CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761261Orig1s000

PRODUCT QUALITY REVIEW(S)

Addendum: This addendum has been prepared following the determination of compliance status for the manufacturing facilities for STN 761261 and the completion of the Office of Pharmaceutical Manufacturing Assessment (OPMA) facilities and microbiology assessments. The final determinations of compliance status for the facilities listed for the manufacture of Xenpozyme (olipudase alfa-rpcp) under STN 761261 have concluded with approval recommendations. For all other assessment information, including the reviews of drug substance and drug product manufacturing process, immunogenicity assays, and microbiology, refer to the OPQ IQA Executive Summary memorandum uploaded to Panorama on April 1, 2022 and the OPQ Technical reviews uploaded to Panorama separately.

Recommendation: Approval

BLA Number: 761261
Assessment Number: 2
Assessment Date: July 27, 2022

Drug Name/Dosage Form	Xenpozyme (olipudase alfa-rpcp)
Strength/Potency	20 mg of olipudase alfa-rpcp as a lyophilized powder in a single-dose vial for reconstitution
Route of Administration	Intravenous (IV) use
Rx/OTC dispensed	Rx
Indication	Enzyme replacement therapy (ERT) for (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients (Niemann-Pick disorder)
Applicant/Sponsor	Genzyme Corporation
US agent, if applicable	Not applicable

Product Overview:

Xenpozyme (olipudase alfa-rpcp) is a recombinant human acid sphingomyelinase (ASM) developed as an ERT to treat non-central nervous system manifestations of ASMD in pediatric and adult patients. Upon treatment, olipudase alfa is internalized by cells primarily through binding to the cation-independent mannose-6-phosphate receptor (CIMPR) with a smaller percentage getting internalized through binding to the mannose receptor. Following internalization and trafficking to lysosomes, olipudase alfa causes breakdown of sphingomyelin, reducing the accumulation of sphingomyelin in the affected organs. Olipudase alfa is manufactured in Chinese hamster ovary cells using recombinant DNA technology. The drug substance (DS) is a clear and colorless liquid. The DS is (b) (4) (b) (4) to manufacture the olipudase alfa drug product (DP). Olipudase alfa DP is supplied in (b) (4) single-use vial with nominal strength of 20 mg/vial. The composition of formulation excipients (b) (4) contains (b) (4) mg/mL olipudase alfa, (b) (4) mg/mL sodium phosphate dibasic (b) (4) mg/mL sodium phosphate monobasic (b) (4) mg/mL (b) (4) methionine, and (b) (4) % (w/v) sucrose at pH 6.5. Olipudase alfa DP is reconstituted with nominal 5.1 mL sterile water for injection and then further diluted before intravenous infusion.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Yongmin Liu	OPQ/OBP/DBRRII
Drug Product	Yongmin Liu	OPQ/OBP/DBRRII
Immunogenicity	Faruk Sheikh	OPQ/OBP/DBRRII
Immunogenicity Secondary Reviewer	Harold Dickensheets	OPQ/OBP/DBRRII
Labeling	Jennifer Kim Yongmin Liu	OPQ/OBP OPQ/OBP/DBRRII
DS Micro and Facilities	Michael Shanks	OPQ/OPMA/DBM/BMB2
DP Micro and Facilities	Yarery Smith	OPQ/OPMA/DBM/BMB2
RBPM	Nowrin Kakon	OPQ/OPRO
Team Lead	Brian Roelofs Virginia Carroll Michael Shanks	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Technical Lead	Brian Roelofs	OPQ/OBP/DBRRII

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Jenny Doan	OND/ORO/DRORDPURM
Cross-disciplinary Team Lead	Anita Zaidi/Katie Donohue	OND/ORDPURM/DRDMG
Medical Officer	Christine Hon	OND/ORDPURM/DRDMG
Nonclinical	Mary Ellen McNerney/Laurie McLeod-Flynn/Mukesh Summan	OND/ORDPURM/DPTRDPURM
Pharmacology/Toxicology, Pharmacometrics	Hongshan Li/Lian Ma	OTS/OCP/DPM
Clinical Pharmacology Genomics: QT: PBPK:	Md Nayeem Hossain/Jie Wang/Michael Pacanowski MD Nayeem Hossain/Christian Grimstein Eliford Kitabi/Girish Bende Guansheng Liu/Yang Yuching	OTS/OCP/DTPM OTS/OCP/DPM and OTS/OCP/DCEP OTS/OCP/DPM
Biostatistics	Andrew Griffin/Yan Wang/Dionne Price	OTS/OB

1. Names:
   a. Proprietary Name: XENPOZYME
   b. Trade Name: XENPOZYME (olipudase alfa-rpcp)
   c. Non-Proprietary Name: olipudase alfa-rpcp
   d. Company Code/Common Name: recombinant human acid sphingomyelinase (rhASM)
   e. INN Name: olipudase alfa
   f. USAN: olipudase alfa
   g. CAS Registry Number: 927883-84-9; Sphingomyelinase C (synthetic human)
   h. OBP systematic name: RPROT P17405 (ASM_HUMAN) SPHINGOMYELIN PHOSPHODIESTERASE [GZ402665]
   i. Other name(s): Sphingomyelin phosphodiesterase (EC-3.1.4.12), GZ402665 (company internal synonym)

2. Pharmacologic Category: Therapeutic recombinant enzyme.

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs: No DMFs are claimed in support of BLA 761261

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

Document	Application Number	Description
IND	012757	Parent IND

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval
The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761261 for Xenpozyme (olipudase alfa-rpcp) manufactured by Genzyme Corporation. The data submitted in this application are adequate to support the conclusion that the manufacture of Xenpozyme (olipudase alfa-rpcp) 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 the conditions specified in the package insert.

The final recommendation on approvability in the original OPQ Executive Summary Integrated Quality Assessment (IQA) completed and signed on April 1, 2022 was pending the completion of the microbiology and facility assessments and inspection of the drug substance manufacturing facility (b) (4) The microbiology and facilities assessments were completed with approval recommendations. The inspection of the drug substance manufacturing facility was performed (b) (4) (b) (4) with an approval recommendation.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance
    (b) (4)

USA
FEI: (b) (4)

- Drug Product:
  Genzyme Ireland Limited
  IDA Industrial Park
  Old Kilmeaden Road
  Waterford, Ireland
  FEI: 3003809840

- Fill size and dosage form: 20 mg of olipudase alfa-rpcp as a lyophilized powder in a 20 mL single-dose vial for reconstitution and intravenous infusion

- Dating period:
  - Drug Product: 24 months at 2 to 8°C
  - Drug Substance: (b) (4) weeks at (b) (4) °C
  - Not Packaged
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process validation drug product lots.
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.

- Exempt from lot release
  - Yes
  - Specified product
    - Olipudase alfa-rpcp is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Xenpozyme (olipudase alfa-rpcp) is a recombinant human ASM developed as an ERT to treat non-central nervous system manifestations of ASMD in pediatric and adult patients. ASMD currently has no approved treatment and there are no disease-specific treatments that can modify the disease or slow the rate of progression. Lack of ASM can lead to a phenotypic range including the Type A severe infantile neurovisceral form or the Type B chronic visceral form. ASM catalyzes the hydrolysis of sphingomyelin to ceramide and phosphocholine and the enzymatic deficiency causes an intracellular buildup of sphingomyelin. Upon treatment, olipudase alfa is internalized by the cells primarily through binding to the cation-independent mannose-6-phosphate receptor (CIMPR) with a smaller percentage getting internalized through binding to the mannose receptor. Following internalization and trafficking to lysosomes, olipudase alfa causes breakdown of sphingomyelin, reducing the accumulation of sphingomyelin in the affected organs. Olipudase alfa has orphan drug designation, rare pediatric disease designation, and received a priority review designation for the treatment of ASMD. Approval of olipudase alfa will address an unmet medical need for ASMD.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a

consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We recommend approval of the commercial manufacture of olipudase alfa DS at (b) (4) FEI: (b) (4) and DP at Genzyme Ireland Limited IDA Industrial Park (Waterford, Ireland) FEI: 3003809840. The OBP product quality and immunogenicity assay assessments, OPMA DS and DP microbiological and facility assessments, and OBP labeling technical assessments are located as separate technical documents in Panorama.

D. Environmental Assessment or Claim of Categorical Exclusion:

A claim of categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(a) and 21 CFR 25.31(c) was provided and is acceptable.

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

1) To establish a working reference standard (WRS) using a (b) (4) batch and qualify this WRS against the current olipudase alfa primary reference standard (PRS) (b) (4) Once the WRS is established, the qualification data for the first WRS together with a WRS requalification protocol specifying how subsequent working reference standards will be qualified will be submitted.

   The WRS will be created from a representative DS batch which has passed all release specifications. The WRS will be qualified according to a predefined protocol using a statistically derived replication strategy for key attributes in addition to a panel of extended characterization methods.

   Final Report Submission: March, 2024 (submission as a Prior Approval Supplement)

2) To develop an endotoxin method for the drug product which mitigates the low endotoxin recovery (LER) effect, to submit method qualification results with 3 lots of drug product, and to provide results of an LER study performed with the updated method with 3 lots of drug product. The rabbit pyrogen test will be replaced by a suitable in vitro endotoxin method upon approval of the supplement.

   Final Report Submission: June, 2026

3) To repeat the performance qualification study for the container closure integrity on the (b) (4) utilizing the current CCIT method which is capable of detecting breaches down to 5 μm.

   Final Report Submission: October, 2023

4) To perform the qualification of the bioburden method using a test volume of 100 mL with 3 batches of drug product.

   Final Report Submission: October, 2023

F. Any Special Product Quality Labeling Recommendations:

- Reconstituted Drug Product: Up to 24 hours when refrigerated (2 to 8˚C) or 12 hours at room temperature (20 to 25˚C)
- Diluted product in infusion solution: Up to 24 hours when refrigerated (2 to 8˚C) and up to 12 hours (including infusion time) when stored at room temperature (20 to 25˚C)
- Store in a refrigerator at 2°C to 8°C
- Do not freeze

G. Establishment Information:

Overall Recommendation: Approval					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Substance Manufacturing (b) (4) Release, In-process, and Stability Testing	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Pre-license inspection required	3-item FDA Form 483 was issued	Approve – Based on Inspection
MCB manufacturing	Genzyme Corporation 76 New York Avenue Framingham, MA, 01701, USA	FEI: 1220423 DUNS: 943130096	No evaluation necessary	N/A	No evaluation necessary
MCB storage, WCB manufacturing and storage, WCB testing (characterization and adventitious virus testing)	Genzyme Corporation 45 New York Avenue Framingham, MA, 01701, USA	FEI: 1220423 DUNS: 968278916	No evaluation necessary	N/A	No evaluation necessary
MCB and WCB Storage	Genzyme Corporation 74 New York Avenue Framingham, MA, 01701, USA	FEI: 1220423 DUNS: 968278932	No evaluation necessary	N/A	No Evaluation Necessary
WCB testing (characterization and adventitious virus testing	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	No evaluation necessary	N/A	No evaluation necessary
		FEI: (b) (4) DUNS: (b) (4)	No evaluation necessary	N/A	No evaluation necessary
Release testing (pyrogen)		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history

	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history
In-Process testing: (b) (4)		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history
Back-up testing for In vitro tests for adventitious viruses, mycoplasma and MVM		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history

DRUG PRODUCT

Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Product Manufacturing (b) (4) (b) (4) Labeling and Packaging Release, In-Process, and Stability Testing Lot Release Storage	Genzyme Ireland Limited IDA Industrial Park Old Kilmeaden Road Waterford, Ireland	FEI: 3003809840 DUNS: 985127419	Facility was found compliant based on file review	N/A	Approve – based on Waiver granted by OPMA/OBP
Drug Product Release Testing (pyrogen)	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – Based on Previous History
		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history
Labeling and Secondary Package Lot Release Storage	Genzyme Corporation 11 Forbes Road Northborough, MA, USA, 01532	FEI: 3009389940 DUNS: 050424395	Facility was found compliant based on file review	N/A	Approve – based on previous history
DP Sterility Testing (back-up site)	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history

H. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) proposed for DS manufacture and Genzyme Ireland Limited IDA, Waterford, Ireland (FEI 3003809840) proposed for DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspection coverage. Based on the site's history, the inspection of the drug product manufacturing site was waived. Refer to the waiver memorandum in Panorama. This submission is recommended for approval from a facilities perspective.

I. Lifecycle Knowledge Management:

1) Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.2.3	(b) (4)		Annual Report
3.2.S.2.5			Annual Report
3.2.S.2.5			Annual Report
3.2.S.5			Annual Report
3.2.S.7.2			Annual Report

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None

2) Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
1.11.1	Active Shipping Protocol	The impact of active shipping on olipudase alfa DP will be assessed.	Annual Report
3.2.P.2	Leachables study	Real-time leachables study results.	Annual Report
3.2.P.8.1 3.2.P.8.2	DP stability updates and shelf-life extension	Primary and supportive stability results as well as Annual stability results will be reported.	Annual Report

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None

Brian Roelofs

Digitally signed by Brian Roelofs
Date: 7/27/2022 06:17:33PM
GUID: 57f29d150070ca84f102970a51133e31

Virginia Carroll

Digitally signed by Virginia Carroll
Date: 7/28/2022 09:35:25AM
GUID: 5898c0190049a524b6af8a93d389a1c0

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/

BRIAN A ROELOFS
07/29/2022 05:41:02 PM

Priority Assessment

Recommendation: Pending

BLA Number: 761261
Assessment Number: 1
Assessment Date: April 1, 2022

Drug Name/Dosage Form	Xenpozyme (olipudase alfa-rpcp)
Strength/Potency	20 mg of olipudase alfa-rpcp as a lyophilized powder in a single-dose vial for reconstitution
Route of Administration	Intravenous (IV) use
Rx/OTC dispensed	Rx
Indication	Enzyme replacement therapy (ERT) for (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency in pediatric and adult patients (Niemann-Pick disorder)
Applicant/Sponsor	Genzyme/Sanofi
US agent, if applicable	Not applicable

Product Overview:

Xenpozyme (olipudase alfa-rpcp) is a recombinant human acid sphingomyelinase (ASM) developed as an ERT to treat non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. Upon treatment, olipudase alfa is internalized by cells primarily through binding to the cation-independent mannose-6-phosphate receptor (CIMPR) with a smaller percentage getting internalized through binding to the mannose receptor. Following internalization and trafficking to lysosomes, olipudase alfa causes breakdown of sphingomyelin, reducing the accumulation of sphingomyelin in the affected organs. Olipudase alfa is manufactured in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology. The drug substance (DS) is a clear and colorless liquid. The DS is (b) (4) to manufacture the olipudase alfa drug product (DP). Olipudase alfa DP is supplied in (b) (4) single-use vial with nominal strength of 20 mg/vial. The composition of formulation excipients (b) (4) (b) (4) contains (b) (4) mg/mL olipudase alfa, (b) (4) mM sodium phosphate, (b) (4) % (w/v) sucrose, and (b) (4) mM (b) (4) methionine at pH 6.5. Olipudase alfa DP is reconstituted with nominal 5.1 mL sterile water for injection and then further diluted before intravenous infusion.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Yongmin Liu	OPQ/OBP/DBRRII
Drug Product	Yongmin Liu	OPQ/OBP/DBRRII
Immunogenicity	Faruk Sheikh	OPQ/OBP/DBRRII
Immunogenicity Secondary Reviewer	Harold Dickensheets	OPQ/OBP/DBRRII
Labeling	Jennifer Kim Yongmin Liu	OPQ/OBP OPQ/OBP/DBRRII
DS Micro and Facilities	Michael Shanks	OPQ/OPMA/DBM/BMB2
DP Micro and Facilities	Yarery Smith	OPQ/OPMA/DBM/BMB2
RBPM	Nowrin Kakon	OPQ/OPRO
Team Lead	Brian Roelofs Virginia Carroll	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Technical Lead	Brian Roelofs	OPQ/OBP/DBRRII

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Jenny Doan	OND/ORO/DRORDPURM
Cross-disciplinary Team Lead	Anita Zaidi/Katie Donohue	OND/ORDPURM/DRDMG
Medical Officer	Christine Hon	OND/ORDPURM/DRDMG
Nonclinical	Mary Ellen McNerney/Laurie McLeod-Flynn/Mukesh Summan	OND/ORDPURM/DPTRDPURM
Pharmacology/Toxicology, Pharmacometrics	Hongshan Li/Lian Ma	OTS/OCP/DPM
Clinical Pharmacology Genomics: QT: PBPK:	Md Nayeem Hossain/Jie Wang/Michael Pacanowski MD Nayeem Hossain/Christian Grimstein Eliford Kitabi/Girish Bende Guansheng Liu/Yang Yuching	OTS/OCP/DTPM OTS/OCP/DPM and OTS/OCP/DCEP OTS/OCP/DPM
Biostatistics	Andrew Griffin/Yan Wang/Dionne Price	OTS/OB

1. Names:
   a. Proprietary Name: Xenpozyme
   b. Trade Name: Xenpozyme (olipudase alfa-rpcp)
   c. Non-Proprietary Name/USAN: olipudase alfa
   d. CAS Registry Number: 927883-84-9; Sphingomyelinase C (synthetic human)
   e. INN Name: olipudase alfa
   f. OBP systematic name: RPROT P17405 (ASM_HUMAN) SPHINGOMYELIN PHOSPHODIESTERASE [GZ402665]
   g. Other name(s): Sphingomyelin phosphodiesterase (EC-3.1.4.12), rhASM (company code), GZ402665 (company internal synonym)

Submissions Assessed:

Submission(s) Assessed	Document Date (disciplines affected)
eCTD 0002/SDN 2 – Original BLA Submission	11/03/2021 (OBP, OPMA)
eCTD 0003/SDN 3 – PQ IR 1 Response	12/08/2021 (OBP, OPMA)
eCTD 0006/SDN 6 – PQ IR 2 Response	01/14/2022 (OPMA)
eCTD 0007/SDN 7 – PQ IR 3 Response	01/21/2022 (OBP, OPMA)
eCTD 0008/SDN 8 – PQ IR 4 Response	01/25/2022 (OBP)
eCTD 0009/SDN 9 – PQ IR 5 Response	02/03/2022 (OBP)
eCTD 0011/SDN 11 – PQ IR 5 Response	02/10/2022 (OBP)
eCTD 0015/SDN 15 – PQ IR 6 Response	03/08/2022 (OBP)
eCTD 0017/SDN 17 – PQ IR 6 Response	03/10/2022 (OBP)
eCTD 0018/SDN 18 – PQ IR 7 Response	03/14/2022 (OBP, OPMA)
eCTD 0019/SDN 19 – PQ IR 7 Response	03/15/2022 (OBP)
eCTD 0021/SDN 20 – Manufacturing Schedule Update	03/16/2022 (OPMA, OBP)
eCTD 0020/SDN 21 – PQ IR 9 Response	03/17/2022 (OBP)
eCTD 0022/SDN 22 – PQ IR 8 Response	03/18/2022 (OPMA)
eCTD 0023/SDN 23 – PQ IR 11 Reponse	03/21/2022 (OPMA)

eCTD 0024/SDN 24 – PQ IR 9/10 Response	03/22/2022 (OBP, OPMA)
eCTD 0025/SDN 25 – PQ IR 12 Response	03/25/2022 (OPMA)

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

APPEARS THIS WAY ON ORIGINAL

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs: No DMFs are claimed in support of BLA 761261

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed

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

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

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

Document	Application Number	Description
IND	012757	Parent IND

3. Consults: None

4. Environmental Assessment

Genzyme is claiming categorical exclusion from preparation of an Environmental Assessment for the BLA for olipudase alfa. Compliance with the categorical exclusion criteria is made pursuant to 21 CFR Part 25, Subpart C, Categorical Exclusions, Section 25.31 (c), Human drugs and biologics, since this application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Olipudase alfa is a recombinant human acid sphingomyelinase and is considered to be readily metabolized in humans and degraded in the environment. The requested action will not result in extraordinary circumstances per 21 CFR section 25.21 since no adverse effect or other significant effect on the quality of the human environment is predicted from approval of this submission.

The request for categorical exclusion is granted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The recommendation for STN 761261 from the Office of Pharmaceutical Quality (OPQ), CDER, is pending the final determination of facility compliance for the DS manufacturing site and the completion of the Office of Pharmaceutical Manufacturing Assessment (OPMA) microbiology assessment. Inspection of the DS manufacturing facility (b) (4) (b) (4) is scheduled (b) (4)

From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER as well as OPMA, OPQ, CDER do not note any product quality deficiencies that would preclude approval of STN 761261 at this time. An addendum to this memorandum will be filed upon completion of the inspection of the DS manufacturing facility and completion of the OPMA microbiology and facility assessments.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance
    (b) (4)
    FEI: (b) (4)
  - Drug Product:
    Genzyme Ireland Limited
    IDA Industrial Park
    Old Kilmeaden Road
    Waterford, Ireland
    FEI: 3003809840

- Fill size and dosage form: 20 mg of olipudase alfa-rpcp as a lyophilized powder in a 20 mL single-dose vial for reconstitution and intravenous infusion.

- Dating period:
  - Drug Product: 24 months at 2 to 8°C
  - Reconstituted Drug Product: Up to 24 hours when refrigerated (2 to 8°C) or 12 hours at room temperature (25±2°C)
  - Diluted product in infusion solution: Up to 24 hours when refrigerated (2 to 8°C) and up to 12 hours (including infusion time) when stored at room temperature (25±2°C)
  - Drug Substance: (b) (4) weeks at (b) (4) °C
  - Not Packaged
  - Stability Option:

- Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process validation drug product lots.
- We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.

- Exempt from lot release
  - Yes
  - Specified product
    - Olipudase alfa-rpcp is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Xenpozyme (olipudase alfa-rpcp) is a recombinant human ASM developed as an enzyme replacement therapy (ERT) to treat non-central nervous system manifestations of ASMD in pediatric and adult patients. ASMD currently has no approved treatment and there are no disease-specific treatments that can modify the disease or slow the rate of progression. Lack of ASM can lead to a phenotypic range including the Type A severe infantile neurovisceral form or the Type B chronic visceral form. ASM catalyzes the hydrolysis of sphingomyelin to ceramide and phosphocholine and the enzymatic deficiency causes an intracellular buildup of sphingomyelin. Upon treatment, olipudase alfa is internalized by the cells primarily through binding to the cation-independent mannose-6-phosphate receptor (CIMPR) with a smaller percentage getting internalized through binding to the mannose receptor. Following internalization and trafficking to lysosomes, olipudase alfa causes breakdown of sphingomyelin, reducing the accumulation of sphingomyelin in the affected organs. Olipudase alfa has orphan drug designation, rare pediatric disease designation, and received a priority review designation for the treatment of ASMD. Approval of olipudase alfa will address an unmet medical need for ASMD.

At this point of the assessment, no approvability issues have been identified. A final determination on the DS manufacturing facility (b) (4) (b) (4) will be made following the inspection scheduled (b) (4)
We recommend approval of the commercial manufacture of olipudase alfa DP at Genzyme Ireland Limited IDA Industrial Park (Waterford, Ireland) FEI: 3003809840. The OBP product quality and immunogenicity assay assessments are located as separate technical documents in Panorama. The OPMA DS and DP microbiological and facility assessments, and OBP labeling technical assessments will be located as separate documents in Panorama.

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

1. To develop an endotoxin method for the drug product which mitigates the low endotoxin recovery (LER) effect, to submit method qualification results with 3 lots of drug product, and to provide results of an LER study performed with the updated method with 3 lots of drug product. The rabbit pyrogen test will be replaced by a suitable in vitro endotoxin method upon approval of the supplement. Due June 2026.
   There is one PMC at the time of this memorandum. If additional PMCs are needed on the basis of OPMA's microbiology assessment, this memorandum will be amended.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Identity	Efficacy and Safety	Intrinsic to the molecule, cell culture	(b) (4)	The assay analysis includes visual comparison, (b) (4)
Potency by Specific Activity	Efficacy	Manufacturing process, cell culture, intrinsic to the molecule, environmental stresses		
Potency by Cellular Uptake Assay				
Potency by Enzyme Kinetics (K_M, µM)				
Potency by Enzyme Kinetics (k_{cat}, 1/sec)				
High molecular weight species (HMWS), aggregates	Efficacy, Safety (immunogenicity)	Manufacturing process, environmental stresses, storage		
Dimer content	Efficacy, Safety (immunogenicity)			
Low molecular weight species (LMWS)	Efficacy	Manufacturing process, (b) (4)		

			(b) (4)
Charge variants, post-translational modifications, glycosylation species	Efficacy, PK/PD	DS manufacturing process, cell culture	
Glycosylation Species	Efficacy, PK/PD	DS manufacturing process, cell culture	
Free Thiol/Free C-terminal cysteine	Efficacy	DS manufacturing process, cell culture	

B. Drug Substance (olipudase alfa) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: DS CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Appearance – Color, clarity/degree of opalescence	Safety, stability	Formulation components and stability	(b) (4)	N/A
Protein Concentration	Efficacy	(b) (4) operations during DS manufacturing		N/A
Osmolality	Stability	Formulation		N/A
pH	Efficacy, Stability	Formulation		N/A

CHO Host Cell Protein (Process Related Impurity)	Safety (immunogenicity)	Production cell line	(b) (4)	N/A
CHO Host Cell DNA (Process related impurity)	Safety	Production cell line		N/A
Adventitious Agents (TSE, virus, mycoplasma)	Safety (systemic infection)	Starting materials, raw materials including (b) (4) cell bank, cell culture process		
Residual hamster acid sphingomyelinase (ASM)	Immunogenicity	Cell culture		N/A
Residual cell culture (b) (4)	Safety	Manufacturing process, cell culture (b) (4)		N/A
Culture medium and buffer components	Safety	(b) (4)		Levels are below toxicological concern based on the risk assessment.
Pyrogens/Endotoxin (contaminant)	Safety and Purity	Raw materials, manufacturing process		PMC to develop a suitable in vitro endotoxin method

			(b) (4)	
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials, manufacturing process		N/A
Mycoplasma	Safety	Raw materials, DS manufacturing process		N/A
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		N/A
Elemental impurities	Safety	Cell culture medium, product-contact surfaces, raw materials, excipients, (b) (4)		N/A

- Description:
  Xenpozyme (olipudase alfa-rpcp) is a recombinant human ASM with an approximate molecular weight of approximately 76,000 Daltons after glycosylation. Olipudase alfa is produced using CHO cells (b) (4) Olipudase alfa is indicated as an ERT treatment for non-central nervous system manifestations of ASMD (Niemann Pick disorder). Lack of ASM can lead to a phenotypic range including the Type A severe infantile neurovisceral form or the Type B chronic visceral form.

- Mechanism of Action (MoA):
  Upon treatment, olipudase alfa is internalized by the cells primarily through binding to the cation-independent mannose-6-phosphate receptor (CIMPR) with a smaller percentage getting internalized through binding to the mannose receptor. Following internalization and trafficking to lysosomes, olipudase alfa causes breakdown of sphingomyelin, reducing the accumulation of sphingomyelin in the affected organs.

- Potency Assays:
  The potency of olipudase alfa is assessed by four assays as part of the DP control strategy. The DS potency is controlled by the Enzyme Activity assay. This assay utilizes the synthetic substrate 2-(N-hexadecanoylamino)-4-nitrophenylphosphorylcholine hydroxide (HDA-PC). This chromogenic substrate is hydrolyzed by olipudase alfa yielding phosphorylcholine and 2-(N-hexadecanoylamino)-4-nitrophenyl (HDA-NP). The

absorbance of the released HDA-NP is monitored at 415 nm as a direct measure of enzyme activity. Potency is reported as Units/mg.

Validation of the Enzyme Activity potency assay was performed with the primary reference standard (PRS), as well as representative process C (b) (4) and process B batches. Additional validation for use of the assay (b) (4) at the DP manufacturing site was performed with process C DP lot C5896 which is representative of the commercial manufacturing process.

Additional potency assays performed as part of the DP control program include:

1. Relative potency by cellular uptake (% of reference standard)
2. Enzyme kinetics (K_M, µM)
3. Enzyme kinetics (k_{cat}, 1/sec)

For the cellular uptake assay, the uptake of olipudase alfa DP in human hepatocarcinoma cells (HepG2) expressing mannose-6 phosphate receptors is monitored. The cells are incubated with recombinant olipudase alfa DP, washed, lysed and the samples are treated with Amplex Red assay kit reagents. The phophorylcholine byproduct generated through cleavage of sphingomyelin by the internalized olipudase alfa is converted to resorufin. The quantity of resorufin is measured by fluorescence as a metric of successful internalization and activity of olipudase alfa in this cell line. The assay was validated using process C DP lot C5896 which is representative of the commercial manufacturing process. Specificity was addressed by comparison to interim reference standard (b) (4) and additional metrics were compared to an internal control generated from DP lot C5896.
In the enzyme kinetics assays, the hydrolysis of the synthetic substrate HDA-PC by olipudase alfa DP is assessed and the K_M and k_{cat} are experimentally determined as specific enzyme parameters for each DP lot and controlled at release. The validation of the assay was performed with representative commercial process DP lots as well as stressed and non-stressed DS batches.

- Reference Materials:
  (b) (4)
- Critical Starting Materials or Intermediates:
  The master cell bank (MCB) is derived from (b) (4) cells (b) (4)

(b) (4)

The procedures for release, stability testing, and generation of a new WCB is adequate for the maintenance of product quality. Viability of both the MCB and the WCB is monitored as part of the stability program.

- Manufacturing Process Summary:
  The manufacture of olipudase alfa is (b) (4)

(b) (4)

- Container Closure:
  The (b) (4) mg/mL olipudase alfa DS is stored [redacted]

- Dating Period and Storage Conditions:
  The dating period for the DS is (b) (4) weeks when stored at [redacted] °C.

C. Drug Product (olipudase alfa) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

Table 3: DP CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Appearance – Lyophilized	Safety	Product formulation, [redacted]	[redacted]	N/A
Reconstitution Time	Efficacy	Product formulation		N/A
Residual Moisture	Efficacy, Safety, Stability	DP manufacturing process		N/A
Appearance – Reconstituted: Color, Clarity, Degree of Opalescence	Safety	Product formulation, [redacted]		N/A
Potency Enzymatic Activity, Cellular Uptake, and Enzyme Kinetics	Potency	Manufacturing process, environmental stresses		Refer to further description in CQA table above.
HMWS species and Dimer content	Efficacy, Safety (immunogenicity)	Manufacturing process, environmental stresses, storage		Refer to further description in CQA table above.
LMWS species	Biological Activity	Manufacturing process, [redacted]		Refer to further description in CQA table above.

			(b) (4)	
Osmolality and pH	Efficacy and stability, safety	Formulation components and stability		N/A
Protein concentration	Efficacy	DS manufacturing process, potential impact (b) (4)		N/A
Visible particles and sub-visible particles	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Pyrogens/Endotoxins (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, manufacturing process		PMC to develop a suitable in vitro endotoxin method
Sterility	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Manufacturing process, failure of the container closure system		N/A
Extractable volume	Efficacy/Dosing	(b) (4)		N/A
Container closure integrity (Sterility assurance)	Safety (maintenance of sterility during shelf-life	Container closure breaches during manufacture or storage		N/A
Elemental Impurities	Safety (Toxicity)	From product contact material during manufacturing and storage		N/A

Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS	(b) (4)	The real-time study results will be submitted as part of subsequent annual reports. Data from the first 12 months were provided.

- Potency and Strength:
  Olipudase alfa is provided as a sterile 20 mg powder in a 20 mL vial for reconstitution and intravenous infusion. Potency is defined by four tests including (1) the enzyme activity, (2) the cellular uptake and activity relative to the current olipudase alfa RS, (3) the enzyme kinetics for binding affinity (K_M), and (4) the catalytic rate constant (k_{cat}). The enzymatic activity assay is the same as that described in the DS section of this memo. Refer to the DS section above for further discussion of the potency assays.

- Summary of Product Design:
  Olipudase alfa is supplied as 20 mg of sterile lyophilized powder for intravenous use. The filling and reconstitution studies demonstrated sufficient control (b) (4) (b) (4) The minimum fill weight of (b) (4) g has been demonstrated to ensure that the label claim of 20 mg/vial will be met (b) (4) and the proposed reconstitution volume of 5.1 mL is sufficient to allow withdrawal of the labeled quantity consistent with USP <697>.

- List of Excipients:
  The olipudase alfa DP excipients per 20 mg vial are (b) (4) mg ((b) (4) mg/mL after reconstitution) sodium phosphate monobasic (b) (4) mg ((b) (4) mg/mL) sodium phosphate dibasic (b) (4) mg ((b) (4) mg/mL) sucrose, (b) (4) mg ((b) (4) mg/mL) (b) (4) methionine, and water for injection to a total volume of (b) (4) mL.

- Reference Materials:
  The same RS are used for DS and DP.

- Manufacturing Process Summary:
  The manufacturing process for olipudase alfa DP includes the following steps:

(b) (4)

- Container Closure:
  The primary container closure system for olipudase alfa DP consists of a clear, colorless 20 mL (b) (4) glass vial with a 20 mm (b) (4) gray elastomeric stopper (b) (4) crimped with an aluminum seal with plastic (b) (4) covers.

  Compatibility studies for olipudase alfa DP administration were performed with diluents and commonly used infusion components. The proposed administration and in-use stability conditions based on the studies performed with protein concentration ranging from 0.1 to 3.5 mg/mL supported commonly used administration bag materials and polypropylene syringe sizes. Product purity, potency, and protein content were maintained through the intended route of administration for intravenous infusion. An in-line 0.2 µm filter is for administration.

- Dating Period and Storage Conditions:
  The dating period for olipudase alfa DP is 24 months when stored at 2-8°C. The in-use compatibility and stability data included in the BLA support the maintenance of reconstituted DP for up to 24 hours when refrigerated (2 to 8°C) or 12 hours at room temperature (25±2°C). The diluted product in infusion solution can be stored for up to 24 hours when refrigerated (2 to 8°C) and up to 12 hours (including infusion time) when stored at room temperature (25±2°C).

- Commercial Presentation:
  The intended commercial presentation will be a single-dose vial containing 20 mg olipudase alfa as a sterilized powder for reconstitution and intravenous use.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
   - Store in a refrigerator at 2°C to 8°C
   - Protect from light
   - Do not freeze

F. Establishment Information:

Overall Recommendation: Pending					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Substance Manufacturing (b) (4) Release, In-process, and Stability Testing	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Pre-license inspection required	TBD	Pending inspection scheduled (b) (4)
MCB manufacturing	Genzyme Corporation 76 New York Avenue Framingham, MA, 01701, USA	FEI: 1220423 DUNS: 943130096	No evaluation necessary	N/A	No evaluation necessary
MCB storage, WCB manufacturing and storage, WCB testing (characterization and adventitious virus testing)	Genzyme Corporation 45 New York Avenue Framingham, MA, 01701, USA	FEI: 1220423 DUNS: 968278916	No evaluation necessary	N/A	No evaluation necessary
MCB and WCB Storage	Genzyme Corporation 74 New York Avenue Framingham, MA, 01701, USA	FEI: 1220423 DUNS: 968278932	No evaluation necessary	N/A	No Evaluation Necessary
WCB testing (characterization and adventitious virus testing	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	No evaluation necessary	N/A	No evaluation necessary
		FEI: (b) (4) DUNS: (b) (4)	No evaluation necessary	N/A	No evaluation necessary
Release testing (pyrogen)		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history
		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history
In-Process testing: (b) (4)		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history

Back-up testing for In vitro tests for adventitious viruses, mycoplasma and MVM	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Product Manufacturing (b) (4) (b) (4) Labeling and Packaging Release, In-Process, and Stability Testing Lot Release Storage	Genzyme Ireland Limited IDA Industrial Park Old Kilmeaden Road Waterford, Ireland	FEI: 3003809840 DUNS: 985127419	Facility was found compliant based on file review	N/A	Approve – based on Waiver granted by OPMA/OBP
Drug Product Release Testing (pyrogen)	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – Based on Previous History
		FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history
Labeling and Secondary Package Lot Release Storage	Genzyme Corporation 11 Forbes Road Northborough, MA, USA, 01532	FEI: 3009389940 DUNS: 050424395	Facility was found compliant based on file review	N/A	Approve – based on previous history
DP Sterility Testing (back-up site)	(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Facility was found compliant based on file review	N/A	Approve – based on previous history

G. Facilities:

A final recommendation for this submission is pending the inspection of the DS manufacturing facility (b) (4) (FEI (b) (4)).

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) (FEI (b) (4)) proposed for DS manufacture and Genzyme Ireland Limited IDA, Waterford, Ireland (FEI 3003809840) proposed for DP manufacture. Based on the site's history, the inspection of the drug product manufacturing site was waived. Refer to the waiver memorandum in Panorama.

All other proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspection coverage.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
1.11.1	(b) (4)		Annual Report
3.2.S.2.3			Annual Report
3.2.S.2.3			Annual Report
3.2.S.2.5			Annual Report
3.2.S.2.5			Annual Report
3.2.S.5			Annual Report
3.2.S.7.2			Annual Report
3.2.P.8.2			Annual Report

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.P.2	Leachables study	Real-time leachables study results.	Annual Report
3.2.P.8.1 3.2.P.8.2	DP stability updates and shelf-life extension	Primary and supportive stability results as well as Annual stability results will be reported.	Annual Report

ii. Outstanding assessment issues/residual risk: An on-site inspection of the (b) (4) (b) (4) DS manufacturing facility is scheduled (b) (4) Additionally, the microbiology and facilities assessment from OPMA is ongoing.

iii. Future inspection points to consider: None

Brian Roelofs

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Virginia Carroll

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/s/

BRIAN A ROELOFS
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