglucosidase alfa.

Drug Characteristics for miglustat⁵

- Drug class: enzyme stabilizer
- Mechanism of action: miglustat binds to and prevents inactivation of the rhGAA enzyme in the blood. Miglustat alone has no specific effects in glycogen reduction.
- Molecular weight: 219 Daltons⁶
- Half-life: approximately 6 to 7 hours
- Does not bind to plasma proteins
- Bioavailability: not determined
- Dose and administration: 195 mg for patients <50 kg and 260 mg for patients ≥ 50 kg. Miglustat is orally administered once every other week one hour prior to cipaglucosidase alfa infusion.

Current Labeling for Miglustat Approved under NDA 021348⁷

- Current labeling is in the Physician's Labeling Rule and PLLR format
- No boxed warning
- No Warnings/Precautions for embryo-fetal toxicity
- No contraindication for pregnancy or lactation
- Severe adverse reactions: peripheral neuropathy, tremor, weight loss, reductions in platelet count.
- Pregnancy: Based on findings from animal reproduction studies, miglustat may cause fetal harm. Miglustat was maternally toxic in rabbits at exposures near the expected therapeutic dose and causes embryo-fetal toxicity in rats at doses twice the recommended

⁴ Draft Integrated Review for BLA 761204 and NDA 215211, Section 5, 1/20/2022.

⁵ Draft Integrated Review for BLA 761204 and NDA 215211, Section 5, 1/20/2022.

⁶ Miglustat | C10H21NO4 - PubChem (nih.gov).

⁷ Approved labeling for Zavesca (NDA 021348; miglustat), last updated 12/8/2020

human dose. Available data from post-marketing reports in humans are insufficient to assess drug-associated risk.

- Lactation: No available data. Breastfeeding is not recommended because of the potential for serious adverse reactions in breastfed infants (e.g., neuropathy, tremors).
- No pregnancy testing or contraception recommendations
- No known drug-drug interactions with hormonal contraceptives

REVIEW

PREGNANCY

PD and Pregnancy

- PD is an autosomal recessive lysosomal storage disease characterized by a GAA mutation that occurs in 1:40,000 births. There is both an infantile-onset from (<1 year with cardiomyopathy) and late-onset Pompe Disease (LOPD) that manifests in adulthood, the latter of which is the intended population for cipaglucosidase alfa. Clinical manifestations in adults include progressive muscle weakness, primarily in the lower limb muscles, paraspinal muscles, and respiratory muscles. Respiratory complications often lead to significant morbidity and mortality.^{8,9}
- Treatment for PD is ERT, which has been shown to stabilize or improve muscular function, pulmonary function, and survival.¹⁰ Alglucosidase alfa was originally approved for use in infantile-onset PD (IOPD) patients in the EU and the US¹¹ in 2006, followed by authorization for LOPD patients in the EU in 2009. Another alglucosidase alfa product was approved in the US in 2010 for patients with LOPD aged 8 years and older and is currently approved for all patients with Pompe disease, including IOPD and LOPD patients less than 8 years of age.¹² Avalglucosidase alfa-ngpt was approved in the US in August 2021.¹³ A European consensus recommendation (Van der Ploeg et al, 2017) for starting and stopping ERT in adult patients with PD determined that there are no data to support stopping enzyme replacement therapy during pregnancy and lactation. The report notes that although there is no evidence that ERT affects the unborn fetus, the decision of whether or not to continue should be left to the discretion of the treating physician and patient.¹⁴
- As a class, ERTs have a risk of hypersensitivity reactions including anaphylaxis, infusion associated reactions, and immunogenicity. A cohort study (Rohman et al, 2016) of four women with PD (seven pregnancies) in the United Kingdom reported that two patients

⁸ Koyuncu K, Turgay B, Aytac R, Soylemez F. Delivery and postpartum management of a patient with Pompe disease: Case report and review of the literature. *Obstet Med.* 2017;10(3):150-151. doi:10.1177/1753495X16688601

⁹ Goker-Alpan O, Kasturi VG, Sohi MK, et al. Pregnancy Outcomes in Late Onset Pompe Disease. *Life (Basel)*. 2020;10(9):194. Published 2020 Sep 11.

¹⁰ Oliveira Santos, Miguel. "Enzyme Replacement Therapy with Alglucosidase Alfa in a Late-Onset Pompe Disease Patient During Pregnancy." *Neuromuscular disorders*. 28.11 (2018): 965–968.

¹¹ Myozyme (BLA 125141).

¹² Lumizyme (BLA 125291).

¹³ Nexviazyme (BLA 761194).

¹⁴ van der Ploeg AT, Kruijshaar ME, Toscano A, et al; European Pompe Consortium. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. *Eur J Neurol.* 2017 Jun;24(6):768-e31.

who stopped ERT during pregnancy developed infusion-related hypersensitivity reactions (i.e., anaphylaxis, itching) once ERT was resumed after delivery.¹⁵

- Patients undergoing ERT develop anti-drug antibodies to the recombinant enzyme. There is concern that switching patients between different enzymes may lead to a risk of immunogenicity.¹⁶
- The clinical course of pregnancy in patients with PD is variable with reports of some patients developing new or worsening PD symptoms during pregnancy. In one international retrospective study (Karabul et al, 2014) of 52 females with PD who had 125 pregnancies, 98% of pregnancies occurred prior to the availability of ERT. The majority of patients became pregnant prior to the onset of PD symptoms (42/52; 80%). Ten patients (20%) had symptoms of PD during pregnancy, including three patients who had worsening muscle symptoms and two patients who had worsening respiratory symptoms. There was no significant difference in the duration of pregnancy, mean birth weight, or pregnancy complications between the asymptomatic and symptomatic groups.¹⁷
- A 2020 retrospective cohort study (Goker-Alpan et al, 2020) described 23 patients with LOPD that reported at least one pregnancy. The majority (20/23) of participants had pregnancies prior to diagnosis of PD and were, therefore, not on ERT. Two participants conceived while on ERT (i.e., alglucosidase alfa) and continued therapy throughout pregnancy and one patient started treatment ERT (not specified) during pregnancy. Among the four fetuses (one pregnancy was twins) exposed to ERT, there were no adverse effects.
- Case reports (described below) of pregnant patients with PD treated with ERT during pregnancy have not reported drug-associated adverse maternal or fetal effects. In some cases, discontinuation of ERT during pregnancy led to worsening of PD symptoms with improvement of these symptoms once ERT was resumed.
 - 31-year-old patient with LOPD with a history of muscular weakness and exertional dyspnea stopped alglucosidase alfa in the first trimester. After five weeks, she developed worsening dyspnea and resumed alglucosidase alfa at 18 weeks with resultant stabilization of symptoms. She delivered a healthy full-term infant via cesarean section.¹⁸
 - 32-year-old patient with LOPD treated with alglucosidase alfa stopped ERT at week 2 of pregnancy. Alglucosidase alfa was restarted at week 20 due to muscle weakness with improvement of symptoms. She delivered a healthy, full-term infant.¹⁹
 - 25-year-old patient with LOPD treated with ERT became pregnant and interrupted ERT from week 5 to week 16 of pregnancy due to precautionary

¹⁵ Rohman, P.J.; Scott, E.; Richfield, L.; Ramaswami, U.; Hughes, D.A. Pregnancy and associated events in women receiving enzyme replacement therapy for late-onset glycogen storage disease type II (Pompe disease). *J. Obstet. Gynaecol. Res.* 2016, 42, 1263–1271.

¹⁶ Draft IRT for BLA 761204 and NDA 215211, page 8, dated February 24, 2022

¹⁷ Karabul, et al. Pregnancy and delivery in women with Pompe disease. *Molecular Genetics and Metabolism*. 2014. 112: 148-153.

¹⁸ Klos et al. Alglucosidase alfa therapy for Pompe disease in pregnancy - Case report. *J Neurol Sci.* 2017 Apr 15;375:167-169.

¹⁹ Santos, et al. Enzyme replacement therapy with alglucosidase alfa in a late-onset Pompe disease patient during pregnancy. *Neuromuscul Disord.* 2018 Nov;28(11):965-968.

concern about first trimester exposure. At 34 weeks, she developed progressively worsening fatigue and weakness. She delivered a healthy infant but delivery was notable for vacuum extraction due to maternal exhaustion.²⁰

- 21-year-old patient with LOPD continued alglucosidase alfa throughout two pregnancies that occurred three years apart. She experienced a mild decrease in motor and pulmonary function during both pregnancies. She delivered a healthy infant in each pregnancy.²¹
- 38-year-old patient with LOPD stopped alglucosidase alfa in week 6 of pregnancy but resumed one month later because she “felt worse.” She continued treatment throughout the remainder of her pregnancy and delivered a healthy infant via cesarean section.²²
- 40-year-old with PD with muscle weakness and nocturnal ventilation used ERT (i.e., non-US-approved alglucosidase alfa) throughout pregnancy. She developed respiratory difficulties and dyspnea in the 25th week which led to additional ventilatory support followed by elective cesarean section at 37.5 weeks due to the dyspnea. She delivered a healthy infant.²³

Nonclinical Experience

In an embryo-fetal development (EFD) study in pregnant rabbits conducted by the applicant, one experimental group of pregnant rabbits was administered cipaglucosidase alfa at doses of 30, 70, or 175 mg/kg every other day during organogenesis. A second experimental group received cipaglucosidase alfa (175 mg/kg) co-administered with oral miglustat (25 mg/kg). A third group received only oral miglustat (25 mg/kg). Clusters of treatment-related cardiac and great vessel malformations were observed in 1 fetus of a rabbit treated with cipaglucosidase alone and 1 fetus of a rabbit treated with miglustat alone. When cipaglucosidase alfa was co-administered with miglustat, 15 fetuses from six litters were noted to have clusters of cardiac and great vessel malformations.

The No Observed Adverse Effect Level (NOAEL) for cipaglucosidase alfa is 70 mg/kg, yielding a margin of 1.1 relative to the human dose normalized for body surface area (BSA). There was no NOAEL for miglustat. The Lowest-Observed Adverse Effect Level (LOAEL) margin for cipaglucosidase alfa is 2.8, while that for miglustat is ~1.9.

In the EFD study in rats, cipaglucosidase alfa was administered by infusion at doses of 70, 150, or 400 mg/kg every other day during organogenesis; 400 mg/kg was also administered in combination with miglustat 60 mg/kg on the same dosing schedule. There was no maternal or developmental toxicity. Maternal and developmental NOAELs were 400 mg/kg and 60 mg/kg, respectively, yielding BSA margins of 3.2 and 2.2, respectively.

²⁰ Holbeck-Brendel, Merete. “Treatment with Enzyme Replacement Therapy During Pregnancy in a Patient with Pompe Disease.” *Neuromuscular disorders*. 27.10 (2017): 956–958.

²¹ Van Houtte J, De Bleecker JL. Two successfully completed pregnancies in adult onset Pompe disease, under continued treatment with alglucosidase alfa. *Acta Neurol Belg*. 2019 Mar;119(1):147-149. doi: 10.1007/s13760-019-01089-4.

²² Zagnoli F, Leblanc A, Blanchard C, Philippe A, Lastennet M. Pregnancy in a Case of Pompe Disease Treated with Recombinant Human Acid Alpha Glucosidase (Myozyme). *Clin Ther*. 2011; 33(6):S22.

²³ DeVries, J et al. First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. *Molecular Genetics and Metabolism*. 2011. 1-14: 552-555.

In a study of pre- and postnatal development in rats, cipaglucoisidase alfa was administered by infusion during gestation at doses of 70, 150, or 400 mg/kg every other day, beginning on gestation day (GD) 6 through GD 20; then again from lactation day (LD)1 through LD19. Cipaglucoisidase alfa 400 mg/kg was also administered in combination with oral miglustat (60 mg/kg) on the same dosing schedule. Excessive maternal and developmental mortality were reported at the highest dose of cipaglucoisidase alfa, whether administered alone or in combination with miglustat. The cipaglucoisidase alfa NOAEL was 150 mg/kg, yielding a BSA-normalized margin of 1.2. There was no NOAEL for miglustat; the margin at the LOAEL margin is 2.2.

Reviewer comment: DPMH discussed these findings with the Pharmacology/Toxicology team. In the rabbit EFD study, while the individual drugs each led to one fetus with cardiac and great vessel malformations, the Pharmacology/Toxicology team believes the findings are likely treatment-related because multiple great vessel and cardiac malformations were observed in the single fetus. In addition, due to the marked increase in cardiac and great vessel malformations in fetuses exposed to cipaglucoisidase alfa co-administered with miglustat, the Pharmacology/Toxicology team is concerned about a synergistic effect between the two drugs. Of note, the rabbit EFD study included normal rabbits with normal glycogen levels and it is not known if depletion of the rabbits' glycogen levels during pregnancy may have contributed to the adverse findings. The team also notes that the original review for miglustat indicates a dose-related and statistically significant increase in the number of fetuses for which "additional blood vessel[s]" emanating from the aortic arch were reported for miglustat.²⁴

For full details, the reader is referred to the Pharmacology/Toxicology review by Babatunde Akinshola, PhD and Mary Ellen McNerney, PhD.

Review of Pharmacovigilance Database

Pregnant persons were excluded from participation in clinical trials. One study participant became pregnant 15 days after the fifth doses of cipaglucoisidase alfa/miglustat and underwent an elective abortion.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in Embase and Medline to identify literature regarding the use of cipaglucoisidase alfa or miglustat during pregnancy.

²⁴ Draft Integrated Review for BLA 761204 and NDA 215211, Section 13, accessed February 10, 2022.

The applicant identified case reports of female patients who received alglucosidase alfa during pregnancy and did not experience adverse maternal or fetal effects.^{25,26,27,28,29,30}

Reviewer comment: Additional details about these case reports are described in the preceding section “PD and Pregnancy.”

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex,³¹ TERIS,³² REPROTOX,³³ and *Drugs in Pregnancy and Lactation*³⁴ to find relevant articles related to the use of cipaglucosidase alfa and miglustat during pregnancy. Search terms included “cipaglucosidase alfa” OR “miglustat” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” “miscarriage,” and “fetal loss.” No publications specific to cipaglucosidase alfa or miglustat were identified.

Cipaglucosidase alfa is not referenced in Micromedex, TERIS, REPROTOX, or *Drugs in Pregnancy and Lactation*.

Miglustat is not referenced in Micromedex, TERIS, REPROTOX, and *Drugs in Pregnancy and Lactation* did not identify relevant literature.

Micromedex pregnancy rating for miglustat: fetal risk cannot be ruled out.

In *Drugs in Pregnancy and Lactation*, the pregnancy recommendation for miglustat is “no human data- contraindicated.”

LACTATION

Nonclinical Experience

Cipaglucosidase alfa and miglustat was detected in the milk of lactating rats. Cipaglucosidase alfa was only detected at low concentrations in the milk of lactating rats. Conversely, in this study miglustat was concentrated in rat milk at a ratio of 1.7-fold that in plasma.

²⁵ DeVries, J et al. First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. *Molecular Genetics and Metabolism*. 2011. 1-14: 552-555.

²⁶ Grosz Z, Javor L, Molnar JM. The safety of enzyme replacement therapy during pregnancy and lactation in Pompe disease-a longitudinal follow up [Conference Abstract, EPO1277]. *Eur J Neurol*. 2020;27(Suppl 1):697. Abstract from 6th Congress of the European Academy of Neurology, 2020.

²⁷ Klos et al. Alglucosidase alfa therapy for Pompe disease in pregnancy - Case report. *J Neurol Sci*. 2017 Apr 15;375:167-169.

²⁸ Oliveira Santos, Miguel. “Enzyme Replacement Therapy with Alglucosidase Alfa in a Late-Onset Pompe Disease Patient During Pregnancy.” *Neuromuscular disorders*. 28.11 (2018): 965–968. Web.

²⁹ Van Houtte J, De Bleecker JL. Two successfully completed pregnancies in adult onset Pompe disease, under continued treatment with alglucosidase alfa. *Acta Neurol Belg*. 2019 Mar;119(1):147-149. doi: 10.1007/s13760-019-01089-4.

³⁰ Zagnoli F, Leblanc A, Blanchard C, Philippe A, Lastennet M. Pregnancy in a Case of Pompe Disease Treated with Recombinant Human Acid Alpha Glucosidase (Myozyme). *Clin Ther*. 2011; 33(6):S22.

³¹ <https://www.micromedexsolutions.com>, accessed 1/13/22.

³² Truven Health Analytics information. TERIS, accessed 1/13/22.

³³ Truven Health Analytics information. REPROTOX, accessed 1/13/22.

³⁴ Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 12th edition. 2022, Philadelphia, PA. online, accessed 1/13/22.

For full details, the reader is referred to the Pharmacology/Toxicology review by Babatunde Akinshola, PhD and Mary Ellen McNerney, PhD.

Review of Pharmacovigilance Database

The applicant did not identify cases relevant to lactation in their pharmacovigilance database.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in Embase and Medline to identify literature regarding the use of cipaglucosidase alfa or miglustat during lactation.

The applicant did not identify literature for cipaglucosidase alfa. The applicant summarized a case report (DeVries, 2011) of a lactating mother with PD who was treated with alglucosidase alfa. Following infusion, alglucosidase alfa was detected in human milk. No complications were noted in the breastfed infant.³⁵

For miglustat, the applicant identified one review (Anderson, 2020) that included a summary of miglustat for Gaucher disease. The review did not identify clinical lactation information relevant to miglustat, but noted that it should be contraindicated in lactating women due to severe side effects, including diarrhea, weight loss, peripheral neuropathy, and tremor.³⁶

Reviewer comment: The Anderson review is based on the dose of miglustat used to treat Gaucher disease (i.e., 300 mg daily). In contrast, the dose of miglustat used for co-administered with cipaglucosidase alfa is 260 mg once every two weeks which is markedly different.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, Micromedex,³⁷ TERIS,³⁸ REPROTOX,³⁹ and *Drugs in Pregnancy and Lactation*,⁴⁰ *Medications and Mothers' Milk*,⁴¹ and LactMed⁴² to find relevant articles related to the use of cipaglucosidase alfa and miglustat during lactation. Search terms included "cipaglucosidase alfa" OR "miglustat" AND "breastfeeding" or "lactation." No relevant publications were identified.

Cipaglucosidase alfa is not referenced in Micromedex, TERIS, REPROTOX, LactMed, or *Medications and Mothers' Milk*.

³⁵ DeVries, J et al. First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. *Molecular Genetics and Metabolism*. 2011. 1-14: 552-555.

³⁶ Anderson PO. Drug therapy of genetic diseases during breastfeeding. *Breastfeed Med*. 2020;15 (7): 426-428.

³⁷ <https://www.micromedexsolutions.com>, accessed 1/13/22.

³⁸ Truven Health Analytics information. TERIS, accessed 1/13/22.

³⁹ Truven Health Analytics information. REPROTOX, accessed 1/13/22.

⁴⁰ Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 12th edition. 2022, Philadelphia, PA. online, accessed 1/13/22.

⁴¹ <https://www.halesmeds.com>

⁴² <https://www.ncbi.nlm.nih.gov/books/NBK501922/>, accessed 1/13/22.

Miglustat is not referenced in *Medications and Mothers' Milk*.

In *Drugs in Pregnancy and Lactation*, the breastfeeding recommendation for miglustat is “no human data- potential toxicity.”

LactMed states, “No published experience exists with miglustat during breastfeeding. Because of the lack of information and its side effects profile, most sources consider breastfeeding to be contraindicated during maternal miglustat therapy.”

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No genotoxicity studies were conducted with cipaglucosidase alfa because cipaglucosidase alfa is a recombinant glycoprotein and is not expected to exhibit genotoxic potential.⁴³

The genotoxicity of miglustat was previously investigated as part of the Zavesca development program by Actelion Pharma LTD. Based on the Zavesca prescribing information, 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.⁴⁴

Cipaglucosidase alfa was administered by infusion to male and female rats, at doses of 70, 150, or 400 mg/kg every other day; cipaglucosidase alfa was co-administered with miglustat to one dose group in both sexes.⁴⁵ Dosing was initiated in males 28 days prior to cohabitation with untreated females. Dosing was initiated in females 14 days prior to cohabitation with untreated males, continuing through GD 7. Cesarean sections were conducted on GD13 in both treated and naïve females. Increased incidence of preimplantation loss was noted among females treated with the combination, as well as in females treated with miglustat alone (> 21%), relative to both concurrent control groups and historical control values. Increased preimplantation loss (25.9%) was also noted among naïve females bred to males treated with the combination after a first mating. This reversed after cessation of dosing.

For full details, the reader is referred to the Pharmacology/Toxicology review by Babatunde Akinshola, PhD and Mary Ellen McNERney, PhD.

Review of Pharmacovigilance Database

The applicant did not identify reports relevant to fertility in their pharmacovigilance database.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in Embase and Medline to identify literature regarding the use of cipaglucosidase alfa or miglustat and effects on fertility.

⁴³ Nonclinical overview for BLA 761204, page 38.

⁴⁴ Approved label for Zavesca (miglustat), 12/8/2020.

⁴⁵ Draft IRT for BLA 761204 and NDA 215211, page 70, based on Study report number 8371927.

Animal data have indicated decreased spermatogenesis in rats. The applicant identified one clinical article relevant to human male fertility. A study (Amory JK et al, 2007) did not identify effects on sperm concentration, motility, or morphology in seven healthy men who received miglustat 100 mg orally twice daily for six weeks.⁴⁶

Reviewer comment: The nonclinical data demonstrating decreased fertility in rats and clinical demonstrating no effects on male fertility in humans are summarized in subsection 8.3 of approved labeling for miglustat.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, Reprotox to find relevant articles related to the use of cipaglucosidase alfa and miglustat and effects on fertility. Search terms included “cipaglucosidase alfa” OR “miglustat” AND “fertility,” “infertility,” “contraception,” and “oral contraceptives.” No relevant publications were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

Embryofetal study findings in rabbits are concerning for an increased risk of cardiac and great vessel malformations at clinically relevant dose levels. When cipaglucosidase alfa and miglustat were each assessed individually, one fetus in each group had cardiac and great vessel malformations. When cipaglucosidase alfa was co-administered with miglustat, there were marked increases in cardiac and great vessel malformations in the exposed fetuses which is concerning for a possible synergistic effect. The increase in malformations occurred at doses approximately 2.8- and 1.9-fold the maximum recommended human dose (MHRD) for cipaglucosidase alfa and miglustat, respectively. Of concern, a NOAEL could not be established in the rabbit embryofetal development studies.

Pregnant persons were excluded from participation in clinical trials for cipaglucosidase alfa and miglustat. One participant became pregnant 15 days after the fifth doses of cipaglucosidase alfa/miglustat and underwent an elective abortion. There are no available published human data on the use of cipaglucosidase alfa or miglustat (alone or in combination) during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There have not been drug-associated adverse outcomes reported in small observational studies and case reports in pregnant patients with PD who have taken other ERTs.

Based on the animal study findings that indicate potential fetal harm at clinically relevant drug dose levels, DPMH recommends a Contraindication for pregnancy and for females of reproductive potential, as well as a Warning and Precaution for Embryofetal Toxicity. The unknown cipaglucosidase alfa half-life⁴⁷ in body tissues precludes recommendations for adequate mitigation of potential embryofetotoxic risks; a basis to determine the duration of contraception use for females of reproductive potential cannot be estimated. In addition, due to the chronic, possibly lifelong, administration of cipaglucosidase alfa in combination with

⁴⁶ Amory JK, Muller, CH, et al. Miglustat has no apparent effect on spermatogenesis in normal men. Human reproduction, 2007; 22(3):702-7

⁴⁷ Based on discussions with Clinical Pharmacology, there are no human tissue data. The bound miglustat is expected to be dissociated from cipaglucosidase alfa after it is internalized and transferred into lysosomes.

miglustat, and in light of the concerns about immunogenicity when patients switch ERTs, alternative treatments are recommended for females of reproductive potential.

While a postmarketing pregnancy safety study would be informative to obtain data in drug-exposed human pregnancies, feasibility is likely to be a significant issue because cipaglucosidase alfa co-administered with miglustat is not recommended during pregnancy in this rare disease population. A postmarketing pregnancy safety study may be informative in the future, particularly if additional nonclinical data further clarifies and/or reduces the potential fetal risk of cardiac malformations.

Lactation

There are no human data regarding the presence of cipaglucosidase alfa or miglustat (alone or in combination) in breastmilk, or about the drugs' effects on the breastfed infant or milk production. Cipaglucosidase alfa and miglustat are present in rat milk. Due to the potential for frequent and serious adverse reactions seen with miglustat, including diarrhea, weight loss, peripheral neuropathy, and tremor, breastfeeding is not recommended.

While a postmarketing milk-only lactation study would be informative to determine if cipaglucosidase alfa and miglustat transfer into human milk, feasibility is likely to be a significant issue in this rare disease population since cipaglucosidase alfa co-administered with miglustat is not recommended during pregnancy or lactation.

Females and Males of Reproductive Potential

There is no published literature regarding cipaglucosidase alfa and its effects on fertility. Animal studies indicate that miglustat decreases spermatogenesis in rats but a published clinical study in seven males did not show adverse effects on spermatogenesis. The nonclinical and clinical information is conveyed in Subsection 8.3 of approved labeling for miglustat, which is also appropriate for this miglustat application.

LABELING RECOMMENDATIONS

DPMH provided input to subsections 4, 5.X, 8.1, 8.2, 8.3 and section 17 of the applicant's proposed labeling for the cipaglucosidase alfa and miglustat products for compliance with the PLLR (see below) and PLR. DPMH discussed our labeling recommendations with the Division and Labeling Policy Team at multiple meetings during February and March 2022. DPMH recommendations are below and reflect these discussions. DPMH refers to the final NDA and BLA actions for final labeling.

DPMH Preamble: TRADENAME and Tradename are used throughout the proposed labeling below. For labeling of each of the respective products, "TRADENAME in combination with Tradename" will be replaced by "POMBILITI in combination with Opfolda" or "OPFOLDA in combination with Pombiliti."

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----CONTRAINDICATIONS-----

- Pregnancy and females of reproductive potential (4, 5.x, 8.1, 8.3)

-----WARNINGS AND PRECAUTIONS-----

- Embryo-Fetal toxicity: May cause fetal harm based on animal studies. Advise pregnant females and females of reproductive potential of the potential risk to the fetus (4, 5.x, 8.1, 8.3)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Breastfeeding not recommended (8.2).

FULL PRESCRIBING INFORMATION

4 CONTRAINDICATIONS

- Pregnancy [*see Warnings and Precautions (5.x) and Use in Specific Populations (8.1)*]
- Females of Reproductive Potential [*see Warnings and Precautions (5.x) and Use in Specific Populations (8.3)*]

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

TRADENAME in combination with Tradename is contraindicated for use in pregnancy because based on findings from animal studies, TRADENAME in combination with Tradename may cause fetal harm. In animal reproduction studies, administration of cipaglucoisidase alfa-atga in combination with miglustat to pregnant rabbits at doses approximately 2.8-fold and 1.9-fold, respectively, the maximum recommended human dose was associated with increased incidence of great vessel and cardiac malformations in rabbit fetuses [*see Use in Specific Populations (8.1)*].

TRADENAME in combination with Tradename is contraindicated for use in females of reproductive potential because based on animal findings, TRADENAME, in combination with Tradename, may cause fetal harm when administered in pregnancy and the unknown half-life of cipaglucoisidase alfa-atga in body tissues precludes adequate mitigation of potential risks to the fetus [*see Use in Specific Populations (8.3)*]. Use an alternative treatment in females of reproductive potential.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TRADENAME in combination with Tradename is contraindicated for use in females of reproductive potential [*see Use in Specific Populations (8.3)*] and in pregnancy because, based on findings in animal studies, TRADENAME in combination with Tradename may cause fetal harm when administered to a pregnant woman. In a rabbit embryo-fetal development study, great vessel and cardiac malformations were increased in offspring of pregnant rabbits treated with

cipaglucoSIDase alfa-atga (dose approximately 2.8-fold the maximum recommended human dose (MRHD) of 20 mg/kg) co-administered with miglustat (dose approximately 1.9-fold the MHRD of 260 mg) during organogenesis (*See Data*). In a pre-and post-natal development study in rats, increases in pup mortality were seen following maternal treatment with cipaglucoSIDase alfa-atga in combination with miglustat (3.2- and 2.2-fold based on BSA, respectively), or with cipaglucoSIDase alfa-atga alone (3.2-fold based on BSA) (*see Data*). There are no available human data on cipaglucoSIDase alfa-atga co-administered with miglustat during pregnancy.

Data

Animal Data

Reproductive toxicity studies of cipaglucoSIDase alfa in rats and rabbits included pretreatment with diphenhydramine (DPH) to prevent or minimize hypersensitivity reactions. The effects of cipaglucoSIDase alfa/miglustat were evaluated based on comparisons with control groups treated with treated with vehicle or DPH alone, as well as groups treated with miglustat and cipaglucoSIDase alfa alone.

In a rabbit embryo-fetal development study, cipaglucoSIDase alfa was administered intravenously to pregnant rabbits, at 30, 70, or 175 mg/kg every other day during organogenesis (GD 7 through GD 19). One experimental group received oral miglustat only at (25 mg/kg). Another group received cipaglucoSIDase alfa-atga (175 mg/kg) co-administered with oral miglustat (25 mg/kg). Clusters of great vessel and cardiac malformations were increased in offspring of pregnant rabbits treated with both cipaglucoSIDase alfa-atga (175 mg/kg; 2.8-fold the MRHD of 20 mg/kg on a body surface area basis (BSA) and miglustat (25 mg/kg; 1.9-fold the MRHD of 260 mg on BSA basis). 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 was administered by intravenously to pregnant rats, at 70, 150, or 400 mg/kg every other day during organogenesis, (GD 6 through GD 18). One experimental group received miglustat alone (60 mg/kg) and one received cipaglucoSIDase alfa-atga (400 mg/kg) with oral miglustat (60 mg/kg) every other day during organogenesis. No evidence of adverse effects to the fetus were observed with cipaglucoSIDase alfa-atga, miglustat alone, or with the combination of drugs up to 400 mg/kg cipaglucoSIDase alfa (3.2-fold the MRHD on a BSA basis) / 60 mg/kg miglustat (2.2fold the MRHD on a BSA basis).

In a pre-and post-natal development study in rats, cipaglucoSIDase alfa was administered intravenously to pregnant rats, at 70, 150, or 400 mg/kg every other day during pregnancy, (GD 6 through GD 20, and from LD 1 through LD 19). One experimental group received cipaglucoSIDase alfa-atga (400 mg/kg) with oral miglustat (60 mg/kg) every other day; and one group received oral miglustat (60 mg/kg) alone. Postnatal mortality was increased with cipaglucoSIDase alfa-atga at 400 mg/kg, (3.2-fold the MRHD on a BSA basis), whether administered alone or with miglustat (60 mg/kg, 2.2-fold the miglustat MRHD on a BSA basis); Maternal mortality was observed with cipaglucoSIDase alfa-atga (400 mg/kg), with oral miglustat (60 mg/kg) (3.2-fold cipaglucoSIDase alfa-atga and 2.2-fold the miglustat MRHD, respectively).

8.2 Lactation

Risk Summary

TRADENAME in combination with Tradename is contraindicated for use in females of reproductive potential [see *Use in Specific Populations* (8.1)]. Based on findings in animal studies, the use of TRADENAME in combination with Tradename, may lead to serious adverse reactions in breastfed infants. Lactating females should avoid breastfeeding during treatment with TRADENAME in combination with Tradename [see *Use in Specific Populations* (8.3)]. There are no data on the presence of [cipaglucoisidase alfa-atga or miglustat] in human milk, the drugs' effects on the breastfed infant, or the effects on milk production. [Cipaglucoisidase alfa-atga or miglustat] are present in rat milk (see *Data*).

Data

[A lactation study in rats showed minimal excretion of cipaglucoisidase alfa-atga in milk, measured 3 hours after dosing; (milk: plasma ratio of 0.038) or miglustat excretion in rat milk, also measured 3 hours after dosing, exceeded plasma levels (milk: plasma ratio of 1.7)]. The concentration of a drug in animal milk does not necessarily predict the concentration of a drug in human milk.

Reviewer comment: The bracketed information under the Risk Summary and Data subheadings will reflect data for the individual product in the respective labeling.

8.3 Females and Males of Reproductive Potential

TRADENAME in combination with Tradename is contraindicated for use in females of reproductive potential [see *Warnings and Precautions* (5.X) and *Use in Specific Populations* (8.1)] because based on animal findings, TRADENAME in combination with Tradename may cause fetal harm when administered to a pregnant woman and the unknown half-life of TRADENAME in body tissues precludes adequate contraception recommendations to mitigate the potential risks to a fetus [see *Warnings and Precautions* (5.X) and *Use in Specific Populations* (8.1)]. Use an alternative treatment in females of reproductive potential.

Females who are NOT of reproductive potential are defined as biological females who are postmenopausal or who have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).

Infertility

No effect on sperm concentration, motility, or morphology was seen in 7 healthy adult men who received miglustat 100 mg orally twice daily for six weeks. In rats, no effects of cipaglucoisidase alfa-atga on male or female fertility was observed. However, co-administration of cipaglucoisidase alfa-atga 400 mg (3.2-fold MRHD) and miglustat (2.2-fold MRHD) to male rats resulted in reversible increases in preimplantation loss. In treated females, coadministration at the same doses or administration of miglustat alone (60 mg/kg, 2.2-fold MRHD), increased pre-implantation loss [see *Nonclinical Toxicology* (13.1)].

Reviewer comment: The first statement under the Infertility subheading is based on a male fertility study of miglustat alone and will, therefore, only be included in the Opfolda labeling.

17 PATIENT COUNSELING INFORMATION

Lactation

Advise lactating females not to breastfeed during treatment with TRADENAME [*see Use in Specific Populations (8.2)*].

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/s/

JEAN L LIMPERT
04/05/2022 10:59:29 AM

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 13, 2022
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761204
Product Name and Strength:	Pombiliti (cipaglucosidase alfa-atga) Lyophilized powder for injection, 105 mg/vial
Applicant/Sponsor Name:	Amicus Therapeutics US, Inc.
OSE RCM #:	2021-1305-1
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 17, 2022 for Pombiliti. The Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container labels and carton labeling for Pombiliti (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 RECOMMENDATIONS FOR AMICUS THERAPEUTICS US, INC.

The carton and container labels are acceptable from a medication error perspective and we have no additional recommendations.

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS)
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^a Mahmoud, S. Label and Labeling Review for Pombiliti (BLA 761204). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 13. RCM No.: 2021-1305.

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/s/

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04/14/2022 09:03:59 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 13, 2022
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761204
Product Name, Dosage Form, and Strength:	Pombiliti (cipaglucosidase alfa-atga) Lyophilized powder for injection, 105 mg/vial
Product Type:	Single ingredient product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amicus Therapeutics US, Inc.
FDA Received Date:	July 29, 2021
OSE RCM #:	2021-1305
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Janine Stewart, PharmD

1 REASON FOR REVIEW

As part of the approval process for Pombiliti (cipaglicosidase alfa-atga) Lyophilized powder for injection, the Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Pombiliti prescribing information (PI), container labels, and carton labeling and US dosing and administration HCP mobile webpage for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review

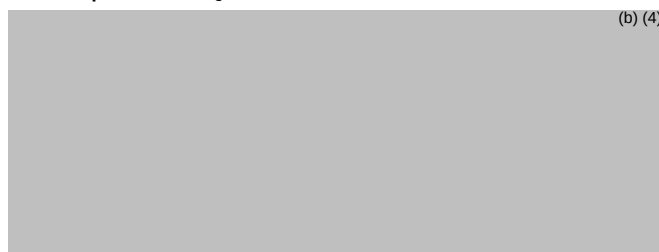
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, container label, carton labeling, for Pombiliti to identify deficiencies that may lead to medication errors and other areas of improvement. We determined that they may be improved to ensure safe product use. Our assessment of Section 2.3 (b) (4) is that it can be revised to eliminate redundancies and to improve the clarity and order of the steps involved in preparing and administering Pombiliti. We identified areas of the container labels and carton labeling that can be modified to improve the prominence and clarity of important product information.

We note the proposed Pombiliti carton contains a QR code on the side panel with a message to healthcare professionals to scan the code (See Snapshot 1). In addition, we acknowledge the BLA submission includes the US Dosing and Administration HCP Mobile Webpage for Pombiliti. Per the Applicant, the mobile webpage is provided as an optional resource for use by providers to aid them in the use of Pombiliti and Opfolda.

Snapshot 1. QR code on Pombiliti Carton



For the QR code (the square image itself), we find that it does not compete with or distract from the presentation of other required or recommended information on the carton. At the time of this review, the Review Team is in discussion with the CDER Non-required/Non-recommended Information (NRI) Labeling Workgroup regarding the QR code, the message next to the QR code, and the US Dosing and Administration HCP Mobile Webpage for Pombiliti. At this time, we recommend in Section 4.2 for the Applicant to ensure that the mobile webpage provides information that is consistent with the approved PI for Pombiliti and Opfolda.

4 CONCLUSION & RECOMMENDATIONS

Our review of the materials found that the proposed Pombiliti PI, container label, and carton labeling may be improved to promote safe and effective use of this product. Thus, we provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF RARE DISEASES AND MEDICAL GENETICS (DRDMG)

A. Highlight of Prescribing Information

1. Revise the Dosage Forms and Strengths section to read:
For Injection: 105 mg lyophilized powder in a single-dose vial
2. Revise the first sentence in the Dosage and Administration section to read:
The recommended dosage of POMBILITI is 20 mg/kg actual body weight administered every other week as an intravenous infusion over 4 hours.

B. Prescribing Information

1. Revise the non-proprietary name to include the conditionally acceptable suffix 'atga' to read "cipaglucosidase alfa-atga" where it appears in the PI.
2. To facilitate understanding of Pombiliti dosing in combination with Opfolda, recommend introducing an overview of Pombiliti dosing and administration in section 2.1 as follows:
"The recommended dosage of POMBILITI is 20 mg/kg (of actual body weight) administered every other week as an intravenous infusion over approximately 4 hours.

Start POMBILITI in combination with Opfolda two weeks after the last ERT dose. Initiate the POMBILITI infusion between 50 to 90 minutes after oral administration of Opfolda.

(Suggest inserting the administration timeline graphic here)



In the event of POMBILITI infusion delay, do not start the infusion more than three hours after oral Opfolda administration.”

3. Dosage and Administration Section

- a. Change (b) (4) to single-dose vial
- b. Consider revising the preparation and administration information for clarity and to eliminate redundancies as proposed below:

2.3 Preparation and Administration Instructions

Preparation

1. Determine the number of POMBILITI vials to be reconstituted based on the calculated dose (based on patient’s actual body weight (kg))
2. Remove vials from the refrigerator and allow to come to room temperature (i.e., approximately 30 minutes).
3. To prepare the infusion bag select the appropriate size bag based on body weight (kg) per table 1. Remove overfill, airspace, and the volume of 0.9% Sodium Chloride Injection, USP that will be equal to the amount (mL) of reconstituted POMBILITI required to achieve the dose.
4. Reconstitute each vial by slowly injecting 7.2 mL of Sterile Water for Injection, USP, down the inside wall of each vial to avoid foaming.
5. Roll and tilt the vial to allow the powder to dissolve completely which typically takes 2 minutes. Each vial will yield a concentration of 15 mg/mL. Do not invert, swirl, or shake.
6. Visually inspect the solution after reconstitution for particulate matter and discoloration. The reconstituted volume appears as a colorless to pale yellow solution, clear to opalescent, and appears almost free of particles but may contain white to

translucent particles. Discard if foreign matter is observed or the solution is discolored.

- a. If the reconstituted POMBILITI vial is not used immediately, store refrigerated at 36°F to 46°F (2°C to 8°C) for up to 24 hours. Do not freeze.
7. Slowly withdraw 7 mL of reconstituted solution from the vials until the patient's dose is obtained. Discard any remaining reconstituted solution in the last vial.
8. Dilute the POMBILITI solution promptly in the prepared 0.9% Sodium Chloride Injection, USP infusion bag.
9. To prevent foaming, avoid vigorous shaking and agitation and gently invert infusion bag to mix the solution. The infusion solution should be administered at room temperature soon after dilution preparation.
 - a. If not administered immediately, diluted POMBILITI infusion is stable for up to 30 hours when stored refrigerated at 36°F to 46°F (2°C to 8°C) or up to 6 hours when stored at room temperature at 68°F to 77°F (20°C to 25°C). Do not freeze.

Administration

1. Prior to administration, inspect the infusion bag for foaming. If foaming is present, let foam dissipate before administering POMBILITI.
2. Use a latex-free and di(2-ethylhexyl)phthalate (DEHP) intravenous administration set with an inline low protein binding 0.2-micron filter to administer POMBILITI.
3. Initiate POMBILITI infusion between 50 to 90 minutes after oral administration of OPFOLDA. In the event of infusion delay, start infusion no more than 3 hours from the oral administration of OPFOLDA.
4. The initial recommended infusion rate is 1 mg/kg/hr. Gradually increase the infusion rate by 2 mg/kg/hr every 30 minutes if there are no signs of infusion-associated reactions (IARs) until a maximum rate of 7 mg/kg/hr is reached; then, maintain the infusion rate at 7 mg/kg/hr until the infusion is complete. The approximate total infusion duration is 4 hours. (See Table 1)
5. Do not infuse POMBILITI in the same intravenous line with other products.

4. How Supplied/Storage and Handling Section

- a. Consider revising the How Supplied information to appear as follows:

POMBILITI (cipaglucosidase alfa-atga) is a white to slightly yellowish lyophilized cake or powder in a single-dose vial available as:

Package size	NDC
Carton containing one (1) single -dose vial	71904-200-01
Carton containing ten (10) single-dose vials	71904-200-02
Carton containing twenty-five (25) single-dose vials	71904-200-03

4.2 RECOMMENDATIONS FOR AMICUS THERAPEUTICS US, INC.

A. General Comments (Container labels & Carton Labeling)

1. Revise the statement, (b) (4) to “Recommended Dosage: See prescribing information.” We recommend this revision to use language that is consistent with the language used in the PI.
2. Revise the statement on the principal display panel (PDP) that reads (b) (4) to read “For intravenous infusion after Reconstitution and Dilution”. We recommend this revision to minimize the risk of wrong administration errors.
3. Move (b) (4) to side panel to reduce clutter on the PDP.
4. Revise storage statement to read. “Must be refrigerated, store at 2°C to 8°C (36°F to 46°F)” to increase the prominence of the storage information. .
5. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as:

YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month.

6. The nonproprietary name, cipagluco^aside alfa-atga, was found conditionally acceptable^a for your proposed product. Should your 351(a) BLA be approved during this review cycle, cipagluco^aside alfa-atga will be the proper name designated in the license. Revise the non-proprietary name on your proposed container label and carton labeling accordingly.
7. Revise the statement, (b) (4) to read “Use POMBILITI™ in conjunction with Opfolda™.” We recommend this phrasing because Pombiliti labeling should reflect Pombiliti as the primary product.

B. Container Label

1. Revise and relocate the statement on the side panel that reads “(b) (4) Discard unused portion” to read “Single-dose vial. Discard unused portion” and to appear on the principal display panel (PDP) for increased prominence. Consider using this revised statement to replace the statement in the top right corner of the PDP that reads “1 Vial”.

C. Carton Labeling

1. Revise the statement (b) (4) that appears on the side panel to use the correct package-type term, “single-dose vial”.
2. We note a QR code embedded with the proposed US dosing and administration HCP mobile webpage appears on the carton labeling. Please ensure that the mobile webpage provides information that is consistent with the approved PI for Pombiliti and the companion product, Opfolda.

^a Harris, Danielle. Letter Subject for cipagluco^aside alfa Nonproprietary Name Suffix Advice. Silver Spring (MD): FDA, CDER, OSE (US); 2022 JAN 26. BLA 761204

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pombiliti received on July 29, 2021 from Amicus Therapeutics US, Inc.

Table 2. Relevant Product Information for Pombiliti	
Initial Approval Date	NA
Nonproprietary Name	cipaglucosidase alfa-atga
Indication	(b) (4)
Route of Administration	Intravenous
Dosage Form	Lyophilized powder for injection
Strength	105 mg/vial
Dose and Frequency	20 mg per kg body weight administered every other week as an intravenous infusion
How Supplied	Sterile, (b) (4) white to slightly yellowish lyophilized (b) (4) powder in single dose vials. Available in one vial in single carton; 10 vials in a multipack carton; and 25 vials in a multipack carton.
Storage	(b) (4)
Container Closure	Glass vial with a rubber stopper

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Pombiliti labels and labeling submitted by Amicus Therapeutics US, Inc..

- Container label received on July 29, 2021
- Carton labeling received on July 29, 2021
- Prescribing Information (Image not shown) received on July 29, 2021, available from <\\CDSESUB1\evsprod\bla761204\0004\m1\us\114-label\1141-draft-label\proposed.docx>
- [US Dosing and Administration HCP Mobile Webpage received on July 29, 2021, available from \\CDSESUB1\evsprod\bla761204\0004\m1\us\114-label\1141-draft-label\carton-qr-code.pdf](\\CDSESUB1\evsprod\bla761204\0004\m1\us\114-label\1141-draft-label\carton-qr-code.pdf)
-

G.2 Label and Labeling Images



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^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SALI MAHMOUD
04/13/2022 02:56:03 PM

JANINE A STEWART
04/14/2022 09:02:05 AM

Clinical Inspection Summary

Date	4/5/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director/(Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jenny Doan, Regulatory Project Manager Daniela Luquetti, M.D., Medical Officer Linda Jeng, M.D., Team Leader Division of Rare Disease and Medical Genetics Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine
BLA #	761204
NDA #	214211
Applicant	Amicus Therapeutics
Drug	Cipaglucosidase alfa, Miglustat
NME	Yes (Cipaglucosidase alfa)
Proposed Indication	Treatment of Pompe disease
Consultation Request Date	9/22/2021
Summary Goal Date	3/29/2022, extended to 4/8/2022
Priority/Standard Review	Standard
Action Goal Date	5/27/2022
PDUFA Date	5/29/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Dr. Quinn was inspected and Drs. Bratkovic and Tchan participated in a Remote Regulatory Assessment (RRA) in support of this application which covered Protocol ATB200-03. Due to travel restrictions from the COVID-19 pandemic, the inspection of Dr. Anderson (Denmark) could not be conducted. Despite protocol deviations noted at Dr. Bratkovic's site, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The inspection/RRAs verified the 6-meter walk test (6MWT) results, the primary efficacy endpoint. Also verified was the key secondary efficacy endpoint, sitting Forced Vital Capacity (FVC) (% predicted). The spirometry reports available at the clinical sites did not include a Quality Control (QC) grade. A QC grade, which is determined based on criteria for acceptability, was assigned later by the vendor (ERT). In response to an information request, the sponsor noted that 13 sitting FVC values for 6 subjects received a QC grade of

unacceptable but were used in data analyses. We recommend that the review division perform a sensitivity analysis with regard to these 6 subjects who had FVC values with unacceptable QC grade to assess the robustness of the results reported by the sponsor.

Dr. Tchan's site was chosen, in part, to obtain more information regarding a subject identified by the sponsor as a statistical outlier for the 6MWT and sitting FVC. The sponsor stated that this subject had admitted to underperforming on both the 6MWT and pulmonary function tests at screening to be eligible for the study and that assessments conducted prior to the study had shown higher values which supported the subject's admission of underperformance. Dr. Tchan had written a Note-to-File six months after the subject had completed the study. This document stated that this subject had admitted to underperforming on these assessments, however, no other documentation was available to support that statement. Dr. Tchan also noted that the 6MWT performed prior to the study was not performed the same as the study 6MWTs and, therefore, could not be reliably compared. This subject had also recently discontinued a concomitant medication which could have impacted screening assessments. Based on information obtained during the RRA, there was insufficient evidence to support exclusion of this subject from the efficacy analyses.

In the sponsor's protocol deviation line listing, some deviations were described as "6MWT not done or not completed correctly as described in the functional assessment manual". At Dr. Bratkovic's site, the deviation for one subject, randomized to cipaglucosidase alfa/miglustat, was described by the site as the subject requesting to use a walking stick starting at Week 14 due to a fall during the 6MWT conducted at Week 12. The sponsor's protocol deviation line listing identified 27 subjects with a deviation described as "6MWT not done or not completed correctly as described in the functional assessment manual". For 15 of those subjects, this deviation occurred either at screening or Week 52/End of Study, the timepoints for efficacy analyses. We recommend that the review division perform a sensitivity analysis regarding these 15 subjects to assess the robustness of the results reported by the sponsor.

II. BACKGROUND

Cipaglucosidase alfa for intravenous use and miglustat oral capsules are being developed under BLA 761204 (IND 127387) and NDA 215211 (IND 127387), respectively, to be co-administered for the treatment of adults with a confirmed diagnosis of Pompe disease (acid α -glucosidase [GAA] deficiency). The only currently approved therapy for adults with Pompe disease is the enzyme replacement therapy (ERT), alglucosidase alfa.

Cipaglucosidase alfa is an ERT with the same mechanism of action as alglucosidase. Like all lysosomal enzymes, cipaglucosidase alfa is unstable at neutral pH and can be

denatured and inactivated in the bloodstream after IV infusion. According to the sponsor, miglustat is a small-molecule enzyme stabilizer that binds to and prevents inactivation of the recombinant human acid α -glucosidase in the blood. This binding is transient and dissociation of the cipaglucosidase alfa-miglustat occurs in the acidic environment of the lysosome. Miglustat alone has no specific effects on glycogen reduction in Pompe disease.

The sponsor has submitted one Phase 3 study, ATB200-03, to support the efficacy and safety of cipaglucosidase alfa co-administered with miglustat for the treatment of adults with Pompe disease.

Protocol ATB200-03

Title: "A phase 3, double-blind randomized study to assess the efficacy and safety of intravenous ATB200 co-administered with oral AT2221 in adult subjects with late-onset Pompe disease compared with alglucosidase alfa/placebo"

Subjects: 123

Sites: 59 sites; Western Europe (22), North America [20; United States (18)], Asia/Pacific (7), Eastern Europe (5), Australia (4), Latin America (1)

Study Initiation and Completion Dates: (b) (6)

This was a double-blind, randomized study of cipaglucosidase alfa + miglustat in adult subjects with late-onset Pompe disease who had received enzyme replacement therapy with alglucosidase alfa (i.e., ERT-experienced) or who never received ERT (i.e., ERT-naïve) compared with alglucosidase + placebo.

Subjects were male or female; ≥ 18 years of age; ≥ 40 kg; diagnosis of late-onset Pompe disease based on either deficiency of acid α -glucosidase (GAA) enzyme or GAA genotyping; sitting forced vital capacity (FVC) $\geq 30\%$ of the predicted value for healthy subjects; and two valid 6-meter walk tests (6MWT) at screening. A valid 6MWT had to meet the following criteria:

- Both 6-meter walk distance (6MWD) were ≥ 75 meters
- Both 6MWD were $\leq 90\%$ of the predicted value for healthy adults, and
- The lower value of 6MWD was within 20% of the higher value 6MWT.

ERT-experienced subjects were defined as currently receiving standard of care ERT, alglucosidase alfa, at the recommended dose and regimen (i.e., 20 mg/kg dose every 2 weeks) for ≥ 24 months.

Excluded were subjects receiving investigational or pharmacological treatment for Pompe (excluding alglucosidase alfa) within 30 days/5 half-lives of the therapy before Day 1, subjects who had received gene therapy for Pompe disease, or subjects

requiring the use of invasive or noninvasive ventilation support for >6 hours per day while awake.

The study was comprised of three phases:

Screening Period: up to 30 days

There were two screening visits during this phase. Efficacy assessments, including pulmonary function tests (e.g., FVC) and the 6MWT were conducted at both screening visits.

Double-Blind Treatment Period: 52 weeks

Subjects were randomized (2:1), stratified by ERT status and baseline 6MWD, to the following treatment arms:

Treatment Arm	Investigational Product	Dosing Regimen
Cipaglucosidase alfa + Miglustat	Cipaglucosidase alfa	20 mg/kg IV infusion over a 4-hour duration every 2 weeks
	Miglustat	Subjects ≥ 50 kg: 260 mg (4 x 65 mg oral capsules) one hour prior to IV infusion every 2 weeks Subjects ≥ 40 kg to <50 kg: 195 mg (3 x 65 mg oral capsules) one hour prior to IV infusion every 2 weeks
Alglucosidase alfa + Placebo	Alglucosidase alfa	20 mg/kg IV infusion over a 4-hour duration every 2 weeks
	Placebo	Subjects ≥ 50 kg: Placebo (4 oral capsules) one hour prior to IV infusion every 2 weeks Subjects ≥ 40 kg to <50 kg: Placebo (3 oral capsules) one hour prior to IV infusion every 2 weeks

Subjects were required to fast at least 2 hours before and 2 hours after administration of miglustat or placebo oral capsules. Subjects were monitored for 3 hours after the end of the first 3 infusions (Day 1, Week 2, Week 4) by study personnel trained in diagnosing and treating acute hypersensitivity reactions and who had immediate access to medication and equipment to treat such reactions. Any signs of symptoms noted during or after the infusion were to be reported as adverse events.

Safety Follow-up Period: 30 days

A 30-day safety follow-up visit for monitoring of any adverse events that were ongoing at the end of study and collection of a blood sample for anti-rhGAA antibodies was scheduled for subjects who were not continuing in the separate open-label extension protocol (ATB200-07).

Subjects who were confirmed positive for anti-rhGAA antibodies at the 30-day safety follow-up visit continued to have follow-up immunological testing for up to 12 months after the last dose of study drug as long as they continued to have a positive result.

The *primary efficacy endpoint* was the change in 6MWD from baseline to Week 52. One of the *key secondary endpoints* was the change in sitting FVC (% predicted) from baseline to Week 52.

Pulmonary Function Tests (PFTs)

PFT measurements were obtained using MasterScope, a portable spirometer device provided by the vendor, ERT. Upon request, the sponsor provided the following documents: Instructions for Use MasterScope for Trial ATB200-03 and ATB200-07” and “PFT OverRead Guidelines for Clinical Trial Protocol ATB200-03” Version 1.0 (10/24/2018).

Spirometry was performed at the clinical sites, and spirometry results were sent electronically directly to the vendor, ERT. The MasterScope records up to 8 separate spirometry efforts per visit and automatically assigns, via an algorithm, one of these efforts as the best spirometry effort for determination of PFT parameters (e.g., supine FVC). According to the document “PFT OverRead Guidelines” after data is transferred to ERT, the following occur:

- ERT Clinical Specialist logs into the “Respiratory OverRead” software to review data
- ERT Clinical Specialist chooses a Quality Control (QC) grade for the data
- If the QC grade indicates that the data are unacceptable, a report is sent to the clinical investigator
- If the QC grade indicates that the data are acceptable, QC results will be available in the ERT Web Portal
- After QC has been performed, ERT determines whether the best Masterscope results were in fact the best acceptable results or whether there was another better acceptable spirometry effort—this was referred to as determining the Best Test Result (BTR)
- The clinical investigator can reject the changes by sending back the BTR Change Report with their signature and a reason for rejecting the changes

Rationale for Site Selection

Sites were selected based on enrollment, outliers for efficacy endpoints, and inspection history. Enrollment at most sites was low due to the rare nature of Pompe Disease.

III. RESULTS

1. Drago Bratkovic, MBBS

Site #4002

PARC Clinical Research Department
Ward S4A North Wing, Royal Adelaide Hospital
Adelaide, SA 5000
Australia

Remote Regulatory Assessment (RRA) Dates: 11/7/2021 – 11/15/2021

Due to the COVID-19 pandemic, travel to this site was not possible. This site was therefore evaluated via a Remote Regulatory Assessment (RRA). Video conferencing via Zoom and document sharing via an online platform (box.com) were used to exchange information.

At this site for Protocol ATB200-03, 11 subjects were screened, all of whom were enrolled, and 10 subjects completed the study. Subject #4002- (b) (6), randomized to cipaglucoisidase alfa/miglustat, discontinued the study due to the adverse event of chills. The narrative for this subject is included in the NDA submission as an adverse event leading to investigational product (IP) discontinuation and as a significant infusion-associated reaction.

This site, Site #4002, was the first site in Australia to start enrolling subjects. Six subjects (#s (b) (6)) were enrolled at this site with the intent to transfer their regular infusions and care to study sites closer to their homes as soon as those sites started enrolling. The transferred subjects were to continue all efficacy assessments at the original site (#4002) to maintain consistency. However, according to the clinical investigator, COVID-19 made travel difficult and/or unsafe for this study population. For most of these subjects, once transferred, efficacy assessments were conducted at the site to which they were transferred. These subjects had efficacy assessments up to and including Week 52; however, data for efficacy assessments conducted at the other sites were not available for verification at Site #4002. For these transferred subjects, their last efficacy assessments performed at Site #4002 were as follows:

- Subject #4002- (b) (6) was transferred to Site #4502. Last efficacy assessment at Site #4002 was Week 12.
- Subject #4002- (b) (6) was transferred to Site #4007. Last efficacy assessment at Site #4002 was Week 38.
- Subject #4002- (b) (6) was transferred to Site #4005. Last efficacy assessment at Site #4002 was Week 38.
- Subject #4002- (b) (6) was transferred to Site #4005. Last efficacy assessment at Site #4002 was Week 38.
- Subject #4002- (b) (6) was transferred to Site #4007. Last efficacy assessment at Site #4002 was Week 38.
- Subject #4002- (b) (6) was transferred to Site #4006. Last efficacy assessment at Site #4002 was Week 52.

Due to data privacy restrictions, consent forms could not be reviewed to determine whether they were signed prior to the conduct of any study procedures. For nine of the 11 enrolled subjects, physician notes documented obtaining consent at the screening visit. An audit of the study records for all 11 enrolled subjects was conducted. As noted above, six subjects were transferred to other sites, such that data collected at these other sites after the date the subject was transferred were not available for review at Site #4002. Records reviewed included, but were not limited to, source documents, site monitoring log, IEC/sponsor communications, financial disclosure, test article dosing, inclusion/exclusion criteria, adverse events, concomitant medications, protocol deviations, key secondary efficacy data (sitting Forced Vital Capacity [FVC], % predicted), and primary efficacy data (6MWD). There was no evidence of underreporting of adverse events.

Results for the 6MWT and sitting FVC (% predicted) were recorded on paper and were verified against the sponsor's data line listings; no discrepancies were identified. As noted above, 6 subjects were transferred to other clinical sites. For 5 of these 6 subjects, data for 6MWT and sitting FVC assessments conducted at these other sites after transfer were not available at Site #4002 and, therefore, could not be verified. The Quality Control grades for spirometry and the ERT Best Test Result (BTR) were not available at the site (*refer to Quality Control Grades for Spirometry Results and Pulmonary Function Tests sections of report*).

There were protocol deviations noted in the sponsor line listings described as "6MWT not done or not completed correctly as described in the FAM" (functional assessment manual). The following information was provided by the clinical investigator:

- Subjects #4002- (b) (6) and #4002- (b) (6): Due to safety reasons, the subject requested to walk on the left of the cones for all their 6MWT assessments as this was the more natural way they walk and turn.
- Subject #4002- (b) (6): The subject requested that they begin using a walking stick at Week 14 because the subject fell during the Week 12 test; this request was approved by the physiotherapist.

Reviewer's comment:

A total of three subjects at this site had a protocol deviation noted as "6MWT not done or not completed correctly as described in the FAM", and all three deviations were due to the 6MWT not being completed correctly. It should be noted that according to one of the protocol deviation line listings (Listing 16.2.2.1), this protocol deviation occurred in 27 of 123 subjects total (22%) in Study ATB200-03. For 15 of those subjects, this deviation occurred either at screening or Week 52/End of Study, the timepoints for efficacy analyses. We recommend that the review division perform a sensitivity analysis regarding these 15 subjects to assess the robustness of the results reported by the sponsor.

2. Colin Quinn, M.D.**Site #2063**

University of Pennsylvania
3400 Spruce Street
3 West Gates Building
Philadelphia, PA 19104

Inspection Dates: 12/6/2021 – 12/10/2021

At this site for Protocol ATB200-03, 3 subjects were screened, all of whom were randomized and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 3 randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (sitting Forced Vital Capacity [FVC], % predicted), and primary efficacy data (6MWD). There was no evidence of under-reporting of adverse events.

Results for the 6MWT were recorded on paper and were verified against the sponsor's data line listings; no discrepancies were identified. Results for FVC were available as print copies from the MasterScope spirometry device. The Quality Control grades for spirometry and the ERT BTR were not available at the site (*refer to Quality Control Grades for Spirometry Results and Pulmonary Function Tests sections of report*). Only the automatically assigned MasterScope best spirometry effort was available at the site.

The sitting FVC (% predicted), obtained from the best spirometry effort chosen automatically by MasterScope via algorithm, was verified against the sponsor line listing. Differences in sitting FVC (% predicted) were identified for one of three randomized subjects (Table 1).

Table 1. Sitting FVC (% predicted) Differences in MasterScope Best Spirometry Effort and Best Test Result in Sponsor Line Listing for Subject #2063- (b) (6)

Study Visit	Date	Sitting FVC (%) Predicted	
		MasterScope Best Spirometry Effort Source document	Best Test Result Sponsor Line Listing
Screening	(b) (6)	47	45
Week 52	(b) (6)	40	36

Reviewer comments: Differences were noted for sitting FVC (% predicted) between the MasterScope assigned best spirometry effort on the source data and the sponsor data line listings for Subject #2063- (b) (6) *These differences were not discrepancies as the source at the*

site did not contain the ERT selected BTRs, which were the basis of the line listings (refer to Quality Control Grades for Spirometry Results and Pulmonary Function Tests sections of report).

3. Michel Tchan, MBBS, Ph.D.

Site #4005

Hawkesbury Road
Westmead Hospital
Westmead, NSW 2145
Australia

RRA Dates: 12/13/2021 – 12/16/2021

Due to the COVID-19 pandemic, travel to this site was not possible. This site was therefore evaluated via a Remote Regulatory Assessment (RRA). Video conferencing via Zoom and document sharing via an online platform (box.com) were used to exchange information.

At this site for Protocol ATB200-03, 3 subjects were screened, all of whom were enrolled and completed the study. Two subjects, #s 4002- (b) (6) and 4002- (b) (6), were transferred from Site #4002 (see above) to this site. According to the RRA report, Dr. Tchan stated that these two subjects transferred to his site when enrolled in the open-label extension study, ATB200-07. However, according to sponsor data line listings, these subjects did have a Week 52 for Protocol ATB200-03. Week 52 presumably occurred at this site since the last efficacy assessment at Site #4002 occurred at Week 38 for both subjects. Efficacy data for Week 52 was not provided by the clinical investigator for these two subjects and therefore could not be verified. There was no evidence of under-reporting of adverse events.

Due to data privacy restrictions, names and signatures of subjects on consent forms were redacted and therefore could not be reviewed to determine whether they were signed prior to the conduct of any study procedures. Records reviewed included, but were not limited to, source documents, IEC/sponsor communications, financial disclosure, inclusion/exclusion criteria, adverse events, concomitant medications, protocol deviations, key secondary efficacy data (sitting Forced Vital Capacity [FVC], % predicted), and primary efficacy data (6MWD).

Results for the 6MWT were recorded on paper and verified against the sponsor's data line listings; no discrepancies were noted. Results for FVC were available as print copies from the MasterScope spirometry device. The Quality Control grades for spirometry and ERT BTR were not available at the site (*refer to Quality Control Grades for Spirometry Results and Pulmonary Function Tests sections of report*).

The sitting FVC (% predicted), obtained from the best spirometry effort chosen automatically by MasterScope via algorithm, was verified against the sponsor line listings. A difference in sitting FVC (% predicted) was identified for one of three randomized subjects (Table 2).

Table 2. Sitting FVC (% predicted) Difference in MasterScope Best Spirometry Effort and Best Test Result in Sponsor Line Listing for Subject #4005- (b) (6)

Study Visit	Date	Sitting FVC (%) Predicted	
		MasterScope Best Spirometry Effort Source document	Best Test Result Sponsor Line Listing
Week 52	(b) (6)	92	89

Reviewer's comment: A difference was noted for sitting FVC (% predicted) between the MasterScope assigned best spirometry effort on the source data and the sponsor data line listings for Subject #4005- (b) (6). This difference was not a discrepancy as the source at the site did not contain the ERT selected BTRs, which were the basis of the line listings (refer to Quality Control Grades for Spirometry Results and Pulmonary Function Tests sections of report).

Subject #4005- (b) (6) – Statistical Outlier

One of the reasons for choosing this site was to verify data for Subject #4005- (b) (6) randomized to alglucosidase/placebo. According to the sponsor, this subject was a statistical outlier for the 6MWT and FVC (% predicted). In Section 11.5 of the Clinical Study Report (CSR), the sponsor stated that “after the database was locked and treatment assignments were unblinded, an outlier subject was identified whose baseline (screening) 6MWD result may have been adversely affected by his use of ostarine prior to study enrollment that resulted in a clinically implausible change at Week 52. Further, this subject admitted to intentionally underperforming during the baseline assessment to gain entry into the study.” The sponsor contends that the ITT population excluding the outlier subject should be considered as the primary analysis population.

Dr. Tchan saw this subject for the first time in February 2019, shortly after the subject was diagnosed with Pompe disease. During that visit, Dr. Tchan discussed potential treatment with alglucosidase alfa or enrollment in Protocol ATB200-03. No decisions about study enrollment were made at that time. He referred the subject to the subject's local physiotherapy team to perform a 6MWT along with other procedures and a plan to follow-up with the subject in 6 months. A 6MWT was performed on (b) (6) by an outside physiologist. The results of this 6MWT were reported to Dr. Tchan and verified during the RRA. The RRA also confirmed that this subject was ERT-naïve.

The 6MWT results for this pre-study assessment and 6MWT results obtained during Protocol ATB200-03 are listed in Table 3 and were verified during the inspection.

Table 3. Six-Minute Walk Test (6MWT) Results for Subject #4005 (b) (6)

Date	Study Visit	6MWD (meters)
(b) (6)	Not study related	585
	Screening 1	337.6
	Screening 2	302.8
	Week 12	360
	Week 26	455
	Week 38	627.4
	Week 52	656.8
	Week 52	694

The inspection confirmed that this subject began taking ostarine powder, purchased through the internet, in (b) (6) and discontinued it in (b) (6). A Note-to-File written and signed by Dr. Tchan, dated 3/16/2021, was obtained during the RRA. This document was written “offering some explanation as to why his trial results differ vastly from the expected and feasible outcomes” with regard to Subject #4005- (b) (6). According to this note, the subject reported a “significant increase in subjective strength and endurance” while taking the ostarine powder; yet the subject approached Dr. Tchan regarding participation in the research study. According to Dr. Tchan, the 6MWT that was performed on (b) (6) was done by an outside physiotherapist who did not make the subject walk around cones (walking around cones is standard procedure for the study). Dr. Tchan noted that “the use of cones during the 6MWT assessment in the study means that this metric cannot be accurately compared to the pre-baseline measurement prior to study entry.” Nonetheless, despite these explanations, according to Dr. Tchan, the subject reportedly did admit that he did not make a full effort with either the 6MWT or the PFT at the screening assessments to ensure that he was eligible for the study.

Reviewer comments

The RRA provided the following information:

1. According to Dr. Tchan, the 6MWT conducted prior to the study was not performed properly and not using the same procedure as the 6MWTs conducted during the study. Therefore, in Dr. Tchan’s opinion, the 6MWT results obtained prior to the study cannot be compared to 6MWT results obtained during the study – including the screening visits. The FVC conducted prior to the study was not reviewed during the RRA, and Dr. Tchan does not provide additional details on this assessment in the Note-to-File.
2. This subject discontinued the investigational steroid, ostarine powder, approximately one month prior to the screening visit. It is not known what impact, if any, this could have had on screening assessments. According to Dr. Tchan, the subject reported an “increase in subjective strength and endurance” while taking this supplement.

3. *According to the sponsor, the subject stated that assessments conducted after the screening visits were with “full effort”. Of note, the 6MWD for Week 12 was 360 meters, only 40 meters greater than the average of the screening 6MWD results.*
4. *Other than the Note-to-File written by Dr. Tchan approximately 6.5 months after the subject had completed the study, there is no other documentation (contemporaneous or otherwise) to support that this subject deliberately underperformed assessments to meet study eligibility criteria.*

Based on information obtained during this RRA, there was insufficient evidence to support exclusion of this subject from the primary analysis population.

Quality Control (QC) Grades for Spirometry Results

The printed spirometry results from the MasterScope included error codes, as applicable, but did not include an overall QC grade. An overall QC grade of F, for example, would indicate that the spirometry results were unacceptable. As described in the Pulmonary Function Test section in the Background section of this CIS, ERT assigned QC grades. On 1/4/2022, an information request was sent to the sponsor requesting additional information about QC grades, specifically, whether any spirometry results deemed unacceptable were used in the efficacy analyses for Study ATB200-03. In their 1/13/2022 response, the sponsor confirmed that 13 sitting FVC values for 6 subjects that received a Best Test Result (BTR) QC grade of “unacceptable” were used in data analyses. Of these 13 sitting FVC values, 9 were for visits used to calculate the key secondary endpoint of change from baseline (8 screening values, 1 Week 52 value). In their response, the sponsor provided a rationale for using these FVC values.

Reviewer comments: We recommend that the reveiw division perform a sensitivity analysis with regard to the subjects with sitting FVC BTR with QC grade “unacceptable” to assess the robustness of the results reported by the sponsor.

{See appended electronic signature page}

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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MEMORANDUM TO FILE

Version Date: February 8, 2022

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Shetarra Walker, MD, MSCR, Clinical Team
Leader, DPMH
John J. Alexander, MD, MPH, Deputy Director
DPMH

BLA Number: 761,204 (Pombiliti, cipaglucosidase alfa; CGA)

NDA Number: 215,211 (Opfolda, miglustat; MIG)

Applicant: Amicus Therapeutics

Indication: Treatment of adult patients with Pompe's disease

**Dosage Forms and
Routes of Administration:** CGA: Lyophilized powder for reconstitution in
solution (105 mg/mL); enzyme replacement therapy
(ERT), intravenous (IV) administration
Miglustat, 65 mg capsules, oral (PO) administration

Proposed Dosing regimens: CGA: 20 mg per kg body weight administered
every other week (EOW), intravenous (IV) infusion.
MIG: Patients ≥ 50 kg, 4 capsules (260 mg);
Patients ≥ 40 kg to < 50 kg, 3 capsules (195 mg
total). Administer EOW, 1 hour (b) (4)
(b) (4) before the start of the CGA
infusion

Division Consult Request: The Division of Rare Diseases and Medical
Genetics (DRDMG) requests DPMH-Pediatrics
input on labeling for this new set of products to be
administered concurrently (one PO and one IV) for
treatment of adults with Pompe's disease.

Background

The Applicant is developing CGA, an ERT for co-administration with MIG for treatment of adults with Pompe disease (PD). PD is a rare autosomal recessive genetic disorder caused by mutations in the gene which encodes human acid α -glucosidase (GAA), a lysosomal enzyme responsible for the breakdown of lysosomal glycogen. On September 13, 2017, FDA granted orphan designation for the combination of CGA-MIG for treatment of PD.

Infantile- and late-onset PD (IOPD and LOPD) exist with overlapping features. IOPD usually presents by 6 to 12 months of age with hypotonia, generalized muscle weakness, respiratory distress, and hypertrophic cardiomyopathy. Prior to availability of ERT, most patients died by 3 years of age. LOPD presents anywhere from 12 months to adulthood with muscle weakness, particularly of the limb-girdle and axial stabilizing muscle groups, and respiratory muscles. Life span in patients with LOPD is shortened and death may occur from failure of pulmonary mechanics.

Three other ERTs are approved for treatment of patients with PD, none of which are co-administered with MIG or any other enzyme stabilizer:

- Myozyme (BLA: 125,141; recombinant human alglucosidase alfa), which was first approved in 2006 and indicated for treatment of IOPD, but which is no longer marketed in the United States (US).
- Lumizyme (BLA: alglucosidase alfa), which is currently marketed in the US, was approved in 2010 and indicated for treatment of patients with IOPD and LOPD.
- Nexvazyme (avalglucosidase alfa-ngpt), which was approved in 2021, is indicated for treatment of patients with LOPD. Studies of pediatric patients with IOPD are planned.

Zavesca (NDA 21,348), another miglustat product administered as PO capsules, is marketed as a glucosylceramide synthase inhibitor indicated as monotherapy for treatment of adult patients with mild/moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.

Neither CGA nor MIG will be indicated in pediatric patients based on data in the current submission. The Applicant is currently conducting an open-label pharmacokinetic (PK), pharmacodynamic (PD), safety and efficacy study in pediatric patients 12 to less than 18 years with LOPD (protocol ATB200-04). The Applicant is planning to conduct a safety, efficacy, PK, PD, immunogenicity study in both ERT-experienced and ERT-naïve pediatric patients 0 to less than 18 Years with IOPD.

Reviewer comment: The ongoing and planned pediatric studies are acknowledged.

(b) (4)



Labeling Review

Labeling recommendations for CGA will be presented first followed by labeling recommendations for MIG. Recommendations for CGA will focus on the proposed boxed warning and sections 1 (Indications and Usage), 2 (Dosage and Administration), 5 (Warnings and Precautions), and 8.4 (Pediatric Use). Recommendations for MIG will focus on the proposed (b) (4) sections 1, 2, 5, and 8.4. For both sets of labeling, review of other sections such as 6 (Warnings and Precautions) and 14 (Clinical Studies) are deferred to DRDMG and other consultant divisions (e.g., Clinical Pharmacology) as required. For this review, text which DPMH recommends deleting is noted by ~~strike out~~, and any text which DPMH recommends adding is noted in **bold red**. The comments below were provided to DRDMG on February 3, 2022. The reader is directed to final approved labeling, which may include revised language not addressed in this review.

Reviewer comment: Similar to combination products with two active components within the same formulation, the safety and efficacy of both CGA and MIG need to be established. However, since each drug will be administered separately, two sets of labeling will be issued, one for each product. Details in some sections (i.e., the indication statement) may be similar or identical, while other sections of labeling (e.g., boxed warning, dosage and administration) may differ.

Pombiliti (cipaglucosidase-alfa)

Boxed Warning



Reviewer comment: Since hypersensitivity/anaphylactic reactions and IARs are class-related for ERTs for PD, the descriptions should mirror the descriptions in labeling for other products (BLA 761194 Nexviazyme, and Lumizyme BLA 125,291). While hypersensitivity/anaphylactic reactions and IARs are described in a single paragraph in Lumizyme labeling, they are described separately in Nexviazyme labeling. Additionally, Nexviazyme labeling includes a separate warning regarding acute cardiorespiratory failure in susceptible patients. The risk of cardiorespiratory failure described in Nexviazyme labeling appears to be attributed to mechanical/volume considerations. Therefore, if the infused volume of CGA is expected to be similar to the infused volume of Nexviazyme, the CGA box warning should include a similar warning regarding acute respiratory failure. A proposed boxed warning based on Nexviazyme labeling is presented below for illustrative purposes.

WARNING: SEVERE HYPERSENSITIVITY REACTIONS, INFUSION-ASSOCIATED REACTIONS, and RISK OF ACUTE CARDIORESPIRATORY FAILURE IN SUSCEPTIBLE PATIENTS

See full prescribing information for complete boxed warning.

Hypersensitivity Reactions Including Anaphylaxis

• Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If a severe hypersensitivity reaction occurs, POMBILITI should be discontinued immediately, and appropriate medical treatment should be initiated. (5.XXXX) Infusion-Associated Reactions (IARs)

• If severe IARs occur, consider immediate discontinuation and initiation of appropriate medical treatment. (5.YYYY) Risk of Acute Cardiorespiratory Failure in Susceptible Patients

• Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function, may be at risk of serious exacerbation of their cardiac or respiratory status during POMBILITI infusion (5.ZZZZ).

1 Indications and Usage

(b) (4)

(b) (4)

(b) (4)

2 Dosage and Administration

Reviewer comment: Review of section 2 will be performed by DRDMG and Clinical Pharmacology. The current version of the text is presented below for illustrative purposes and is subject to further revision.

2.1 Recommended Dosage and Administration

POMBILITI is to be administered in combination with Opfolda. Refer to OPFOLDA prescribing information prior to reconstituting POMBILITI.

The recommended dosage of POMBILITI is 20 mg/kg body weight administered every other week as an intravenous infusion over approximately 4 hours.

Start infusion of POMBILITI between (b) (4) after oral administration of OPFOLDA. In the event of infusion delay, the start of infusion should not exceed 3 hours from the oral administration of OPFOLDA.

The initial recommended infusion rate is 1 mg/kg/hr. Gradually increase the infusion rate by 2 mg/kg/hr every 30 minutes if there are no signs of infusion-associated reactions (IARs) until a maximum rate of 7 mg/kg/hr is reached; then, maintain the infusion rate at 7 mg/kg/hr until the infusion is complete. The approximate total infusion duration is 4 hours.

For patients who experience infusion-associated reactions to POMBILITI, premedicate with corticosteroids, antihistamines, and antipyretics. Monitor patients for the occurrence of new IARs. [see *CONTRAINDICATIONS (4)* and *WARNINGS AND PRECAUTIONS (5.1)*].

2.2 Dosage and Administration Modifications Due to Hypersensitivity Reactions and/or Infusion-Associated Reactions

(b) (4)

2.3 Preparation and Administration Instructions

Reconstitution and Dilution Using Aseptic Technique

1. Determine the number of POMBILITI vials to be reconstituted based on the patient's body weight.
2. Remove vials from the refrigerator and allow to come to room temperature (i.e., approximately 30 minutes)
3. Reconstitute each vial by slowly injecting 7.2 mL of Sterile Water for Injection, USP, down the inside wall of each vial to avoid foaming.
4. Roll and tilt the vial to allow the powder to dissolve completely which typically takes 2 minutes. Each vial will yield a concentration of 15 mg/mL. Do not invert, swirl, or shake.
5. Visually inspect the solution after reconstitution for particulate matter and discoloration. (b) (4)
Discard if foreign matter is observed or the solution is discolored.
6. Slowly withdraw 7 mL of reconstituted solution from the vials until the patient's dose is obtained. Discard any remaining reconstituted solution in the last vial.
7. Dilute the POMBILITI solution promptly with 0.9% Sodium Chloride Injection, USP, to a final volume according to Table 1.
8. To prevent foaming, avoid vigorous shaking and agitation and gently invert infusion bag to mix the solution. Do not use a pneumatic tube to transport the infusion bag. The infusion solution should be administered at room temperature soon after dilution preparation [see *DOSAGE AND ADMINISTRATION (2.1)*].

Administration

1. Prior to administration, inspect the infusion bag for foaming. If foaming is present, let foam dissipate before administering POMBILITI.
2. Use (b) (4) intravenous administration set with an inline low protein binding 0.2-micron filter to administer POMBILITI.

3. Infuse POMBILITI (b) (4) after oral administration of OPFOLDA. In the event of infusion delay, start infusion no more than 3 hours from the oral administration of OPFOLDA.
4. The initial recommended infusion rate is 1 mg/kg/hr. Gradually increase the infusion rate by 2 mg/kg/hr every 30 minutes if there are no signs of infusion-associated reactions (IARs) until a maximum rate of 7 mg/kg/hr is reached; then, maintain the infusion rate at 7 mg/kg/hr until the infusion is complete. The approximate total infusion duration is 4 hours.
5. See Table 1 for the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

Table 1. Recommended Infusion Volumes and Rates

Patient Weight Range (kg)	Total infusion volume (mL)	Step 1 1 mg/kg/hr (mL/hr)	Step 2 3 mg/kg/hr (mL/hr)	Step 3 5 mg/kg/hr (mL/hr)	Step 4 7 mg/kg/hr (mL/hr)
40–50	250	13	38	63	88
50.1–60	300	15	45	75	105
60.1–100	500	25	75	125	175
100.1–120	600	30	90	150	210
120.1–140	700	35	105	175	245
140.1–160	800	40	120	200	280
(b) (4)					

6. Do not infuse POMBILITI in the same intravenous line with other products.

Storage and Handling

- If the reconstituted POMBILITI vial is not used immediately, store refrigerated at 36°F to 46°F (2°C to 8°C) for up to 24 hours. Do not freeze.
- After dilution, POMBILITI is (b) (4) stored refrigerated at (b) (4) 36°F to 46°F (2°C to 8°C) (b) (4) Do not freeze.

5 Warnings and Precautions

5.1 (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Mild and transient IARs may not require medical treatment or discontinuation of the POMBILITI infusion. Reduction of the infusion rate, temporary interruption of the infusion, or symptomatic treatment with oral antihistamine, antipyretics and/or corticosteroids, have effectively managed most IARs.

(b) (4)

(b) (4) Acute Cardiorespiratory Failure in Susceptible Patients

Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during the POMBILITI infusion. More frequent monitoring of vitals should be performed during POMBILITI infusion in these patients. Some patients may require prolonged observation times.

(b) (4)

(b) (4)

(b) (4)

8.4 Pediatric Use

The safety and effectiveness of (b) (4) **POMBILITI, alone or in conjunction with OPFOLDA, for the treatment of pediatric patients with LOPD** (b) (4) have not been established (b) (4)

Reviewer comment: The above revision reflects the indication and the conditions of study.

Opfolda (miglustat)

(b) (4)

(b) (4)

Reviewer comment:

(b) (4)

(b) (4)

Though CGA and MIG will be administered in close temporal proximity,

(b) (4)

(b) (4)

DPMH will discuss this issue with DRDMG prior arriving at consensus recommendations.

1 Indications and Usage

OPFOLDA

(b) (4)

(b) (4)

2 Dosage and Administration

Reviewer comment: Review of section 2 is performed by DRDMG and Clinical Pharmacology. The current version of the text is presented below for illustrative purposes and is subject to further revision.

2.1 Recommended Dosage and Administration

OPFOLDA is to be administered in combination with Pombiliti. Refer to Pombiliti prescribing information prior to administering OPFOLDA.

The recommended dosage of OPFOLDA is based on body weight:

•

(b) (4)

•

(b) (4)

Take OPFOLDA on an empty stomach (b) (4) before intravenous administration of Pombiliti and swallow capsules with unsweetened beverages (i.e., water, tea/coffee with no cream, sugar, or sweeteners). (b) (4)

(b) (4) Consumption of these beverages is permitted during this 4-hour fasting period. (b) (4)

5 Warnings and Precautions

Reviewer comment: The above issues most likely relate to CGA rather than MIG. The Applicant or DRDMG should review the safety data to determine what, if any, safety issues from the MIG component warrant description in Warnings and Precautions. Providing the Warnings and Precautions from other miglustat labeling is likely not appropriate since the dosage regimen for Gaucher disease (100 mg PO, three times daily) differs from the regimen for LOPD (195 mg every other week (EOW) for patients weighing ≥ 40 kg to <50 kg, and 260 mg EOW for patients weighing ≥ 50 kg).

8.4 Pediatric Use

The safety and effectiveness of OPFOLDA, (b) (4) **in combination with POMBILITI,** (b) (4) have not been established.

Reviewer comment: The above revision reflects the indication and the conditions of study.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ETHAN D HAUSMAN
02/08/2022 10:52:40 AM

SHETARRA E WALKER
02/08/2022 12:11:29 PM

JOHN J ALEXANDER
02/08/2022 01:11:56 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 14, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Jenny Doan, RPM
DRDMG

Subject: QT Consult to NDA215211/BLA761204 (SDN 001 / 003)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/8/2021 regarding the sponsor's QT related question. We reviewed the following materials:

- Previous IRT review(s) for IND 127387 dated [10/19/2020](#) and [04/02/2021](#) in DARRTS;
- Draft label under NDA215211 (SDN 001, [link](#)) and BLA761204 (SDN 003, [link](#));
- Highlights of clinical pharmacology and cardiac safety (IND127387 / SDN 0149; [link](#));
- Pharmacology written summary (NDA 215211, eCTD 0001; [link](#));
- Nonclinical summary of toxicology (BLA 761204, eCTD 0001; [link](#));
- In vitro GLP hERG assay report 201027 (b) (4) (NDA 215211 / SDN 001, [link](#)) and related raw data (NDA215211 / SDN 010, [link](#));
- 13-Week Repeat Dose Study in Cynomolgus Monkeys study (b) (4)-423-10 (BLA 761204 eCTD 0001; [link](#)); and
- Cardiac Safety Report (NDA 215211 / eCTD 0003; [link](#)).

1 Responses for the Division

Question: The Division (DRDMG) receives an original BLA for ATB 200 and new NDA for miglustat (to be co-administered with ATB200) (b) (4)

DRDMG requests IRT to review and comment on the submitted ECG data for ATB200-03 trial and the final report Cardiac Safety of Cipaglucosidase alfa/Miglustat provided in module 5.3.5.4 of NDA 215211. Input to the labeling will also be appreciated. The QTc study was pre-agreed, during the pre-BLA meeting (for Miglustat), to be a PMR.

IRT's response: We previously recommended a clinical QT study for miglustat + cipaglucosidase alfa because of higher mean maximal concentration ($C_{\max}$) for miglustat (~3000 ng/mL) compared to the mean $C_{\max}$ with an already approved product (ZAVESCA: 1920 ng/mL) and limited supporting clinical and nonclinical information.

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 and we therefore recommend removing labeling statements as proposed below.

While the clinical ECG data are not informative, we consider the potential for QTc prolongation low for cipaglucosidase alfa and miglustat and it is appropriate to conduct the QT assessment as a PMR because:

1. Miglustat is an approved product, and the exposure is not significantly higher compared to the already approved product ZAVESCA. Per the product labeling for OPFOLDA, there are no known intrinsic or extrinsic factors that will increase exposure to miglustat, but we defer the final assessment to the Office of Clinical Pharmacology.
2. Nonclinical data suggests low potential for QTc prolongation for miglustat an *in vitro* assay that met most best practice elements per ICH S7B Q&A 2 showed no direct inhibition of hERG current at clinical exposures (hERG safety margin >73 – no effect at 1000 μ M) and no signal for QTc prolongation in an *in vivo* toxicology study at 5.6x the clinical exposures.
3. Cipaglucosidase alfa is a large protein and is therefore expected to have a low risk of direct ion channel interaction (ICH E14 Q&A R3 6.3).

Based on the totality of evidence of data submitted thus far and the low risk for QT prolongation for this product the Applicant could consider collecting ECGs at $T_{\max}$ in ongoing trials in a subset of patients to support the PMR for a QT evaluation. We recommend that the Applicant submits their plan for QT assessment for review.

We are including our recommended suggestions below for both labels. Our changes are highlighted (**addition**, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

Proposed labeling for miglustat (NDA215211 (SDN 001, [link](#)))

Cardiac Electrophysiology

The effect of DRUG on the QTc interval has not been adequately characterized.

(b) (4)

The proposed labeling language is based on the information described in the Cardiac Safety Report which is inadequate to allow for characterization of the clinical QT prolongation potential for miglustat. For products that require a QT assessment and the effect on the QTc interval has not been characterized or insufficient data are available to characterize the effect, the proposed edits are recommended in the draft Guidance for Industry, "QT Information in Labeling for Drug and Biological Products" which is currently undergoing internal clearance.

(b) (4)

Large proteins have a low risk for cardiac ion channel interaction (ICH E14 Q&A R3 6.3) and for these products we therefore generally do not include QTc language in the label. This is consistent with the recommendations in the draft guidance cited above.

Not applicable.

Amicus Therapeutics, the Applicant, is developing cipaglucosidase alfa to be concomitant administered with miglustat for the (b) (4) treatment of adult (b) (4) (b) (4) patients with late-onset Pompe disease (LOPD). The Applicant is asserting that miglustat binds to cipaglucosidase alfa, protects cipaglucosidase alfa from denaturation in the blood and enhances the pharmacokinetics of cipaglucosidase alfa. The proposed therapeutic dosing regimen is miglustat 260 mg plus 20 mg/kg cipaglucosidase alfa every other week.

Because miglustat is an already approved product the need for a QTc assessment depends on whether the exposure is significantly higher for this new product, additional ECG data are considered necessary for the new indication or patient population or if there is a post-marketing concern (ICH E14). In our initial review, we noted that the C_{max} for the new dosing was reported to be 3176 ng/mL at the maximum clinical dosing regimen proposed. Because of the higher exposure, lack of a dedicated QT study in the past and lack of convincing nonclinical data we recommended a clinical study to be conducted (DARRTS 10/19/2020). We were subsequently consulted concerning the timing of the thorough QT study and deferred the timing of the thorough QT study to the review division (DARRTS 04/02/2021). Per the consult request a QT study was pre-agreed during the pre-BLA meeting as a PMR.

The nonclinical QTc evaluation includes a hERG assay (201027 (b) (4)) and ECGs collected in a 13-week repeat dose toxicity study in Cynomolgus Monkeys ((u) (4) -423-10).

3

related gene (hERG) were determined. Two concentrations of AT2221 (100 μ M and 1000 μ M) were tested at near-physiological temperature. AT2221 inhibited hERG current by (Mean $\pm$ SEM; n = 3) $-3.1 \pm 1.1\%$ at 100 μ M and $-3.4 \pm 2.2\%$ at 1000 μ M versus $1.1 \pm 1.2\%$ in control. hERG inhibition at 100 μ M and 1000 μ M were not statistically significant ($p < 0.05$) when compared to vehicle control values. The IC₅₀ for the inhibitory effect of AT2221 on hERG potassium current was not calculated but was estimated to be greater than 1000 μ M.

The positive control article terfenadine inhibited hERG potassium current by (Mean $\pm$ SD; n = 2) $88.9 \pm 2.4\%$ at 60 nM. This result confirms the sensitivity of the test system to hERG inhibition.

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

Reviewer's Comments: *The hERG assay met most of best practice recommendations for an in vitro assay according to the new draft ICH S7B Q&As 2.1 ([link](#); Table 5). We re-analyzed the original electrophysiological records for this study to assess data quality and verify study report conclusions (Appendix 4). The results of our independent analysis are consistent with the applicant's and show that miglustat has a low potential to prolong the QT interval by inhibition the hERG current at the anticipated therapeutic exposures (hERG safety margin >73 – no effect at 1000 μ M).*

Cipaglucosidase alfa, both with and without miglustat, was administered once every other week (QOW) for 13 weeks to cynomolgus monkeys. Cipaglucosidase alfa was administered by 2-hour intravenous (IV) infusion and was either co-administered with oral miglustat (nasogastric gavage) [Group 2 (50 mg/kg cipaglucosidase alfa, 25 mg/kg miglustat; Group 3 (100 mg/kg cipaglucosidase alfa, 175 mg/kg miglustat)] or administered alone as monotherapy [Group 5 (100 mg/kg cipaglucosidase alfa)]. Miglustat was administered 30 minutes prior to the start of the infusion of cipaglucosidase alfa in Groups 2 and 3 and in Group 4 miglustat was administered alone (175 mg/kg) at the same time the other groups received miglustat.

There were no changes attributable to cipaglucosidase alfa or miglustat or to their co-administration on physical examination endpoints, food consumption, clinical observations, detailed clinical observations, body weights, ophthalmology, or ECG parameters.

Reviewer's Comment: *The in vivo QTc assessment in this study includes ECGs collected pre- and post-dose on days 15 and 85 for each dose group and animals were sedated per the study report. Based on the PK data collected in this study (Table 1), the exposures at the timing of ECG collection post-dose (0.5 to 1 h) the combined C_{max} for female and male Cynomolgus monkeys (100 mg/kg cipaglucosidase alfa + 175 mg/kg miglustat: 16900 ng/mL) covers ~5.6x the clinical exposure. No consistent increase in HR (Table 2) or QTcB (Table 3) was observed in this study when comparing pre to post-dose on days 1 and 71.*

Table 1: Mean miglustat PK in male and female Cynomolgus monkeys

Group Sex	Day 1		Day 85	
	Pre	1h post	Pre	1h post
Vehicle				
Female	<0.5	<0.5	N/R	N/R
Male	<0.5	<0.5	N/R	N/R
50 mg/kg cipaglucosidase alfa + 25 mg/kg miglustat				
Female	<0.5	5510	<0.5	2560

Male	<0.5	6910	<0.5	4970
100 mg/kg cipaglucoisidase alfa + 175 mg/kg miglustat				
Female	<0.5	10100	0.79	6470
Male	<0.5	22000	1.3	23000
175 mg/kg miglustat				
Female	<0.5	12800	0.67	8500
Male	<0.5	9240	0.60	11600
100 mg/kg cipaglucoisidase alfa				
Female	<0.5	N/R	N/R	N/R
Male	<0.5	<0.5	N/R	N/R

Source: (b) (4) -423-10, Table 9 in Final Toxicokinetics Report

Abbreviations: N/R: Not reported

Table 2: Mean (SD) HR in male and female Cynomolgus monkeys

Group Sex	Day 15		Day 71	
	Pre	Post ¹	Pre	Post ¹
Vehicle				
Female	164 (16)	196 (18)	159 (11)	184 (14)
Male	142 (20)	170 (22)	137 (22)	148 (20)
50 mg/kg cipaglucoisidase alfa + 25 mg/kg miglustat				
Female	175 (20)	191 (17)	186 (19)	189 (19)
Male	174 (16)	173 (32)	168 (33)	170 (35)
100 mg/kg cipaglucoisidase alfa + 175 mg/kg miglustat				
Female	187 (36)	192 (31)	195 (19)	201 (18)
Male	183 (8)	177 (14)	161 (27)	193 (19)
175 mg/kg miglustat				
Female	174 (18)	185 (9)	169 (5)	163 (17)
Male	169 (18)	168 (20)	151 (16)	158 (31)
100 mg/kg cipaglucoisidase alfa				
Female	186 (15)	179 (9)	172 (11)	177 (13)
Male	167 (13)	170 (16)	155 (17)	149 (8)

¹: 0.5 to 1 h post-dose

Source: (b) (4) -423-10, Table 1 in Final Electrocardiography Report

Table 3: Mean (SD) QTcB in male and female Cynomolgus monkeys

Group Sex	Day 15		Day 71	
	Pre	Post ¹	Pre	Post ¹
Vehicle				
Female	354 (15)	349 (16)	353 (11)	350 (8)
Male	347 (14)	348 (17)	347 (11)	351 (11)
50 mg/kg cipaglucoisidase alfa + 25 mg/kg miglustat				
Female	349 (7)	351 (9)	348 (5)	349 (7)

Male	348 (9)	348 (8)	352 (18)	350 (16)
100 mg/kg cipaglucosidase alfa + 175 mg/kg miglustat				
Female	353 (10)	351 (7)	348 (6)	345 (13)
Male	343 (11)	344 (15)	350 (9)	348 (16)
175 mg/kg miglustat				
Female	342 (8)	344 (7)	345 (9)	347 (9)
Male	338 (13)	333 (19)	340 (11)	337 (8)
100 mg/kg cipaglucosidase alfa				
Female	352 (12)	353 (13)	348 (13)	350 (12)
Male	347 (10)	346 (8)	351 (12)	350 (13)

¹: 0.5 to 1 h post-dose

Source: ^{(b) (4)} -423-10, Table 1 in Final Electrocardiography Report

3.2 Clinical Cardiac Safety

The clinical QTc is based on two clinical studies ATB200-02 and ATB200-03.

In study ATB200-02, the first in human trial in adults with Pompe Disease, ECGs were collected and managed by the investigational sites. Cipaglucosidase alfa was administered in single doses of 5, 10, and 20 mg/kg for the first 3 doses in Stage 1 for cohort 1. In Stage 2 for cohort 1, multiple doses of 20 mg/kg IV every 14 days, with miglustat 3 doses of 130 mg administered 1 hour prior to the start of infusion followed by the next 3 doses of 260 mg (n=29). Cohorts 2, 3 and 4 only received the 20 mg/kg dose of cipaglucosidase and 260 mg of miglustat. There were no significant changes in QTcF or other ECG parameters on ECGs collected immediately following the end of cipaglucosidase alfa infusion through up to 24 months of treatment. No patients had QTcF > 450 ms or QTcF increase from baseline > 60 ms, and only 2 patients had QTcF increases from baseline between 30 – 40 ms.

Reviewer's Comment: This study included 4 cohorts and patients received 260 mg (the therapeutic dose) starting in stage 2 (cohort 1) and stage 3 (cohorts 2 – 4). Miglustat was dosed 1 hr prior to starting the 4 hr infusion of cipaglucosidase alfa. ECGs were only collected at pre-dose and end of infusion for cipaglucosidase alfa and therefore misses the Tmax of miglustat (~3h).

Study ATB200-03 (completed) was a Phase 3 double-blind randomized study to assess the efficacy and safety of intravenous cipaglucosidase alfa co-administered with oral miglustat in adult subjects with late-onset Pompe Disease compared with alglucosidase alfa/placebo. The study consisted of a screening period up to 30 days, a 12-month treatment period, and a 30-day safety follow-up period.

A total of 130 subjects were screened, 123 subjects were randomized and dosed (95 ERT-experienced and 28 ERT-naïve), and 117 completed the study (with 6 discontinuations in the ERT-experienced population) at 62 clinical sites across 24 countries. Eligible patients were randomly assigned in a 2:1 ratio to cipaglucosidase alfa /miglustat or alglucosidase alfa/placebo and stratified by ERT status (ERT-experienced, ERT-naïve) and baseline 6-minute walk distance (6MWD) (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters).

12-lead ECGs were collected at Screening and on Day 1, Weeks 12, 26, 38, and 52 (or at early termination) prior to dosing.

A review of the ECGs collected to date from the Double Blind Treatment period reveals the following:

- No patients have had substantial increases in heart rate, PR, or QRS duration
- 7 patients have had one or more QTcF values >450, of whom 2 had preexisting complete right bundle branch block, 1 had preexisting complete left bundle branch block, and 1 had a preexisting nonspecific intraventricular conduction defect with QRS durations between 120-130 ms. There were 3 patients who had normal QRS duration, and had maximum QTcF values between 450 and 460 ms. 2 of these patients had QTcF > 450 ms at Screening as well as on one or more post Screening ECGs, while 5 patients had QTcF > 450 ms only on post Screening ECGs. There were therefore 5 patients with new QTcF > 450 ms.
- 2 patients have had one or more QTcF values > 480 ms, including 1 patient with preexisting left bundle branch block (and QTcF > 480 ms at Screening) and 1 patient with a preexisting nonspecific intraventricular conduction defect and QRS durations between 120-130 ms (but with QTcF ≤ 480 ms at Screening). There was thus one patient with new QTcF > 480 ms.
- 1 patient randomized to alglucosidase alfa has had a QTcF value > 500 ms in the presence of preexisting complete left bundle branch block and a QTcF of 490 ms at Screening.
- No patients had QTcF change from baseline > 60 ms.
- 11 patients had QTcF change from baseline >30-60 ms (the largest QTcF change from baseline was 40 ms).
- One patient randomized to alglucosidase alfa (subject 1108-2691) developed new atrial fibrillation at week 52.
- No patients developed new right bundle branch block, new left bundle branch block, new myocardial infarction, or new ST segment depression.
- One patient randomized to cipalglucosidase alfa/miglustat (subject 1106-1641) developed new Twave inversion in leads I and aVL at week 52.

Reviewer's Comment: *The ECGs collected in ATB200-03 were only at pre-dose and therefore does not provide information about the QTc prolongation at the time of peak miglustat concentration.*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrdcrpqt@fda.hhs.gov

4 APPENDIX I: REVIEW OF SUPPORTING NONCLINICAL DATA

4.1 SPONSOR'S SUBMISSION

4.1.1 In vitro hERG assays

The sponsor evaluated the effects of ATB2221 (miglustat) on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The GLP hERG study report 201027^{(b) (4)} ([link](#)) describes the potential effects of ATB2221 on the hERG current in HEK cells. The hERG current was assessed at near-physiological temperature (33 - 35°C), using a voltage protocol that is similar to the recommended hERG current protocol at IRT's website ([link](#)). The positive control (60 nM terfenadine) inhibited hERG potassium current by 88.9%. Samples of the test article formulation solutions collected from the outflow of the perfusion apparatus were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of ATB2221 at all test concentrations were within $\pm$ 15.0% of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects.

ATB2221 inhibited the hERG current by 3.1% and 3.4%, at concentrations of 100 μ M 1000 μ M, respectively. Higher concentrations were not tested due to the limits of the validated analytical method. The IC₅₀ for the inhibitory effect of AT2221 on hERG potassium current is estimated to be greater than 1000 μ M.

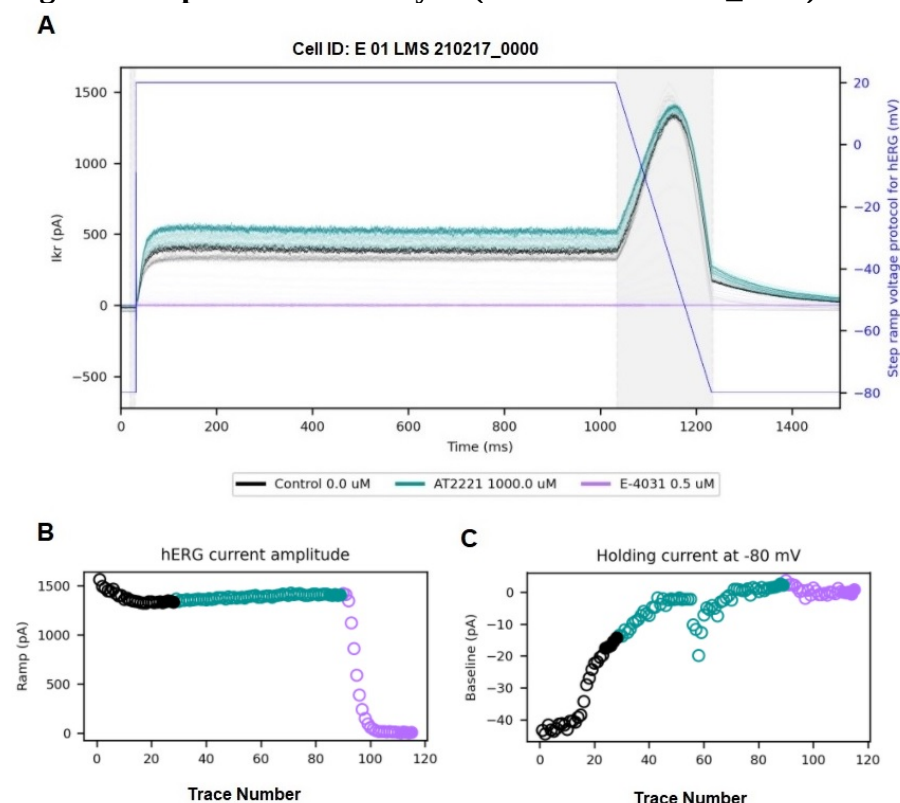
4.2 REVIEWER'S ASSESSMENT AND DATA REANALYSIS

Original electrophysiology records for the hERG assays (201027^{(b) (4)}) were provided by the sponsor. IRT reanalyzed these records and assessed data quality by examining current traces from all cells, and verifying assay recording stability/quality.

The hERG current was assessed at physiological temperature (33-35°C), at the stimulating frequency of 0.2 Hz, using a voltage protocol that is similar to the recommended hERG protocol available at IRT's website ([link](#)). The reviewer doesn't expect the difference of voltage protocol will impact the hERG current pharmacology. Only one concentration of the positive control (60 nM terfenadine), which inhibited hERG potassium current by 88.9%, was used in the study. However, this is not sufficient to meet current ICH S7B Q&As best practice recommendations, which state that "two or more concentrations [of the positive control] spanning 20% to 80% block should be used". Moreover, no safety margins computed under the same experimental protocol for a series of drugs known to cause TdP were included.

Representative analysis from cell E 01 LMS 210217_0000 is shown in Figure 1. Panel A shows last five recorded traces of each treatment group from this cell with background current subtraction. The voltage waveform used to evoke hERG current is shown in blue. The gray shade on the right highlights the region where peak hERG tail current was measured. Shaded gray area on the left shows measurement cursor used to calculate holding current throughout the experiment. Traces recorded in control solution are shown in black, following 1000 μ M ATB2221 application in green; and following application of E-4031 (0.5 μ M), a selective hERG blocker, in pink. Time course plots for peak ramp current and holding current are shown on panels B and C, respectively.

Figure 1: Representative analysis (E 01 LMS 210217_0000)



The hERG current amplitudes from the last 5 traces acquired in control (black solid circles) and in drug solution (green) were then averaged to calculate % inhibition by that concentration. Results of ATB2221 after background current subtraction on hERG current are summarized in Table 4.

Table 4: Effects of ATB2221 on hERG current

Test article	N	Mean (%)	SEM (%)
ATB2221 100 μ M	3	-5.1	1.3
ATB2221 1000 μ M	3	-6.6	0.9

While there are numerical differences in the results from IRT's independent analysis compared to the sponsor's, these do not change overall conclusions. That is, IRT's independent analysis of the submitted electrophysiology data shows that ATB2221 have low potential to interact with the hERG current at concentrations up to 1000 μ M and that the hERG IC_{50} of ATB2221 is expected to be larger than 1000 μ M.

4.3 SUMMARY

The comparisons of sponsor's hERG assay and the best practice recommendations by the new draft ICH S7B Q&A 2.1 are summarized in Table 5.

Table 5: Comparison of sponsor's hERG assays with the new draft ICH S7B Q&As best practice recommendations

Elements	Sponsor's hERG assays	ICH Best Practice recommendations	Present?
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Temperature	Near Physiological(33-35°C)	physiological (35 – 37°C)	Yes
Voltage protocol	Similar voltage protocol for hERG assays available at IRT's website	The voltage protocols used to evoke ionic currents should approximate the appropriate elements of a ventricular action potential and be repeated at physiologic intervals to ensure examination and capture of frequency-dependent effects of the test drug. The voltage protocol should include steps that enable monitoring of cell health and consistent electrophysiological recordings throughout the experiment.	Yes
Recording quality	Currents reached steady-state in control solution and after drug applications. There seems to be some run-up in the peak current after AT2221 addition, but the reviewer deemed this to be small and not significant.	A sufficient number of traces should be recorded in control solution to illustrate that steady state level is achieved prior to drug application, and that drug effect reached steady state. Seal resistance should be high enough so that the leak conductance at all voltages specified by the voltage protocol and series resistance do not compromise voltage control.	Yes
Background current subtraction	E-4031 (0.5 µM) added at the end of experiment in each cell.	A full blocker (E-4031 at 0.5 to 1.0 µM) should be added at the end of the experiment	Yes
Data summary	Data in tabular form from each cell showing the effects of the test articles at each concentration and the effect of the positive control, with summary statistics. The report will include example traces of currents, time-course plots (I-T plots).	The primary endpoints are half inhibitory concentration or IC50 value (reported in both micromolar and ng/mL units) and the Hill coefficient. A table with each individual cell's fractional block value to estimate the variability of experimental data and quantify the uncertainty of calculated block potency parameters should be provided. The study report should contain example traces of specific currents and examples of time-course plot of current amplitude, input resistance, and holding current for individual cells, in the absence and presence of test drug.	Yes
Concentration verification	Drug concentration verification were conducted. Solution samples were collected from the outflow of perfusion apparatus (immediately after the chamber).	The concentrations of drug to which the cells were exposed should be verified by a validated analytical method.	Yes

Positive Control	Terfenadine 60 nM. There was no rationale to support defining the hERG safety margin nor a series of reference compounds with known TdP risk	two or more concentrations of a spanning 20–80% block.	No
Negative Control (vehicle)	Vehicle control included in the study	Vehicle (negative) controls should be included in the study to provide an assessment of recording stability and level of background current.	Yes

Table 6: Safety Margin of ATB2221 on hERG Current

	C _{max} (ng/mL)	Protein Binding	Free C _{max} (ng/mL)	hERG IC ₅₀ (μM)	Mol Weight (g/mol)	Safety Margin (Ratio)
ATB2221	3000	0%	3000	>1000	219.28	>73x

C_{max}: Per the label, the C_{max} is ~3000 ng/mL

In summary, the hERG assay met most of best practice recommendations for an *in vitro* assay according to the new draft ICH S7B Q&A 2.1 ([link](#)). The hERG results showed that ATB2221 has a hERG safety margin of > 73x (no effect at 1000 μM), suggesting it has low potential to prolong the QT interval by directly inhibiting the hERG current at the anticipated therapeutic exposures.

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/s/

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