CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761204Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 127387

MEETING MINUTES

Amicus Therapeutics, Inc.
Attention: Jamie L. Gault, RAC
Executive Director, Global Regulatory Affairs
3675 Market Street
Philadelphia, PA 19104

Dear Ms. Gault:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ATB200 co-administered with miglustat.

We also refer to the teleconference between representatives of your firm and the FDA on April 20, 2021. The purpose of the meeting was to discuss the data package and regulatory pathway for ATB200 co-administered with miglustat as (b) (4) treatment in adult patients with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jenny Doan, Regulatory Project Manager, at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Kathleen M Donohue, MD, MSc
Director
Division of Rare Diseases and Medical Genetics
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: April 20, 2021; 10:15 AM – 11:15 AM EDT
Meeting Location: Teleconference

Application Number: IND 127387
Product Name: ATB200 co-administered with miglustat

Sponsor Name: Amicus Therapeutics, Inc.
Indication: Treatment of Pompe disease
Regulatory Pathway: 351(a) of the Public Health Service Act for ATB200
505(b)(1) of the Food, Drug, and Cosmetics Act for miglustat

Meeting Chair: Jacqueline Karp, MD, Medical Team Leader (Acting)
Meeting Recorder: Jenny Doan, Regulatory Health Project Manager

FDA ATTENDEES

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Janet Maynard, MD, Deputy Director

Division of Rare Diseases and Medical Genetics
Kathleen Donohue, MD, Director
Patroula Smpokou, MD, Deputy Director
Jacqueline Karp, MD, Medical Team Leader (Acting)
Dina Zand, MD, Medical Reviewer
Anna Choe, MD, Medical Reviewer
Cheronda Cherry-France, MSN, BSN, Safety Regulatory Project Manager

Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine
Mukesh Summan, PhD, Director
Babatunde Akinshola, PhD, Toxicologist

Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
Pamela Lucarelli, Director, Project Management Staff
Michael G. White, PhD, Chief Project Management Staff
Jenny Doan, MSN, BSN, Regulatory Health Project Manager
Avinash Kalsi, PharmD, Regulatory Health Project Manager
Diego Diaz, Regulatory Health Project Manager

Office of Clinical Pharmacology/ Division of Translational and Precision Medicine
Jie Wang, PhD, Clinical Pharmacology Team Leader
Sarah Dorff, PhD, Clinical Pharmacology Reviewer
Travis Ready, PharmD, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/ Division of Biometrics IV
Yan Wang, PhD, Biostatistics Team Leader
Wonyul Lee, PhD, Statistical Reviewer

Office of Drug Evaluation Sciences / Division of Biomedical Informatics, Research, and Biomarker Development (BIRBD)
Y. Veronica Pei, MD, MEd, MPH, Associate Director of Biomedical Informatics (Acting)

Office of Surveillance and Epidemiology (OSE)
Laura Zendel, PharmD, BCPS, Team Leader, Division of Risk Management (DRM)
Sarah Vee, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Su-Lin Sun, RPh, PharmD, GWCPM, Safety Regulatory Project Manager

SPONSOR ATTENDEES
John Crowley, Chairman and Chief Executive Officer
Mitchell Goldman, MD, PhD, Senior Vice President, Clinical Research
Jeff Castelli, PhD, Chief Development Officer
Jamie Gault, RAC, Executive Director, Global Regulatory Affairs
Anthony Sileno, MS, Senior Vice President, Clinical Operations and Translational Sciences
Zoheb Kazi, MD, Associate Director, Clinical Research
Hai Jiang, PhD, Senior Director, Biostatistics
Sheela Sitaraman, PhD, Vice President, Program Management
Peng Zhou Senior, Manager, Global Regulatory Affairs
(b) (4) Regulatory Consultant
(b) (4)
Amanda Sowinski, Senior Manager, Patient Advocacy
Emma Crowley, Patient Representative

1.0 BACKGROUND

FDA Regulatory Background

Amicus Therapeutics, Inc. (Amicus) is developing ATB200, an intravenously (IV) second generation enzyme replacement therapy (ERT), to be co-administered with oral miglustat for the treatment of late onset Pompe disease (LOPD) in adult patients. ATB200, also referred to as cipaglucosidase alfa, is a recombinant human acid α-glucosidase suggested to have improved uptake into lysosomes of muscle cells. Miglustat capsules, known as N-butyl-deoxynojirimycin, and also referred to by the company's code AT2221, is an iminosugar suggested to function as chaperone protein that stabilizes and prolongs the enzymatic activity of ATB200 in tissues. Amicus proposes that ATB200 co-administered with miglustat addresses the canonical pathophysiology of Pompe disease by increasing intracellular GAA activity and preventing glycogen accumulation in the lysosomes.

Since the initial IND submission on November 20, 2015, the FDA has had multiple interactions with Amicus to discuss the program's development. Orphan drug designation for ATB200 co-administered with miglustat was granted on September 13, 2017, and Breakthrough Therapy designation was granted on February 20, 2019. Additional regulatory history is detailed in the meeting minutes from the type B meeting held on September 1, 2020 (meeting minutes issued September 14, 2020).

In communications dated May 30, 2018 and October 11, 2019, Amicus indicated that while ATB200 and miglustat will be co-labeled, they did not intend to co-package these products. Based upon this intention, the FDA communicated to Amicus on November 9, 2020, that ATB200 co-administered with miglustat would not be considered at Part 3 combination product.

FDA granted rolling review designation for ATB200 biologic license application (BLA) on April 30, 2020. Amicus submitted part I of BLA 761204, which contained the non-clinical modules, on November 20, 2020. Amicus anticipates submitting the remaining components, including the clinical and CMC modules, in June of 2021.

Amicus also intends to submit a new drug application (NDA) via the 505(b)(1) regulatory pathway for miglustat in June of 2021. Miglustat is currently an approved drug under the commercial name Zavesca which is indicated for the treatment of Type 1 Gaucher disease (NDA 021348, Actelion Pharmaceuticals US, Inc.). Amicus has obtained the right of reference from Actelion and plans to cross reference module 2, 4, and 5 of NDA 021348.

On February 12, 2021, Amicus Therapeutics requested a pre-marketing application meeting to discuss their proposed data package for ATB200 and miglustat. A type B teleconference was granted on February 19, 2021, to take place on April 20, 2021. The meeting briefing package was received on March 19, 2021.

FDA sent the preliminary comments to Amicus on April 14, 2021. Amicus provided a slide presentation as read-ahead materials for the meeting on April 19, 2021. The teleconference took place as scheduled on April 20, 2021.

FDA Clinical Background

Pompe disease (also known as acid maltase deficiency or glycogen storage disease [GSD] type II) is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid alpha-glucosidase (GAA), an enzyme that degrades glycogen. The global prevalence is estimated at approximately 200,000 patients. In this lysosomal disorder, glycogen accumulation in affected tissue (primarily skeletal and/or cardiac muscle) can result in progressive hypotonia, respiratory failure, and cardiomyopathy. The disease spectrum ranges from the severe, rapidly progressive infantile onset Pompe disease (IOPD), and the slowly progressive, heterogeneous late LOPD.

In the U.S., the first enzyme replacement therapy (ERT) for Pompe disease was approved in 2006 for IOPD (alglucosidase alfa) and in 2010 for LOPD. Alglucosidase alfa is the current standard of care for both IOPD and LOPD, dosed at 20 mg/kg IV infusion every two weeks. Recent literature describes the natural history of patients on alglucosidase alfa to plateau or worsen in their pulmonary or gross motor function after 2-5 years on current standard of care. The Amicus-engineered second generation rhGAA, ATB200, is identical to wild-type GAA but is post-translationally modified to contain additional mannose 6-phosphate (M6P) residues to improve cellular uptake by cation independent M6P receptors (CI-MPR).

Amicus requested this pre-BLA meeting to discuss the current status of the ATB200/AT2221 development program. The clinical data to support this rolling BLA submission will derive from the following two LOPD studies:

- **ATB200-03**: This is a phase 3 multinational, double-blind, active comparator controlled trial that enrolled 123 adult patients with LOPD (95-ERT-experienced and 28 ERT-naïve), with completion by 117 patients (6 ERT-experienced subjects discontinued). Patients were randomized 2:1 (ATB200/miglustat to alglucosidase alfa/placebo). The primary endpoint of this trial is the change in the 6-minute walk distance (6MWD) at 52 weeks from baseline. The change in the percent predicted forced vital capacity (% predicted FVC) at 52 weeks from baseline is the first key secondary endpoint.

- **ATB200-02**: This is an open-label, fixed-sequence, ascending-dose, first-in-human study to assess the safety, PK, PD, and exploratory efficacy of ATB200/miglustat in adults with LOPD.

The pre-BLA briefing package contained top-line summary data from Study ATB200-03 for both for the primary endpoint (6MWD) and first key secondary endpoint (% predicted FVC) in the full study population and subgroup analyses in ERT-experienced and ERT-

naïve patients. In the overall population, a 13.6 meter improvement in the 6MWD (SD = 8.3, p = 0.072) and a 3% increase in predicted FVC (SD = 1.2; p = 0.023) was observed with ATB200/miglustat compared to alglucosidase alfa/placebo. These data excluded an ERT- naive patient recently exposed to an anabolic steroid who had a 355 meter improvement in 6WMD and no change in his % predicted FVC assessment. Of note, when this patient is included in the analysis, the treatment difference in the 6MWD in the overall population was smaller, with a p-value of 0.55. Subgroup analysis for ERT-experienced patients (n=95) showed an increase of 16.9 meters in 6MWD (SD = 8.8; p = 0.046) and an increase of 4.1 % in predicted FVC (SD = 1.2; p = 0.0.23). There was no difference in 6MWD or % predicted FVC in the smaller ERT-naïve population (n= 27).

Amicus intends to submit additional data to support efficacy from the following LOPD studies:

- **ATB200-07**: Open label extension for patients enrolled in study ATB200-03.

- **ATB200-04**: Multinational, open label study in subjects aged 12 to < 18 years to evaluate PK, PD, safety, and efficacy, enrolling approximately 12 ERT experienced and ERT naïve patients.

Amicus requests discussion of the available evidence from study ATB200-03 and long term data from study ATB200-02 to support registration of ATB200/miglustat in patients diagnosed with LOPD. (b) (4)

2.0 DISCUSSION

FDA Introductory Comment
It appears that your primary analysis results of the primary endpoint from study ATB200-03 did not reach statistical significance (i.e., p-value > 0.05) and the data may therefore not suffice to support the efficacy for ATB200/miglustat in patients diagnosed with LOPD aged 18 years and older. Additionally, the removal of the "outlier" subject will require further justification than what was provided in the meeting briefing document, especially since this removal substantially changes the result for the primary endpoint in the overall population.

Your applications should address the following if you choose to submit them:

- Justify the degree of change in 6MWD and % predicted FVC that is clinically meaningful to patients.

- Compare ATB200/miglustat exposure in treatment naïve vs. treatment experienced patients in Study ATB200-04 (b) (4)

[redacted] (b) (4) (Refer to the June 19, 2019, type B meeting minutes for our previous advice.)

- The non-clinical data suggest that miglustat, when co-administered with ATB200, debulks intracellular glycogen. However, the long-term contribution is unclear. Provide justification for continued use in the application. (Refer to November 15, 2018, type C meeting minutes for previous discussion).

- [redacted] (b) (4) clarify the source of alglucosidase alfa used in Studies ATB200-02, ATB200-03, ATB200-04, and ATB200-07.

- Since there has only been one clinical trial in your development program (Study ATB200-03) that may be considered adequate and well-controlled, your applications must clearly describe the confirmatory evidence required to establish substantial evidence of effectiveness (refer to the FDA draft guidance, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, December 2019).

- As discussed in the type C guidance written responses dated October 23, 2020, assessments in the integrated summary of safety (ISS) containing subjects from study ATB200-02, ATB200-03, and ATB200-07 should be reviewed in total and stratified by history of previous exposure to alglucosidase alfa. In addition, the ISS should contain analyses specific for the risks associated with first generation ERT and miglustat. We recommend that you include an evaluation of hypersensitivity and anaphylaxis and the narratives for anaphylaxis/hypersensitivity should contain the following information:

    - Patient history of hypersensitivity with any ERT
    - History of pretreatment with steroids or antihistamine prior to event
    - History of pretreatment with steroids or antihistamine after event, with subsequent commentary if there were additional events thereafter

  Refer to section 4.0 "ASSESSMENTS FOR ISS" for specific table shells for adverse events of interest.

Meeting Discussion: ***The Sponsor responded to the FDA's preliminary comments (refer to Section 8.0 for the slide presentation). The Agency appreciated the helpful patient perspective comments provided by the patient representative and clinical physician representative.***

During the discussion, the FDA requested further clarification regarding the source of alglucosidase alfa used in study ATB200-03. [redacted] (b) (4)

[redacted] (b) (4) ***Amicus stated that they would contact Sanofi for additional source information regarding the alglucosidase alfa used in study ATB200-03. FDA stated that they would provide further information*** [redacted] (b) (4)

Additionally, during the meeting Amicus agreed to include in the marketing application data for all patients in the completed datasets and analyses, both with and without the outlier patient.

Post-Meeting Comments: ***We acknowledge receipt via email on April 21, 2021, of a letter dated February 5, 2018, from Genzyme Europe BV to Myoderm Limited, "Subject: Equivalency of Myozyme product." Further FDA internal discussion is needed to determine what data will be necessary to establish a bridge between EU-licensed alglucosidase alfa and US-licensed alglucosidase alfa to support a comparative efficacy claim between ATB200/miglustat and alglucosidase alfa. The FDA will provide comments on this matter in a subsequent correspondence (i.e., advice letter).***

Question 1: Does the Agency agree that the adequate and well-controlled study ATB200-03 for cipaglucosidase alfa/miglustat plus the totality of data from Studies ATB200-03 and ATB200-02 are sufficient to support the submission of a BLA/NDA for the [redacted] (b) (4) treatment of adult patients with LOPD?

FDA Response to Question 1: See Introductory Comment.

Meeting Discussion: ***No further discussion occurred.***

Question 2: Does the Agency agree that the totality of data from Studies ATB200-03 and ATB200-02 support the initial indication in the overall population of [redacted] (b) (4) treatment in adult patients with LOPD?

FDA Response to Question 2: See Introductory Comment and guidance provided in the type B meeting on November 12, 2019. A successful marketing application provides substantial evidence of efficacy from two adequate and well-controlled trials, or one adequate and well-controlled trial and confirmatory evidence; there is no "totality of data" standard for drug approval in FDA statutes, regulations or guidances. Open-label extension studies generally do not meet the standard for well-controlled trials.

Meeting Discussion: ***No further discussion occurred.***

Question 3: Does the Agency agree that the projected size of safety database is adequate to assess the safety of cipaglucosidase alfa/miglustat for the proposed indication?

FDA Response to Question 3: The projected size of the safety database appears adequate.

Meeting Discussion: ***No further discussion occurred.***

Question 4: Amicus is providing clarification that the 120-day safety update will be an addendum to the SCS, not the CSR. Is the Agency in agreement with this approach?

FDA Response to Question 4: This is acceptable.

Meeting Discussion: ***No further discussion occurred.***

Question 5: Does the Agency agree that data from Study ATB200-04 does not need to be included in the pooled data for the Summary of Clinical Safety?

FDA Response to Question 5: Inclusion of data from Study ATB200-04 in the pooled data for the Summary of Clinical Safety will not be a requirement for filing of the applications. However, specific data pooled from multiple ongoing studies may be necessary to clarify safety concerns identified during the review.

Meeting Discussion: ***No further discussion occurred.***

Question 6: Does the Agency agree that a REMS is not required?

FDA Response to Question 6: At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and, if a REMS is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

We acknowledge your plan to place a black box warning on ATB200 labeling, similar to the current labeling for alglucosidase alfa. As hypersensitivity and anaphylaxis are anticipated safety signals for ERTs, the Division concurs with your proposal for a black box warning describing both hypersensitivity and anaphylaxis for ATB200.

Meeting Discussion: ***No further discussion occurred.***

Question 7: Does the Agency agree with our approach and that the QTc study can be a post-marketing requirement?

FDA Response to Question 7: We agree that the submission of QTc study data may be done as a PMR. However, the results of the QTc study should be submitted prior to submission of an efficacy supplement for IOPD. Refer to the type C written responses dated October 23, 2020, for more information.

Meeting Discussion: ***No further discussion occurred.***

Question 8: Can the Agency confirm, based on the fact that the BLA and NDA submissions will occur on the same day and the labeling requirement is that cipaglucosidase alfa must be used in conjunction with miglustat, that the PDUFA date will be the same for both products?

FDA Response to Question 8: If the BLA and NDA are submitted on the same day then any PDUFA action will most likely take place on the same day for both applications.

Meeting Discussion: ***No further discussion occurred.***

Question 9: Does the Agency agree that alternative packaging configurations are possible in addition to the individual and separate packaging for cipaglucosidase alfa and miglustat?

FDA Response to Question 9: The alternative packaging configurations are possible; however, we would expect a separate marketing application for any proposed new combination of active ingredients (b) (4) in addition to the already planned BLA and NDA original application submissions. Refer to the FDA guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*[1,2] which provides advice on submitting applications with different combinations of active ingredients. Please note (b) (4) Also, refer to the draft guidance *Principles of Premarket Pathways for Combination Products*.[3]

Meeting Discussion: ***No further discussion occurred.***

Question 10: Does the Agency agree that Amicus has provided adequate support for child-resistance of the 65 mg miglustat packaged in 40 cc and 120 cc bottle?

FDA Response to Question 10: Your proposal appears reasonable.

Meeting Discussion: ***No further discussion occurred.***

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/media/72397/download
[3] https://www.fda.gov/media/119958/download

3.0 ADDITIONAL FDA COMMENTS

Comments Related to Data and Safety Analyses:

- CDISC standards should be followed when preparing the define file. The define files should include possible responses for all variables when the meaning is not obvious. Discuss the need for programs for other derived datasets with the review division. (TCG 4.1.4.5 Data Definition Files for SDTM, SEND, and ADaM; TCG Section 8.3 Study Data Traceability). General considerations include the following:
    - Topline summary/description of what is included in each analysis dataset (i.e., a dataset table of contents)
    - For each analysis dataset, document the following:
        - For derived or imputed variables, a description and/or algorithm of how the variable was derived or imputed from the source data
        - Clear definition of analysis flags
        - Codes and decodes of all categorical variables (e.g., 1=mild, 2=moderate, 3=severe; 0 = age < 18, 1 = age ≥ 18)

- Submit all statistics programs/scripts and datasets used to create the analyses found in the main sections of the Summary of Clinical Efficacy, Summary of Clinical Safety, and phase 3 trial CSRs. If script contains a macro, include the macro script. The scripts and define files should be sufficient to facilitate understanding of how the analyses were conducted. Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the script used to create the table or figure. For the principle tables and figures, include a table that contains the following:
    - Name of statistical analysis code with hyperlink
    - Name of table or figure with hyperlink or its location in CSR if not hyperlinked
    - Names of datasets used to create the table or figure (hyperlinks are helpful)

- For ease of navigation of the review, include a dataset that indicates those subjects for whom a CRF and/or narrative was submitted, and the reason it was submitted (e.g., death, SAE, AE leading to medication discontinuation, adjudication package submitted). We recommend you provide this information in tabular format with the patient identifier hyperlinked to the narrative and/or CRF in the ISS.

- When creating the disposition dataset, for discontinuations due to "other," perform medical review to ensure appropriate categorization (e.g., discontinuation due to AE or meeting study discontinuation criteria, etc.). For

discontinuations due to "other" that are not appropriate for pre-defined categories, provide the specific reason.

- For your safety analyses, provide a prioritized list of adverse events of special interest (AESIs), including those previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any MedDRA SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

- For each study, provide a flag in the AE dataset or a separate dataset that maps preferred terms to the AESIs.

- Evaluate adverse events based on logical groupings of preferred terms using standard MedDRA queries or other appropriate means. Include in your submission the procedures and rationale used for grouping of preferred terms (PTs). The intent of grouping PTs for safety analyses is to avoid splitting of PTs to ensure that adverse events are adequately captured (e.g., PTs such as "ABDOMINAL PAIN LOWER", "ABDOMINAL PAIN UPPER", "ABDOMINAL PAIN" should be grouped in the assessment for abdominal pain).

4.0 ASSESSMENTS FOR ISS

Table 1: AEs of interest for Primary Analysis Period

FMQ Terminology	Alglucosidase Alfa/placebo N =	cipaglucosidase alfa/ miglustat		
		All subjects N=	ERT - Treatment Experienced Subjects N=	ERT - Treatment Naïve Subjects N=
Anaphylaxis include all PT from the anaphylaxis broad SMQ				
Hypersensitivity reaction include all PTs from the hypersensitivity broad SMQ				

Table 2a: AEs of over time in patients receiving cipaglucosidase alfa/ miglustat in ERT experienced subjects

FMQ Terminology	ERT Experienced Subjects						
	0-4 mo N=	4-8 mo N=	8-12 mo N=	12-16 mo N=	16-20 mo N=	20-24 mo N=	>24 mo N=
Anaphylaxis							

include all PT from the anaphylaxis broad SMQ							
Hypersensitivity reaction include all PTs from the hypersensitivity broad SMQ							

Table 2b: AEs of over time in patients receiving cipaglucosidase alfa/ miglustat in ERT treatment naïve subjects

FMQ Terminology	ERT – Naïve Subjects						
	0-4 mo N=	4-8 mo N=	8-12 mo N=	12-16 mo N=	16-20 mo N=	20-24 mo N=	>24 mo N=
Anaphylaxis include all PT from the anaphylaxis broad SMQ							
Hypersensitivity reaction include all PT from the hypersensitivity broad SMQ							

5.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 19, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[4]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug products for this indication have an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

[4] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*[7].

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345,

[7] https://www.fda.gov/media/90160/download

Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

6.0 ISSUES REQUIRING FURTHER DISCUSSION

Additional requirements to establish a bridge between EU-licensed alglucosidase alfa and US-licensed alglucosidase alfa to support a comparative efficacy claim between ATB200/miglustat and alglucosidase alfa (refer to the meeting discussion).

7.0 ACTION ITEMS

FDA: Provide guidance on what data is required to establish a bridge between EU-licensed alglucosidase product and US-licensed alglucosidase product.

[10] https://www.fda.gov/media/85061/download

8.0 ATTACHMENTS AND HANDOUTS

1) On April 19, 2021, in response to the FDA's preliminary comments dated April 14, 2021, Amicus provided via email a slide presentation as read-ahead materials for the telecon.
2) On April 21, 2021, Amicus provided via email a letter dated February 5, 2018, from Genzyme Europe BV to Myoderm Limited "Subject: Equivalency of Myozyme Product."

17 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

JENNY N DOAN
04/27/2021 09:33:59 AM
Signed on behalf of Dr. Donohue.

IND 127387

MEETING MINUTES

Amicus Therapeutics
Attention: Jamie Gault, RAC
Executive Director, Global Regulatory Affairs
1 Cedar Brook Drive
Cranbury, NJ 08512

Dear Jamie Gault:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for recombinant human acid alphaglucosidase (ATB200) and miglustat (AT2221).

We also refer to the teleconference between representatives of your firm and the FDA on November 10, 2020. The purpose of the meeting was to gain agreement on Module 3 content description of the ATB200 BLA and AT2221 NDA and specific questions on each product in the meeting request.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Marquita Burnett, Regulatory Business Process Manager at (b) (6)

Sincerely,

{See appended electronic signature page}

Maria Gutierrez-Lugo, PhD
Review Chief
Division of Biotechnology Review and Research III
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: November 10, 2020 3:00PM – 4:00PM EST
Meeting Location: Teleconference

Application Number: 127387
Product Name: recombinant human acid alphaglucosidase (ATB200) and miglustat (AT2221)

Indication: Treatment of Late-onset Pompe disease
Sponsor Name: Amicus Therapeutics

Meeting Chair: Maria (Tere) Gutierrez-Lugo, PhD
Meeting Recorder: Marquita Burnett, MPH

FDA ATTENDEES

Maria Gutierrez-Lugo, PhD	Branch Chief, OPQ/OBP
Frances Namuswe, PhD	ATL, OPQ/OBP/DBRRIII
Davinna Ligons, PhD	Drug Product Reviewer, OPQ/OBP/DBRRIII
Hitesh Shroff, PhD	Team Lead, OPQ/ONDP/DNDPII/NDPB4
Yubing Tang, PhD	Branch Chief, OPQ/OPMA/DPMAII/PMB5
Candace Gomez-Broughton, PhD	Branch Chief, OPQ/OPMA/DBM/BMB2
Virginia Carroll, PhD	Team Lead, OPQ/OPMA/DBM/BMB2
Marquita Burnett, MPH	RBPM, OPQ/OPRO

SPONSOR ATTENDEES

Jason Cameron	Senior Vice President, Technical Operations
Sergey Tesler, RAC, PMP	Executive Director, Regulatory Affairs CMC
Jamie Gault, RAC	Executive Director, Global Regulatory Affairs
Sheela Sitaraman, PhD, PMP	Vice President, Program Management
Qing-Hong Dai, PhD, RAC (ATB200)	Associate Director, Regulatory Affairs CMC
Xin Yao, PhD, RAC (AT2221)	Senior Manager, Regulatory Affairs CMC
Joseph Berry	Vice President, MSAT
Jon Jessmer	Vice President, Quality Assurance

1.0 BACKGROUND

On September 11, 2020, Amicus Therapeutics submitted a type B meeting request. The purpose of the meeting is to discuss and gain agreement on Module 3 content description of the ATB200 BLA and AT2221 NDA and specific questions on each

product. On September 21, 2020, the FDA Office of Pharmaceutical Quality (OPQ) granted a teleconference meeting for November 10, 2020.

FDA sent Preliminary Comments to Amicus Therapeutics on November 3, 2020.

2. DISCUSSION

The Sponsor used slides to outline the meeting and order of discussion for the questions desired. The Agency advised post-meeting comments may be appropriate based on discussion for some questions, which would be included in the meeting minutes document if necessary.

Question 1: *Does the Agency agree with the proposed content for the ATB200 BLA?*

FDA Response to Question 1:
Overall, the general content you plan to include in the BLA CMC module for ATB200 appears reasonable. We have the following specific comments and recommendations for the BLA based on the information included in the meeting package. These comments do not reflect complete assessment of the CMC sections. The adequacy of all CMC data will be a review issue of the BLA:

1. *You indicate* (b) (4) *In the BLA, clearly indicate which* (b) (4) *are intended for commercial use and provide the process validation data to support use* (b) (4) *In addition, provide comparability assessment(s) to support comparability of ATB200 manufactured with the proposed commercial* (b) (4) *and the ATB200 used in clinical studies.*

2. *Regarding the drug substance (DS) and drug product (DP) specifications:*

    a. *You propose a specification* (b) (4) *Revise the* (b) (4) *specification for commercial manufacturing to include an adequately validated method (refer to Question 3 for more comments) and acceptance criteria that are consistent with your clinical experience and industry standards.*
    b. *The specifications acceptance criteria for the two potency assays, specific activity and fibroblast uptake,* (b) (4) *The specifications for the commercial process should reflect your clinical and manufacturing experience. Revise these specifications accordingly.*

c. *You do not indicate a specification for extractable volume for DP release. The BLA should include a specification for extractable volume following reconstitution with data (e.g. extractable volume data) supporting that the labeled volume can be extracted upon reconstitution.*

3. *Your post-approval stability protocols for DS and DP will assess stability of DS and DP at the 12-, 24-, and 36-month timepoints. According to ICH Q5C, stability of DS and DP should be assessed every 3 months during the first year, every 6 months during the second year, and annually thereafter. Revise your post approval stability protocols to be consistent with ICH Q5C.*

4. *You propose a shelf-life* (b) (4) *The shelf-life of DS and DP will be a review issue and will depend on adequate demonstration that the real-time stability data were collected from lots that are representative of the material at commercial manufacturing scale, including the container closure system. This assessment should be supported by comparability between DS and DP PPQ and the representative lots.*

5. Refer to the CMC microbiology comments below for additional information.

Amicus's Response 2c:

- *The preparation of ATB200 drug product prior to administration is in line and complies with the harmonized USP and Ph. Eur. Monographs for "Parenteral preparations".*
- *Following the proper reconstitution instruction during sample preparation for either analytical testing or patient dosing will consistently ensure that labeled extractable volume will be met.*
- *Robust control is built in and supported by an Expansion/extractable volume study, Instructions for use and significant amount of batch release data.*
- *Therefore, Amicus proposed to remove "Extractable volume" testing from the drug product specification as justified on slide 10.*

Does the Agency agree with Amicus's justification to remove extractable volume from DP specification?

Discussion:

The Agency stated that based on the information provided, an extractable volume specification may not be needed if the Sponsor can demonstrate that the control strategy can ensure the label claim for the product. The Agency advised Amicus to conduct extractable/deliverable volume studies as part of development studies and to demonstrate (b) (4)

Amicus's Response 3.:

(b) (4)

Does the Agency agree with Amicus's proposal (b) (4) *for post-approval stability?*

Discussion:

The Agency indicated that at this time, we cannot agree to the proposed stability program and this will be a review issue. The Agency advised (b) (4)

(b) (4)

The Sponsor should provide stability data

(b) (4)

The Agency asked the Sponsor

The adequacy of the stability program will be a review issue.

Question 2: *Does the FDA agree with Amicus's proposed approach to justify* (b) (4)

FDA Response to Question 2:

You conducted (b) (4)

(b) (4)

The adequacy of this information and how it impacts the control strategy of ATB200 will be a review issue of the BLA.

Amicus's Response:

(b) (4)

Does the FDA agree with Amicus's additional clarification to justify (b) (4) (b) (4)

Discussion:

The Agency asked for clarification (b) (4) The information and data provided will inform the control strategy of the product, which will be a BLA review issue.

Question 3: *Does the FDA agree with Amicus's proposed approach* (b) (4) (b) (4) *for product release testing in commercial manufacturing?*

FDA Response to Question 3:

You propose (b) (4)

In general, the Agency recommends (b) (4)

You did not provide information (b) (4)

(b) (4)

(b) (4)

Amicus's Response:

(b) (4)

(b) (4)

Does the FDA agree with Amicus's proposal (b) (4)

Discussion:
Based on the data provided (b) (4)

(b) (4)

Question 4: *Does the FDA agree with Amicus's proposal on the facility site listing and concur that none of the development facilities are required to be PAI ready?*

FDA Response to Question 4:
Yes, we agree with your proposed plan of listing the facility sites in the BLA. In the initial BLA submission, please provide preliminary manufacturing schedules for the ATB200 drug substance and drug product to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

We also agree that R&D facilities are not required to be PAI ready. However, CGMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages. To assure the product quality of the materials used in the clinical studies, the facility(ies) used to manufacture these materials must operate in compliance with CGMP requirements 21 CFR 211 with respect to quality, production, facility and equipment, laboratory control, material control

and packaging and labeling systems. You indicate in the meeting package that some of the development facilities are non-GMP sites; however, you did not indicate the role(s) of the non-GMP sites. It is your responsibility to ensure that the facilities manufacturing clinical materials operate under phase appropriate CGMPs.

For more details, refer to Preparation of Investigational New Drug Products (Human and Animal) published on FDA.gov (https://www.fda.gov/media/71017/download).

Discussion:
Sponsor accepted the response with no further discussion requested.

Question 5: *Does the Agency agree with the proposed overall content of the AT2221 NDA?*

FDA Response to Question 5:
In general, the proposed overall content of the AT2221 NDA submission appears reasonable. However, its adequacy will be determined at the time of the NDA review. We have the following recommendations for your NDA submission:

1. We recommend that you add specifications for elemental impurities (b) (4) (b) (4) to your proposed drug product specification.

2. In your NDA the drug product specification should be based on the ingredients, (b) (4) manufacturing process, results of the stability tests of the registration and supportive batches as well as ICH Guidelines Q6A. The drug product impurities should be listed in specification table as specified, unspecified and total impurities and controlled per ICH Guidelines Q3B (b) (4) (b) (4) The elemental impurities should be controlled per USP <232>, USP <233> and ICH Q3D. All mutagenic impurities should be controlled per ICH M7. Provide validated analytical methods used for the drug product release in accordance with ICH Guidelines Q2 (R1) and demonstrate that they are suitable for the intended use. The final determination of the drug product specification will be based on the thorough review of the data provided in your NDA.

3. For preparation of the CMC sections in your NDA refer to the relevant CDER Pharmaceutical quality, CMC Guidances, ICH Quality Guidelines and the USP chapter:

- https://www.fda.gov/drugs/pharmaceutical-quality-resources/guidances-andmanuals-pharmaceutical-quality
- https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
- https://ich.org/
- USP <2> Oral Drug Products – Product Quality Tests

Discussion:

1. The Agency advised the Sponsor that their proposal to include in their NDA submission summaries of the risk assessments per ICH Q3D and verification testing data in lieu of elemental impurities specification appears reasonable. The Sponsor may provide justification for (b) (4) specification in your NDA submission. The final determination of the drug product specification will be based on the thorough review of the data provided in your NDA. The Sponsor understood and agreed.

Question 6: *Does the Agency agree that stability (b) (4) data are considered minor components and can be submitted within 30 days of the original submission?*

FDA Response to Question 6:
In accordance with ICH Q1A (R2), at the time of NDA submission you need to provide at least 12 months of long-term and 6 months of accelerated stability data on three registration batches of the drug product. However, at the time of your NDA submission you may provide at least 9 months of long-term and 6 months of accelerated stability data on 3 batches of the drug product if you commit to submit additional 3 months of long-term stability data within 30 days of NDA submission. The registration batches should be manufactured by the same manufacturers using the same manufacturing process and packaged in the same container closure system as to-be marketed product. The registration batches should be manufactured by the same manufacturers using the same manufacturing process and packaged in the same container closure system as to-be marketed product.

For the (b) (4) study and supporting data package, we agree that the information can be submitted within 30 days of the NDA submission with your commitment (b) (4)

Discussion:
Sponsor accepted the response with no further discussion requested.

Question 7: *Does the FDA agree with the proposed content plan for the 3.2.S.4 sections?*

FDA Response to Question 7:
Your plan to file two separate sections for the batches manufactured by each manufacturer appears acceptable if the quality of the batches from the two manufacturers is comparable. Provide the comparison in the NDA and Letter of Authorizations for both DMFs. In addition, refer to the advice provided on 04/30/2020.

Discussion:
Sponsor accepted the response with no further discussion requested.

Question 8: *Does the FDA agree with Amicus's proposed initial commercial shelf life of 36 months in the original NDA?*

FDA Response to Question 8:
The drug product shelf-life will be determined at the time of NDA review based on the stability data provided in your NDA.

Discussion:
Sponsor accepted the response with no further discussion requested.

Additional Comments:

BLA CMC Microbiology comments:
The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).*
- *Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
- *Chromatography resin and UF/DF membrane lifetime study protocols and*

acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).

- *Information and summary results from the shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*
- *Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).*

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- *Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.*
- *Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.*
- *Parameters for filling and capping for the vials.*
- *A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.*
- *Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.*
- *Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.*

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- *Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.*

- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.*
- *In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*
- *Isolator decontamination summary data and information, if applicable.*
- *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.*
- *Information and summary results from shipping validation studies.*
- *Validation of capping parameters, using a container closure integrity test.*
- *Lyophilizer sterilization validation summary data and information.*

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- *Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.*
- *Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.*
- *Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).*
- *Low endotoxin recovery studies. Certain product formulations have been*
- *reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.*

Microbiological studies in support of the post-reconstitution and post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product

concentrations that would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> Antimicrobial Effectiveness Testing, plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-reconstitution and post-dilution storage period is not more than 4 hours.

Amicus's Response:

(b) (4)

Does the Agency agree with Amicus's risk mitigation plan for LER?

Amicus acknowledges the recommendation for microbiological studies in support of the post-reconstitution and post-dilution storage conditions. A study is planned to include microbial challenges against recommended organisms prior to BLA. Amicus would like to receive FDA's feedback on the selection of the challenge organisms as listed on slide 19.

Does the Agency agree that the proposed list of micro-organisms selected for in-use stability is acceptable?

Discussion:

LER (slide 15-17): The Agency stated that there isn't enough information to make this determination and the adequacy of the risk mitigation strategy for endotoxin will be a review issue. In general, the plan should include (b) (4) (b) (4) appropriate bioburden/endotoxin limits (b) (4) (b) (4) to limit potential contamination (b) (4) (b) (4). If a suitable in vitro endotoxin method which mitigates LER is not identified during the BLA review cycle, rabbit pyrogen testing (RPT) may need to be implemented as an interim release method.

The Agency asked whether an experiment has been done to determine whether endotoxin-spiked drug product is pyrogenic in rabbits. The Sponsor stated that the

(b) (4) This type of experiment may be useful to understand if the masking effect occurs in vivo. If endotoxin-spiked product held under defined conditions is not pyrogenic in rabbits, RPT may not be required for release.

The Agency asked (b) (4) The Agency recommended that LER studies be performed with reference standard endotoxin (RSE) or control standard endotoxin (CSE), (b) (4) The Agency encouraged to continue to develop a suitable in vitro endotoxin method which mitigates LER and referenced PDA Technical Report No. 82 for additional information. A summary of the mitigation methods that have been tested to date should be provided in the BLA.

Organisms for In-use Study (slide 18 and 19): Yes, the list of microorganisms for the in-use study appears reasonable.

Additional Discussion:
The Agency inquired on the estimated time of submission of the BLA, to which the Sponsor informed the Agency the plan is to submit the BLA by the end of June 2021.

3.0 SECURE EMAIL

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ATTACHMENTS AND HANDOUTS

The slides used to guide the meeting are included at the end of the meeting minutes.

20 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

MARIA T GUTIERREZ LUGO
12/10/2020 08:58:52 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 127387
Request Receipt Date	December 21, 2018
Product	ATB200 and AT2221
Indication	Late-Onset Pompe Disease (LOPD)
Drug Class/Mechanism of Action	Primary (ATB200): Enzyme replacement therapy Secondary (AT2221): Substrate Reduction Therapy
Sponsor	Amicus Therapeutics, Inc
ODE/Division	ODE III/Division of Gastrointestinal and Inborn Errors products
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	February 21, 2019

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Treatment of patients with Late-Onset Pompe Disease (LOPD) (b) (4)

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**
   ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
      ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
      ☐ Undetermined
      ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

         i. Only animal/nonclinical data submitted as evidence ☐

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

Executive Summary

This is the second request for Breakthrough Therapy Designation (BTD) for IND 127387 for the use of enzyme replacement therapy (ATB200) concurrently with an iminosugar (AT2221) in patients diagnosed with Late Onset Pompe disease (LOPD).

The Sponsor's initial request for BTD was denied in February 2018 for the same products and indication because the Sponsor presented results from a short-term, open-label, single-arm study without comparison to an adequate control. A full copy of that denial is attached to this document for review.

This second BTD request was received in December 2018, and we now recommend granting Breakthrough designation based on new data and analyses showing:

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

1. A longer duration of treatment notable for improvements in the percent predicted six-minute walk distance (%P6MWD) for patients treated with ATB200/AT2221 compared to two external historical control cohorts treated with enzyme replacement therapy.
2. Nonclinical data supporting the clinical evidence of drug activity. Data from a murine model suggest that the chaperone component, AT2221 has an additive effect on the enzyme component, ATB200.

Pompe is a rare, serious, and life-threatening disease. Mutations in the gene for lysosomal acid alpha glucosidase (GAA) cause glycogen accumulation in the lysosomes, leading to myocyte destruction, progressive muscle weakness, and eventual respiratory failure. The clinical course of LOPD is highly variable. Some patients face severe early morbidity and mortality as adolescents or young adults, whereas others face a more protracted course and may live a normal lifespan albeit with significant morbidity. Enzyme replacement therapy (ERT) with alglucocidase alfa was approved for LOPD patients in 2010 on the basis of improvements in lung function and six-minute walk distance. However, patients with LOPD have substantial unmet medical need, as lung function and walk distance may begin to decline again after the first few years of ERT, though this too is highly variable.

The Division concludes that LOPD is serious and life-threatening, that patients have significant unmet medical need, and that the preliminary clinical evidence shows that ATB200/AT2221 may demonstrate substantial improvement over available therapy on the percent predicted six-minute walk distance when compared to historical controls.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), an any relevant regulatory history. Consider the following in your response.

The reader is referred to our appended prior Breakthrough Designation Review for a detailed description of disease course and drug mechanism of action. Briefly:

Disease
See especially **Figure 1** from Kuperus et al. and **Figure 2** from Schosser et al. showing that on average patients begin to decline in walk distance and lung function after two to three years on alglucosidase alfa enzyme replacement therapy. Note the wide confidence intervals around this inflection point, suggesting that the time course to recurrent decline is highly variable from patient to patient.

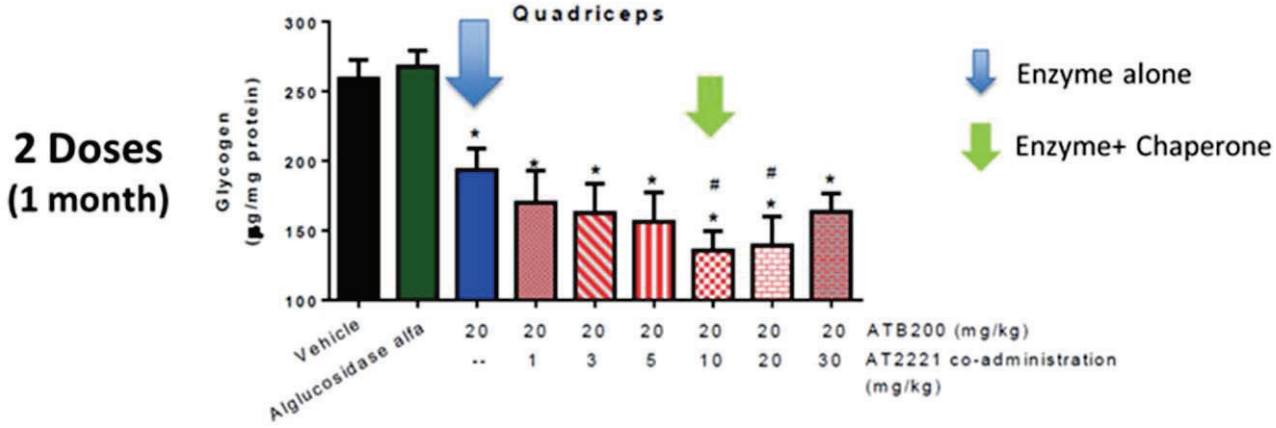
Mechanism of Action
ATB200 is a new recombinant acid-alpha glucosidase enzyme replacement therapy for IV infusion. Its sequence is identical to wild type human, apart from the addition of mannose-6-phosphate residues that improve uptake into lysosomes. AT2221 is a chaperone protein that stabilizes ATB200 and prolongs the enzymatic activity of ATB200 in tissues.

This submission includes new nonclinical data that suggest that ATB200/AT2221 addresses the canonical pathophysiology of Pompe disease by increasing intracellular GAA activity and preventing glycogen accumulation in the lysosomes. The preliminary clinical evidence of improved six-minute walk distances suggests that ATB200/AT2221 may be addressing the damage to muscle cells that leads to progressive muscle weakness, reduced ambulation, and eventual respiratory failure in Pompe patients.

Non-clinical data submitted since the prior Breakthrough designation denial demonstrated that ATB200 increased GAA activity and reduced glycogen levels in quadriceps, triceps, and heart tissues in Gaa KO mice. The studies also demonstrated improvement in disease factors such as protein accumulation, aberrant lysosomal proliferation, and increased autophagy in *Gaa* KO mice. The chaperone, AT2221, showed additive effects on the efficacy of ATB200, enabling the enzyme to function more quickly than it would otherwise alone. However, as a monotherapy, AT2221 did not demonstrate pharmacological effects on glycogen reduction. In vitro, AT2221 increased the stability of ATB200 at pH 7.0, delaying protein denaturation and unfolding, indicating that the chaperone has the potential to increase the

availability and, therefore, efficacy of ATB200. In vivo, an additive effect on the reduction of glycogen levels and increase in GAA activity in the quadriceps was observed after co-administration of AT2221 with ATB200, beginning after two co-administered doses or 1 month of exposure.

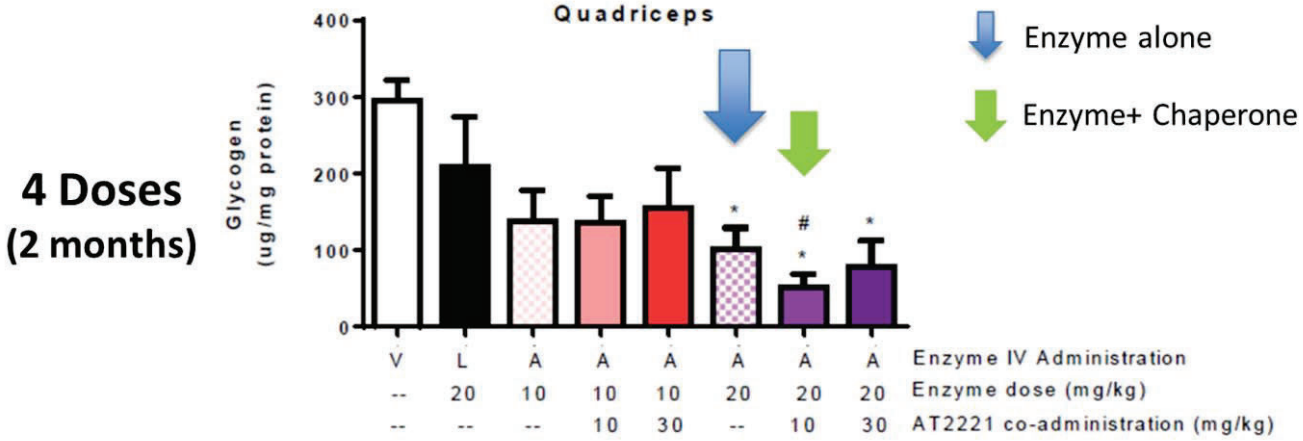
Figure 1: Efficacy of ATB200 + AT2221 in male *Gaa* KO mice after 2 doses (1 month)



Male *Gaa* KO mice (~16 weeks old) were administered two biweekly IV bolus tail vein injections of vehicle, 20 mg/kg alglucosidase alfa, or 20 mg/kg ATB200 alone. Some ATB200 groups of mice were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 administration. Tissues were collected 14 days after the last injection (2nd dose). The data shown represent pooling of several studies, with the mean ± SEM of 4-21 mice. Statistical significance was determined using unpaired t-tests, where # represents $p<0.05$ vs. ATB200 alone; * represents $p<0.05$ vs. alglucosidase alfa alone.

Source: IND 127387; Sections 4.2.1 and 4.2.2

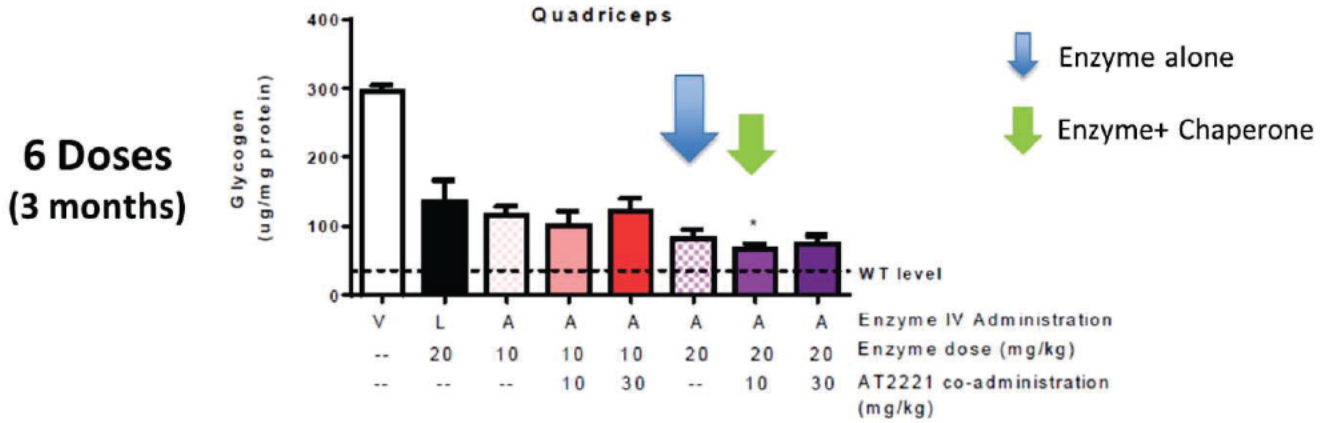
Figure 2: Efficacy of ATB200 + AT2221 in male Gaa KO mice after 4 doses (2 months)



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

Source: IND 127387; Sections 4.2.1 and 4.2.2

Figure 3: Efficacy of ATB200 + AT2221 in male Gaa KO mice after 6 doses (3 months)



Male *Gaa* KO mice (~16-weeks old) (n=6) were administered a total of 6 biweekly IV bolus injections of vehicle (V), 20 mg/kg alglucosidase alfa (L), or ATB200 (A) at 10 or 20 mg/kg. Some ATB200 groups were also orally administered the indicated doses of AT2221 30 minutes prior to ATB200 IV administration. Tissues were collected 14 days after the last injection (6th dose). Each column represents mean ± SEM of 4-6 animals. Statistical significance was determined using unpaired t-tests, where; * represents $p<0.05$ vs. alglucosidase alfa and # represents $p<0.05$ vs. same-dose ATB200 alone.

Source: IND 127387; Sections 4.2.1 and 4.2.2

Relevant Regulatory History:

The relevant regulatory history for IND 127387 is summarized below in **Table 1**:

Table 1: IND 127387 Relevant Regulatory History

Date	Type of Meeting	Concerns Addressed
6-Oct-2015	Pre-IND Face-to-Face	The Division clarified to the Sponsor that ATB200/AT2221 is a drug/biologic combination product and provided advice regarding CMC, clinical pharmacology and trial design issues.
31-Dec-2016	--	IND 127387 was considered safe to proceed.
13-Mar-2016	WRO	The Agency provided suggestions regarding proposed manufacturing changes for ATB200 for comparability of batches. Additional recommendations for a face-to-face meeting were made.
25-Oct-2017	T-con	Preliminary advice regarding a Breakthrough Therapy Designation Request (BTDR): The Division commented upon the review of preliminary data and encouraged the sponsor to proceed with a formal BTDR submission.
4-Dec-2017	BTDR	Denied on 4-Feb-2018
3-Jul-2018		Submission of additional non-clinical information
22-Aug-2018		Submission of additional non-clinical information
16-Jul-2018	Face-to-Face	The Division concurred with the Sponsor that a blinded, randomized study (ATB200/AT2221 vs. alglucosidase alfa/placebo) would be the best opportunity for interpretation of an effect. Further discussion was focused upon additional concerns such as upon endpoint selection, duration and enrollment criteria.
30-Oct-2018	Face-to-Face	The Division continued discussion with the Sponsor regarding their proposed Phase 3 study.
21-Dec-2018	BTDR	*Under review*
9-Jan-2019		IR to Sponsor for clarification on BTDR
18-Jan-2019		IR to Sponsor for clarification on BTDR
25-Jan-2019		IR to Sponsor for clarification on BTDR
1-Feb-2019		T-con with Sponsor for clarification on BTDR

Source: DARRTS, IND 127387

To address the Division's stated concerns in the denial of first Breakthrough Designation Request, the Sponsor submitted additional longitudinal clinical data in the second Breakthrough Therapy Designation Request on 21 December 2018. The Sponsor also initiated discussion with the Division to optimize a possible trial design that would yield sufficient power and interpretability as a marketing trial.

7. Information related to endpoints used in the available clinical data:

The six-minute walk test (6MWT) is an acceptable endpoint to the Division as it measures a clinically relevant function (ambulation). The 6MWT was one of the primary endpoints used for approval of Lumizyme (alglucosidase alfa) in 2010 for patients with LOPD (refer to **Section 8** for details). While the sponsor's trial and data from Study ATB200-02 use 6MWD, the historical data extracted from the literature presented in this BTDR uses the percent predicted 6MWD (%P6MWD). The derived endpoint was created for the sponsor's data to ease comparison with historical literature. The %P6MWD has not been reviewed previously by the COA Staff.

Thus far, no biomarkers have been identified that the Division would consider likely to predict a clinical benefit for Pompe disease.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

The reader is referred to the initial Breakthrough Designation Denial for a detailed discussion of the available enzyme replacement therapy, Lumizyme. Lumizyme was approved based upon the demonstration of a treatment effect relative to placebo of 3.4 % (95% CI: 1.3% to-5.5%) improvement in % predicted upright FVC and a 28-meter (95% CI: -1 to 52 meters) treatment effect in 6MWD. Durability of effect was noted over 12 months.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

The Division received a breakthrough therapy designation request on February 7, 2019, for avalglucosidase (neoGAA) in IND 109569. NeoGAA is an enzyme replacement therapy indicated for patients with Pompe disease. The protein sequence of neoGAA is identical to alglucosidase alfa but differs in that it contains additional mannose-6-phosphate residues, to enhance intracellular uptake. As the determination of this request is due by April 8, 2019, the data is currently under review.

10. Information related to the preliminary clinical evidence:

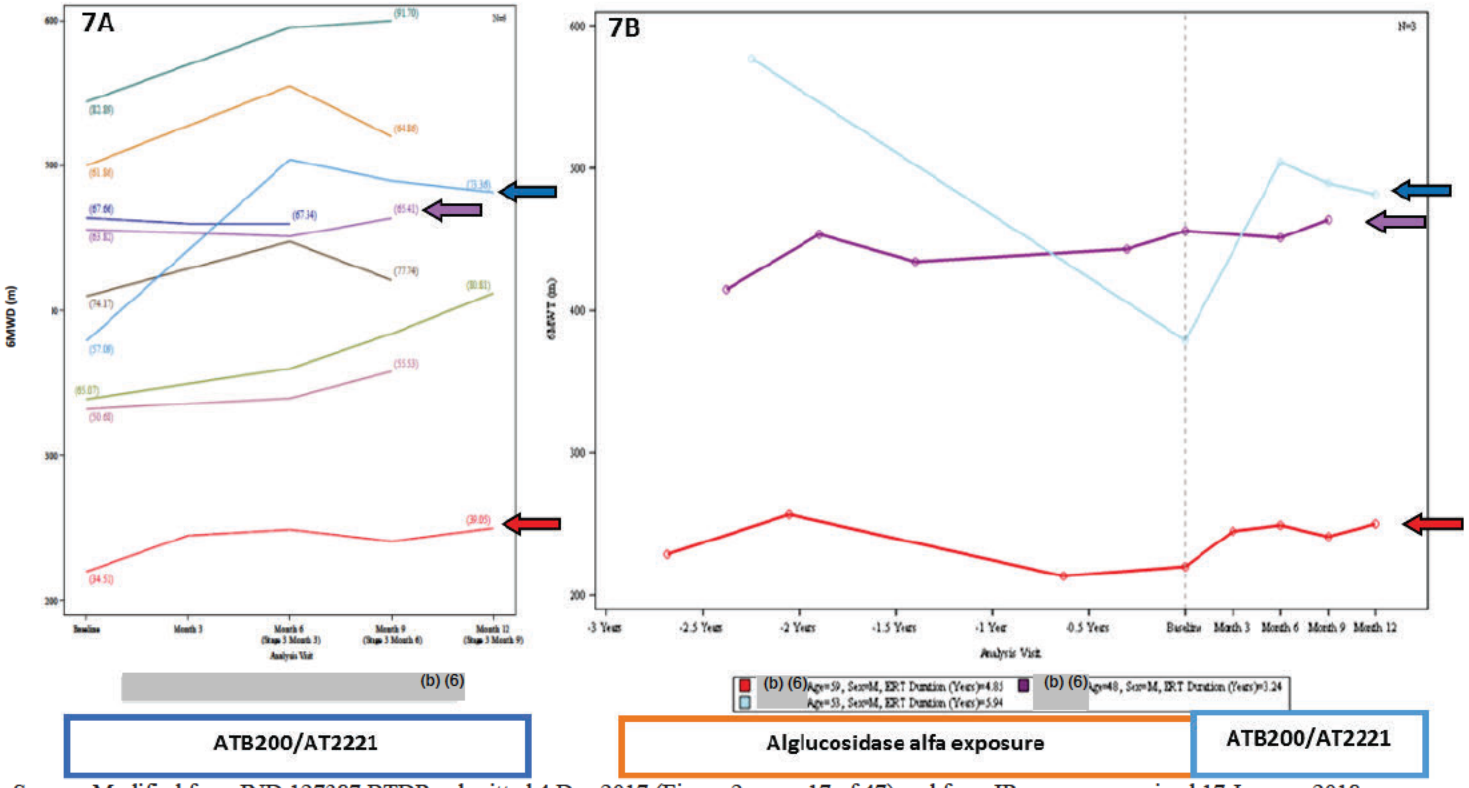
The Sponsor's initial request for BTD was denied in February 2018 for the same products and indication. See appended prior review for details.

Briefly, all patients in the initial Breakthrough submission were previously exposed to at least 2 years of ERT (alglucosidase alfa) and then switched over to an equivalent dose of Amicus's α-glucosidase (ATB200), although the

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

functional equivalence of the two α-glucosidase products has not been established. The Sponsor presented results from a six-month, open-label, single-arm study in nine patients (See **Figure 7A**) without comparison to an adequate control, and pre-baseline natural history data were only available for three of the nine patients to visualize an overall clinical trajectory (**Figure 7B**).

Figure 4A and 7B: Study ATB200-02 ERT-Experienced Patients – Six Minute Walk Test (6MWT)



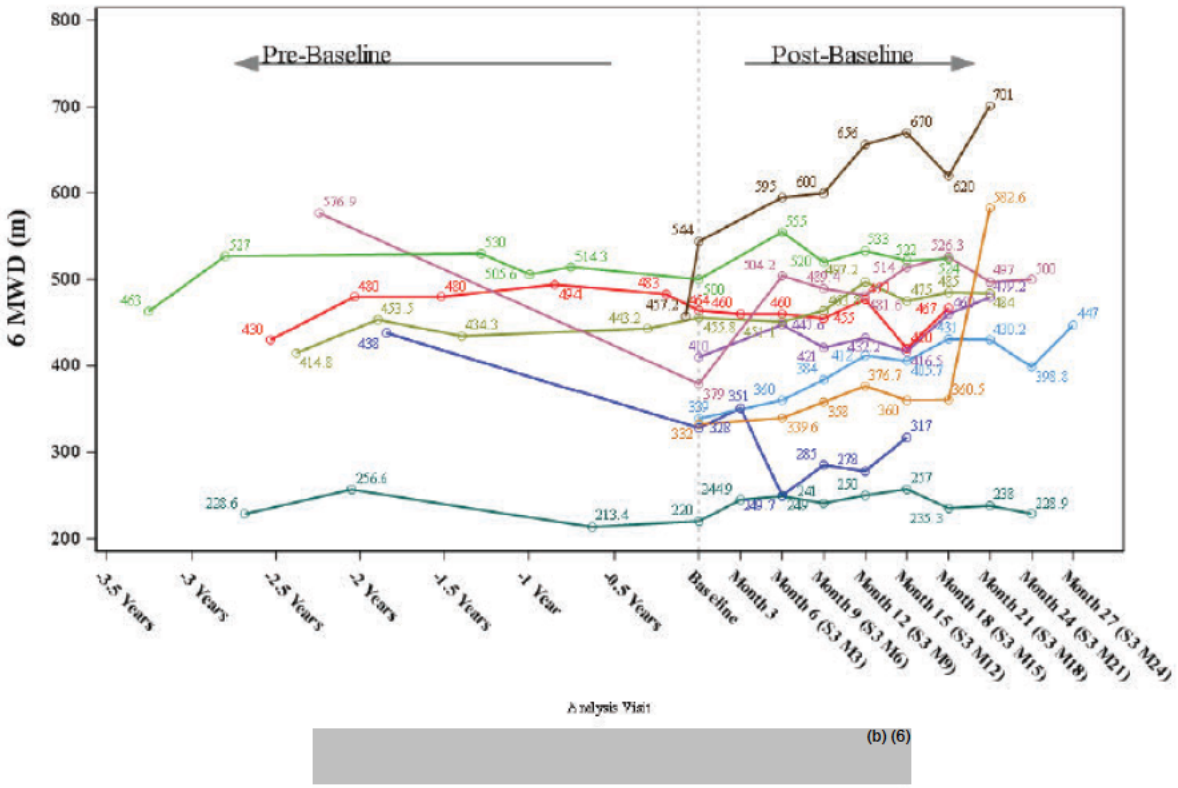
Source: Modified from IND 127387 BTDR submitted 4 Dec 2017 (Figure 2; page 17 of 47) and from IR response received 17 January 2018

[a] All patients described were ERT- experienced ambulatory subjects who had received alglucosidase alfa for 2- to 6-years prior to enrollment and could walk at least 200 meters in the 6-minute walk test (6MWT)

To address the concerns stated by the Division in the initial denial of the initial BTDR, the Sponsor submitted a second request for BTD in December 2018. To better understand individual patient trends in 6MWD, updated longitudinal 6MWD results on the 11 available patients who continued enrollment were reviewed. Pre-crossover data is now available in 6 of 11 patients. All patients were exposed to ATB200/AT2221 for a minimum of 15 months and a maximum of 27 months at the time of the data cut. Refer to **Figure 8**.

As the second Breakthrough submission was lacking key details describing the methodology and comparability of the external control cohorts, three IRs were sent, and a teleconference held on February 1st, 2019 (refer to **Table 1**). The most recent response to IR was received February 7th presenting revised analyses, a more detailed description of the methodology, and the demographic details of the external control cohorts. Our summary below reflects the revised analyses and responses to IR obtained during the review cycle more so than what was presented in the second Breakthrough submission.

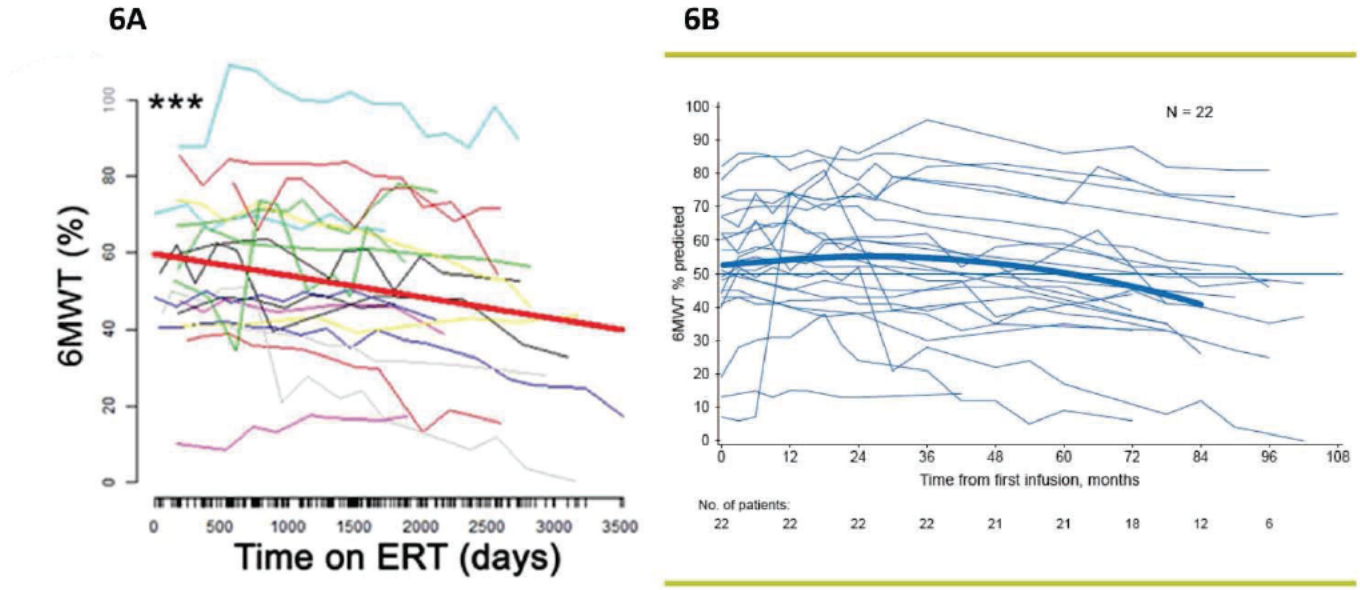
Figure 5: 6MWD in ERT Experienced Patients Receiving ATB200/AT2221; Pre- and Post- Study ATB200-02 Initiation



Source: IR response IND 127387; received 15 Jan 2019

To support this second BTD request the patient data from Study ATB200-02 were compared with a French cohort of patients receiving long-term alglucosidase alfa therapy (Masat et al. 2016) and a different cohort of international patients receiving long-term alglucosidase alfa therapy (Van der Ploeg et al. 2017 WORLD poster/abstract). Refer to **Figure 9A** and **Figure 6B**.

Figure 6A and 9B: % Predicted 6MWT in Lon -Term Al lucosidase Alfa ERT with LOPD



Source: 9A, Figure B in Masat et al (2016); 9B, Figure 5 in Van der Ploeg et al. (2017)

Comparison of baseline demographics suggests that patients enrolled in Study ATB200-02 may be healthier as judged by mean % predicted 6MWD and the percentage of patients who use assistive devices. Overall, the patients enrolled in Study ATB200-02 had less duration of exposure to alglucosidase alfa, at baseline (**Table 2**).

Table 2: Baseline Demographics for Patients evaluated in Study ATB200-02, Masat et al and Van der Ploeg et al.

	Amicus Study ATB200-02 (N=11)	Van der Ploeg et al. (2017) (N=68)	Masat et al. (2016) (N=19)
Mean Age (years) ± SD (min, max)	49.4 (SD=9.5) (28,66)	[a]45.8 (SD=11.2) (16,70)	[b]58.2 (SD=2.4) No range was provided
Country, n (%)	US 8 (73%) UK 1 (9%) Netherlands 1(9%) Germany 1(9%)	[a^]France 38 (56%), Netherlands 21 (31%), US 9 (13%)	[b]France 19 (100%)
Baseline % predicted 6MWD	61.0 (13.4)	[a]52.5 (19.0) N=22	[b,c]59.6
Mean Baseline 6MWD ±SD. (min, max)	392.0 (SD=93.4) (220, 544)	Not available	Not available
% male, n (%)	9/11 (82%)	[a^]36/68 (53%)	[b]13/18 (72%) N=18
Duration of ERT (years), mean ± SD (min, max)	4.8 (SD=1.4) 2.2, 6.4	*7.1 (SD = 1.3) N=22 Range 3.5, 9.0	*7.0 (SD=1.6) N=19 Range 4.7, 97
Ambulatory support at initial treatment, n (%)	2/11 (18%)	[a^]35/68 (51%)	Not available
Respiratory support at initial treatment, n (%)	3/11 (27%)	[a]26/68 (38%)	Not available
Mutations (e.g. n, % with c.32-13T > G etc.)	c.32-13T>G: 9 c.45T>G: 2	Not available	Report stated that almost all LOPD subjects carried at least one c.32-13T>G allele

IND 127387; Response to IR submitted 30 Jan 2019, Table 2 (page 4 of 6); Some data was amended to reflect review of original report

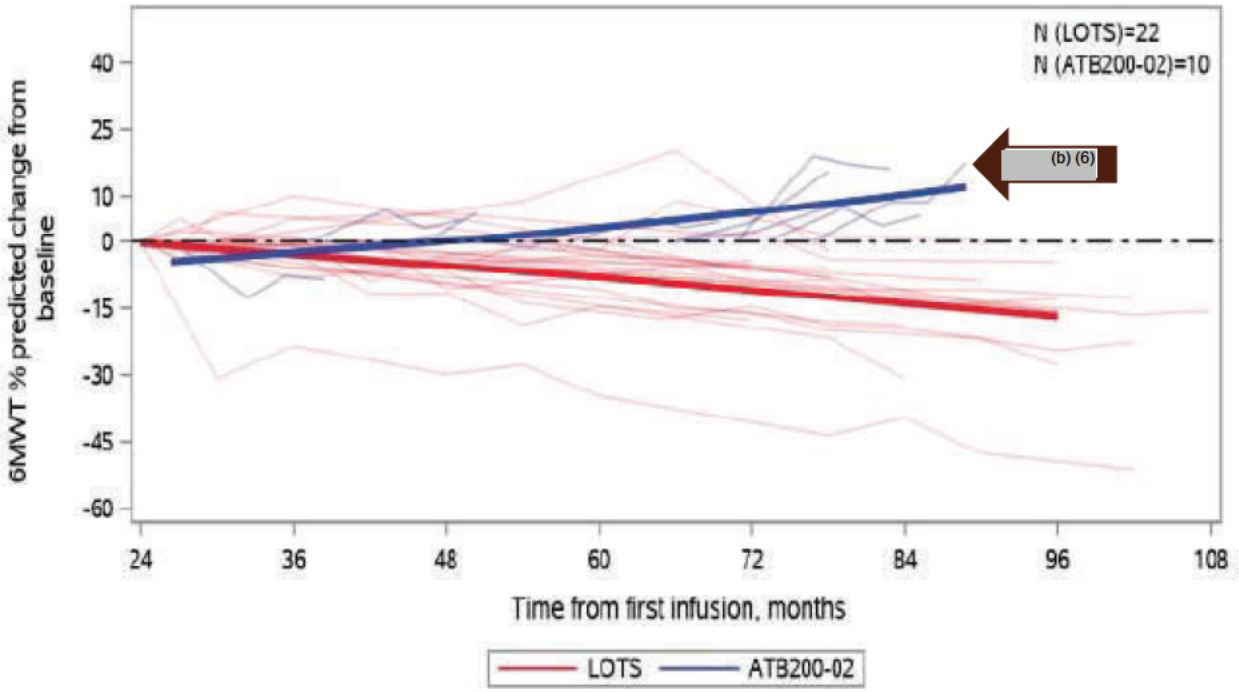
[a] Data obtained from the LOTS publication; Baseline age and gender data in the LOTS extension study were obtained from the original analysis population of 68 subjects.

[b] Data obtained from the MASAT publication Baseline % predicted 6MWD values study were obtained from the 60 subjects randomized to receive alglucosidase alfa.
[c] This value for baseline % predicted 6MWD is the estimated intercept from Masat, Lafloret 2016
[*] Data generated from digitized graphs
[^] Not all patients described by Van der Ploeg et al. were able to complete 6MWD; some were followed for pulmonary function only.

Full data sets were only available for the patients enrolled in Study ATB200-02. Amicus digitally extracted data points for %P6MWD and duration of ERT from patient-level line plots in the Masat & Van der Ploeg papers. Amicus then matched the patients in ATB200-02 to patients in the two external historical control cohorts by duration of prior exposure to alglucocidase alfa and baseline %P6MWD. Matches were required to have data on either side of the 12-month period of exposure to alglucosidase alfa in addition to data in the 12-month window. Matches were required to be within ±10% for the % predicted 6MWD at the start of the 12-month window. Cubic splines were generated for each of the historical control patients to impute %P6MWD at timepoints comparable to those collected for ATB200-02. Amicus then calculated the slopes from the cubic splines for each patient in the ATB200-02 study and in the two historical control cohorts and compared them.

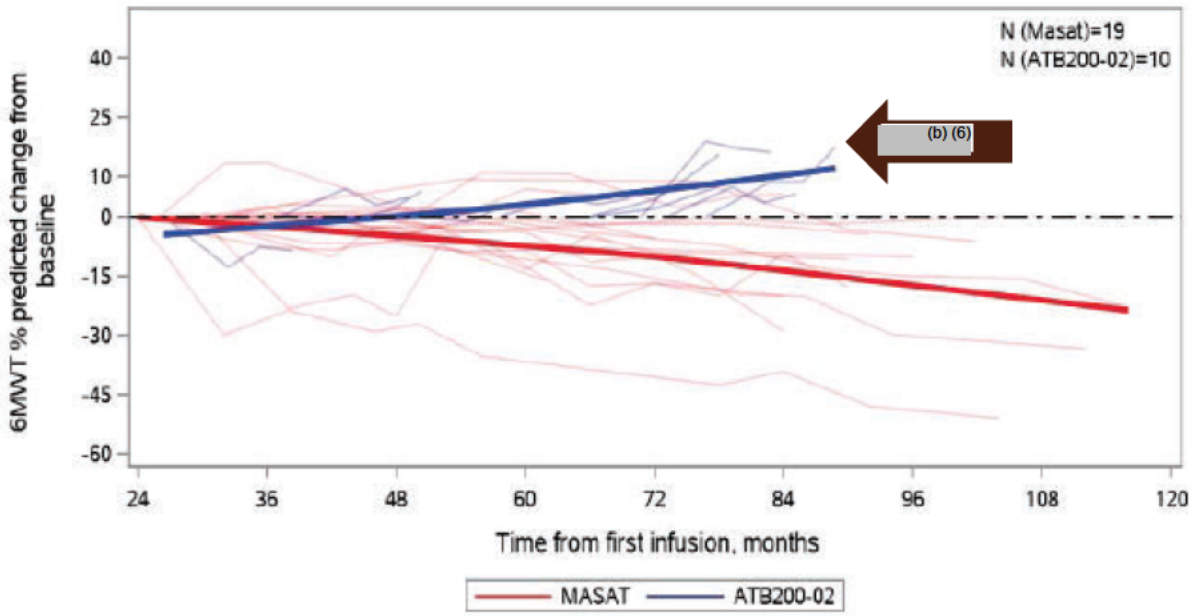
Figures 10 & 11 below show that on average, patients treated with ATB200/AT2221 demonstrated improvements in %P6MWD, compared to historical controls who demonstrated declines in %P6MWD, when matched for duration of prior ERT therapy and baseline %P6MWD.

Figure 7: Comparison of % Predicted 6MWD in Study ATB200-02 vs Van der Ploeg et al.



Source: IND 127387 BTDR received 21 Dec 2018 (Figure 6; Page 25 of 123)
All patients enrolled in Study ATB200-02 were required to have received at least 24 months of ERT treatment with alglucosidase alfa, so the X-axis initiates at 24 months of exposure ERT. Patient 2017-1052 from Study ATB200-02 is identified with the brown arrow as they had the longest exposure to alglucosidase alfa prior to switchover (76.8 months).

Figure 8: Comparison of % Predicted 6MWD in Study ATB200-02 vs Masat et al.



Source: IND 127387 BTDR received 21 Dec 2018 (Figure 7; Page 26 of 123)
All patients enrolled in Study ATB200-02 were required to have received at least 24 months of ERT treatment with alglucosidase alfa, so the X-axis initiates at 24 months of exposure ERT. Patient (b) (6) from Study ATB200-02 is identified with the brown arrow as they had the longest exposure to alglucosidase alfa prior to switchover (76.8 months).

The Division re-evaluated the slopes for individual patients enrolled in Study ATB200/AT2221 compared to matched patients from Van der Ploeg et al. and Masat et al. Slope is defined as the estimate monthly rate of change in the % predicated 6MWT where positive values imply improvement and negative values imply decline. Refer to **Table 3**.

Table 3: Comparison of the Monthly Rate of Change in the % Predicted 6MWD in patients enrolled in Study ATB200-02 and those reported by Van der Ploeg et al. and Masat et al.

Patient ID	Months on Alglucosidase Alfa	% Predicted 6MWD at Baseline	Study ATB200-02 Slope	Van der Ploeg et al. Matched Slope	Masat et al. Matched Slope
(b) (6)	26.4	52.2	-0.88	-0.139, -.727	-0.005, 0.267
	45.6	67.7	0.103	-0.272	-0.305, -0.606, 0.325
	57.6	34.5	0.296	0.193	-0.189
	76.8	82.9	1.120	-0.170, -0.073	(-0.058)
	73.2	74.2	0.397	-0.073	None
	38.4	63.8	0.418	-0.032, -0.245	-0.807, -0.180, -0.186, -0.236, -0.116
	66.0	65.1	0.560	-0.413	-0.441
	70.8	57.1	1.124	-0.319, -0.423, -0.243	-0.063, -0.148, -0.455
	66.0	50.7	1.341	-0.304, -0.105, -0.245	-0.343, -0.067
	37.2	61.9	0.332	-0.308, -0.494	-1.083, -0.167, -0.211

Source: Calculations were completed by E. Russek-Cohen with additional information submitted responses to IR submitted to IND 127387. Of note, The Masat et al. data did not provide a match for two patients enrolled in Study ATB200-02, but when the matching criteria were relaxed to be within 20% of baseline % predicted 6MWD, one patient was able to be matched (parenthesis).

Safety

Safety and tolerability were assessed in 20 patients who were exposed to ATB200/AT2221 in the first request for BTD. In general, there were no new safety signals during this limited review and the reported AEs appeared to be consistent with anticipated AEs for both ATB200 and AT2221.

Limitations

This analysis is marked by several limitations. Selection bias is a concern in any comparison to external controls. First, the natural history of 6MWD in Pompe patients treated with avalglucodise alfa ERT is highly variable; on average patients initially improve and then begin to decline after about three years, but the time to decline is marked by considerable heterogeneity between patients. The patients enrolled in the Amicus cohort had, on average, a shorter duration of prior exposure to ERT and less need for ambulatory and respiratory support than those in the two historical control cohorts. Thus, some of the Amicus patients may have been expected to continue improving even on the first generation avalglucocidase alfa ERT. By matching for both baseline %P6MWD and duration of prior ERT, Amicus addressed the two most powerful predictors of clinical course, even if we cannot eliminate the possibility of some residual confounding. A second limitation is that the two historical control cohorts may not be fully independent; it appears that a few patients may have been included in both. Nonetheless, it is reassuring that the results for ATB200/AT2221 are comparable when compared to two (nearly) separate historical control cohorts.

Conclusion

Overall, patients treated with ATB200/AT2221 demonstrated an improvement in %P6MWD when compared to patients from two external historical control cohorts matched for baseline %P6MWD and duration of prior ERT. This preliminary clinical evidence is supported by nonclinical evidence from a murine model of Pompe disease, which showed that combination treatment with ATB200/AT2221 produced an additive effect in reducing the canonical features Pompe disease pathophysiology, including reductions in protein accumulation, aberrant lysosomal proliferation, and autophagy. Given the limitations noted earlier regarding the potential for selection bias, we would not conclude that these results represent substantial evidence of efficacy. However, we do conclude that these results constitute preliminary clinical evidence of a substantial improvement over available therapy.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

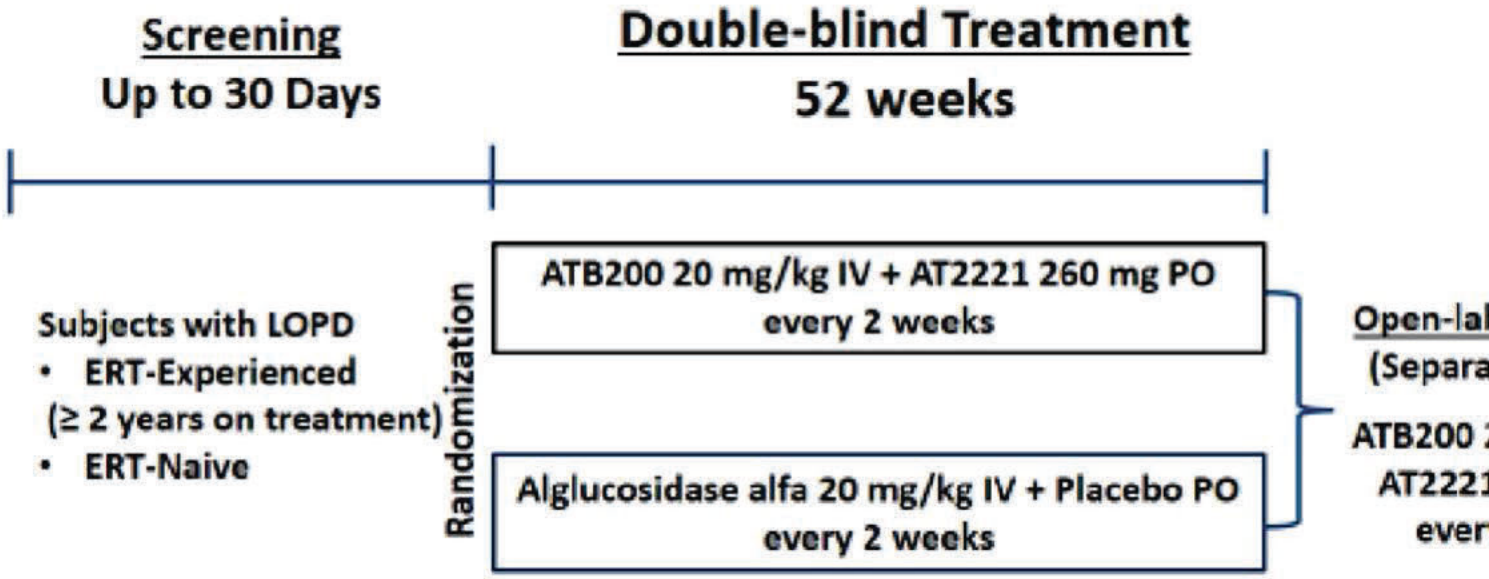
Provide summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

Amicus initially proposed a within-patient comparison to baseline for the registration trial. Planning the development program for this second generation, combination therapy, for a rare disease posed several challenges. The Division agreed that a conventional four-arm trial that randomized to ATB200, AT2221, ATB200/AT2221, and Lumizyme would not be feasible given the rarity of the disease. Over the course of two meetings in August and November of 2018, The Division agreed that the nonclinical data were sufficient to demonstrate that AT2221 was not efficacious as a solo therapy, eliminating the need for one of the four arms. The Division further agreed that it was not feasible to perform a three-arm trial, and ultimately favored retaining the Lumizyme comparator over the ATB200 arm. Amicus agreed to perform a randomized, double-blind, active-controlled trial comparing ATB200/AT2221 to Lumizyme (See **Figure 9**). The trial will enroll n= 110 LOPD patients, including both treatment naïve (n~30) and experienced patients; randomized 2:1 to ATB200/AT2221 or Lumizyme (aglucosidase alfa). The year long trial is powered to detect superiority on six-minute walk distance as the primary endpoint with lung function as the first secondary.

Figure 9: Proposed Phase 2 Trial ATB200-03



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Abbreviations: 6MWD = 6-minute walk distance; ERT = enzyme replacement therapy; IV = intraver
LOPD = late-onset Pompe disease; PO = oral

Source: IND 128387; ATB200-03 protocol amendment submitted February 1, 2019.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

Hagemanns M.L.C., et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain. (2005) 128:671-677.

Kuperus E., et al. Long-term benefit of enzyme replacement therapy in Pompe disease: a 5-year prospective study. Neurology. 2017; 89:1–9

Lim JA, Li L and Raben N. Pompe disease: from pathophysiology to therapy and back again. Front Aging Neuroscie (2014) 6:177

Masat, E. et al. Long-term exposure to Myozyme results in a decrease of anti-drug antibodies in late onset Pompe disease patients. Sci Rep (2016) 4; 6:36182

Regenery C., et. al. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. J Inherit Metab Dis. (2012) 35:5; 837-845.

Schoser B., et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systemic review and meta-analysis. J Neurol (2017) 264:621–630

Stepien K.M., et al. Observational clinical study of 22 adult-onset Pompe disease patients undergoing enzyme replacement therapy over 5 years. Mol Gen Metab. (2016) 117:413–418

Van der Ploeg, A.T. et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. (2010) N Engl J Med. 362(15): 1396-1406.

Van der Ploeg, A.T, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. (2017) European Journal of Neurology http://dx.doi.org/10.1111/ene.13285

Van der Ploeg, A.T, et al. Long-term efficacy of alglucosidase alfa in late-onset Pompe disease. Poster at WORLD Symposium on Lysosomal Disease (2017)

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☐ NO ☒

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 6/15/17/M. Raggio

17 Pages of Duplicate Copy of 1.31.18 BTD Review have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

DINA J ZAND
02/20/2019 11:30:52 AM

KATHLEEN M DONOHUE
02/20/2019 11:37:06 AM

DRAGOS G ROMAN
02/20/2019 05:19:24 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 127387
Request Receipt Date	December 4 2018
Product	ATB200 and AT2221
Indication	Late-Onset Pompe Disease (LOPD)
Drug Class/Mechanism of Action	Primary (ATB200): Enzyme replacement therapy Secondary (AT2221): Substrate Reduction Therapy
Sponsor	Amicus Therapeutics, Inc
ODE/Division	ODE III/Division of Gastrointestinal and Inborn Errors products
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	February 4, 2017

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Treatment of patients with Late-Onset Pompe Disease (LOPD)

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

Executive Summary

The Division does not recommend granting breakthrough therapy designation (BTD) to IND 127387 as the preliminary results from a single-arm, open-label study do not suggest significant clinical improvement after exposure to the Sponsor's drug-biologic combination product ATB200/AT2221.

Patients with Late-Onset Pompe Disease (LOPD) clinically improve upon initiation of the currently available enzyme replacement therapy (ERT). However, after treatment for a few years, newly published reports describe either a plateau in clinical improvement or a slowly progressive deterioration in ambulation (six-minute walk distance (6MWD)) and pulmonary function testing (% predicted FVC). The Sponsor has submitted data from a single arm, open-label study (Study ATB200-02) that evaluated patients switched to ATB200/AT2221 after at least three years of treatment with ERT (alglucosidase alfa) prior to enrollment. The primary efficacy in the study was a comparison of 6MWD from switchover baseline to the longest treatment evaluation (6 to 12 months). The change from baseline was also compared to the available published natural history data. The Sponsor argues that the patients enrolled are presumed to be in the plateau/decline phase of disease, and that if improvement or stability are shown in the 6MWD after starting ATB200/AT2221, then it is reasonable to conclude efficacy relative to historical controls.

The Sponsor was asked to provide pre-switchover clinical data. Such data were provided for three of nine patients who completed the 6MWT. These data called into question whether patients enrolled in the study were in a plateau or a decline phase of disease, and thus whether it is appropriate to compare the results from the trial to natural history data. The Division concludes that the limited information submitted to date, the uncertainties related to the inherent variability in disease progression, and the additional limitations associated with an efficacy assessment that is effort dependent (6MWD) make a claim of efficacy on the basis of the results of this single-arm study very tentative.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Disease:

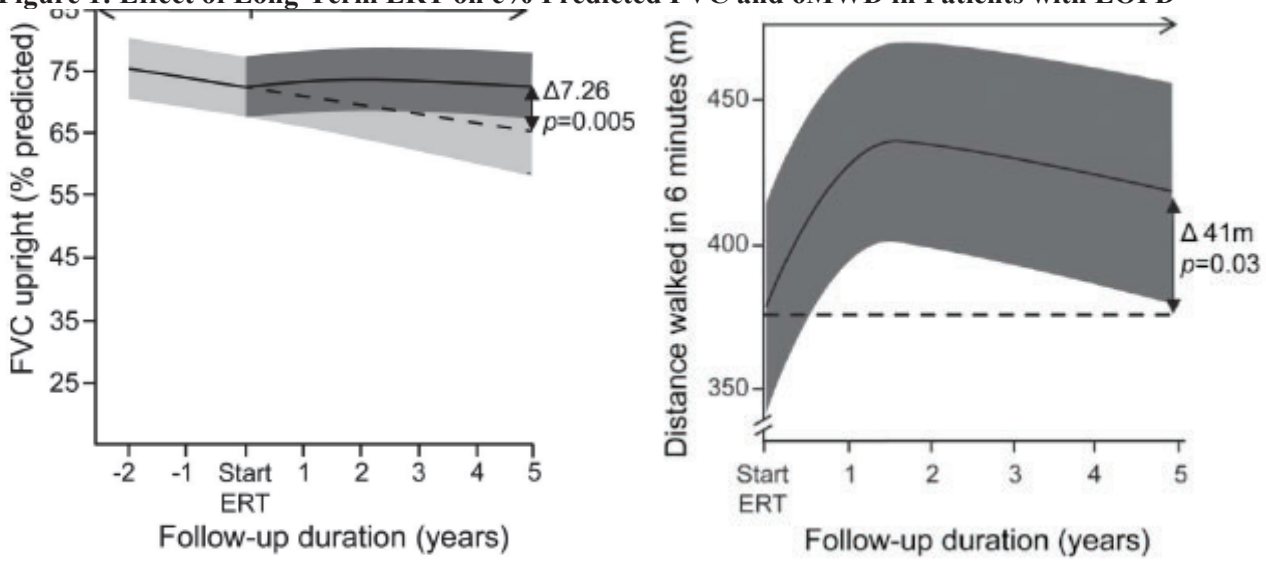
Pompe disease (OMIM#232300), also known as acid maltase deficiency or glycogen storage disease type 2, is a rare lysosomal storage disorder estimated to affect 1 in 40,000 live births, with autosomal recessive inheritance. Patients who present clinically within one-year of age are diagnosed with Infantile-Onset Pompe Disease (IOPD). Patients who present after one year of age are diagnosed with Late-Onset Pompe Disease (LOPD). All diagnosed patients have low or deficient acid α-glucosidase (GAA) activity resulting in glycogen filled lysosomes that ultimately impair all tissues. The mechanism of impairment is not clearly understood. Large accumulation of glycogen appears to cause lysosomes to swell and rupture, and results in cellular damage. In addition, autophagic buildup and lipofuscin inclusions appear to impact the muscle architecture to a greater extent than in other cells. It is also postulated that lysosomal glycogen accumulation has a secondary toxicity on mitochondrial function, which may have a greater impact upon muscle cells (Lim JA, et al). Both IOPD and LOPD significantly impact skeletal and smooth muscle tissue but cardiac muscle is more commonly impaired in patients with IOPD.

Disease progression in patients with LOPD is slower compared to patients with IOPD. Most patients demonstrate progressive limb-girdle weakness and respiratory failure related to disease involvement of muscles in the proximal lower and upper limbs, paraspinal muscles and diaphragm.

Alglucosidase alfa (Myozyme), enzyme replacement therapy (ERT) for patients with IOPD, was initially approved in 2006. Approval was based upon improvement in ventilator-free survival in patients with IOPD. Alglucosidase alfa (under the name Lumizyme) was subsequently approved for patients 8-years and older with LOPD who did not have evidence of cardiac hypertrophy. Approval was based upon improvement in both the 6MWT and % predicted FVC. For additional details regarding approval, refer to Section 8. Recent publications suggest that while long-term ERT with alglucosidase alfa improves muscle strength and pulmonary function, this improvement may peak after a few years of treatment.

- **Kuperus et al., 2017:** A review of long-term efficacy in 102 patients with LOPD treated in the Netherlands suggests that after three years, patients either plateau or steadily decline in measures of muscle strength or pulmonary function and quality of life. (**Figure 1**) The authors evaluated patients for about five years and noted a large degree of variability in 6MWD based upon 95% confidence interval.

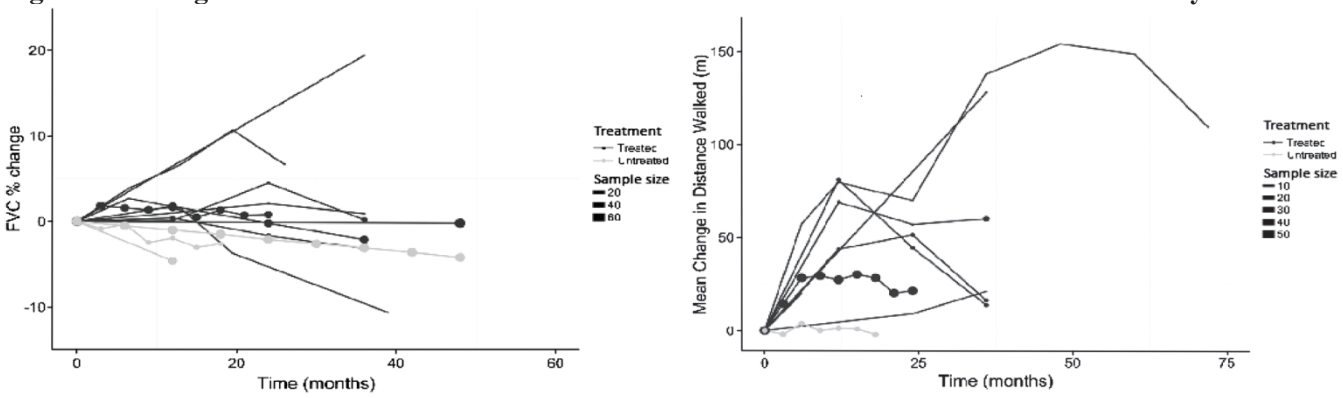
Figure 1: Effect of Long-Term ERT on c% Predicted FVC and 6MWD in Patients with LOPD



Source: Kuperus et al. (2017)
Note: 53 patients evaluated for 6MWD; 94 subjects evaluated prior to ERT start, 84 subjects evaluated after ERT start. The 95% confidence intervals are shown. The dashed line represents the natural course extrapolated on the basis of natural course data. A total of 53 patients were evaluated for 6MWD and 88 patients were evaluated for FVC after initiation of ERT.

- **Schoser et al., 2017:** The authors screened 808 citations and assessed 19 for the long-term efficacy of ERT in patients with LOPD. A total of 298 patients on treatment and 153 patients without treatment informed 11 individual studies that were reviewable for long term information on % predicted FVC. (**Figure 2)** By comparison, 201 patients (171 on treatment and 30 without placebo) informed 8 individual studies reviewable for long-term information on 6MWD. (**Figure 2**)

Figure 2: Change in % Predicted FVC and 6MWD Over Time for Treated and Untreated Study Arms

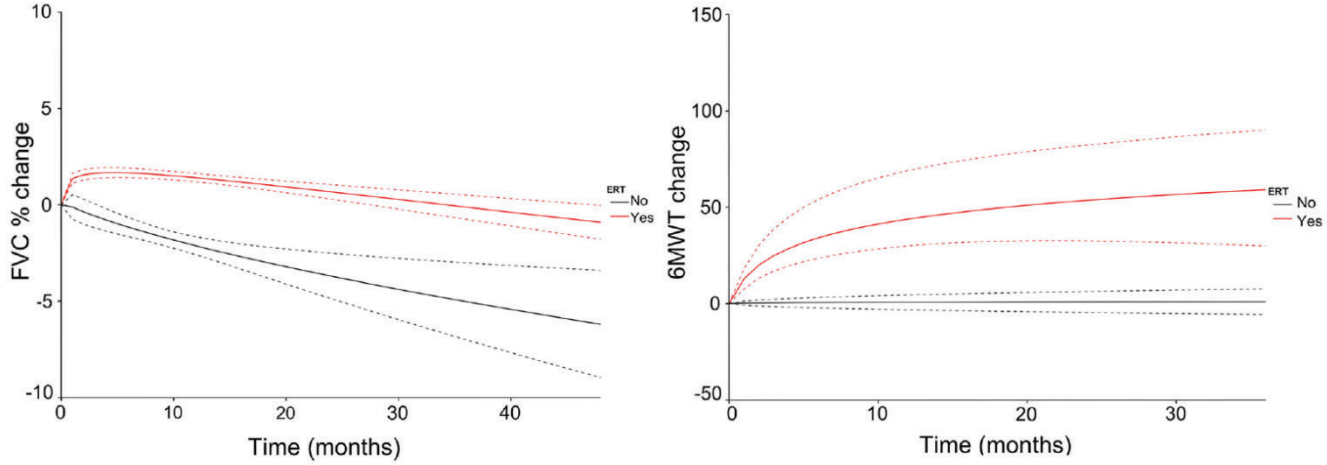


Source: Schoser et al. (2017)

Each line represents a single study. ERT patients (black); Placebo (light grey). The size of the circles represents the approximate sample sizes at each time point. On the left, the absolute change in percent predicted FVC over time among studies, including patients on (black lines) and not on (grey lines) treatment. On the right is the mean change (in meters) over time in distance walked, including patients on treatment (black lines) and not on treatment (grey lines).

Modeling of the data represented in **Figure 2** was used to estimate changes in time for %FVC (11 studies) or 6MWT (8 studies) and is represented in **Figure 3**. These data appear to suggest a plateau or a slowing in improvement in the 6MWT over time, while the change in %FVC gradually decreased over time. Of note, these modeling data project to a shorter duration (40 months) than the patient data provided by Kuperus et al. in **Figure 1** (5 years)**.**

Figure 3: Modeled Mean Changes in % Predicted FVC and 6MWT Over Time for Treated and Untreated - Study Arms



Source: Schoser et al. (2017)

ERT study arm (red); Placebo study arm (black) ; Dotted lines represent 95% confidence interval based on modeling. A total of 12 studies were used for modeling to estimate the change in FVC and a total of 8 studies were used to estimate the change in 6MWD (Studies were single lines in Figure 2)

In general, recent literature evaluating patients on long-term ERT for LOPD suggests that the ERT related functional improvement has limited durability, with an additional caveat that there may be wide variability in the trajectory of individual patient changes. The Sponsor states that there is an unmet medical need for patients with LOPD, as patients who have received alglucosidase alfa for an extended period will ultimately decline clinically on that treatment.

Drug Mechanism:

ATB200/AT2221 is a drug-biologic combination product. The co-administration of AT2221 with ATB200 is hypothesized to stabilize ATB200 within the cells, thereby enhancing efficacy. Each component is described in more detail below:

ATB200 (rhGAA):

ATB200 is a recombinant form of the human enzyme acid α-glucosidase (rhGAA) provided by IV infusion. It is an analog of wild-type (WT) human sequence. ATB200 was also engineered to contain higher amounts of mannose-6-phosephase (M6P) residues to increase affinity for the cation-dependent mannose-6-phosphate receptor (CI-MPR), compared to the mannose receptor. The Sponsor postulates that the increased percentage of Bis-M6P N-glycan residues in ATB200 improves cell surface receptor mediated internalization and targeted delivery to lysosomes.

By comparison, alglucosidase alfa (Myozyme and Lumizyme) contains three amino acid changes from the human WT sequence that have not impacted the specific activity of the protein. The majority of the alglucosidase alfa N-glycan residues are non-phosphorylated.

AT2221 (N-butyl-deoxynojirimycin):

Thermostability data suggest that AT2221 acts as a pharmacological chaperone of ATB200, improving enzyme stabilization and delivery to the lysosome (DARRTS Section 2.6.2 and Section 2.6.4). AT221 is an iminosugar with a composition identical to miglustat, the active ingredient in Zavesca, which was approved in 2003 for type 1 Gaucher disease. It is an inhibitor of the glucosylceramide synthase, the initial enzyme in a series of reactions that inhibits the synthesis of most glycosphingolipids. Both AT2221 and Zavesca are administered orally. The impact of co-administration of AT2221 on alglucosidase alfa or ATB200 was previously assessed via thermostability assays. The data suggested that AT2221 may improve the stability of exogenous ERT in the neutral pH environment of blood and the Sponsor postulates that improved stability may result in improved efficacy *in vivo*. The Sponsor also evaluated the impact of ATB200 and/or AT2221 administration in Gaa knockout mice and observed the greatest decrease in tissue glycogen with ATB200 at 20 mg/kg and AT2221 at 10 mg/k.

Based on the glycogen reduction data from the Gaa knockout mice, the Sponsor generated an exposure response curve as a function of the AT2221/ATB200 exposure ratio. The Sponsor chose the ratios of either 0.01 and 0.02 as optimal, and doses of 233 mg and 466 mg ATT2221 co-administered with 20 mg/kg ATB200 in a 70-kg adult were identified based upon these ratios.[3] A dosage of 260 mg AT2221 was chosen to co-administer with ATB200 infusions.

Relevant Regulatory History:

The Sponsor submitted their Breakthrough Therapy Designation Request on 4 December 2017. The relevant regulatory history for IND 127387 is summarized below in **Table 1**:

[3] IND 127387, initial Clin Pharm review dated 12/22/2015 (Christine Hon)

Table 1: IND 127387 Relevant Regulatory History

Date	Type of Meeting	Concerns Addressed
6-Oct-2015	Pre-IND Face-to-Face	The Division clarified to the Sponsor that ATB200/AT2221 is a drug/biologic combination product and provided advice regarding CMC, clinical pharmacology and trial design issues.
31-Dec-2016	--	IND 127387 was considered safe to proceed.
13-Mar-2016	WRO	The Agency provided suggestions regarding proposed manufacturing changes for ATB200 for comparability of batches. Additional recommendations for a face-to-face meeting were made.
25-Oct-2017	T-con	Preliminary advice regarding a Breakthrough Therapy Designation Request (BTDR): The Division commented upon the review of preliminary data and encouraged the sponsor to proceed with a formal BTDR submission.

Source: DARRTS, IND 127387

7. Information related to endpoints used in the available clinical data:

The endpoints of six-minute walk test (6MWT) and % predicted forced vital capacity (FVC) are acceptable to the Division as both measure clinically relevant functions (ambulation, pulmonary function). They were the primary endpoints used for approval of Lumizyme (alglucosidase alfa) in 2010 for patients with LOPD (refer to Section 8 for details).

Thus far, no biomarkers have been identified that the Division would consider likely to predict a clinical benefit for Pompe disease.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Currently, Myozyme and Lumizyme (both alglucosidase alfa) are the only approved therapies to treat patients diagnosed with Pompe disease. Both products are enzyme replacement therapy (ERT) and both are manufactured by Sanofi Genzyme. Due to changes in manufacturing during the alglucosidase development program, their labeling indications are different.

- **Myozyme:**
  Myozyme was approved in 2006 for patients with IOPD as usage improved ventilator-free survival in patients who ranged from 1 month to 3.5 years of age at the time of initial infusion. Efficacy was assessed by comparing the proportion of patients who died or needed invasive ventilator support with the survival information of a historical cohort of untreated IOPD with similar disease age and severity. Historically, patients diagnosed with IOPD died by age two from disease related cardiopulmonary complications. Secondary outcome measures included unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS).[4]

- **Lumizyme:**
  Lumizyme was approved in 2010 for patients ≥8 years of age who are diagnosed with LOPD without evidence of cardiac hypertrophy. Safety and efficacy were assessed in ambulatory patients aged 10 to 70 years of age who did not require invasive ventilator support or non-invasive ventilation while awake. Patients

[4] Myozyme label (05/2014)

were required to walk at least 40 meters in a 6MWT and have a forced vital capacity (FVC) between 30 and 79% at baseline. Lumizyme was approved based upon the demonstration of a treatment effect relative to placebo of 3.4 % (95% CI: 1.3% to-5.5%) improvement in % predicted upright FVC and a 28-meter (95% CI: -1 to 52 meters) treatment effect in 6MWD.[5] Durability of effect was noted over 12 months.

The greatest concern regarding the use of alglucosidase alfa is the effect of immunogenicity on efficacy long-term. Most patients diagnosed with IOPD with severely low or no residual activity receive immunosuppressants to counter or prevent an immune mediated response to ERT. While in both IOPD and LOPD, treatment with alglucosidase alfa reduces the rate of disease progression, the literature (Refer to Section 6) suggests that following an initial improvement in respiratory and motor function, there is a slow down or decline after about 2-3 years treatment.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[6].

None, currently.

10. Information related to the preliminary clinical evidence:

The Sponsor provided preliminary data from a single study (ATB200-02) in their request for Breakthrough Therapy Designation (**Table 2**). The study was an open-label, ascending-dose (ATB200), first-in-human study to assess the safety, tolerability and pharmacokinetics of IV infusion of ATB200 co-administered with ATB2221. All patients were previously exposed to at least 3 years of ERT (alglucosidase alfa) and then switched over to an equivalent dose of Amicus's α-glucosidase (ATB200) IV infusions at enrollment (please note that the functional equivalence of the two α-glucosidase products has not been established). The IV dosing interval for ATB200 was every 2 weeks, consistent with the previous ERT dosing. Oral administration of AT2221 was provided one hour prior to IV infusion (**Table 3**).

Eleven ambulatory adults were enrolled in Study ATB200-02. Prior to enrollment each subject was required to demonstrate a baseline ability to walk between 200 and 500 meters and an upright FVC between 30% and 80% predicted normal value. Study ATB200-02 did not have a comparator arm (either previous ERT, or AT2221 alone). (**Table 3**) At the time of BTDR, 11 subjects were still enrolled, aged 25 to 65 years. One subject discontinued the study after completion of Stage 2 (**Table 3**). One subject was not able to complete assessments for the 6MWT at months 6 and 9 and another subject did not have FVC data (due to faulty equipment, per the Sponsor).

[5] Lumizyme label (05/2010)
[6] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Table 2: Studies Reviewed for Consideration of Breakthrough Therapy Designation

Study	Study Title	N	Duration	Endpoints
ATB200-02	Open-label, fixed-sequence, ascending-dose, multicenter, international, first-in-human study to assess the safety, tolerability, PK/PD and efficacy of intravenous infusions of ATB200 co-administered with oral AT2221 in ERT-experienced[a] adult subjects with Pompe disease	11	Up to 12 months	• 6MWT • % pred FVC

Source: IND 127387 BTDR submitted 4 Dec 2017

[a] All patients described were ERT- experienced ambulatory subjects who had received alglucosidase alfa for 2- to 6-years prior to enrollment and could walk at least 200 meters in the 6-minute walk test (6MWT)

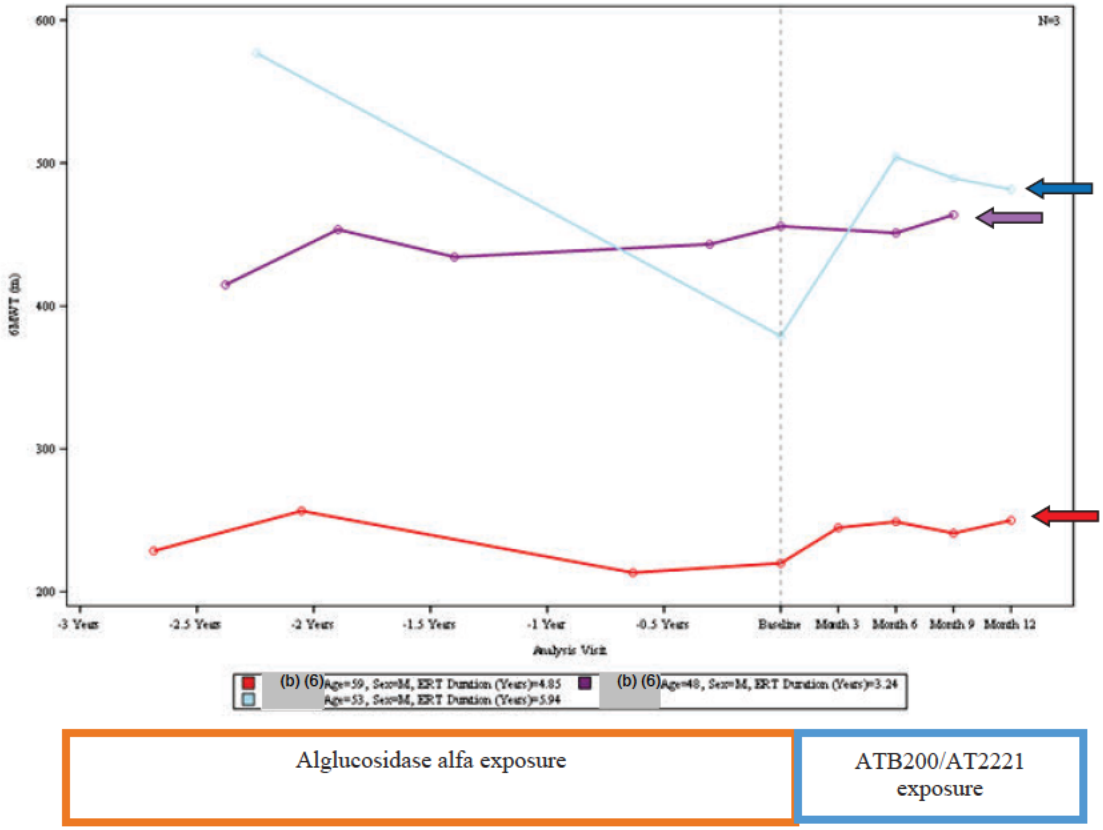
Table 3: Study ATB200-02 Description of Dose Escalation at Two Week Intervals

Stage 1 (6 weeks)			Stage 2 (12 weeks)		Stage 3 (2 years)
Period 1 Single-Dose	**Period 2 Single-Dose**	**Period 3 Single-Dose**	**Period 4 3 Multiple Doses Co-administration**	**Period 5 3 Multiple Doses Co-administration**	**Multiple Dose, Long-term Extension Co-administration**
5 mg/kg ATB200	10 mg/kg ATB200	20 mg/kg ATB200	20 mg/kg ATB200 +130 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221

Source: IND 127387 BTDR submitted 4 Dec 2017 (Table 2; page 12 of 47)

Data from nine subjects who received at least 6 months of exposure to both ATB200 and AT2221 (Stage 2 and Stage 3 of Study ATB200-02) were available for review. All patients had been previously exposed to alglucosidase alfa for at least 3.14 years and no more than 6.42 years prior to study initiation. Study ATB200-02 did not include a run-in period, The Sponsor was able to provide at Division's request pre-enrollment 6MWD for three patients of 9 patients. (Figure 4).

Figure 4: Pre- and after Switchover 6MWD Data for 3 Patients in Clinical Study ATB200-02



Source: IND 127387; Modified from IR response received 17 January 2018

Review of six-minute walk distances (6MWD) completed during the trial suggested that 8 of the 9 patients were either stable or improved in 6MWD by at least 8 meters from baseline to the last time point after 9 months of treatment with ATB200/AT2221. (**Table 4** and **Figure 5**). Note that the table does not include data points prior to initiating treatment that are shown in Figure 4.

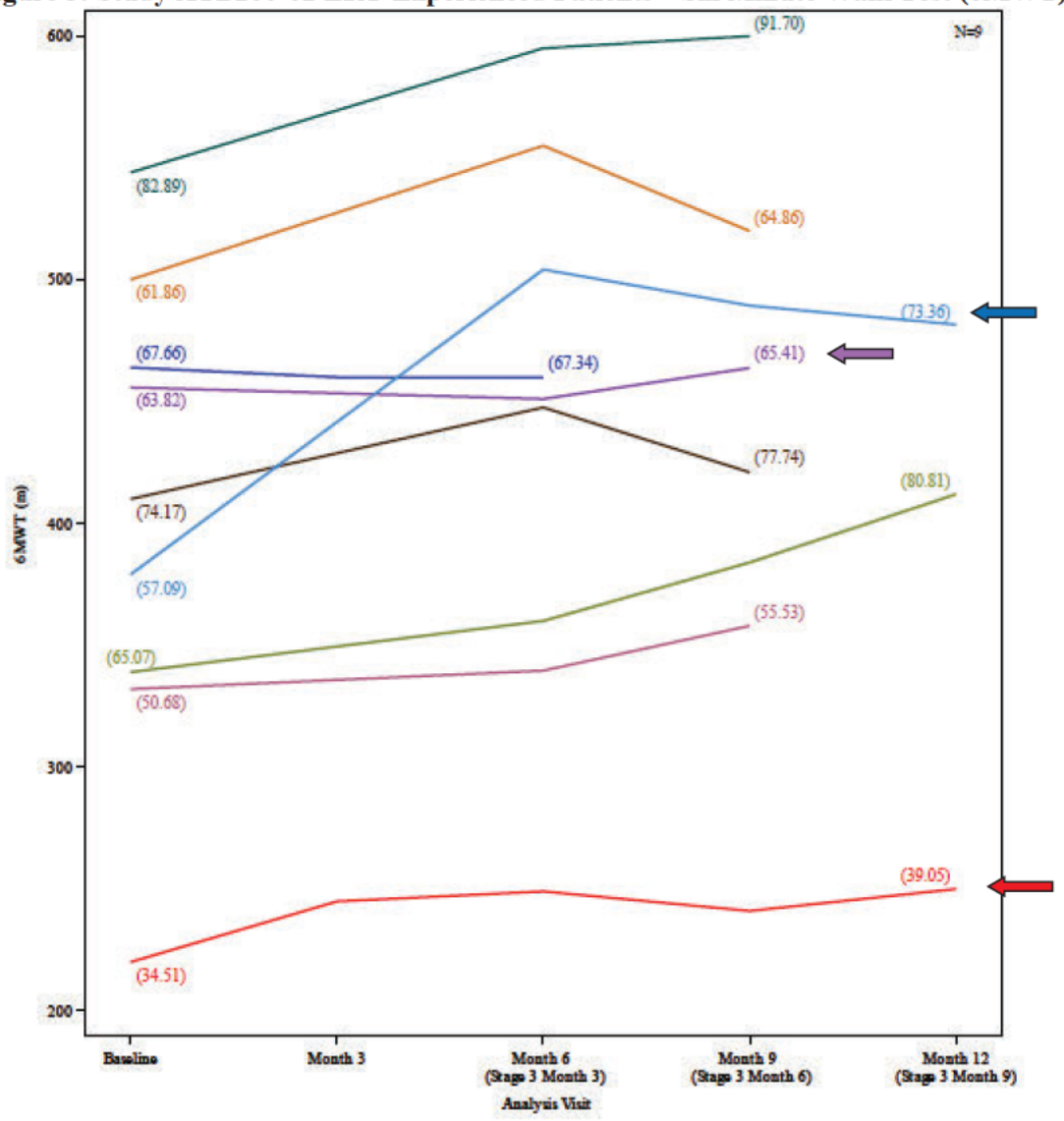
Table 4: 6MWT and Change from Baseline through 9-month Follow-up

Patient-Level Data **ERT- Experienced (Cohort 1) (N=11):** **Six-minute walk test (6MWT) & Change from Baseline (CFBL)**			
Subject Number	**Baseline (m), n=9**	**Change from Baseline at Month 6[a], n=9**	**Change from Baseline at Month 9[b], n=8**
(b) (6)	464.0	-4.0	N/A[c]
	220.0	29.0	21.0
	544.0	51.0	56.0
	410.0	37.6	11.0
	455.8	-4.7	8.0
	339.0	21.0	45.0
	379.0	125.2	110.4
	332.0	7.6	26.0
	500.0	55.0	20.0
Mean (SD)	404.9 (99.4)	35.3 (40.1)	37.2 (33.8)

[a] M6 =S3M3 data on xpt files
[b] M9 =S3M6 data on xpt files
[c] did not have M9 data available at the time of interim analysis
Source: IND 127387 BTDR, Table 5 (page 16 of 47)

Given the relatively changes observed on ATB200/AT2221 treatment and the inherent uncertainties related to a comparison to a non-concurrent cohort, the Division asked for any available pre- ATB200/AT2221 treatment 6MWD data. Such data were available for only 3 patients (indicated by the colored arrows in both **Figure 4** and **Figure 5**), and did not provide convincing evidence of improvement. In two patients (purple and red arrows) the overall trend on treatment was not markedly different from that observed prior to treatment switchover. For the third subject (blue arrow) interpretation of the data is challenging because there is only one data point on previous treatment; the single data point at baseline and the two data points after switchover suggest an initial brief improvement followed by deterioration. Given that the 6MWD is effort dependent, the lack of formal standardization, and the limited number of pre-switchover assessments, ascribing the results for this patient (blue arrow) as improvement due to ATB200/AT2221 remains tentative.

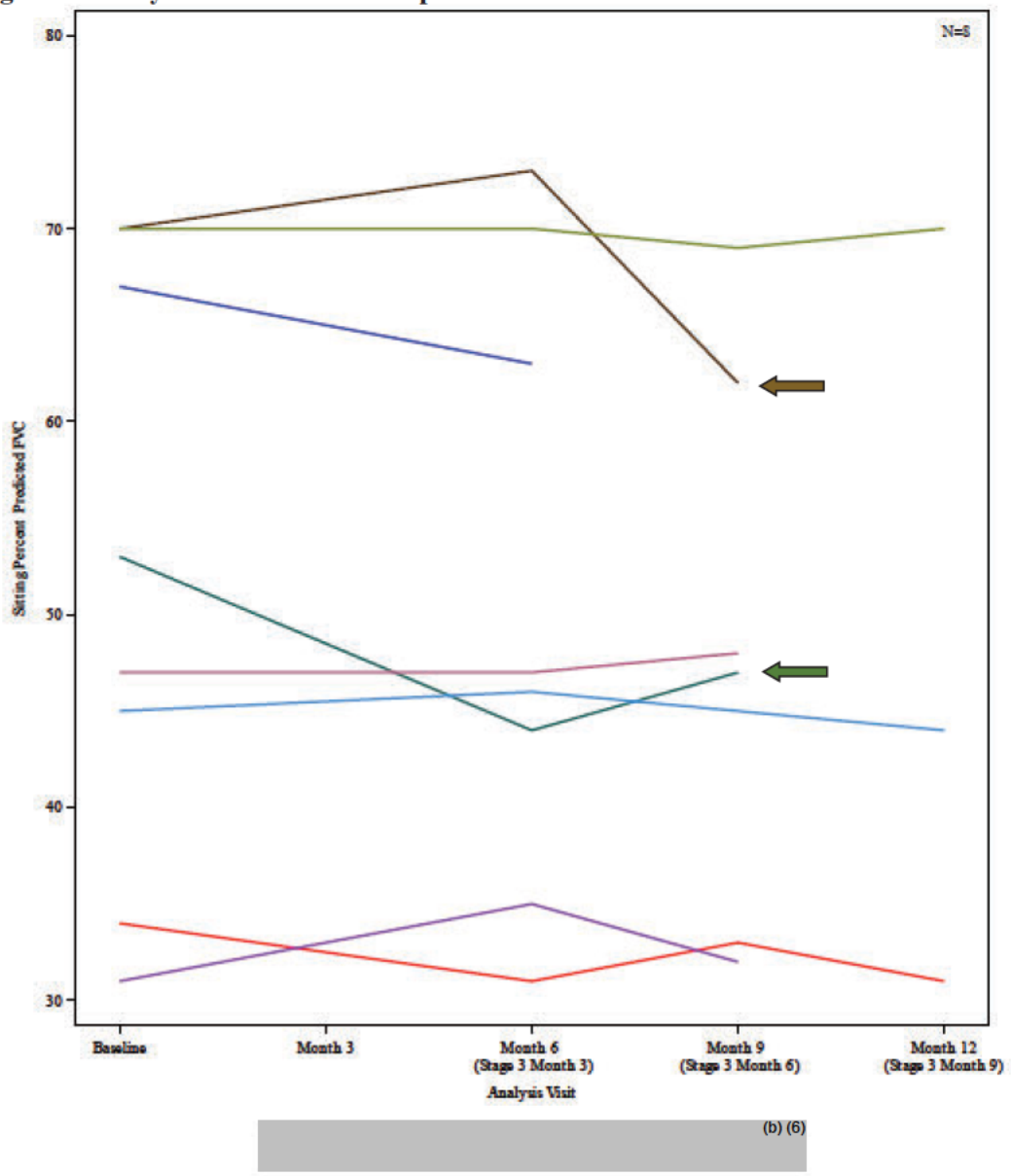
Figure 5: Study ATB200-02 ERT-Experienced Patients – Six Minute Walk Test (6MWT)



Note: Values shown in parenthesis are Percent predicted 6MWD.
Note: Predicted 6MWD values are obtained from the following equations:
Males: (7.57 x height cm) - (5.02 x age) - (1.76 x weight kg) - 309 m.
Females: (2.11 x height cm) - (2.29 x weight kg) - (5.78 x age) + 667 m.
Percent predicted 6MWD values are calculated as: 100 x (Observed value) / (Predicted value).
Source: Modified from IND 127387 BTDR submitted 4 Dec 2017 (Figure 2; page 17 of 47)

In contrast, only 8 of 11 patients could perform % predicted FVC. Overall, there was no significant improvement after 6-to 12-months exposure to ATB200/AT2221. (**Figure 6**)

Figure 6: Study ATB200-02 ERT-Experienced Patients -- Percent Predicted Forced Vital Capacity (FVC)



Note: The values for FVC measurement in subject 2036-1751 are not included in this analysis. Reliable measurements were not obtained at 6 and 9 month visits due to equipment failure.

ATB200/AT2221 Exposure

Source: IND 127387 BTDR submitted 4 Dec 2017 (Figure 3; page 220 of 47)

Of the 8 patients who completed % predicated FVC testing at baseline and one timepoint thereafter, 5 of 8 demonstrate a progressive decline in pulmonary function, while three appeared to stabilize or improve somewhat relative to baseline. Two of the 3 patients with decline were also noted to utilize a nighttime respiratory device (CPAP or BiPAP) prior to study enrollment. Patient (b) (6) (green arrow) remained on BiPAP throughout the study. Patient (b) (6) (brown arrow) entered Study ATB200-02 while on CPAP, but switched to BiPAP nine months after enrollment due to inadequate CO_2 clearance at night.

A lack of concordance between walk distance and pulmonary function is not unexpected. Hagemans et al., (2005) notes that the natural history of the disease is marked by differential progression for walk distance and pulmonary function.

Other studies have noted that gains in 6MWD and FVC are not consistently parallel or of similar magnitude (Stepien et al 2016, Kuperus et al 2017).

Safety

Safety and tolerability were assessed in 20 patients who were exposed to ATB200/AT2221. The data submitted for review reflect a maximum of 72-weeks exposure with over 400 infusions of ATB200. No deaths occurred. The adverse events (AEs) reported in at least 15% of subjects were diarrhea, increased blood uric acid, tremor, headache, upper respiratory tract infection, nausea, muscle spasms, myalgia, back pain, fall, fatigue, flatulence, abdominal distension, abdominal pain, and pain in extremity.

Infusion associated reactions (IARs) were noted in two subjects who experienced a total of three events. One IAR occurred in a non-ambulatory ERT experienced subject who reported skin discoloration following infusion. By report, this subject experienced a similar IAR with previous therapy. Two events of IARs occurred in an ERT naïve subject who had hand pruritus, erythema and burning sensation. IARs were controlled with pre-medications.

In general, there were no new safety signals during this limited review and the reported AEs appeared to be consistent with anticipated AEs for both ATB200 and AT2221.

11. Division's recommendation and rationale (pre-MPC review):

☐ GRANT :

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☒DENY:

Provide brief summary of rationale for denial:

The Division does not recommend that breakthrough therapy designation be granted to ATB200/AT2221. While the literature suggests that patients with LOPD who have received ERT may demonstrate a slowdown in 6MWD over time, individual patients may not decline at the same velocity. The lack of a concurrent control, the absence of reliable pre-treatment information or any pre-treatment information for most patients, the expected variability of the assessment (6MWD), and the uncertainties related to a comparison with the literature data without appropriate matching, make data interpretation extremely challenging if not speculative. Therefore, without a reliable comparator arm, it is difficult to attribute the improvements noted in some patients in study ATB200-02 to the effects of ATB200/AT222.

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

We continue to work closely with the sponsor on this drug development program. The Sponsor has submitted written questions regarding the planned phase 3 study in patients with LOPD for this product. It is currently under review with an anticipated telephone conference for additional discussion in April 2018.

As ATB200/AT2221 is a drug-biologic combination product, the Sponsor has been advised regarding the necessary elements for a marketing submission, including the need to evaluate of the contribution of the individual components along with the combination in the LOPD population.

Upon multidisciplinary review of the submitted protocol, more specific commentary will be provided to the Sponsor.

13. List references, if any:

Hagemanns M.L.C., et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain. (2005) 128:671-677.

Kuperus E., et al. Long-term benefit of enzyme replacement therapy in Pompe disease: a 5-year prospective study. Neurology. 2017;89:1–9

Lim JA, Li L and Raben N. Pompe disease: from pathophysiology to therapy and back again. Front Aging Neuroscie (2014) 6:177

Regenery C., et. al. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. J Inherit Metab Dis. (2012) 35:5; 837-845.

Schoser B., et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systemic review and meta-analysis. J Neurol (2017) 264:621–630

Stepien K.M., et al. Observational clinical study of 22 adult-onset Pompe disease patients undergoing enzyme replacement therapy over 5 years. Mol Gen Metab. (2016) 117:413–418

Van der Ploeg, A.T. et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. (2010) N Engl J Med. 362(15): 1396-1406.

Van der Ploeg, A.T, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. (2017) European Journal of Neurology http://dx.doi.org/10.1111/ene.13285

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☐ NO ☒

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 6/15/17/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DINA J ZAND
01/31/2018

KATHLEEN M DONOHUE
01/31/2018

DRAGOS G ROMAN
01/31/2018