

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761204Orig1s000

PRODUCT QUALITY REVIEW(S)

Breakthrough/Orphan Designation Recommendation: Approval

BLA Number: 761204

Review Number: 1

Review Date: April 4, 2022; Revised: July 12, 2022; August 5, 2022; September 19, 2023

Drug Name/Dosage Form	Pombiliti® [cipaglucosidase alfa-atga] for Injection Co-labeled for use with Opfolda (miglustat, AT2221, N-butyldeoxynorjirimycin under review in NDA 215211)¹
Strength/Potency	105 mg lyophilized powder in a single-dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Pombiliti is indicated, in combination with Opfolda, for the treatment of adult patients with late-onset Pome disease weighing ≥40 kg and who are not improving on their current enzyme replacement therapy
Applicant/Sponsor	Amicus Therapeutics US, LLC

Product Overview

Pombiliti (cipaglucosidase alfa-atga, ATB200) is a recombinant form of human acid α -glucosidase, an enzyme responsible for the breakdown of lysosomal glycogen. Cipaglucosidase alfa was developed as an enzyme replacement therapy (ERT) for treatment of late-onset Pompe Disease, a lysosomal storage disorder that results from deficiency in acid α -glucosidase activity. Cipaglucosidase alfa is produced as a 110 kDa glycoprotein in Chinese hamster ovary (CHO) cells by perfusion technology. The amino acid sequence of cipaglucosidase alfa is identical to the human wild type acid α -glucosidase. Its glycan profile includes mannose 6-phosphate (M6P) and bis-phosphorylated high mannose (bis-M6P) oligosaccharide structures, which facilitate its transportation to lysosomes through the cation independent mannose 6-phosphate receptor (CI-MPR).

Pombiliti drug product is supplied as a sterile, white to slightly yellowish lyophilized powder with a cake-like appearance in a single-dose vial containing 105 mg of cipaglucosidase alfa. Cipaglucosidase alfa will be co-administered with an oral dose of Opfolda (miglustat), a small molecule that is proposed to bind to and stabilize the enzyme in plasma.

Quality Review Team

	BLA	
Discipline	Reviewer	Branch/Division
Drug Substance	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Drug Product	Davinna Ligons/Frances Namuswe	DBRRIII/OBP

¹ This review memo only covers Pombiliti. For Opfolda, refer to the review memo for NDA 215211.

Microbiology Drug Substance	Richard Ledwidge/ Virginia Carroll/Candace Gomez-Broughton	DBM/OPMA
Microbiology Drug Product	Richard Ledwidge/Virginia Carroll/ Candace Gomez-Broughton	DBM/OPMA
Facility	Richard Ledwidge/Virginia Carroll/ Candace Gomez-Broughton	DBM/OPMA
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Immunogenicity	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Application Team Lead	Frances Namuswe	DBRRIII/OBP
Application Tertiary reviewer	Maria Teresa Gutierrez-Lugo	DBRRIII/OBP
OPQ RBPM	Kelly Ballard	OPRO/DRBPMI/RBPMB
NDA		
Drug Substance	Jeffery Medwid/ Donna Christner	DNDAPI/ONDP
Drug Product	Zhengfang Ge/ Hong Cai	DNDPII/ONDP
Biopharmaceutics	Kamrun Nahar/ Vidula Kolhatkar	DB/ONDP
Application Team Lead	Hamid Shafiei	DNDPII/ONDP

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
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Clinical Pharmacology Secondary	Jie (Jack) Wang Lian Ma (pharmacometrics)	OTS/OCP/DTPM
Statistics	Primary: Emily Morris Secondary: Yan Wang	OTS /OB/DBIV
DMEPA	Valerie Vaughan/Sevan Kolejian	OSE/OMEPRM/DMEPA

1. Names:

- a. Proprietary Name: Pombiliti
- b. Trade Name: Pombiliti
- c. Non-Proprietary/USAN: cipaglucosidase alfa-atga
- d. CAS name and number: 2359727-71-0
- e. Common name: ATB200
- f. INN Name: cipaglucosidase alfa
- h. OBP systematic name: RPROT P10253 (LYAG_HUMAN) LYSOSOMAL ALPHA-GLUCOSIDASE [ATB200]
- i. Other names: recombinant human acid alpha-glucosidase (rhGAA), α -glucosidase, (acid) maltase, glucoinvertase, glucosidosucrase, maltase-glucoamylase, α -glucopyranosidase, glucosidoinvertase, α -D-glucosidase, α -glucoside hydrolase, α -1,4-glucosidase, lysosomal α -glucosidase

2. Pharmacological class: Hydrolytic lysosomal glycogen-specific enzyme

Submissions Reviewed

Submission:	Date Received:	Assessment Completed (yes or no)
SN 0004	7/29/2021	Yes
SN 0007	9/14/2021	Yes
SN 0008	9/22/2021	Yes
SN 0015	11/19/2021	Yes
SN 0017	12/3/2021	Yes
SN 0018	12/9/2021	Yes
SN 0019	12/15/2021	Yes
SN 0020	12/22/2021	Yes
SN 0021	1/7/2022	Yes
SN 0022	1/13/2022	Yes
SN 0023	1/21/2022	Yes
SN 0024	1/28/2022	Yes
SN 0026	2/16/2022	Yes
SN 0027	2/18/2022	Yes
SN 0029	2/25/2022	Yes
SN 0030	2/28/2022	Yes
SN 0031	3/02/2022	Yes
SN 0032	3/15/2022	Yes
SN 0034	4/08/2022	Yes
SN 0037	5/11/2022	Yes
SN 0038	5/18/2022	Yes
SN 0041	6/15/2022	yes
SN 0043	7/7/2022	yes
SN 0045	7/25/2022	yes
SN 0056	12/16/2022	yes
SN 0057	1/31/2023	Yes
SN 0058	3/15/2023	yes
SN 0059	3/31/2023	yes
SN0060	4/19/2023	Yes
SN 0061	5/12/2023	Yes
SN 0062	5/25/2023	Yes
SN 0064	7/21/2023	Yes
SN 0065	8/3/2023	yes
SN 0067	9/18/2023	yes

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents

A. DMFs

DMF#/ (Type)	DMF Holder	Item Referenced	Code ¹	Date Assessment completed	LOA	Comment (status)
(b) (4) (V)		(b) (4)	2	02/15/2019	Yes	Adequate
(b) (4) (III)			3	N/A	Yes	Review not needed. Relevant information submitted in the BLA.
(b) (4) (III)			3	N/A	Yes	Review not needed. Relevant information submitted in the BLA.

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows:
2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to
reference not granted; 5- DMF not available; 6- Other (explain under "comments")

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application

Application Number	Description
IND 127387	ATB200
NDA 215211	Opfolda (miglustat)
NDA 021348	Zavesca (miglustat)

3. Consults

None issued

4. Environmental Assessment or Claim of Categorical Exclusion

Amicus claims categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(c). Per 21 CFR 25.31(c), categorical exclusion can be granted for Pombiliti; therefore, the claim of categorical exemption is accepted.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- i. Recommendation: Approval with PMCs

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

B. Approval Action Letter Language

- Manufacturing location:
 - **Drug Substance and Drug Product manufacture:** WuXi Biologics Co., Ltd., 108 Meiliang Road, Mashan, Binhu District, Wuxi, Jiangsu 214092, China

DP labeling and Secondary packaging:

(b) (4)

(b) (4)

- Fill size and dosage form: 105 mg lyophilized powder in a single-dose vial for injection
- Dating period:
 - Drug Product: 36 months at 2-8°C
 - Drug Substance: (b) (4) months at (b) (4) °C
 - For packaged Products: Not packaged but co-labeled for use in combination with Opfolda
- Exempt from lot release
 - Yes. Pombiliti is exempted from lot release per Docket No 95-29960 because it is a specified product

C. Benefit/Risk Considerations

Pompe disease (PD) is a rare and serious lysosomal storage disease that can lead to death from cardiac or respiratory failure if untreated in the infantile-onset form (IOPD) and to motor impairment and premature death from respiratory failure in the late-onset form (LOPD). PD is caused by autosomal recessive variants in the acid alpha glucosidase (GAA) gene that result in deficient GAA activity and accumulation of glycogen in cells. This in turn leads to myopathy, respiratory weakness, physical disability, and can lead to premature death. The currently approved therapies for PD are recombinant GAA enzymes, alglucosidase alfa and avalglucosidase alfa. Alglucosidase alfa does not lead to a sustained improvement in muscle weakness, and thus, patients tend to develop progressive disease, which can lead to respiratory failure. (b) (4)

(b) (4) Therefore, treatment and cure of PD continue to represent unmet medical needs.

Efficacy of cipaglucosidase alfa coadministered with miglustat was evaluated in one well-controlled trial (ATB200-03) in 123 adult patients with LOPD (95 treatment-experienced, 28

treatment-naïve) randomized to cipaglucosidase alfa/miglustat or a non-U.S.-approved alglucosidase alfa product coadministered with placebo. The benefit of cipaglucosidase alfa/miglustat is based on comparison of the distance walked on the 6-min walk test, the primary endpoint, and forced vital capacity (% predicted), a key secondary endpoint. The estimated treatment difference in the mean change from baseline to Week 52 in the 6-min walk test and in forced vital capacity favored the cipaglucosidase alfa/miglustat arm; the results of the primary end point are driven by the treatment experienced subgroup. Confirmatory evidence of effectiveness is derived from other studies showing cipaglucosidase alfa coadministered with miglustat reduces glycogen levels in tissues and improves muscle function in GAA knockout mice compared to alglucosidase alfa, consistent with the mechanism of action and pathophysiology of the disease.

Based on these studies, the Agency concluded that the benefits of cipaglucosidase alfa coadministered with miglustat on lung function, an important target for drug treatment for patients with LOPD, outweigh its risks when used according to the agreed-upon labeling. The Agency recommends cipaglucosidase alfa coadministered with miglustat as a second-line therapy for adult patients with LOPD who are not improving on other ERT, because of the potential increased risk when receiving two drugs instead of one drug, safety concerns identified as possibly related to miglustat, and the availability of two other approved ERTs for the treatment of Pompe disease. Refer to the OND review and labeling for the final approved indication.

The data submitted in this application are adequate to demonstrate that the manufacture of Pombiliti is well-controlled and leads to a product that is safe, pure, and potent. Therefore, from a product quality perspective, this product is approvable for human use as described in the product labeling. The Applicant agreed to three post-marketing commitments (PMCs) to improve the robustness of the drug substance (DS) and drug product (DP) manufacturing processes and overall product control strategy as outline in Section D below.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

The following post marketing commitments have been proposed and accepted by the Applicant:

Product Quality

PMC 4322-1: To perform extractables/leachables studies and risk assessments to evaluate leachables from the container closure system(s) and manufacturing product contact surfaces of cipaglucosidase alfa drug substance and drug product and assess the potential impact of leachables on product quality at the end of drug product shelf-life. The analyses will be performed using drug substance and drug product lot(s) and/or representative samples (e.g., (b) (4) if justified) analyzed at appropriate time points, including at the end of drug product shelf life. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of the potential impact of leachables on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be provided in the final study report per 21 CFR 601.12.

Final report submission date: 12/2023

PMC 4322-2: To develop, validate, and implement a test method with justified numerical acceptance criteria for control of cipaglucoisidase alfa kinetic parameters during drug product release and stability testing. Critical kinetic parameters (e.g., Km, Kcat, etc.,) will be determined, justified, and included in the control strategy. If applicable, justification and data supporting (b) (4) will be provided. The method validation report for the enzyme kinetic assay, the revised drug product release and stability specifications, and all supporting studies and data will be provided in a final study report per 21 CFR 601.12.

Final report submission date: 06/2024

Microbiology

PMC 4322-3: To develop an endotoxin method for the drug product which mitigates the low endotoxin recovery (LER) effect, submit method qualification results with three lots of drug product and provide results of an LER study performed with the updated method with three lots of drug product.

Final Report Submission: 01/2024

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Tables 1 and 2 summarize the CQAs intrinsic to cipaglucoisidase alfa API and the drug substance manufacturing process, respectively. These CQAs are based on both the Applicant's determined CQAs and quality attributes the Agency considers CQAs for this class of products, regardless of how they were classified by the Applicant. Attributes that are controlled only by the manufacturing process as well as attributes that the Applicant considers non-CQAs will be assessed in risk-based comparability assessments as requested by the Agency.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy (Additional comments)
Identity (General)	Safety and Efficacy	Intrinsic to the molecule	(b) (4)
Primary Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule - Expression construct and cell line	
Higher Order Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule	

CI-MPR binding and cellular uptake (potency)	Efficacy	- Intrinsic to the molecule - May be impacted by the DS manufacturing process and changes to the glycan profile
Enzymatic activity and specific activity (potency)	Efficacy	- Intrinsic to the molecule - Impacted by the DS manufacturing process
Glycosylation (M6P and Bis M6P)	Efficacy	- Intrinsic to the molecule - Impacted by the DS manufacturing process
Glycosylation (Sialic acid)	May impact PK and Efficacy	- Intrinsic to the molecule - Impacted by the DS manufacturing process
High Molecular Weight Species (product impurities)	Efficacy and Safety, including Immunogenicity	- Manufacturing process - May increase on storage
Low Molecular Weight Species (product impurities)	Efficacy and Safety	- Manufacturing process - May increase on storage
Charge Heterogeneity (product variants)	Potential impact on Efficacy and Safety	- Intrinsic to the molecule (e.g., from glycan species) - DS and DP manufacturing process - May increase on storage (e.g. oxidation, deamidation)
Post-translation Modification (PTMs) (oxidation, deamidation, succinimide, & isomerization)	May impact potency or safety	-DS and DP manufacture - May increase on storage

(b) (4)

B. Pombiliti [cipaglucosidase alfa-atga] Drug Substance Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy (Additional comments)
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Appearance (general)	Safety	- Manufacturing process
pH (general)	Safety and DS stability	- Manufacturing process/formulation
Protein Content (general)	Efficacy	- Manufacturing process/formulation
Osmolality (general)	Patient discomfort (No further formulation to generate DP)	- Manufacturing process/formulation
(b) (4)	Product Stability	- Manufacturing/formulation
Host Cell Proteins (process impurity)	Safety and immunogenicity	Production cell line/Cell culture
Host Cell DNA (Process impurity)	Safety	Production cell line/Cell culture
Adventitious virus (Contaminant)	Safety	Raw materials and contamination during manufacturing
Mycoplasma (Contaminant)	Safety	Raw materials and contamination during manufacturing
Bioburden (Contaminant)	Safety, purity, and efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process
Endotoxin (Contaminant)	Safety and purity	Raw materials and manufacturing process
Pyrogens	Safety	Raw materials and manufacturing process
(b) (4)	Safety	DS manufacture

(Process impurities)			
Leachables (Impurities)	Safety and product stability	Manufacturing equipment and container closure	(b) (4)

- a. **Description:** Cipaglucosidase alfa is a 110 kDa recombinant hydrolytic lysosomal human acid α -glucosidase enzyme produced in CHO cells by perfusion technology. Its 896 amino acid sequence corresponds to amino acid residues 57 to 952 of wild-type (WT) human acid α -glucosidase (GAA) after proteolytic processing that removes the initial 56 residues comprising the signal peptide and precursor peptide. It has 7 N-glycosylation sites and contains M6P and bis-M6P glycans that are critical for binding to the CI-MPR. Its N-terminal forms pyroglutamate and its tertiary structure is stabilized by 5 disulfide bonds.
- b. **Mechanism of Action:** Cipaglucosidase alfa is indicated for treatment of PD, a lysosomal storage disorder that results from deficiency in GAA activity. GAA deficiency results in lysosomal accumulation of glycogen in various tissues. Cipaglucosidase alfa is an exogenous source of GAA. It binds to the CI-MPR, which internalizes the product and delivers it to the lysosomes. In the lysosomes, cipaglucosidase alfa degrades glycogen to glucose and thus, reduces glycogen substrate levels. CI-MPR binding is mediated by M6P and bis-M6P on cipaglucosidase alfa. According to the Applicant, cipaglucosidase alfa has higher levels of M6P and bis-M6P than alglucosidase alfa, which result in high binding affinity for the CI-MPR. Potency of cipaglucosidase alfa is controlled by monitoring specific activity using an enzymatic activity assay and a fibroblast uptake cell-based assay. In addition, M6P and bis-M6P levels are controlled.

Cipaglucosidase alfa will be co-administered with an oral dose of miglustat, a small molecule proposed to bind to and improve stability of ATB200 in plasma (at neutral pH), thereby improve enzyme uptake and delivery of ATB200 to muscle and lysosomes. When cipaglucosidase alfa was coadministered with miglustat, in vitro and animal studies showed improved dose-dependent stability of cipaglucosidase alfa and studies in *Gaa* knockout mice showed significant reduction in glycogen. However, miglustat has no direct treatment effect on patients with LOPD.

c. **Potency Assay**

Fibroblast cell uptake: The fibroblast cell uptake assay measures the ability of cipaglucosidase alfa to hydrolyze the substrate 4-Methylumbelliferyl- α -D-glucopyranoside (4-MU-Glc) to its fluorescent product 4-methylumbelliferone (4-MU) after cellular uptake of cipaglucosidase alfa

by human normal fibroblasts cells via the CI-MPR. This assay reflects cipaglusosidase alfa's mechanism of action. Plated cells are incubated with serially diluted DS and DP samples, reference standard (RS), and assay control in duplicate. Cells are lysed, incubated with 4-MU-Glc, and evaluated for enzyme activity. The measured fluorescence (RFUs) is converted to 4-MU content using a 4-MU standard curve. Protein concentration in each sample well is determined using a bovine serum albumin standard curve. Enzymatic activity (4-MU per well/mL enzyme/hour) and specific enzyme activity (nmol/mg/h) are calculated for the samples and RS. Potency is reported relative to that of the RS based on the ratio of EC50 values. New lots of the critical raw materials and reagents used for the assay must be qualified prior to use. The Applicant established an adequate link between the potency assay proposed for commercial use and other potency assays used to release clinical material.

Specific activity: In a different (non-cell based) assay, specific activity of cipaglusosidase alfa is determined by its ability to catalyze the 4-MU-Glc substrate to 4-MU. Diluted DS and DP samples (prepared in triplicate), control (reference standard), and dilution buffer (blank) in 96-well plates are incubated with 4-MU-Glc substrate, alongside 4-MU standards and control samples. The plate is incubated at $37 \pm 1^\circ\text{C}$ for 60 ± 1 minutes and read at 370 nm excitation/460 nm emission. RFUs are converted to amount of 4-MU using a 4-MU standard curve. Enzyme activity is calculated as 4-MU nmol/mL of enzyme/hour. Specific enzyme activity is calculated from the enzyme activity and enzyme concentration as 4-MU nmol released/mg of enzyme/hour.

Glycan analysis: The M6P and Bis M6P glycans important for CI-MPR binding and cellular uptake are also controlled (b) (4)

Enzyme kinetics: The control strategy for cipaglusosidase alfa does not include assessment of enzyme kinetics. To further support lot-to-lot consistency and comparability of enzyme activity following manufacturing changes, the Applicant agreed to a PMC to implement control of critical enzyme kinetic parameters in the drug product release and stability specifications.

- d. **Reference Materials:** DS and DP potency and identity results are reported relative to the RS. The Applicant established a (b) (4) system for control of commercial DS and DP. The current primary and working RSs, (b) (4) respectively, were generated (b) (4). The current working RS was used to release the phase 3 clinical materials and PPQ lots. Qualification of these RSs is adequate to support their current use and approval. The Sponsor established an adequate link between these RSs and the RSs used to release earlier clinical material. Protocols for qualification and requalification of primary and working RSs are adequate and will be approved with this BLA.
- e. **Critical starting materials or intermediates:** The Applicant established a (b) (4) system. (b) (4). The cell banks were adequately qualified and are acceptable for use, and the protocols for stability testing of the MCB and WCB are adequate.

(b) (4)

(b) (4)

A protocol for qualification of future WCBs was submitted and will be approved with this BLA.

f. **Manufacturing process summary:** DS is manufactured

(b) (4)

The manufacturing process is validated and adequately controlled through defined operating and performance parameters. Control of adventitious agents is ensured

(b) (4)

Microbial quality is controlled

(b) (4)

Bioburden

(b) (4)

and endotoxin are monitored

Microbial control

(b) (4)

was

demonstrated by microbial monitoring in lifetime studies. Adequate controls are in place to maintain microbiological product quality and throughout the manufacturing process.

(b) (4)

g. **Container closure:** DS is stored

(b) (4)

h. **Dating period and storage conditions:** (b) (4) months at (b) (4) °C.

C. Pombiliti Drug Product Quality Summary:

Table 3 provides a summary of the CQAs that derive from the drug product manufacturing process and general drug product attributes, their origin and associated risk, and control strategy.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy (Additional comments)
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Protein Quantity (General)	Efficacy	DS and DP Manufacturing processes
Appearance, color, clarity (General)	Safety, Efficacy, Product Stability	Manufacturing process, formulation, contamination, degradation
Identity	Safety and Efficacy	Intrinsic to the molecule
Sterility (Contaminant)	Safety, Purity, Efficacy	-Manufacturing process or failure of container closure integrity
Endotoxin (Contaminant)	Safety, Purity	Raw materials and manufacturing process
Pyrogens	Safety	Raw materials and manufacturing process
Container Closure Integrity (Sterility Assurance)	Safety (Sterility assurance)	Breach during manufacture or storage
pH (General)	Stability	- DS manufacture (no additional formulation during DP manufacture)
Osmolality (General)	Patient Discomfort	DS manufacture (no additional formulation during DP manufacture)
Particulate Matter: Visible and Sub-Visible Particulates (General)	Safety and Immunogenicity	-Manufacturing process, container closure system, storage, dose preparation
Extractable volume - (General)	Dosing	-Manufacturing process -Reconstitution
Leachables (Impurities)	Safety and product stability	Manufacturing product contact equipment and container closure system

(b) (4)

			(b) (4)
PS80	Product Stability	- DS manufacturing - May be impacted by steps in the DP manufacturing process	
Moisture Content (General)	Safety and DP stability	DP manufacturing process and storage	
Reconstitution time (General)	Product quality	-DP manufacturing process -May be impacted by storage	

- a. **Potency and Strength:** Pombiliti is supplied as a 105 mg lyophilized product in a single-dose vial that provides a 15 mg/mL solution of cipaglugosidase alfa upon reconstitution. Potency is determined using the same fibroblast cell uptake and specific activity assays as for DS.
- b. **Summary of Product Design:** A sterile white to slightly yellow lyophilized product in a 20 mL (b) (4) glass vial containing 105 mg of cipaglugosidase alfa. Each vial is reconstituted with 7.2 mL of sterile water for injection to allow for an extractable volume of 7 mL of a clear to opalescent, colorless to yellowish solution containing 15 mg/mL cipaglugosidase alfa, (b) (4) mM sodium citrate, (b) (4) mg/mL mannitol, and (b) (4) mg/mL PS-80 at pH (b) (4). Reconstituted DP is further diluted in 0.9% sodium chloride for administration by intravenous infusion.
- c. **List of Excipients:** Citric acid monohydrate (4.57 mg), mannitol (140 mg), polysorbate 80 (3.5 mg), sodium citrate (39 mg), and Sterile Water for Injection, USP (for reconstitution), final pH 5.7 – 6.3.
- d. **Reference Materials:** The same reference standards are used for DS and DP testing.
- e. **Manufacturing process summary:** The DP manufacturing process at WuXi Biologics consists of (b) (4).
(b) (4) Final DP is packaged in boxes containing one, 10, or 25 vials. The final identity test per 21 CFR 610.14 consists of visual inspection of unique physical properties for the container closure, color, and lyophilized cake appearance. Finished DP is stored at 2-8°C.
- The DP commercial manufacturing process is adequately controlled. The control strategy includes (b) (4).
(b) (4)

To ensure sterility, all sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. (b) (4)

Bioburden and endotoxin are tested during manufacture, and sterility, pyrogens, and endotoxin are tested at release. Container closure integrity using a validated method is included in the stability program.

- f. **Container closure:** DP is provided in a clear, 20 mL (b) (4) glass vial with a 20 mm (b) (4) rubber stopper fitted with a 20 mm aluminum crimp seal. Bulk DP is packed (b) (4)

The final labeled DP vials are packed in cartons consisting of one, 10, and 25 vials.

- g. **Dating period and storage conditions:** 36 months at 2-8°C protected from light. Data also support short term excursions up to 25°C of up to 1 month.
- h. **List of co-package components, if applicable:** Pombiliti is not co-packaged with other components. However, it is co-labeled and co-administered with Opfolda (miglustat).

D. Novel Approaches/Precedents:

Use of foreign comparator in clinical studies : A non-U.S.-approved alglucosidase alfa product was used in the clinical studies supporting the BLA and some analytical data comparing U.S.-licensed alglucosidase alfa to the non-U.S.-approved alglucosidase product were provided in the BLA. Refer to Office of Regulatory Policy (ORP) and the final labeling for assessment of the relevance of the data obtained with non-US-approved alglucosidase alfa.

Exclusivity determination per 21 CFR 316.3(b)(14): Pombiliti was developed as a second-generation ERT for treatment of late-onset PD. The currently approved therapies for PD are recombinant GAA enzymes, Lumizyme (alglucosidase alfa) and Nexviazyme (avalglucosidase alfa).

Regarding assessment of whether Pombiliti is the same drug as Lumizyme and Nexviazyme per 21 CFR 316.3(b)(14), (b) (4) Pombiliti differs from that of Lumizyme and Nexviazyme (u) (4) Other differences include (b) (4)

Additional

data (e.g., side-by-side comparison of functional characteristics between Pombiliti and Nexviazyme) are needed to determine whether the differences (b) (4) (b) (4) between these two drugs would provide evidence to determine if Pombiliti could potentially be clinically superior to Nexviazyme or not. Data from other disciplines (e.g., clinical) can help to further establish and support whether Pombiliti is clinically superior to Lumizyme and/or Nexviazyme.

E. Any Special Product Quality Labeling Recommendations:

- Store unconstituted vials at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.
- Prior to use, allow vials to reach ambient temperature, reconstitute each vial with 7.2 mL sterile WFI and dilute in 0.9% sodium chloride. Avoid foaming, forceful impact, shaking, agitation. Do not use a pneumatic tube to transport the infusion bag.
- Reconstituted product may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 h and diluted product may be stored at 2°C to 8°C (36°F to 46°F) for up to 16 h. Storage at room temperature is not recommended. Do not freeze or shake. After removal of the diluted solution from the refrigerator, completely infuse within 6 hours and do not restore in the refrigerator.

F. Establishment Information

OVERALL RECOMMENDATION: Approval			
Drug Substance and Drug Product			
Function	Site Information	DUNS/FEI Number	Current Recommendation
• Drug substance and drug product manufacturing • Drug substance and drug product release and stability testing • MCB and WCB storage	WuXi Biologics Co., Ltd. 108 Meiliang Road, Mashan, Binhu District, Wuxi, Jiangsu 214092, China	DUN: 421298354 FEI: 3010606982	Approve Based on Inspection
• MCB and WCB storage	(b) (4)	DUNS: (b) (4) FEI: (b) (4)	No Evaluation Necessary
• MCB and WCB manufacturing, testing and storage • (b) (4) Testing	WuXi Advanced Therapies Inc. 4751 League Island Blvd. Philadelphia, PA, 19112, USA	DUNS: 117331245 FEI: 1000122198	Approve - Based on Previous History
• (b) (4) testing • (b) (4) Testing	WuXi Biologics Biosafety Testing Co., Ltd. 1336 Wuzhong Road, Wuzhong Economic Development Zone, Suzhou, Jiangsu 215104, China	DUNS: 544312968 FEI: 3015655844	Approve - Based on Previous History
Rabbit Pyrogen Testing	(b) (4)	DUNS: (b) (4) FEI: (b) (4)	Approve - Based on Previous History
Labeling and Secondary Packaging	(b) (4)	DUNS: (b) (4)	Approve - Based on

	(b) (4)	FEI: (b) (4)	Previous History
WCB manufacturing site	WuXi Biologics (Shanghai) Co., Ltd. 31 Yiwei Road, Pilot Free Trade Zone, Shanghai 200131, China	FEI 3012317728	No Evaluation Necessary

Facilities: Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for WuXi Biologics Co. Ltd., Wuxi, China (FEI: 3010606982) proposed for DS and DP manufacturing.

All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facilities perspective.

G. Lifecycle Knowledge Management

a. Drug Substance

- i. **Protocols approved:** The following protocols are approved:
 1. Annual post-approval stability protocol
 2. Protocols for qualification and requalification of primary and working reference standards
 3. Protocols for concurrent validation (b) (4)
 4. Master cell bank and working cell bank stability protocols
 5. Protocol for qualification of new working cell banks
- ii. **Outstanding review issues/residual risk:** See Post Marketing Commitments and Agreements in Section 1D
- iii. **Future inspection points to consider:** None

b. Drug Product

- i. **Protocols approved:** The following protocols are approved:
 1. Annual post-approval stability protocol
 2. Final DP shipping qualification protocol
- ii. **Outstanding review issues/residual risk:** See Post Marketing Commitments and Agreements in Section 1D
- iii. **Future inspection points to consider:** None

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/

FRANCES NAMUSWE
09/20/2023 05:32:19 PM



U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 29, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Davinna Ligons, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 3
Application:	BLA 761204
Applicant:	Amicus Therapeutics US, LLC
Submission Date:	July 29, 2021
Product:	Pombiliti (cipaglucosidase alfa-atga)
Dosage form(s):	For injection
Strength and Container-Closure:	105 mg lyophilized powder in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information (submitted on September 28, 2022), container labels (submitted on May 18, 2022) and carton labeling (submitted on June 21, 2022) were assessed and found to be acceptable from an OBP Labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information (submitted on September 28, 2022), container labels (submitted on May 18, 2022) and carton labeling (submitted on June 21, 2022) were assessed and found to be acceptable from an OBP Labeling perspective (see Appendix C).

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on July 29, 2021)

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Container Labels (submitted on July 29, 2021)

(b) (4)

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise proper name to include placeholder for 4 letter suffix. Consider adding the dosage form to appear beneath the proper name as follows:
POMBILITI
(cipaglucoisidase alfa-xxxx)
For injection
105 mg/vial
Applicant revised as requested

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Comment/Recommendation: Revise the manufacturer statement using the qualifying phrase "Manufactured by:" *Applicant revised as requested*
 Relocate the U.S. License No. to go directly beneath the manufacturer's name and address.
 Replace (b) (4) with a placeholder "xxxx" for the US license number.
Applicant revised as requested

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. <i>Applicant's response: Amicus confirms there is no text on the ferrule and cap overseal of the vials.</i>

Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located
Applicant's response: Amicus confirms that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container. The bottle label does not overwrap and the visual inspection area is located near the primary display, between the variable data area and the UPC. There is a 1/8-inch gap for visual inspection.

Route of administration (container label)	Acceptable
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise from (b) (4) to read "For intravenous infusion only" to appear beneath the strength presentation *Applicant revised similarly as requested*

NDC numbers (container label)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (container label)	Acceptable
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i>	☐ Yes ☐ No ☒ N/A

Package type term (container label)	Acceptable
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the correct package-type term to read "Single-dose vial. Discard unused portion." *Applicant revised as requested*

Misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☒ Yes ☐ No ☐ N/A

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Remove "1 vial" *Applicant revised as requested*

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise form (b) (4) to read as follows: "Dosage: See Prescribing Information.". *Applicant revised as requested*

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to "Store refrigerated at 2°C to 8°C (36°F to 46°F) in carton to protect from light. Do not freeze." *Applicant revised as requested*

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package⁶ Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise proper name to include placeholder for 4 letter suffix. Consider adding the dosage form to appear beneath the proper name as follows:

POMBILITI
(cipaglucosidase alfa-xxxx)
For injection
105 mg/vial
Applicant revised as requested

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A

⁶ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
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Comment/Recommendation: Revise to the name and address of the manufacturer listed as the applicant on FDA form 356h "Amicus Therapeutics US, LLC 3675 Market Street Philadelphia, PA 19104 using the qualifying phrase "Manufactured by:" <i>Applicant revised as requested</i> Relocate the U.S. License No. to go directly beneath the manufacturer's name and address. Replace "761204" with a placeholder "xxxx" for the US license number. <i>Applicant revised as requested</i> Confirm if (b) (4) to be considered as the distributor, if so then you may use the qualifying phrase "Manufactured for" <i>Applicant deleted (b) (4)</i>	
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Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	☒ Yes ☐ No ☐ N/A

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to "Store refrigerated at 2°C to 8°C (36°F to 46°F) in carton to protect from light. Do not freeze." *Applicant revised as requested*

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to read "For intravenous infusion after reconstitution and dilution." *Applicant revised as requested*

Known sensitizing substances (package labeling)	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the list of inactive ingredients to appear in alphabetical order and ensure that it is consistent with your prescribing information, also add the pH as follows:

"Each vial contains 105 mg of cipaglugosidase alfa-xxxx and the inactive ingredients:

Citric Acid monohydrate (4.57 mg)

Mannitol (140 mg)

Polysorbate 80 (3.5 mg)

Sodium Citrate (39 mg)

The pH is xx.

Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes the citric acid monohydrate and sodium citrate (b) (4) Ensure that all inactive ingredients with a USP monograph are provided as such.

The applicant revised as requested (b) (4)

(b) (4)

(b) (4)

The Applicant revised as requested. Amicus accepts FDA's request to revise the ingredient information

(b) (4)

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(r)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: We note that (b) (4) appears on the proposed container and carton labeling. We request that the statement be removed from labeling. Our view is that (b) (4) is not applicable, and thus the no statement is required for the container and carton labeling.⁷ *Applicant revised as requested*

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

⁷ Weiner J. Memorandum. Applicability of 21 CFR 610.61(r). BLA 761204. Silver Spring (MD): FDA, CDER, ORP (US); June 22, 2022.

Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: <i>Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider including the preparation instructions after the temperature/storage statement to read as follows: "After reconstitution with 7.2 mL of Sterile Water for Injection, USP, the resultant concentration is 105 mg/ 7 mL (15 mg/mL). If not used immediately, the reconstituted product can be stored up to 24 hours when refrigerated at 36°F

to 46°F (2°C to 8°C)." *Applicant revised as requested but the carton has (b) (4) mL instead of 7.2 mL revise accordingly*

We note that the preparation instructions have the volume of Water for Injection as (b) (4) mL'.
Revise to '7.2 mL' *Applicant revised as requested*

Package type term (package labeling)	Acceptable
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the correct package-type term to read "Single-dose vial. Discard unused portion." *Applicant revised as requested*

Misleading statements (package labeling)	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No

	☒ N/A
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Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise form (b) (4) to read as follows: "Dosage: See Prescribing Information.". <i>Applicant revised as requested</i>
--

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Added the dosage form in the customary position <i>Applicant revised as requested</i>

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)] <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the</i>	☒ Yes ☐ No ☐ N/A

reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."	
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to as a clear to opalescent, colorless to yellowish solution <i>Applicant revised as requested</i>	
Added (b) (4) as "Add the reconstituted solution slowly and directly into (b) (4)	
(b) (4) <i>Applicant proposed to delete</i>	(b) (4)
(b) (4) <i>OBPL and OBP product quality agree with this change. We agree</i>	(b) (4)
Revised the (b) (4)	
(b) (4) <i>Applicant proposed to delete</i>	(b) (4)
(b) (4) <i>OBPL and OBP product quality agree with this change.</i>	
<i>Deletion</i> (b) (4) <i>is acceptabl</i> (b) (4)	
Revised to the storage time that is supported by microbial data for the diluted drug product (refer to IR dated 2/25/2022): (b) (4)	
(b) (4)	
(b) (4) <i>Applicant revised</i> (b) (4)	
<i>er OPMA Storage time of diluted solution at 2°C to 8°C is limited to 16 hours based on microbial challenge study data and storage at room temperature is not recommended. Applicant accepted revised language "Discard the diluted solution if refrigerated more than 16 hours or if the diluted solution is not able to be completely infused within 6 hours after removal from the refrigerator."</i>	

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A

Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements USP General Chapters: <7> Labeling	☒ Yes ☐ No ☐ N/A
---	--

Comment/Recommendation: Added dosage form *Applicant revised as requested*
Added "powder with cake-like appearance" revising from (b) (4) *Applicant revised as requested*

Full Prescribing Information	
11 DESCRIPTION	Acceptable
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: added "lysosomal" *Applicant revised as requested*
Added MW *Applicant added MW as 110 kDa as requested*
Added dosage form *Applicant revised as requested*
Revised inactive ingredients to appear in alphabetical order *Applicant revised as requested*

Revised inactive ingredients to their compendial name which required recalculation of quantitative amount based on the USP monograph definition. *Applicant revised back to the previous established names and amounts for citric acid monohydrate and sodium citrate*
(b) (4) OBPL response: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients). The established name for the inactive ingredient in your product is citric acid monohydrate per the USP/NF monograph title. (b) (4)
(b) (4)

(b) (4) Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes the citric acid (b) (4)

(b) (4) Ensure that all inactive ingredients with a USP monograph are provided as such. To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients). Revise the established name for the inactive ingredient in your product, sodium citrate, per the USP/NF monograph title. (b) (4)

OBPL response: We acknowledge this revision. Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes the sodium citrate (b) (4) Ensure that all inactive ingredients with a USP monograph are provided as such. Added the pH *Applicant revised as requested*

Full Prescribing Information	
15 & 16 Hazardous Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. ¹	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Added the proper name and dosage form to the first paragraph *Applicant revised as requested*
Added the strength to the table *Applicant revised as requested*
Revised the storage statement as one sentence. *Applicant revised as requested*

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to the qualifying phrase that indicates the manufacturer or licensed applicant. *Applicant revised as requested*
Revised as a placeholder for the US license number *Applicant revised as requested*

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on September 28, 2022)

<\\CDSESUB1\EVSPROD\bla761204\0050\m1\us\114-label\1141-draft-label\proposed-clean-changes-pi.docx>)

Container Labels (submitted on May 18, 2022)

(b) (4)



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 9/29/2022 11:35:47AM
GUID: 50814c7000007a3d59329f660d8ddf02



Davinna
Ligons

Digitally signed by Davinna Ligons
Date: 9/29/2022 11:40:50AM
GUID: 5822293b004ccdbf2f2e504746be3f82

Breakthrough/Orphan Designation Recommendation: Pending

BLA Number: 761204

Review Number: 1

Review Date: April 4, 2022; Revised: July 12, 2022; August 5, 2022

Drug Name/Dosage Form	Pombiliti® [cipaglucosidase alfa-atga] for Injection Co-labeled for use with Opfolda (miglustat, AT2221, N-butyldeoxynorjirimycin under review in NDA 215211)¹
Strength/Potency	105 mg lyophilized powder in a single-dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Pombiliti is indicated, in combination with Opfolda, for the treatment of adult patients with late-onset Pompe disease weighing ≥40 kg and who are not improving on their current enzyme replacement therapy
Applicant/Sponsor	Amicus Therapeutics US, LLC

Product Overview

Pombiliti (cipaglucosidase alfa-atga, ATB200) is a recombinant form of human acid α -glucosidase, an enzyme responsible for the breakdown of lysosomal glycogen. Cipaglucosidase alfa was developed as an enzyme replacement therapy (ERT) for treatment of late-onset Pompe Disease, a lysosomal storage disorder that results from deficiency in acid α -glucosidase activity. Cipaglucosidase alfa is produced as a 110 kDa glycoprotein in Chinese hamster ovary (CHO) cells by perfusion technology. The amino acid sequence of cipaglucosidase alfa is identical to the human wild type acid α -glucosidase. Its glycan profile includes mannose 6-phosphate (M6P) and bis-phosphorylated high mannose (bis-M6P) oligosaccharide structures, which facilitate its transportation to lysosomes through the cation independent mannose 6-phosphate receptor (CI-MPR).

Pombiliti drug product is supplied as a sterile, white to slightly yellowish lyophilized powder with a cake-like appearance in a single-dose vial containing 105 mg of cipaglucosidase alfa. Cipaglucosidase alfa will be co-administered with an oral dose of Opfolda (miglustat), a small molecule that is proposed to bind to and stabilize the enzyme in plasma.

Quality Review Team

	BLA	
Discipline	Reviewer	Branch/Division
Drug Substance	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Drug Product	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Microbiology Drug Substance	Richard Ledwidge/ Virginia Carroll	DBM/OPMA

¹ This review memo only covers Pombiliti. For Opfolda, refer to the review memo for NDA 215211.

Microbiology Drug Product	Richard Ledwidge/Virginia Carroll	DBM/OPMA
Facility	Richard Ledwidge/Virginia Carroll	DBM/OPMA
Labeling	Vicky Borders-Hemphill	IO/OBP
Immunogenicity	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Application Team Lead	Frances Namuswe	DBRRIII/OBP
Application Tertiary reviewer	Maria Teresa Gutierrez-Lugo	DBRRIII/OBP
OPQ RBPM	Kelly Ballard	OPRO/DRBPMI/RBPMB
NDA		
Drug Substance	Jeffery Medwid/ Donna Christner	DNDAPI/ONDP
Drug Product	Zhengfang Ge/ Hong Cai	DNDPII/ONDP
Biopharmaceutics	Kamrun Nahar/ Vidula Kolhatkar	DB/ONDP
Application Team Lead	Hamid Shafiei	DNDPII/ONDP

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
OND RPM	Jenny Doan	OND/ORO/DRORDPURM
Cross-disciplinary Team Lead	Linda Jeng	OND/ORDPURM/DRDMG
Medical Officer	Daniela Varela Luquetti	OND/ORDPURM/DRDMG
Pharm/Tox	Primary: -Emmanuel Akinshola - Mary Ellen McNeerney, Secondary: Laurie McLeod-Flynn	OND/ORDPURM/DPTRDPURM
Clinical Pharmacology	Primary: - Oluseyi Adeniyi (BLA) - Travis Ready (NDA) - Ruojing Li (Pharmacometrics)	OTS/OCP/DTPM
Clinical Pharmacology Secondary	Jie (Jack) Wang Lian Ma (pharmacometrics)	OTS/OCP/DTPM
Statistics	Primary: Emily Morris Secondary: Yan Wang	OTS /OB/DBIV
DMEPA	Valerie Vaughan/Sevan Kolejian	OSE/OMEPRM/DMEPA

1. Names:

- a. Proprietary Name: Pombiliti
- b. Trade Name: Pombiliti
- c. Non-Proprietary/USAN: cipaglucoisidase alfa-atga
- d. CAS name and number: 2359727-71-0
- e. Common name: ATB200
- f. INN Name: cipaglucoisidase alfa
- h. OBP systematic name: RPROT P10253 (LYAG_HUMAN) LYSOSOMAL ALPHA-GLUCOSIDASE [ATB200]
- i. Other names: recombinant human acid alpha-glucosidase (rhGAA), α -glucosidase, (acid) maltase, glucoinvertase, glucosidosucrase, maltase-glucoamylase, α -glucopyranosidase, glucosidoinvertase, α -D-glucosidase, α -glucoside hydrolase, α -1,4-glucosidase, lysosomal α -glucosidase

2. Pharmacological class:

Hydrolytic lysosomal glycogen-specific enzyme

Submissions Reviewed

Submission:	Date Received:	Assessment Completed (yes or no)
SN 0004	7/29/2021	Yes
SN 0007	9/14/2021	Yes
SN 0008	9/22/2021	Yes
SN 0015	11/19/2021	Yes
SN 0017	12/3/2021	Yes
SN 0018	12/9/2021	Yes
SN 0019	12/15/2021	Yes
SN 0020	12/22/2021	Yes
SN 0021	1/7/2022	Yes
SN 0022	1/13/2022	Yes
SN 0023	1/21/2022	Yes
SN 0024	1/28/2022	Yes
SN 0026	2/16/2022	Yes
SN 0027	2/18/2022	Yes
SN 0029	2/25/2022	Yes
SN 0030	2/28/2022	Yes
SN 0031	3/02/2022	Yes
SN 0032	3/15/2022	Yes
SN 0034	4/08/2022	Yes
SN 0037	5/1/2022	Yes
SN 0038	5/18/2022	Yes
SN 0041	6/15/2022	yes
SN 0043	7/7/2022	yes
SN 0045	7/25/2022	yes

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents

A. DMFs

DMF#/ (Type)	DMF Holder	Item Referenced	Code ¹	Date Assessment completed	LOA	Comment (status)
(b) (4) (V)		(b) (4)	2	02/15/2019	Yes	Adequate

(b) (4) (III)	(b) (4)	3	N/A	Yes	Review not needed. Relevant information submitted in the BLA.
(b) (4) (III)	(b) (4)	3	N/A	Yes	Review not needed. Relevant information submitted in the BLA.

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application

Application Number	Description
IND 127387	ATB200
NDA 215211	Opfolda (miglustat)
NDA 021348	Zavesca (miglustat)

3. Consults

None issued

4. Environmental Assessment or Claim of Categorical Exclusion

Amicus claims categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(c). Per 21 CFR 25.31(c), categorical exclusion can be granted for Pombiliti; therefore, the claim of categorical exemption is accepted.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

i. Recommendation: Approval pending outcome of pre-licensing inspection

The Office of Pharmaceutical (OPQ), CDER, recommendation on approvability of STN 761204 for Pombiliti manufactured by Amicus Therapeutics US, LLC is pending final determination of the compliance status of WuXi, Biologics, Co., Ltd, WuXi, China (FEI: 3010606982) manufacturing site. From a product quality perspective, the Office of Pharmaceutical Quality, CDER, does not note any product quality deficiencies that would preclude approval of BLA 761204 for Pombiliti manufactured by Amicus Therapeutics US, LLC. at this time. The data submitted in this application are adequate to support the conclusion that the manufacture of Pombiliti is well-controlled and leads to a product that is pure and potent. However, due to restrictions on travel during the ongoing COVID-19 pandemic, the pre-license inspection (PLI) of the drug substance and drug product manufacturing facility WuXi, Biologics, Co., Ltd, China

(FEI: 3010606982) cannot be conducted by the time of finalizing this memorandum. The outcome of the facility inspection will be captured in a future addendum to this Executive Summary review memo.

B. Approval Action Letter Language

- Manufacturing location:
 - **Drug Substance and Drug Product manufacture:** WuXi Biologics Co., Ltd., 108 Meiliang Road, Mashan, Binhu District, Wuxi, Jiangsu 214092, China

DP labeling and Secondary packaging:

(b) (4)

(b) (4)

- Fill size and dosage form: 105 mg lyophilized powder in a single-dose vial for injection
- Dating period:
 - Drug Product: 36 months at 2-8°C
 - Drug Substance: (b) (4) months at (b) (4) °C
 - For packaged Products: Not packaged but co-labeled for use in combination with Opfolda
- Exempt from lot release
 - Yes. Pombiliti is exempted from lot release per Docket No 95-29960 because it is a specified product

C. Benefit/Risk Considerations

Pompe disease (PD) is a rare and serious lysosomal storage disease that can lead to death from cardiac or respiratory failure if untreated in the infantile-onset form (IOPD) and to motor impairment and premature death from respiratory failure in the late-onset form (LOPD). PD is caused by autosomal recessive variants in the acid alpha glucosidase (GAA) gene that result in deficient GAA activity and accumulation of glycogen in cells. This in turn leads to myopathy, respiratory weakness, physical disability, and can lead to premature death. The currently approved therapies for PD are recombinant GAA enzymes, alglucosidase alfa and avalglucosidase alfa. Alglucosidase alfa does not lead to a sustained improvement in muscle weakness, and thus, patients tend to develop progressive disease, which can lead to respiratory failure. (b) (4)

(b) (4) Therefore, treatment and cure of PD continue to represent unmet medical needs.

Efficacy of cipaglucosidase alfa coadministered with miglustat was evaluated in one well-controlled trial (ATB200-03) in 123 adult patients with LOPD (95 treatment-experienced, 28 treatment-naïve) randomized to cipaglucosidase alfa/miglustat or a non-U.S.-approved alglucosidase alfa product coadministered with placebo. The benefit of cipaglucosidase alfa/miglustat is based on comparison of the distance walked on the 6-min walk test, the primary

endpoint, and forced vital capacity (% predicted), a key secondary endpoint. The estimated treatment difference in the mean change from baseline to Week 52 in the 6-min walk test and in forced vital capacity favored the cipaglucoaldose alfa/miglustat arm; the results of the primary end point are driven by the treatment experienced subgroup. Confirmatory evidence of effectiveness is derived from other studies showing cipaglucoaldose alfa coadministered with miglustat reduces glycogen levels in tissues and improves muscle function in GAA knockout mice compared to alglucoaldose alfa, consistent with the mechanism of action and pathophysiology of the disease.

Based on these studies, the Agency concluded that the benefits of cipaglucoaldose alfa coadministered with miglustat on lung function, an important target for drug treatment for patients with LOPD, outweigh its risks when used according to the agreed-upon labeling. The Agency recommends cipaglucoaldose alfa coadministered with miglustat as a second-line therapy for adult patients with LOPD who are not improving on other ERT, because of the potential increased risk when receiving two drugs instead of one drug, safety concerns identified as possibly related to miglustat, and the availability of two other approved ERTs for the treatment of Pompe disease. Refer to the OND review and labeling for the final approved indication.

The data submitted in this application are adequate to demonstrate that the manufacture of Pombiliti is well-controlled and leads to a product that is safe, pure, and potent. Therefore, from a product quality perspective, this product is approvable for human use as described in the product labeling. The Applicant agreed to five post-marketing commitments (PMCs) to improve the robustness of the drug substance (DS) and drug product (DP) manufacturing processes and overall product control strategy as outline in Section D below.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

The following post marketing commitments have been proposed and accepted by the Applicant:

Product Quality

PMC #1: To perform extractables/leachables studies and risk assessments to evaluate leachables from the container closure system(s) and manufacturing product contact surfaces of cipaglucoaldose alfa drug substance and drug product and assess the potential impact of leachables on product quality at the end of drug product shelf-life. The analyses will be performed using drug substance and drug product lot(s) and/or representative samples (e.g., (b) (4) if justified) analyzed at appropriate time points, including at the end of drug product shelf life. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of the potential impact of leachables on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be provided in the final study report per 21 CFR 601.12.

Final report submission date: 03/2023

PMC #2: To develop, validate, and implement a test method with justified numerical acceptance criteria for control of cipaglusosidase alfa kinetic parameters during drug product release and stability testing. Critical kinetic parameters (e.g., K_m , K_{cat} , etc.) will be determined, justified, and included in the control strategy. If applicable, justification and data supporting (b) (4) will be provided. The method validation report for the enzyme kinetic assay, the revised drug product release and stability specifications, and all supporting studies and data will be provided in a final study report per 21 CFR 601.12.

Final report submission date: 03/2024

Microbiology

(b) (4)

PMC #5: To develop an endotoxin method for the drug product which mitigates the low endotoxin recovery (LER) effect, submit method qualification results with 3 lots of drug product and results of an LER study performed with the updated method with 3 lots of drug product.

Final Report Submission: 0/2023

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Tables 1 and 2 summarize the CQAs intrinsic to cipaglusosidase alfa API and the drug substance manufacturing process, respectively. These CQAs are based on both the Applicant's determined CQAs and quality attributes the Agency considers CQAs for this class of products, regardless of how they were classified by the Applicant. Attributes that are controlled only by the manufacturing process as well as attributes that the Applicant considers non-CQAs will be assessed in risk-based comparability assessments as requested by the Agency.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy (Additional comments)
Identity (General)	Safety and Efficacy	Intrinsic to the molecule	(b) (4)

Primary Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule - Expression construct and cell line
Higher Order Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule
CI-MPR binding and cellular uptake (potency)	Efficacy	- Intrinsic to the molecule - May be impacted by the DS manufacturing process and changes to the glycan profile
Enzymatic activity and specific activity (potency)	Efficacy	- Intrinsic to the molecule - Impacted by the DS manufacturing process
Glycosylation (M6P and Bis M6P)	Efficacy	- Intrinsic to the molecule - Impacted by the DS manufacturing process
Glycosylation (Sialic acid)	May impact PK and Efficacy	- Intrinsic to the molecule - Impacted by the DS manufacturing process
High Molecular Weight Species (product impurities)	Efficacy and Safety, including Immunogenicity	- Manufacturing process - May increase on storage
Low Molecular Weight Species (product impurities)	Efficacy and Safety	- Manufacturing process - May increase on storage
Charge Heterogeneity (product variants)	Potential impact on Efficacy and Safety	- Intrinsic to the molecule (e.g., from glycan species) - DS and DP manufacturing process - May increase on storage (e.g. oxidation, deamidation)
Post-translation Modification (PTMs) (oxidation, deamidation, succinimide, & isomerization)	May impact potency or safety	-DS and DP manufacture - May increase on storage

(b) (4)

B. Pombiliti [cipaglucosidase alfa-atga] Drug Substance Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy (Additional comments)
Appearance (general)	Safety	- Manufacturing process	(b) (4)
pH (general)	Safety and DS stability	- Manufacturing process/formulation	
Protein Content (general)	Efficacy	- Manufacturing process/formulation	
Osmolality (general)	Patient discomfort (No further formulation to generate DP)	- Manufacturing process/formulation	
(b) (4)	Product Stability	- Manufacturing/formulation	
Host Cell Proteins (process impurity)	Safety and immunogenicity	Production cell line/Cell culture	
Host Cell DNA (Process impurity)	Safety	Production cell line/Cell culture	
Adventitious virus (Contaminant)	Safety	Raw materials and contamination during manufacturing	
Mycoplasma (Contaminant)	Safety	Raw materials and contamination during manufacturing	
Bioburden (Contaminant)	Safety, purity, and efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process	
Endotoxin (Contaminant)	Safety and purity	Raw materials and manufacturing process	

Pyrogens	Safety	Raw materials and manufacturing process	(b) (4)
(b) (4) (Process impurities)	Safety	DS manufacture	
Leachables (Impurities)	Safety and product stability	Manufacturing equipment and container closure	

- a. **Description:** Cipaglucosidase alfa is a 110 kDa recombinant hydrolytic lysosomal human acid α -glucosidase enzyme produced in CHO cells by perfusion technology. Its 896 amino acid sequence corresponds to amino acid residues 57 to 952 of wild-type (WT) human acid α -glucosidase (GAA) after proteolytic processing that removes the initial 56 residues comprising the signal peptide and precursor peptide. It has 7 N-glycosylation sites and contains M6P and bis-M6P glycans that are critical for binding to the CI-MPR. Its N-terminal forms pyroglutamate and its tertiary structure is stabilized by 5 disulfide bonds.
- b. **Mechanism of Action:** Cipaglucosidase alfa is indicated for treatment of PD, a lysosomal storage disorder that results from deficiency in GAA activity. GAA deficiency results in lysosomal accumulation of glycogen in various tissues. Cipaglucosidase alfa is an exogenous source of GAA. It binds to the CI-MPR, which internalizes the product and delivers it to the lysosomes. In the lysosomes, cipaglucosidase alfa degrades glycogen to glucose and thus, reduces glycogen substrate levels. CI-MPR binding is mediated by M6P and bis-M6P on cipaglucosidase alfa. According to the Applicant, cipaglucosidase alfa has higher levels of M6P and bis-M6P than alglucosidase alfa, which result in high binding affinity for the CI-MPR. Potency of cipaglucosidase alfa is controlled by monitoring specific activity using an enzymatic activity assay and a fibroblast uptake cell-based assay. In addition, M6P and bis-M6P levels are controlled.

Cipaglucosidase alfa will be co-administered with an oral dose of miglustat, a small molecule proposed to bind to and improve stability of ATB200 in plasma (at neutral pH), thereby improve enzyme uptake and delivery of ATB200 to muscle and lysosomes. When cipaglucosidase alfa was coadministered with miglustat, in vitro and animal studies showed improved dose-dependent stability of cipaglucosidase alfa and studies in *Gaa* knockout mice showed significant reduction in glycogen. However, miglustat has no direct treatment effect on patients with LOPD.

c. Potency Assay

Fibroblast cell uptake: The fibroblast cell uptake assay measures the ability of cipaglucosidase alfa to hydrolyze the substrate 4-Methylumbelliferyl- α -D-glucopyranoside (4-MU-Glc) to its fluorescent product 4-methylumbelliferone (4-MU) after cellular uptake of cipaglucosidase alfa by human normal fibroblasts cells via the CI-MPR. This assay reflects cipaglucosidase alfa's mechanism of action. Plated cells are incubated with serially diluted DS and DP samples, reference standard (RS), and assay control in duplicate. Cells are lysed, incubated with 4-MU-Glc, and evaluated for enzyme activity. The measured fluorescence (RFUs) is converted to 4-MU content using a 4-MU standard curve. Protein concentration in each sample well is determined using a bovine serum albumin standard curve. Enzymatic activity (4-MU per well/mL enzyme/hour) and specific enzyme activity (nmol/mg/h) are calculated for the samples and RS. Potency is reported relative to that of the RS based on the ratio of EC50 values. New lots of the critical raw materials and reagents used for the assay must be qualified prior to use. The Applicant established an adequate link between the potency assay proposed for commercial use and other potency assays used to release clinical material.

Specific activity: In a different (non-cell based) assay, specific activity of cipaglucosidase alfa is determined by its ability to catalyze the 4-MU-Glc substrate to 4-MU. Diluted DS and DP samples (prepared in triplicate), control (reference standard), and dilution buffer (blank) in 96-well plates are incubated with 4-MU-Glc substrate, alongside 4-MU standards and control samples. The plate is incubated at $37 \pm 1^\circ\text{C}$ for 60 ± 1 minutes and read at 370 nm excitation/460 nm emission. RFUs are converted to amount of 4-MU using a 4-MU standard curve. Enzyme activity is calculated as 4-MU nmol/mL of enzyme/hour. Specific enzyme activity is calculated from the enzyme activity and enzyme concentration as 4-MU nmol released/mg of enzyme/hour.

Glycan analysis: The M6P and Bis M6P glycans important for CI-MPR binding and cellular uptake are also controlled (b) (4)

Enzyme kinetics: The control strategy for cipaglucosidase alfa does not include assessment of enzyme kinetics. To further support lot-to-lot consistency and comparability of enzyme activity following manufacturing changes, the Applicant agreed to a PMC to implement control of critical enzyme kinetic parameters in the drug product release and stability specifications.

- d. Reference Materials:** DS and DP potency and identity results are reported relative to the RS. The Applicant established a (b) (4) system for control of commercial DS and DP. The current primary and working RSs, (b) (4) respectively, were generated (b) (4)

The current working RS was used to release the phase 3 clinical materials and PPQ lots. Qualification of these RSs is adequate to support their current use and approval. The Sponsor established an adequate link between these RSs and the RSs used to release earlier clinical

material. Protocols for qualification and requalification of primary and working RSs are adequate and will be approved with this BLA.

- e. **Critical starting materials or intermediates:** The Applicant established a system. (b) (4)

The cell banks were adequately qualified and are acceptable for use, and the protocols for stability testing of the MCB and WCB are adequate.

- f. **Manufacturing process summary:** DS is manufactured (b) (4)

The manufacturing process is validated and adequately controlled through defined operating and performance parameters. Control of adventitious agents is ensured (b) (4)

Microbial quality is controlled (b) (4). Bioburden (b) (4) and endotoxin are monitored (b) (4). Microbial control (b) (4) was demonstrated by microbial monitoring in lifetime studies. Adequate controls are in place to maintain microbiological product quality (b) (4) and throughout the manufacturing process.

- g. **Container closure:** DS is stored (b) (4)

- h. **Dating period and storage conditions:** (b) (4) months at (b) (4) °C.

C. Pombiliti Drug Product Quality Summary:

Table 3 provides a summary of the CQAs that derive from the drug product manufacturing process and general drug product attributes, their origin and associated risk, and control strategy.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy (Additional comments)
Protein Quantity (General)	Efficacy	DS and DP Manufacturing processes	(b) (4)
Appearance, color, clarity (General)	Safety, Efficacy, Product Stability	Manufacturing process, formulation, contamination, degradation	
Identity	Safety and Efficacy	Intrinsic to the molecule	
Sterility (Contaminant)	Safety, Purity, Efficacy	-Manufacturing process or failure of container closure integrity	
Endotoxin (Contaminant)	Safety, Purity	Raw materials and manufacturing process	
Pyrogens	Safety	Raw materials and manufacturing process	
Container Closure Integrity (Sterility Assurance)	Safety (Sterility assurance)	Breach during manufacture or storage	
pH (General)	Stability	- DS manufacture (no additional formulation during DP manufacture)	
Osmolality (General)	Patient Discomfort	DS manufacture (no additional formulation during DP manufacture)	

			(b) (4)
Particulate Matter: Visible and Sub-Visible Particulates (General)	Safety and Immunogenicity	-Manufacturing process, container closure system, storage, dose preparation	
Extractable volume - (General)	Dosing	-Manufacturing process -Reconstitution	
Leachables (Impurities)	Safety and product stability	Manufacturing product contact equipment and container closure system	
PS80	Product Stability	- DS manufacturing - May be impacted by steps in the DP manufacturing process	
Moisture Content (General)	Safety and DP stability	DP manufacturing process and storage	
Reconstitution time (General)	Product quality	-DP manufacturing process -May be impacted by storage	

- a. **Potency and Strength:** Pombiliti is supplied as a 105 mg lyophilized product in a single-dose vial that provides a 15 mg/mL solution of cipaglugosidase alfa upon reconstitution. Potency is determined using the same fibroblast cell uptake and specific activity assays as for DS.
- b. **Summary of Product Design:** A sterile white to slightly yellow lyophilized product in a 20 mL (b) (4) glass vial containing 105 mg of cipaglugosidase alfa. Each vial is reconstituted with 7.2 mL of sterile water for injection to allow for an extractable volume of 7 mL of a clear to opalescent, colorless to yellowish solution containing 15 mg/mL cipaglugosidase alfa, (b) (4) mM sodium citrate, (b) (4) mg/mL mannitol, and (b) (4) mg/mL PS-80 at pH (b) (4). Reconstituted DP is further diluted in 0.9% sodium chloride for administration by intravenous infusion.
- c. **List of Excipients:** Citric acid monohydrate (4.57 mg), mannitol (140 mg), polysorbate 80 (3.5 mg), sodium citrate (39 mg), and Sterile Water for Injection, USP (for reconstitution), final pH 5.7 – 6.3.
- d. **Reference Materials:** The same reference standards are used for DS and DP testing.
- e. **Manufacturing process summary:** The DP manufacturing process at WuXi Biologics consists of (b) (4)

(b) (4)

Final DP is packaged in boxes containing one, 10, or 25 vials. The final identity test per 21 CFR 610.14 consists of visual inspection of unique physical properties for the container closure, color, and lyophilized cake appearance. Finished DP is stored at 2-8°C.

The DP commercial manufacturing process is adequately controlled. The control strategy includes

(b) (4)

To ensure sterility, all sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes.

(b) (4)

Bioburden and endotoxin are tested during manufacture, and sterility, pyrogens, and endotoxin are tested at release. Container closure integrity using a validated method is included in the stability program.

- f. **Container closure:** DP is provided in a clear, 20 mL (b) (4) glass vial with a 20 mm (b) (4) rubber stopper fitted with a 20 mm aluminum crimp seal. Bulk DP is packed (b) (4)

The final labeled DP vials are packed in cartons consisting of one, 10, and 25 vials.

- g. **Dating period and storage conditions:** 36 months at 2-8°C protected from light. Data also support short term excursions up to 25°C of up to 1 month.
- h. **List of co-package components, if applicable:** Pombiliti is not co-packaged with other components. However, it is co-labeled and co-administered with Opfolda (miglustat).

D. Novel Approaches/Precedents:

Use of foreign comparator in clinical studies : A non-U.S.-approved alglucosidase alfa product was used in the clinical studies supporting the BLA and some analytical data comparing U.S.-licensed alglucosidase alfa to the non-U.S.-approved alglucosidase product were provided in the BLA. Refer to Office of Regulatory Policy (ORP) and the final labeling for assessment of the relevance of the data obtained with non-US-approved alglucosidase alfa.

Exclusivity determination per 21 CFR 316.3(b)(14): Pombiliti was developed as a second-generation ERT for treatment of late-onset PD. The currently approved therapies for PD are recombinant GAA enzymes, Lumizyme (alglucosidase alfa) and Nexviazyme (avalglucosidase alfa).

Regarding assessment of whether Pombiliti is the same drug as Lumizyme and Nexviazyme per 21 CFR 316.3(b)(14), (b) (4) Pombiliti differs from that of Lumizyme and Nexviazyme (b) (4) Other differences include (b) (4)

(b) (4)

Additional

data (e.g., side-by-side comparison of functional characteristics between Pombiliti and Nexviazyme) are needed to determine whether the differences (b) (4) between these two drugs would provide evidence to determine if Pombiliti could potentially be clinically superior to Nexviazyme or not. Data from other disciplines (e.g., clinical) can help to further establish and support whether Pombiliti is clinically superior to Lumizyme and/or Nexviazyme.

E. Any Special Product Quality Labeling Recommendations:

- Store unconstituted vials at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.
- Reconstituted product may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 h and diluted product may be stored at 2°C to 8°C (36°F to 46°F) for up to 16 h. Storage at room temperature is not recommended. Do not freeze or shake.
- Prior to use, allow vials to reach ambient temperature, reconstitute each vial with 7.2 mL sterile WFI and dilute in 0.9% sodium chloride. Avoid foaming, forceful impact, shaking, agitation. Do not use a pneumatic tube to transport the infusion bag.

F. Establishment Information

OVERALL RECOMMENDATION: Deferred-Travel Restrictions-COVID			
Drug Substance and Drug Product			
Function	Site Information	DUNS/FEI Number	Current Recommendation
• Drug substance and drug product manufacturing • Drug substance and drug product release and stability testing • MCB and WCB storage	WuXi Biologics Co., Ltd. 108 Meiliang Road, Mashan, Binhu District, Wuxi, Jiangsu 214092, China	DUN: 421298354 FEI: 3010606982	PLI Deferred due to COVID Travel Restrictions
• MCB and WCB storage	(b) (4)	DUNS: (b) (4) FEI: (b) (4)	No Evaluation Necessary
• MCB and WCB manufacturing, testing and storage • (b) (4) Testing	WuXi Advanced Therapies Inc. 4751 League Island Blvd. Philadelphia, PA, 19112, USA	DUNS: 117331245 FEI: 1000122198	Approve - Based on Previous History

• (b) (4) testing • (b) (4) Testing	WuXi Biologics Biosafety Testing Co., Ltd. 1336 Wuzhong Road, Wuzhong Economic Development Zone, Suzhou, Jiangsu 215104, China	DUNS: 544312968 FEI: 3015655844	Approve - Based on Previous History
Rabbit Pyrogen Testing	(b) (4)	DUNS: (b) (4) FEI: (b) (4)	Approve - Based on Previous History
Labeling and Secondary Packaging	(b) (4)	DUNS: (b) (4) FEI: (b) (4)	Approve - Based on Previous History

G. **Facilities:** An overall recommendation for the GMP facilities associated with the manufacture of Pombiliti drug substance and drug product is pending.

WuXi Biologics Co. Ltd., Wuxi, China FEI: 3010606982

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for WuXi Biologics Co. Ltd., Wuxi, China (FEI: 3010606982) proposed for DS and DP manufacturing.

An inspection will be necessary before WuXi Biologics Co. Ltd. can be approved for DS and DP manufacturing operations as described in the submission. Due to travel restrictions in China, we may not be able to conduct the inspection of the WuXi Biologics Co. Ltd. facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application. We will continue to monitor the public health situation, as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections once safe travel may resume and based on public health need and other factors.

Other facilities: All other proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

H. Lifecycle Knowledge Management

a. Drug Substance

- i. **Protocols approved:** No protocols are approved at this time since OPQ's recommendation on approvability is pending final determination of the compliance status of the DS and DP manufacturing site. However, the following protocols are approvable if/when the BLA is approved:
 1. Annual post-approval stability protocol
 2. Protocols for qualification and requalification of primary and working reference standards
 3. Protocols for concurrent validation (b) (4)
 4. Master cell bank and working cell bank stability protocols

- ii. **Outstanding review issues/residual risk:** See Post Marketing Commitments and Agreements in Section 1D
- iii. **Future inspection points to consider:** Due to COVID-19 inspection travel restrictions, a pre-licensing inspection of the DS manufacturing facility has not yet been conducted.

b. Drug Product

- i. **Protocols approved:** No protocols are approved at this time since OPQ's recommendation on approvability is pending final determination of the compliance status of the DS and DP manufacturing site. However, the following protocols are approvable if/when the BLA is approved:
 - 1. Annual post-approval stability protocol
 - 2. Final DP shipping qualification protocol
- ii. **Outstanding review issues/residual risk:** See Post Marketing Commitments and Agreements in Section 1D
- iii. **Future inspection points to consider:** Due to COVID-19 inspection travel restrictions, a pre-licensing inspection of the DP manufacturing facility has not yet been conducted.

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/

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