CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125141/0

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

genzyme

Patent Information and Certification

Genzyme Corporation is not including in this Biologics License Application, any patent information or patent certification pertaining to Myozyme. This is consistent with 21 U.S.C. Section 355(b) or (c) and Title 21 CFR 314.50(h) and (i) and 314.53, which requires patent information be submitted for New Drug Applications.

Genzyme Corporation

Alexander E. Kuta, Ph.D., Vice President, Regulatory Affairs

July 29, 2005
Date

Not Applicable

Under the PHS Act we do not require any patent information to accompany the submission

genzyme

Debarment Certification

Certification Pursuant to 21 U.S.C Section 335 a(k)(1)

Genzyme Corporation certifies that there was no use in any capacity of the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. Section 335 (a) (b)) within this application.

Genzyme Corporation

Alexander E. Kuta

Alexander E. Kuta, Ph.D., Vice President, Regulatory Affairs

July 29, 2005
Date

genzyme

Exclusivity Claim

In accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 CFR 314.108(b)(2), Genzyme Corporation claims exclusivity for Myozyme (alglucosidase alfa). The active moiety in Myozyme is a new chemical entity, and has not been previously approved for marketing under section 505(b). Under the Orphan Drug Act of January 4, 1983, and its amendments in 1984, 1985 and 1988, the developer of an ophan product is guaranteed seven years of market exclusivity following the approval of the product by the FDA. This product that is the subject of this Biologics License Application was granted Orphan Drug Designation on June 17, 1997 (designation 97-1065). Therefore, Genzyme requests and claims 7 years of market exclusivity following approval of this Biologics License Application.

Genzyme Corporation

Alexander E. Kuta

Alexander E. Kuta, Ph.D., Vice President, Regulatory Affairs

July 29, 2005
Date

Not Applicable

Under the PHS Act we only have orphan exclusivity

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: 4/25/06

To: Jennifer Panagoulias	**From:** Cristi Stark
Company: Genzyme Corporation	Division of Gastroenterology Products
Fax number: (617) 768-6419	**Fax number:** (301) 796-9905
Phone number: (617) 768-6704	**Phone number:** (301) 796-2120

Subject: approval letter/approved PI/approved carton/approved vial

Total no. of pages including cover: 31

Comments: Attached is a copy of your approval for STN 125141/0. Please confirm receipt.

Document to be mailed: ☒ YES ☐ NO

4/27/06

Division of Gastroenterology Products

PROJECT MANAGER'S ADDENDUM REVIEW

Application Number: STN 125141/0

Name of Drug: Alglucosidase alfa

Sponsor: Genzyme Corporation

Material Reviewed:

Submission Date: April 12, 2006 – revised Carton and Vial Labeling
April 26, 2006 – revised Carton Label

Receipt Date: April 13, 2006 – revised Carton and Vial Labeling
April 27, 2006 – revised Carton Label

Background and Summary

STN 125141/0 for Alglucosidase alfa is an original application intended as an enzyme replacement therapy for patients with Pompe disease who are deficient in or lack the endogenous enzyme, acid alpha-glucosidase (GAA). The sponsor proposed indication for Alglucosidase alfa is for —

Review

I. Vial – revisions from the April 12, 2006 submission

A. Per FDA request, the statement "Protect from light," has been added to the label. This conforms to 21 CFR 610.61 and 21 CFR 201.100.

B. Per FDA suggestion, the proper name and proprietary name font sizes are revised. The proper name has a font size of 11.5 points and the proprietary name has a font size of 14.2 points. This conforms to the regulation.

II. Carton – revisions from the April 12, 2006 and April 26, 2006 submissions

A. Per FDA request, the statement "Protect from light," has been added to the label. This conforms to 21 CFR 610.61 and 21 CFR 201.100.

B. Per FDA suggestion, the proper name and proprietary name font sizes are revised. The proper name has a font size of 11.0 points and the proprietary name has a font size of 13.2

points. This conforms to the regulation.

C. The ingredient listing has changed on the side of the carton. The carton label read,

"Each vial contains
alglucosidase alfa – mg
Mannitol 210
mgpolysorbate 80 0.5 mg
Sodium phosphate dibasic
heptahydrate – mg
Sodium phosphate
monobasic monohydrate 31.2 mg."

It now reads,

"Each vial contains
Alglucosidase alfa 52.5 mg,
Mannitol 210 mg,
Polysorbate 80 0.5mg,
Sodium Phosphate Dibasic
Heptahydrate 9.9 mg,
Sodium Phosphate
Monobasic Monohydrate 31.2mg."

This is consistent with the package insert.

D. Per FDA suggestion, the trailing zeros have been removed. The label read,

"Following reconstitution with 10.3 mL … a total extractable volume of 10 mL and 5.0 mg/mL."

It now reads,
"Following reconstitution with 10.3 mL … a total extractable volume of 10 mL and 5.0 mg/mL."

Conclusions

The proposed carton and vial labeling revisions are acceptable.

4/27/06

Cristi L. Stark, M.S.
Regulatory Project Manager

PM LABELING REVIEW

A

3 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

1 § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Thursday, April 27, 2006 4:04 PM
To: Stark, Cristi L
Subject: Myozyme cover letter
Attachments: seq 0020 coverletter.pdf; emfinfo.txt

Dear Cristi,

Attached is a PDF copy of the cover letter for yesterday's submission containing the final labeling and post-marketing commitments.

Fed Ex tracking information indicates that the submission has been delivered to the Doc Control room.

Let me know if you need anything else.

Kind regards,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

genzyme

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
T 617-252-7500

April 26, 2006

Ms. Cristi Stark
Regulatory Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: Biologics License Application 125141/0 Myozyme® (acid alpha–glucosidase)
Recombinant Human Acid Alpha-Glucosidase (rhGAA)
Amendment 0020: Final product labeling and post-marketing commitments

Dear Ms. Stark:

Reference is made to our Biologics License Application (BLA) for Myozyme® (alglucosidase alfa) for the treatment of Pompe disease that was submitted to the Agency on 28 July 2005 (STN 125141/0). Further reference is made to our teleconference of 25 April 2006 regarding the post-marketing commitments for Myozyme.

As discussed during our teleconference, enclosed please the final list of 24 post-marketing commitments for Myozyme which Genzyme agrees to fulfill in accordance with the timelines indicated for each commitment. Also enclosed is the finalized package insert for Myozyme which has been provided in Microsoft Word, Adobe PDF and Specified Product Labeling format.

Finally, I have provided a revised mock-up of the carton for Myozyme. The carton has been revised from the version submitted to the BLA on 12 April 2006 (see Sequence 0017) to provide a listing of ingredients contained in each vial of Myozyme consistent with the final package insert.

Please contact me at 617-768-6704, or Betty Wiley at 617-768-6699, with any questions regarding this submission.

Sincerely,

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs
Ph: 617-768-6704
Fax: 617-768-6419
jennifer.panagoulias@genzyme.com

A1

5 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Wednesday, April 26, 2006 4:56 PM
To: Stark, Cristi L
Cc: Wiley, Betty
Subject: Tracking information for Myozyme Amendment
Attachments: emfinfo.txt

Dear Cristi,

Sequence 0020 to BLA 125141/0 has been sent to you today via Federal Express. This amendment contains the final product labeling and post-marketing commitments for Myozyme. The shipping information is as follows:

Tracking no: —

Please let me know if there is anything that remains outstanding our our end.

Thanks,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 25, 2006

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Telecon

PARTICIPANTS:

CDER: Cristi Stark, Jasti Choudary Julie Beitz, Brian Harvey, Jean Temeck, Anil Rajpal, Anne Pariser, Fred Mills, Gibbes Johnson, Jin Hai Wang

Genzyme: Richard Moscicki, Alison Lawton, Alex Kuta, Betty Wiley, Jennifer Panagoulias, Deya Corzo, Edward Kaye, Claire Morgan, MaryAlice Worden, Nancy Silliman, Paul Merrigan, David Meeker, Brian Conner, Wytske Kingma, Jennifer Hunt, Alison McWylie

A telecon for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides treatment of patients with a confirmed diagnosis of Pompe disease (GAA deficiency), was held on April 25, 2006.

This telecon was held to reach concurrence regarding post marketing commitments.

FDA: Since we have made a few changes to the post marketing commitments lets start again from the beginning. Does Genzyme concur with the proposed language in #1?

Genzyme: Commitments 1 through 7 we concur with. Lets skip the pharm/tox and head on to the product commitments. Commitments 14 – 22 we made a few changes by adding dates. Does FDA concur with these dates?

FDA: We are in agreement. In regards to commitment #23, is it mediated by IgG antibody?

Genzyme: Yes.

FDA: Ok then we are fine with #23 and #24. Now moving back to the pharm/tox commitments, we have discussed #8 internally and agree that if necessary pre-treatment with diphenhydramine (DPH) is ok. Please allow for two control groups: one as a control by itself, and one with the antihistamine.

Genzyme: Please note that we have data with mice up to 14-weeks with pre-treatment. Even with pre-treatment of DPH there is severe loss (approximately 30%). This may be an issue when trying to run the chronic study.

FDA: We understand this; however, we will find this out in the study.

Genzyme: We are struggling with the idea of this study as the cost is extensive. This study can cost us in the upwards of —

FDA: We are sensitive to these issues and are trying to move forward with the minimum number of pre-clinical tests.

Genzyme: If we find during treatment that we are running into mortality issues, how do we proceed?

FDA: If you find issues with mortality we would like to hear from you. We can then discuss the issue.

Genzyme: Please note that in the 16-week efficacy study we saw almost a 30% mortality. We will agree at this time to #8 and revisit the issue later if we have mortality issues.

FDA: We do recommend you use the maximum feasible dose in your study,

Genzyme: Ok.

FDA: Lets move on to commitment #9. What are the outcomes of this study?

Genzyme: This is for strength and administration. In the female only study we found no observed effect.

FDA: Ok. Lets move on to commitment #10. Do you agree?

Genzyme: We will attempt in the dose-ranging study to not pretreat with DPH. If an issue arises we will notify the Agency and work from there.

FDA: Ok. In regards to #11 do you concur?

Genzyme: Agreed.

FDA: In regards to #12 do you concur with the FDA proposed changes?

Genzyme: Agreed.

FDA: In regards to #13 do you concur? Please note that as long as you have a group with DPH alone, it will be useful with interpreting data to see if there is an effect.

Genzyme: We would rather
instead of performing the study.

FDA: We feel that the current label is balanced. Unless there is data supporting that labeling we cannot place it in. Looking at the bigger picture, this study becomes important to an approval of all indications.

Genzyme: Ok. Do you agree with our proposed timelines?

FDA: The timelines are acceptable. Also you noted that you will perform the study in rats and not mice?

Genzyme: Correct.

FDA: Moving back to commitment #6, we agree to the proposed language. Just note that our product division is anxious to see the data. Does Genzyme concur with #6?

Genzyme: Yes.

FDA: Ok, all post marketing commitments are concurred upon. The label that was sent on Friday, April 21, 2006 was concurred upon. Genzyme needs to send the concurred upon labeling and post marketing commitments to the BLA prior to the action date. In addition, please send the required items by secure messaging to the project manager. Also include the FedEx tracking number to the project manager so that we can track the submission and ensure delivery at the document room.

Genzyme: Now that we have concluded, we have one additional comment we would like to bring up. In the future we would like to consider commitments #5 and #7

FDA: We can discuss this in the future but there are legal issues here as well.

The call ended.

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Tuesday, April 25, 2006 4:12 PM
To: Stark, Cristi L
Cc: Wiley, Betty
Subject: Labeling and PMCs STN 125141/0
Attachments: FINAL PI 4_25_06.doc; FINAL PI 4_25_06.pdf; Final PMCs April_25_06.doc; Final PMCs April_25_06.pdf; 6828 r12 Myozyme Ctn.pdf; emfinfo.txt

Dear Cristi,

Pursuant to our telephone conversation of today, attached please find the following items:

1. Final labeling for Myozyme provided in Word and PDF formats;
2. Final list of post-marketing commitments provided in Word and PDF formats; and
3. PDF version of Myozyme carton.

I will submit an amendment to BLA 125141/0 tomorrow which contains SPL, Word and PDF versions of the final labeling, along with the final list of PMCs. I will forward you the Federal Express tracking number for the submission as soon as it it mailed.

In the interim, would you please confirm receipt of this submission?

We look forward to hearing from you on Friday with respect to FDA's action on the Myozyme BLA.

Kind regards,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

B

23 Page(s) Withheld

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___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Monday, April 24, 2006 4:51 PM
To: Stark, Cristi L
Cc: Wiley, Betty
Subject: RE: current PI and PMCs:STN 125141/0:Myozyme
Attachments: Genz revised DraftPMCs April_24_062.doc; emfinfo.txt

Dear Cristi,

Attached are revised PMC's per our discussion today. As discussed during our teleconference, we have added further comments to the nonclinical commitments. In addition to the changes we discussed, we have updated numbers 14, 19, 23 and 24.

Speak to you tomorrow.

Thanks,
Jennifer

-----Original Message-----
From: Stark, Cristi L [mailto:cristi.stark@fda.hhs.gov]
Sent: Friday, April 21, 2006 4:30 PM
To: Panagoulias, Jennifer
Cc: betty.wiley@genzyme.com
Subject: current PI and PMCs:STN 125141/0:Myozyme

Good afternoon Jennifer and Betty,

Attached is the current PI as it stands with FDA. Also we have attached our full list of PMCs with comments. The PMCs are listed in bold and separated by web-reportable and non web-reportable. There are a total of 24 PMCs.

Please note that due to the fact that your action is one week away, the label as sent is the final draft. Our negotiations set for Monday should now focus around the PMCs.

<<labeling changes sent to Genzyme on 4_21_06.doc>> <<DraftPMCs April_21_06.doc>>

Please confirm receipt.

Thanks,
Cristi

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___ § 552(b)(5) Deliberative Process

1 § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 24, 2006

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Telecon

PARTICIPANTS:

CDER: Cristi Stark, Jasti Choudary Joyce Korvick, Julie Beitz, Brian Harvey, Jean Temeck, Anil Rajpal, Anne Pariser, Lisa Kammerman, Fred Mills, Gibbes Johnson, Amy Rosenberg, Jin Hai Wang

Genzyme: Richard Moscicki, Alison Lawton, Alex Kuta, Betty Wiley, Jennifer Panagoulias, Deya Corzo, Edward Kaye, Claire Morgan, MaryAlice Worden, Nancy Silliman, Paul Merrigan, David Meeker, Brian Conner, Wytske Kingma, Jennifer Hunt, Alison McWylie

A telecon for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides treatment of patients with a confirmed diagnosis of Pompe disease (GAA deficiency), was held on April 24, 2006.

This telecon was held to reach concurrence regarding the package insert and post marketing commitments.

Genzyme: We are in agreement with all FDA proposed changes to the package insert except the indication. We have sent you an email outlining 3 new proposals for the wording of the indication.

INDICATIONS AND USAGE:

FDA: This past Friday we had internal discussions and feel the label reflects the data correctly. Based upon the regulations, the data, and the past precedents, we feel the indication statement is justified. We are concerned with your most recent proposals as they are heading in the wrong direction. As of this past Friday the label has been sent up the chain. If you feel the label is not adequate, do you want to consider a future cycle?

Genzyme: We do have concerns about [redacted] in the boxed warning. Also we believe that the current indication will limit access to patients based on reimbursement.

FDA: Your current proposed options are variations on a theme we have seen earlier. Based on the current data we could only indicate for the infantile-only population. This is outside our team's current comfort level.

Genzyme: We accept your idea; however, some of the proposed wording may help with the [redacted]

FDA: You are speaking about the third option. The concern with that option is that it only emphasizes the benefits.

Genzyme: What if we say risks and benefits?

FDA: We have gone over the label internally and this is where we stand. The current label is based on the data that have been submitted. These three options you submitted do not meet our criteria based upon the data. The proposal we sent you on Friday was our final label.

Genzyme: We hear your points. At this time we will leave the label as it was sent on Friday.

FDA: We do look forward to future data and can remove and/or change the labeling later as the data reflect.

Now lets move on to post marketing commitments. Where does Genzyme stand on the proposals for #1 and #2?

Genzyme: We are currently looking at We will submit a protocol soon. If the clinical study goes out , then we will

In regards to #3 and #4, we agree with the proposed wording.

In regards to #5, there are some practical issues here. We think we can

We propose to leave the commitments as written and send a protocol in September. Once the protocol is in, we can have ensuing discussions with the Agency and examine the issue again.

FDA:

The post marketing commitments will stay as written. You can submit your protocol in September with your proposals. We will then review and discuss your proposal.

Please also note that when you are reporting growth assessments for infants less than 18 months of age, we need growth assessments by chronological age and corrected for gestational age.

Genzyme: We acknowledge and agree. We agree to leave #5 and #7 as written but will submit

to handle these commitments.

FDA: No. Commitments #5 and #7 will remain as written and when you submit your protocol we will review and discuss with you if We are not agreeing at this time, but agree to receive and review your proposal.

Genzyme: In regards to #6 we do plan to have an effective regimen preclinically. We can submit these results in support of clinical use.

FDA: What additional kinds of animal studies will be helpful? What is already out there gives us all knowledge from animals.

Genzyme: The currently available animal studies do not necessarily work with Myozyme. Some of the other regimens that work with other products, do not work with Myozyme. Our most effective regimen thus far is — We do have studies in-house and would like to submit our data to support this. We are looking at a CRIM negative protocol using — at suitable levels.

FDA: Ok, if this is how you choose to move forward, we have no choice, but we urge you to consider less toxic experimental agents.

Genzyme: We will submit a timeline and a statement that at a later date we will submit an outline for the clinical protocol to be added as an additional post marketing commitment.

In regards to #7, we have talked internally and will send a date for the protocol by close of business today.

FDA: ok

Genzyme: In regards to #8, what is the rationale? This is a foreign protein in rodents and will lead to an immune response.

FDA: You do not have any rodent studies beyond 4 weeks. We understand you will get an immune response; however, you get an immune response in all species, including humans.

Genzyme: The rodents develop anaphylactic reactions to Myozyme. Unless we pretreat with diphenhydramine they will die. Even with pretreatment we lose 30% of the animals.

FDA: Unfortunately we will table this conversation. Our time is up and we will finish discussion tomorrow at 9:00am EST.

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: April 21, 2006

To: Administrative File, STN 125141/0, and 125141/0/10

From: Nicholas Buhay, Acting Division Director, CDER/OC/DMPQ, HFD-320 04/21/06

Through: Tia Harper-Velazquez, Pharm.D., Project Manager, CDER/OC, HFD-300 4/21/06

Subject: Division Director Memo: Biological License Application (BLA): New BLA

US License #1596

Applicant Genzyme Corporation

Product Alglucosidase alfa (Myozyme®)

Indication —

Due date: April 28, 2006

Recommendation: The Office of Compliance has reviewed the information submitted, and concurs with the recommendation of approval for this Biological License Application, as amended, under 21 CFR 601.

Cc: HFD-328: Brenda Uratani
HFM-328: Michelle Clark-Stuart
HFD-328: TFRB Blue Files (STN 125141)

Original to be forwarded to:
Bronwyn Collier
Associate Director for Regulatory Affairs
FDA/CDER/ODE II

Archived File: S:\125141\125141.0.rev.mem.div.dir.04-21-06

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Friday, April 21, 2006 3:40 PM
To: Wang, Jin Hai
Cc: Stark, Cristi L; Wiley, Betty
Subject: Myozyme STN 125141/0
Attachments: emfinfo.txt

Dear Dr. Wang,

Per our conversation with Dr. Rosenberg today, below is Genzyme's proposed post-marketing commitment regarding the antibody uptake inhibition assay.

Genzyme commits to [redacted]. In addition, Genzyme commits to analyze sera from all patients in Studies 1602 and 1702, as well all patients in clinical studies or the expanded access program for Myozyme who have become invasively ventilated since February 2, 2006, and provide these data to FDA by [redacted], 2006.
We will add this to the formal commitments to be submitted to the BLA next week.

Please let me know if you have any questions.

Sincerely,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

Stark, Cristi L

From: Hoyt, Colleen
Sent: Thursday, April 20, 2006 10:25 AM
To: Stark, Cristi L; Merritt, Babette A
Subject: RE: compliance check needed asap (it expires several days before the first action):STN 125141/0

Hi Cristi - hope all is well with you and the baby!

There have been no changes in the compliance status of the firms listed below since the issuance of the last compliance check.

Colleen

From: Stark, Cristi L
Sent: Monday, April 17, 2006 3:38 PM
To: Hoyt, Colleen; Merritt, Babette A
Cc: Harper Velazquez, Tia M
Subject: compliance check needed asap (it expires several days before the first action):STN 125141/0
Importance: High

Good afternoon Colleen and Babette,

I need a compliance check run once more on original BLA STN 125141/0 (unfortunately the last check expires shortly before the action date). We will be taking a formal action (approval and license issuance) on April 28, 2006. Please complete this compliance check by April 24, 2006. Note: Nothing should change as this is after the PAI; however, I am just covering bases. This is STN 125141/0, Alglucosidase alfa or MYOZYME, for the treatment of Pompe disease. The license number is 1596 (this is not approved yet). The manufacturing sites are as follows:

Genzyme Corporation
Allston Landing Facility
500 Soldiers Field Road
Allston, MA 02134
FEI#: 1000305672

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
FEI#: 1220423

Genzyme Corporation
80 New York Avenue
Framingham, MA 01701
FEI#: ?

Genzyme Corporation
45 New York Avenue
Framingham, MA 01701
FEI#: ?

Genzyme Corporation
76 New York Avenue
Framingham, MA 01701
FEI#: ?

Genzyme Corporation
51 New York Avenue
Framingham, MA 01701
FEI#:?

Genzyme Corporation
74 New York Avenue
Framingham, MA 01701
FEI#:?

Thanks,
Cristi

Appears This Way
On Original

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Thursday, April 20, 2006 10:14 AM
To: Stark, Cristi L
Cc: Wiley, Betty
Subject: Package Insert STN 125141/0
Attachments: labeling changes from Genzyme 4_20_06.doc; emfinfo.txt

Dear Cristi,

Attached is a revised package insert with changes and comments from Genzyme. I have provided the document to you in red-line mode. Please let me know if you need any additional information from Genzyme. We look forward to receiving your further comments on Friday and to speaking with you on Monday.

Sincerely,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

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21 Page(s) Withheld

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✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Friday, April 14, 2006 3:12 PM
To: Stark, Cristi L
Cc: Wiley, Betty
Subject: STN 125141/0 label materials
Attachments: coverletter A0017 4-12-06.pdf; emfinfo.txt

Dear Cristi,

Attached is the revised carton and vial label for Myozyme. Font sizes are indicated in the cover letter. The full amendment was submitted on Wednesday. Please let me know if you have any questions.

Have a nice weekend,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

genzyme

Genzyme Corporation
500 Kendall Street
Cambridge MA 02142
T 617-252-7500

April 12, 2006

Ms. Cristi Stark
Regulatory Project Manager
Center for Drug Evaluation and Research
CDER Therapeutics Biologic Document Control Room
U.S. Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Biologics License Application 125141/0 Myozyme® (alglucosidase alfa), Recombinant Human Acid Alpha-Glucosidase (rhGAA)
Sequence 0017: Response to FDA Request for Information

Dear Ms. Stark:

Reference is made to our Biologics License Application (BLA) for Myozyme® (alglucosidase alfa), recombinant human acid alpha-glucosidase (rhGAA) for the treatment of Pompe disease submitted to the Agency on July 28, 2005 (STN 125141/0).

Enclosed is correspondence in response to a request for information regarding patients who were tested for IgE antibodies. Specifically there are MedWatch reports for 2 IgE positive patients, a tabular listing of test results for all patients who underwent specialty testing and communications between Genzyme and the Allergic Reaction Review Board (ARRB). These items were previously submitted via email to Dr. Pariser.

Also provided in this submission are revised mock-ups of the Myozyme carton and vial label. Per your request, the statement, "Protect from light", has been added to both the carton and vial label. In addition, tradename and generic name font sizes are revised as follows:

Carton

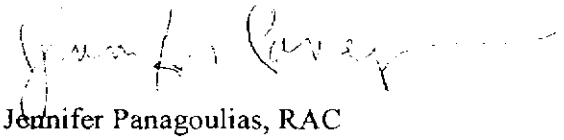
- Tradename: 13.2 points
- generic name: 11 points

Vial label

- tradename: 14.2 points
- generic name: 11.5 points

Please contact me at 617.768.6704 or Betty Wiley at 617.768.6699 with any questions regarding this submission.

Sincerely,



Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs

D

3 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Thursday, April 13, 2006 5:12 PM
To: Stark, Cristi L
Subject: Revised Package Insert STN 125141/0
Attachments: 4-13-06 revised labeling from Genzyme.doc; emfinfo.txt

Dear Cristi,

Attached is the revised PI for Myozyme. As Alison noted during our teleconference this morning, Genzyme has made changes to the WARNINGS and Adverse Reactions sections. Specifically, we have included the language that FDA originally proposed regarding anaphylaxis.

If you have any questions, please do not hesitate to call me.

Kind regards,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

E

19 Page(s) Withheld

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___ § 552(b)(5) Deliberative Process

√ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Wiley, Betty [Betty.Wiley@genzyme.com]
Sent: Thursday, April 13, 2006 10:33 AM
To: Stark, Cristi L
Cc: Panagoulias, Jennifer
Subject: Myozyme - BLA STN 125141 - Post Marketing Commitments
Attachments: comments-v3_DraftPMCs April_13_06.doc; emfalert.txt

Hi Cristi,

Attached are Genzyme's comments for the post-marketing commitments. Proposed changes are in track-changes mode. I wanted to get these to you before our conference call today at 11:00 am. I assume that we will need to set up a separate conference call early next week to further discuss our comments.

Speak to you soon

Sincerely,

Betty Wiley, Director, Regulatory Affairs
Genzyme Corporation
phone 617-768-6699
fax 617-768-6420

F

4 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Mills, Frederick [frederick.mills@fda.hhs.gov]
Sent: Wednesday, April 12, 2006 4:05 PM
To: Stark, Cristi L
Subject: RE: Product PMC for Myozyme

Attachments: v2 ProductPMCs0401206DTP.doc

Hi Cristi,

We had a teleconference with Genzyme this afternoon 3-4 pm, in which we disccused this draft, which I've sent to Lesie Rhubin. The schedule is that they will get back to us with a letter-ready version on Monday, April 17, sending to me, Ralph Bernstein, and you. Presumably we're getting quite close to finalizing.

I'll out of town from tomorrow through Monday morning visitng my father and other elderly relatives in Ohio. Talk Monday, probably,

Best wishes,
Fred

v2
tPMCs0401206DTP.

-----Original Message-----
From: Stark, Cristi L
Sent: Friday, April 07, 2006 5:41 PM
To: Mills, Frederick
Cc: Cherney, Barry; Rosenberg, Amy; Johnson, Gibbes; Bernstein, Ralph
Subject: RE: Product PMC for Myozyme

Thanks Fred! I will be in touch with everyone early next week. The plan is as follows:

-COB Monday Genzyme will send me all items they concur on and all items of which they still have issues (along with their justification)
-I will circulate this to the team to prepare for our upcoming telecon (Wed, 4/12)
-Wed, 4/12, our labeling meeting is going to be used to discuss outstanding label (and if time, PMC) issues with Genzyme
-by close of next week we hope to have all reviews in and reach a consensus to alert the press office to start work on the release and test paper

Thanks,
Cristi

From: Mills, Frederick [mailto:frederick.mills@fda.hhs.gov]
Sent: Friday, April 07, 2006 5:34 PM
To: Stark, Cristi L
Cc: Cherney, Barry; Rosenberg, Amy; Johnson, Gibbes; Bernstein, Ralph
Subject: Product PMC for Myozyme

Hi Cristi,

Here is Genzyme's draft of the PMCs, and our revised draft, which was edited to correspond to our understandings from our telecon this afternoon from 3:30-4:30 pm. Although it would ideally be communicated through you, in the interest of Genzyme working on this over the weekend we sent our draft by secure email this evening at 5:10 pm. We'll communicate the remaining drafts through you.

Thanks for you patience,

Stark, Cristi L

From: Rhubin, Leslie [Leslie.Rhubin@genzyme.com]
Sent: Tuesday, April 11, 2006 11:33 AM
To: Mills, Frederick
Cc: Stark, Cristi L
Subject: Suggested Edits Myozyme PMCs

Importance: High

Attachments: emfinfo.txt

emfinfo.txt (699 B)

Hi Dr. Mills,
As discussed, the suggested changes are in track changes. Rationales and other comments are provided using the "comments" feature. Please call me if there are any technical issues with the file.
Thanks,
Leslie
RA CMC, Genzyme Corporation
Framingham, MA 01701
508 271-3940

6

5 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Monday, April 10, 2006 5:28 PM
To: Stark, Cristi L
Subject: RE: STN 125141/0 label revisions and PMCs
Attachments: 4-10-06 revised labeling from Genzyme.doc; clean 4-10-06 revised labeling from Genzyme.doc; emfinfo.txt

Dear Cristi,

Attached is the revised labeling from Genzyme following our latest review. I have enclosed two versions; a copy in red-lined mode which notes changes made by Genzyme to the file received from FDA on 4-7-06 along with comments which explain our changes and/or questions, and a clean copy with only our comments/question in the margin. Please let me know if you need any additional information for our teleconference on Wednesday. Would you please confirm receipt of this message?

Thank you,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corp.
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

-----Original Message-----
From: Stark, Cristi L [mailto:cristi.stark@fda.hhs.gov]
Sent: Friday, April 07, 2006 5:25 PM
To: Panagoulias, Jennifer
Cc: betty.wiley@genzyme.com
Subject: STN 125141/0 label revisions and PMCs
Importance: High

Good afternoon Jennifer and Betty,

Attached are the FDA revisions to the label Genzyme sent on March 31, 2006. In addition, the post marketing commitment language is included as a second attachment (drug substance/drug product are not included--they will be sent separately). Please meet with your group and let me know what Genzyme concurs with and where there are issues regarding labeling and PMCs. In identifying the issues, please give us a brief justification so that we can prepare our responses for the telecon on Wednesday. Also please give us the call-in number and passcode for our teleconference on Wednesday (4/12/06 from 10:00-11:00am EST).

<<labeling changes sent to Genzyme on 4_7_06.doc>> <<DraftPMCs April_07_06.doc>>
Thanks,
Cristi Stark

4

19 Page(s) Withheld

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___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Mills, Frederick [frederick.mills@fda.hhs.gov]
Sent: Friday, April 07, 2006 5:34 PM
To: Stark, Cristi L
Cc: Cherney, Barry; Rosenberg, Amy; Johnson, Gibbes; Bernstein, Ralph
Subject: Product PMC for Myozyme

Attachments: PMC-Draft.pdf; ProductPMCs040706.doc

Hi Cristi,

Here is Genzyme's draft of the PMCs, and our revised draft, which was edited to correspond to our understandings from our telecon this afternoon from 3:30-4:30 pm. Although it would ideally be communicated through you, in the interest of Genzyme working on this over the weekend we sent our draft by secure email this evening at 5:10 pm. We'll communicate the remaining drafts through you.

Thanks for you patience,
Fred


PMC-Draft.pdf (81 KB)


ProductPMCs040706.doc (63 KB)

Stark, Cristi L

From: Rhubin, Leslie [Leslie.Rhubin@genzyme.com]
Sent: Thursday, April 06, 2006 1:24 PM
To: Mills, Frederick
Cc: Stark, Cristi L
Subject: PMC draft and Conf. Call Number

Attachments: PMC-Draft.pdf; emfinfo.txt


PMC-Draft.pdf (78 KB)


emfinfo.txt (699 B)

Hi Dr. Mills,

Attached please find draft language for Myozyme product PMCs for discussion at tomorrow's (4/7) telephone call. The call-in number for our 3:30 pm call tomorrow is provided below.

US - 866-732-4932
Passcode - 194907

Please call me with any questions.
Regards,
Leslie
RA CMC, Genzyme Corporation
Framingham, MA 01701
508 271-3940

I

3 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

genzyme

Genzyme Corporation
15 Pleasant Street Connector
Metrowest Place
Framingham, MA 01701-9322
T 508-872-8400
F 508-271-2692

April 06, 2006

Frederick Mills, Ph. D.
DHHS/FDA/CDER/OPS/OBP/DTP
NIH Campus Building 29A,
9000 Rockville Pike, HFD-122
Rockville, MD 20892

RE: Biologics License Application 125141/0 Myozyme® (alglucosidase alfa), Recombinant Human Acid Alpha-Glucosidase (rhGAA)- CMC Post-Approval Commitments

Dear Dr. Mills:

As briefly discussed in the March 6, 2006 teleconference between Genzyme and representatives from the Division of Therapeutic Proteins (DTP) and pursuant to your telephone message of March 24, 2006, please find draft language for the proposed CMC post-approval commitments:

J

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___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

3/31/06

Division of Gastroenterology Products

PROJECT MANAGER'S REVIEW

Application Number: STN 125141/0

Name of Drug: Alglucosidase alfa

Sponsor: Genzyme Corporation

Material Reviewed:

Submission Date: July 28, 2005 – original Carton and Vial Draft Labeling

Receipt Date: July 28, 2005

Background and Summary

STN 125141/0 for Alglucosidase alfa is an original application intended as an enzyme replacement therapy for patients with Pompe disease who are deficient in or lack the endogenous enzyme, acid alpha-glucosidase (GAA). The sponsor proposed indication for

Review

I. Vial

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
   a. The proper name of the product –Alglucosidase alfa is displayed along with the proprietary name, Myozyme. This conforms to the regulation.

   b. The name, address, and license number of the manufacturer – Genzyme Corporation is the manufacturer. The correct address per the 356h is listed. The license holder, XXXX, is listed underneath the address. In addition the license holder is listed on the bottom right corner of the label. This conforms to the regulation.

   c. The lot number or other lot identification – The lot number is located next to the proper name of the product. This conforms to the regulation.

   d. The expiration date – The expiration date is located below the lot number. This conforms to the regulation.

e. The recommended individual dose, for multiple dose containers – This is for intravenous infusion (to be reconstituted) and for single use only. The statement "For single use only" is located at the top left of the label. This conforms to the regulation.

f. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the top right of the label. This conforms to the regulation.

g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – A Medication Guide is not required under 208.1 as this will not be used on an outpatient basis without direct supervision by a health professional. Therefore, this package label does not need to conform to the regulation.

2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This section does not apply.

3. 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. – The container bears a full label. Please see comments under items 1 (a) - (g) above.

4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a full label. Please see comments under items 1 (a) – (g) above.

5. Visual inspection. When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – A 20 cc. vial will be used for containing the drug. The label length is approximately 3 3/8'' and the vial circumference is approximately 3 ¾''. Therefore, the label gap is 3/8''. The gap runs the entire length of the vial to permit visual inspection of the contents. This conforms to the regulation.

B. 21 CFR 610.61 Package label – This is a container label. Therefore, this does not need to

conform to the regulation.

C. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulations including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This is under one of the four categories of a "specified" biological product: Therapeutic DNA plasmid products; Therapeutic synthetic peptide product of 40 or fewer amino acids, Monoclonal antibody products for in vivo use; and Therapeutic recombinant DNA-derived products. Therefore the label does not need to conform to this regulation.

D. 21 CFR 610.63 Divided manufacturing responsibility to be shown – This only has one manufacturer, Genzyme Corporation. Therefore, the label does not need to conform to this regulation.

E. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by ____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. – The distributor is Genzyme Corporation which is also the manufacturer. All manufacturing information is labeled correctly and conforms with 21 CFR 610.60. Therefore, this conforms with the regulation.

F. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.

G. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – The barcode is located on the left of the label. This conforms with the regulation.

H. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor – Genzyme Corporation is the manufacturer, packer, and distributor. The label requirement conform to 21 CFR 610.60. Therefore, this conforms to the regulation.

I. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58468-XXXX-X. The NDC number conforms to 21 CFR 207.35 as a 4-1 Product-Package Code configuration. This conforms to the regulation.

J. 21 CFR 201.5 Drugs; adequate directions for use - On the left of the label the statement "See package insert for dosage and administration" appears. This conforms to the regulation.

K. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary name, Myozyme, and the established name, Alglucosidase alfa. Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.

L. 21 CFR 201.10 Drugs; statement of ingredients – The proprietary name is used in a larger size text when compared to the established name. The proprietary name, Myozyme, is size 15.25 pt font. The established name, Alglucosidase alfa, is size 7.7 pt font. Alglucosidase alfa is used in type at least half as large as the most prominent presentation of Myozyme. This conforms to the regulation.

M. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements ("Rx Only," "For Intravenous Infusion Only," "For single use only," "Store refrigerated at 2-8°C") are prominent and do not overlap. This conforms to the regulation.

N. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot identification number on the right portion of the label. This conforms to 21 CFR 610.60. In addition, as per 21 CFR 211.166 the storage conditions are stated (Store refrigerated at 2-8°C (36-46°F). This conforms to the regulation.

O. 21 CFR 201.25 Bar code label requirements – The bar code is located on the left of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

P. 21 CFR 201.50 Statement of identity – The established name, Alglucosidase alfa, is stated on the label. The established name and proprietary name, Myozyme, conform to 21 CFR 201.10. This conforms to the regulation.

Q. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents as 50mg directly under the proprietary and established name. This conforms to the regulation.

R. 21 CFR 201.55 Statement of dosage – The label states "See package insert for dosage and administration." This conforms to the regulation.

S. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only," "For Intravenous Infusion Only," an identifying lot number, storage conditions, and reference to the package insert. Photostability studies are not complete for Alglucosidase alfa. Please refer to the chemistry, manufacturing, and controls reviews. An additional statement, "Protect from Light," will need to be added to the label in order to conform with the regulation.

II. Carton

A. 21 CFR 610.60 Container Label – This is a package label. Therefore, this does not need to conform to the regulation.

B. 21 CFR 610.61 Package Label

a. The proper name of the product – The proper name, Alglucosidase alfa, is displayed on the front and back of the carton. In addition the proprietary name, Myozyme, is displayed prominently on the front and back of the carton. This conforms to the regulation.

b. The name, address, and license number of manufacturer – Genzyme corporation is the manufacturer. The correct address is listed on the side of the carton (the far right on the pdf layout). The license number is listed with the license number holder, XXXX, directly below the address. A second license number holder is listed on the side, bottom flap of the carton. This conforms to the regulation.

c. The lot number or other lot identification – The lot number is listed on the bottom flap of the carton. This conforms to the regulation.

d. The expiration date – The expiration date is listed below the lot number on the bottom flap of the carton. This conforms to the regulation.

e. The preservative used and its concentration, of if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative" – There are no preservatives used in the drug. The statement "Contains No Preservatives" is displayed on the front, center of the carton. This conforms to the regulation.

f. The number of containers, if more than one – There is only one package container per drug. Each package contains one vial of drug. The statement "Package contains one vial of" is listed on the front, top of the carton. This conforms to the regulation.

g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – It is prominently listed as 50 mg on the front, back, and top flap of the carton. In addition, the ingredients of the vial are listed on the side flap in the top 1/3. The amount of product following reconstitution is listed on the side flap in the bottom 1/3. This conforms to the regulation.

h. The recommended storage temperature – The statement "Store refrigerated at 2-8C (36-46F)" is on the front of the carton under the proprietary and established name.

Please refer to the chemistry, manufacturing, and controls review regarding appropriate storage temperature. This conforms to the regulation.

i. The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; - The statement "Do Not Freeze or Shake" is located on the front, center of the carton. This conforms to the regulation.

j. The recommended individual dose if the enclosed container(s) is a multiple-dose container; - This is for one-time use only. Therefore, this does not apply.

k. The route of administration recommended, or reference to such directions in an enclosed circular; - The statement "For Intravenous Infusion Only" is located on the back and side flap of the carton. In addition, the statement "See package insert for dosage and administration" is located on the front of the carton at the bottom. This conforms to the regulation.

l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information; - The statement "See package insert for dosage and administration" is located on the front of the carton at the bottom. Photostability studies are not complete for Alglucosidase alfa. Please refer to the chemistry, manufacturing, and controls reviews. An additional statement, "Protect from Light," will need to be added to the label in order to conform with the regulation.

m. The type and calculated amount of antibiotics added during manufacture; - There are no antibiotics added during manufacture. Please refer to chemistry, manufacturing, and controls reviews. Therefore, this regulation does not apply.

n. The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information; - The statement "Each vial contains…" is located on the side of the carton. In addition, the statement "See package insert for dosage and administration" is located on the front, bottom of the carton. This conforms to the regulation.

o. The adjuvant, if present; - There are no substances that modify the effect of the drug, thereby enhancing the pharmacological effect. Please refer to the chemistry, manufacturing, and control reviews for all substances in manufacture. Please refer to the clinical pharmacology review for the pharmacological effect of the drug. This conforms to the regulation.

p. The source of the product when a factor in safe administration; - Directions for aseptic technique and administration are contained in the package insert. The statement "See package insert for dosage and administration" is located on the front

of the carton at the bottom. This conforms to the regulation.

q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; - The statement "See package insert for dosage and administration" is located on the front of the carton at the bottom. This conforms to the regulation.

r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency." – The statement "No U.S. Standard of Potency" is located on the front of the carton at the bottom. This conforms to the regulation.

s. The statement: "'Rx only'" for prescription biologicals. – The statement "Rx Only" is located on the back and side of the carton. This conforms to the regulation.

C. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulations including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This is under one of the four categories of a "specified" biological product: Therapeutic DNA plasmid products; Therapeutic synthetic peptide product of 40 or fewer amino acids, Monoclonal antibody products for in vivo use; and Therapeutic recombinant DNA-derived products. Therefore the label does not need to conform to this regulation.

D. 21 CFR 610.63 Divided manufacturing responsibility to be shown – This only has one manufacturer, Genzyme Corporation. Therefore, the label does not need to conform to this regulation.

E. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. – The distributor is Genzyme Corporation which is also the manufacturer. All manufacturing information is labeled correctly and conforms with 21 CFR 610.60. Therefore, this conforms to the regulation.

F. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.

G. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter.

– The barcode is located on the top flap and side of the label. There is sufficient surrounding white space to allow for scanning. This conforms to the regulation.

H. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor – Genzyme Corporation is the manufacturer, packer, and distributor. The label requirement conform to 21 CFR 610.60. Therefore, this conforms to the regulation.

I. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located above the proprietary name on the back of the carton. In addition it is listed directly under the large barcode on the side of the carton. It is noted as NDC 58468-XXXX-X on the back of the carton and as 58468XXXXX under the barcode. The NDC number conforms to 21 CFR 207.35 as a 4-1 Product-Package Code configuration. This conforms to the regulation.

J. 21 CFR 201.5 Drugs; adequate directions for use - On the front, bottom of the carton the statement "See package insert for dosage and administration" appears. This conforms to the regulation.

K. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary name, Myozyme, and the established name, Alglucosidase alfa. Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.

L. 21 CFR 201.10 Drugs; statement of ingredients – The proprietary name is used in a larger size text when compared to the established name. The proprietary name, Myozyme, is size 14.22 pt font. The established name, Alglucosidase alfa, is size 7.15 pt font. Alglucosidase alfa is used in type at least half as large as the most prominent presentation of Myozyme. This conforms to the regulation.

M. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements ("Rx Only," "For Intravenous Infusion Only," "For Single Use Only," "Store refrigerated at 2-8C," "Contains No Preservatives," "Do Not Freeze or Shake," "No U.S. Standard of Potency") are prominent and do not overlap. This conforms to the regulation.

N. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot identification number on the bottom flap of the carton. This conforms to 21 CFR 610.60. In addition, as per 21 CFR 211.166 the storage conditions are stated (Store refrigerated at 2-8C (36-46F). This conforms to the regulation.

O. 21 CFR 201.25 Bar code label requirements – The bar code is located on the top flap and side of carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

P. 21 CFR 201.50 Statement of identity – The established name, Alglucosidase alfa, is stated on the label. The established name and proprietary name, Myozyme, conform to 21 CFR 201.10. This conforms to the regulation.

Q. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents as 50mg directly under the proprietary and established name and on the top flap of the carton. A direct listing of what is included in every vial is located on top third of the side of the carton. On the bottom third of the side of the carton are the net quantity after reconstitution. This conforms to the regulation.

R. 21 CFR 201.55 Statement of dosage – The label states "See package insert for dosage and administration." This conforms to the regulation.

S. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only," "For Intravenous Infusion Only," an identifying lot number, storage conditions, and reference to the package insert. Photostability studies are not complete for Alglucosidase alfa. Please refer to the chemistry, manufacturing, and controls reviews. An additional statement, "Protect from Light," will need to be added to the label in order to conform with the regulation.

Conclusions

The proposed carton and vial labeling are acceptable only upon the following changes:

-The addition of the statement "Protect from Light" on both the carton and vial labels. The photostability studies are not complete. Please refer to chemistry, manufacturing, and controls reviews. This will conform to 21 CFR 610.61 and 21 CFR 201.100.

-The carton label currently reads, "Each vial contains
alglucosidase alfa ⁻ mg
Mannitol 210
mgpolysorbate 80 0.5 mg
Sodium phosphate dibasic
heptahydrate ⁻ mg
Sodium phosphate
monobasic monohydrate 31.2 mg."

It should read, "Each vial contains
alglucosidase alfa ⁻ mg
Mannitol 210 mg
Polysorbate 80 0.5 mg
Sodium phosphate dibasic
heptahydrate ⁻ mg

Sodium phosphate
monobasic monohydrate 31.2 mg."

It is suggested that all trailing zeros should be deleted from the labeling (e.g., 5.0 mg/mL should read as 5 mg/mL). Please refer to the DMETS review.

The carton label currently reads, "Following reconstitution with 10.3 mL … a total extractable volume of 10 mL and 5.0 mg/mL." It is suggested that this should read, "Following reconstitution with 10.3 mL Sterile Water for Injection, USP, —. — Please refer to the DMETS review.

3/31/06
Cristi L. Stark, M.S.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Brian Strongin, R.Ph., M.B.A.
Brian Strongin, R.Ph., M.B.A 3/31/06
Chief, Project Management Staff

PM LABELING REVIEW

Stark, Cristi L

From: Panagoulias, Jennifer [Jennifer.Panagoulias@genzyme.com]
Sent: Wednesday, March 29, 2006 11:52 AM
To: Stark, Cristi L
Cc: Wiley, Betty
Subject: Myozyme STN 125141/0
Attachments: Myozyme clean package insert 3-29-06.doc; Myozyme red-lined package insert 3-29-06.doc; emfinfo.txt

Dear Cristi,

Per our telephone conversation of today, attached are clean and red-lined versions of the Myozyme package insert. As I mentioned, we have taken the components of the package insert sent to us by FDA on 3-13-06, 3-17-06 and 3-23-06, combined them, and included additional edits following our internal review. You will note these specific changes in the red-lined version of the document. We do have some questions for discussion at our subsequent labeling teleconferences and I will submit these to you by email later today.

Would you please confirm receipt of this message?

If you have any questions, please do not hesitate to contact me.

Kind regards,
Jennifer

Jennifer Panagoulias, RAC
Associate Director, Regulatory Affairs • Genzyme Corporation
500 Kendall Street • Cambridge, MA 02142
617-768-6704 • jennifer.panagoulias@genzyme.com

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__√__ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Stark, Cristi L
Sent: Thursday, March 23, 2006 11:57 AM
To: 'Panagoulias, Jennifer'
Subject: final sections of PI:STN 125141/0:Myozyme

Attachments: labeling changes sent to Genzyme on 3_23_06.doc

Good afternoon Jennifer,

Attached are the final sections of the package insert. The attachment includes: description, laboratory tests (under precautions section), drug interactions (under precautions), carcinogenesis mutagenesis impairment of fertility (under precautions), pregnancy (under precautions), nursing mothers (under precautions)

labeling changes sent to Genzy...

Please confirm receipt of this.

Thanks,
Cristi

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Stark, Cristi L

From: Stark, Cristi L
Sent: Friday, March 17, 2006 4:10 PM
To: 'Panagoulias, Jennifer'
Cc: 'betty.wiley@genzyme.com'
Subject: second set of labeling:STN 125141/0

Attachments: labeling changes sent to Genzyme on 3_17_06.doc

Good afternoon Jennifer,

Attached you will find an additional piece of draft labeling from your package insert. Here is what is included in this email:

DRAFT PI sections sent to Genzyme on 3/17/06: clinical studies, indications and usage, contraindications, warnings, precautions, adverse reactions, overdosage, dosage and administration

labeling changes sent to Genzy...

Please confirm receipt of this.

Note: Below is a listing of what has already been sent out of your package insert and what is currently still under review:

DRAFT PI sections sent to Genzyme on 3/13/06: clinical pharmacology, immunogenicity (under adverse reactions section), instructions for use (under dosage and administration), reconstitution dilution and administration (under dosage and administration), storage (under dosage and administration), how supplied, references

DRAFT PI sections still under review/not sent: description, laboratory tests (under precautions section), drug interactions (under precautions), carcinogenesis mutagenesis impairment of fertility (under precautions), pregnancy (under precautions), nursing mothers (under precautions)

Thanks,
Cristi Stark

M

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Brony, Michael

To: Stark, Cristi L
Subject: RE: STN 125141/0 carton and vial labels

Hi Cristi,

This is just to let you know that DDMAC has no comments on the carton and vial labels.

Thanks

Michael

From: Stark, Cristi L
Sent: Thursday, March 16, 2006 11:27 AM
To: Brony, Michael
Subject: RE: STN 125141/0 carton and vial labels

Ok great. So we are ok with the logo/trademark? Could you send me a hardcopy signed off review so I can refer to it? I am located in White Oak Building 22, room 5137 (HFD-180). In addition I do not have a review for the PI. Could you please check on getting me a hard copy review of that as well? I need to start circulating the action package on Monday. Attached is the current PI where we are at. Debi did make quite a few DDMAC comments on the PI throughout the process.

Thanks,
Cristi

-----Original Message-----
From: Brony, Michael
Sent: Thursday, March 16, 2006 11:04 AM
To: Stark, Cristi L
Subject: RE: STN 125141/0 carton and vial labels

Hi Cristi,

DDMAC has no comments.

Thanks

Michael

From: Stark, Cristi L
Sent: Wednesday, March 15, 2006 12:03 PM
To: Brony, Michael
Subject: STN 125141/0 carton and vial labels

Michael,

Attached are the Alglucosidase alfa carton container and vial labels. Please note that we are

Thanks,
Cristi

N

2 Page(s) Withheld

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✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Stark, Cristi L
Sent: Monday, March 13, 2006 4:41 PM
To: 'Panagoulias, Jennifer'
Subject: label sections for STN 125141/0:Alglucosidase alfa

Attachments: labeling changes sent to Genzyme on 3_13_06.doc

Good afternoon Jennifer,

As promised I have received concurrence on certain sections of the label. Attached are those particular sections for the start of our labeling exchanges. Please let me know if you have any questions. I ask that when Genzyme makes the appropriate labeling changes, you email me a word copy to work off of (also we will need a follow-up to the submission--we will try to do as few of these as possible). Please confirm receipt of this email.

labeling changes sent to Genzy...

Thanks,
Cristi Stark

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125141/0

MAR 3 2006

Genzyme Corporation
Attention: Alexander Kuta, Ph.D.
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act for "Alglucosidase alfa," and to the meeting held on February 2, 2006, between representatives of your firm and this agency. As requested in your letter of January 11, 2006, a copy of our memorandum of that meeting is attached for your information.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact me at (301) 796-1007.

Sincerely yours,

Cristi L. Stark, M.S.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

OTRR:DARP:CLStark:3.3.2006
(N:\Stark\Genzyme Corporation\STN 125141_0\Type A 2_2_06 meeting letter.doc)

MEETING SUMMARY ENCLOSED (MS)

Office	Name/Signature	Date
DGP		3/3/06

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: MAR 3 2006

From: *Cristi Stark, DGP, ODEIII*

To: STN 125141/0

Subject: Type A Meeting Summary

Meeting Date: February 2, 2006 **Time:** 10:00-11:30am

Location: White Oak Conference Room 1417, Building 22

Meeting Requestor/Sponsor: Genzyme Corporation

Product: Alglucosidase Alfa (Myozyme)

Proposed Use: —

—

Type of meeting: Critical path to discuss indication

Meeting Purpose: To discuss the indication statement, extrapolation of data and product concerns.

FDA Attendees: Brian Harvey, Joyce Korvick, Marc Walton, Anne Pariser, John Hyde, Julie Beitz, Barbara Wilcox, Cristi Stark, Jinhai Wang, Frederick Mills, Jeffrey Fritsch, Nicole Wagner, Brian Langhary, Debi Tran, Constantine Markos, Anil Rajpal, Hong Zhao, Jean Temech, Henry Startzman, Jasti Choudary, Deb Avant, Amy Rosenberg

Sponsor Attendees: Bob Mattaliano, Betty Wiley, Nancy Silliman, Alison Skrinar, Jennifer Hunt, Mary Alice Worden, Ali Afman, Edward Kaye, Richard Moscicki, Alison Lawton, Jennifer Panagoulias, Deya Corza, Alex Kuta, Priya Kishnani, Robert Leshner, Mark Hayes

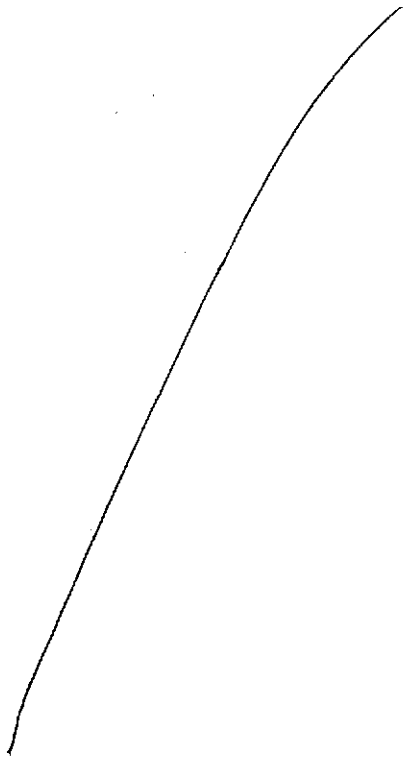
Note: ***FDA provided Genzyme with draft responses to questions via fax on January 27, 2006. The following minutes include those responses along with additional comments from the meeting discussions.***

FDA comments/questions and Sponsor response:

1. Note that according to 21 CFR 601.2(d) "Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products." Our review has determined that the release testing for rhGAA drug substance and product as proposed in the original Myozyme BLA submission does not meet the applicable requirements to ensure continued potency. However, we will make every effort to work with Genzyme to address this issue and the following CMC comments should be helpful in correcting this deficiency.

   Response to November 18, 2005, information request (IR) letter Question 35:

   Implement a potency assay which ——



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validation and setting additional specifications.

Sponsor questions and FDA response:

1. Genzyme believes that it is appropriate to extrapolate findings obtained in patients with the most rapidly progressing form of Pompe disease (infantile-onset) to those with a less rapidly progressing form of the disease (late-onset), especially considering the positive data obtained to date in late-onset patients. Therefore, does the Agency agree with the proposed indication statement for Myozyme which is as follows:

No, we cannot agree on your proposed indication. Your application remains under review and specific phrasing will be discussed in the future. At this point we can say that your application appears to support an indication for the treatment of infantile-onset patients with the observed benefit of a ventilator-free survival advantage in these patients. However, it does not appear that the information you have submitted supports an indication for the treatment of late-onset patients.

You have submitted information on 13 late-onset patients, all of whom received open-label, uncontrolled treatment with Myozyme or Myozyme and other rhGAA preparations. The assessments of these patients were subjective. The effect of alglucosidase treatment on these patients is not clear. The historical control dataset you collected was designed primarily to provide a reliable comparison for non-randomized treatment of the most severe patients. This dataset is not able to provide valid control-comparison data for the late-onset population. Since the late-onset patient data submitted are of non-randomized treatment, and no valid comparison can be made to the historical dataset, no conclusions regarding treatment benefits in the late-onset patients may be formed based on the data you have submitted to us at present.

The regulations for extrapolation of data from adult patients to pediatric patients state that "Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies..."

While extrapolation in the reverse direction, from younger to older patients can be

considered, similar constraints on the suitability must be assessed. However, the courses of disease are not the same in the infantile-onset and late-onset patients. For example, survival in late-onset patients is typically measured in decades, not months as for infantile-onset patients. Additionally, cardiac hypertrophy is not described in late-onset patients, glycogen storage in skeletal muscle is patchy, and there is extreme heterogeneity of clinical presentation and progression of late-onset disease. In contrast, the success of the historical comparison method for the infantile-onset patients is dependent upon a progression to fatal outcome that has very little variability. We note that these disease course differences were specifically discussed with you in multiple communications under the IND, including in the pre-BLA period. These differences lead to a substantially different study design being necessary for the late-onset population.

With regard to the proposed statement of treatment benefits, the expected benefits of the treatment in the infantile-onset and in late-onset patients are also not the same. The indication you have proposed includes prolonged ventilator-free survival,

With regard to the

so this does not appear to be a treatment effect that is appropriate to include in an indication statement.

You have also proposed claims

However, we do find that the information you have gathered on developmental assessments of these infants over time has value for descriptive purposes. The data illustrate that, while these infants survive, they are not restored to a fully normal, healthy condition.

Discussion at meeting: Genzyme agreed to remove the ventilator-free survival,

move it to the Clinical Studies section. In addition, Genzyme agreed that the late-onset data are limited, there is a heterogeneity of progression, and they agreed to perform antibody mediated uptake inhibition analysis (including a retrospective analysis of 1602 & 1702 by the , and an evaluation of patients who become invasively ventilated, until the 1602 & 1702 analysis is assessed).

2. Genzyme commits to the completion of the late-onset treatment study (Study AGLU02704) and providing results as soon as they are available (anticipated for late . In addition, Genzyme will provide updated data on late-onset patients as part of the U.S. Expanded Access Program (AGLU02603). Does the Agency agree with this approach?

   We recommend that you submit the results of the late-onset treatment study (Study AGLU02704) as

   Discussion at meeting: Genzyme agreed with FDA that the late-onset data are limited (a total of late onset expanded access program, n=15, and uncontrolled studies, n=8), subjective, and that the historical control database is not a satisfactory comparator for late-onset results. They plan to have enrollment complete for the late-onset trial (LOTS) by ' with the last patient completing by

   FDA asked what Genzyme's plan was if they were granted approval for Myozyme, completed the LOTS trial, and received negative data, or if they could not complete the LOTS trial. Genzyme replied that they view the LOTS trial as a post-approval activity and a key to the Myozyme label. Genzyme is committed to completing the LOTS trial and reminded FDA that they have performed and completed trials in the past after an approval (e.g., Fabrazyme). Also Genzyme stated that if the LOTS trial does not yield positive data they will contact and notify the community with the results and follow-up with a formal submission to the Agency.

3. Does the Agency agree with the use of the proposed tradename, Myozyme?

   No objections have arisen as of yet, but the issue is still under review. A final decision has not yet been made.

4. Does the Agency have any significant comments with respect to the proposed package insert for Myozyme?

   Submission is still undergoing review. Label discussions will be held at a future date.

Pediatric Consult Comments regarding Genzyme Questions 1 & 2:

In general efficacy can be extrapolated between two populations when the course of disease and the effect of the drug, both beneficial and adverse are sufficiently similar. Additional supporting data such as bridging pharmacokinetic/pharmacodynamic data and safety assessments are usually required (see 21 CFR 201.57(f)(9)(iv) and Subpart B 314.55). In this case, the course of disease in the infantile patient differs significantly in that the disease is rapidly progressive and that cardiac symptomatology is evident. Moreover, even if the agency agreed to extrapolate efficacy, the safety of neutralizing antibody development from Myozyme in patients dependent on endogenous GAA production is unproven.

The data from the late-onset treatment study are essential to establishing efficacy and safety in the late-onset population.

Additional Comments:

1. You reported more than 95% uptake inhibition by serum of one patient who is under invasive ventilation, indicating that uptake inhibition may play important role in the failure of replacement therapy. You should examine sera of all other patients with a qualified uptake assay to examine whether antibodies that inhibit enzyme uptake are more prevalent in sera from patients on invasive ventilation versus patients not requiring ventilation. Preferably we would like to see a careful analysis to assess whether development of such antibodies predicts a negative outcome and whether development of neutralizing antibodies correlates with genetic mutation. Muscle GAA activity should be re-examined in patients who developed entry-inhibitory antibody or who are under invasive ventilation.

2. Our ability to perform a timely and thorough review of your submission is highly dependent on the quality of the submission and the timeliness and completeness of your responses to our questions. Your submission contained numerous errors and was incomplete in many basic aspects, which lead to a large number of information requests. At the time of the original submission, applications are expected to be complete, with all required data needed to support the proposed indication, they should address the issues raised at any pre-BLA meetings, and they should have undergone thorough quality checking such that the data can be relied upon. We would like to arrange a future meeting with you to discuss more specifically and in more detail our recommendations for future regulatory submissions.

Additional Discussion Items at Meeting:

1. FDA asked which subjects were receiving product from the 2000 L process.

   Genzyme stated that all late-onset patients were being treated with product from the 2000 L

process. In addition, some of the infantile and expanded access subjects were treated with product from both the 160 L and 2000 L processes.

2. FDA asked if Genzyme were to receive Lot Release approval for the 160 L process, how will that impact availability? In addition, how many lots need to be released over the next 12 months?

   Genzyme replied that the 160 L process scale can provide the US population with enough Myozyme product for [redacted]. (A total of [redacted] over the course of 12 months should address patient needs.) This will allow Genzyme the time to work on the 2000 L process. Genzyme emphasized that the main item regarding availability is the indication.

3. FDA asked if Genzyme will need to adjust the dose of the 2000 L process product because it is 20% less bioreactive (PK/PD differences).

   Genzyme stated that the initial PK/PD that was performed showed comparability. Looking at serum pharmacodynamics is not clinically relevant. Therefore, Genzyme is not convinced that it will lead to any clinical difference.

4. During the slide presentations, Genzyme mentioned that there is a total of 310 patient-years experience with Myozyme. FDA asked if all of that information was submitted to the BLA.

   Genzyme did not provide all 310 patient-years to FDA. Much of the experience is in the expanded access program in Europe, from which it is difficult to obtain efficacy data. Genzyme stated that they provided FDA with a total of 23 late-onset patients (10 are in the form of patient narratives; the subjects were on Myozyme for six months or longer), and 95% of the safety data for all 310 patient-years. Genzyme did not submit any information from the LOTS (late-onset) trial as it is ongoing and should have full enrollment in March 2006 (with a total of 85 subjects).

5. Genzyme presented the recently approved European label as an indication statement for the FDA to consider:

   Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid alpha-glucosidase deficiency). The benefits of Myozyme in patients with late-onset Pompe disease have not been established.

   FDA responded that [redacted]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 3, 2006

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Regulatory Briefing

PARTICIPANTS:

CDER: **Renata Albrecht, Julie Beitz, Jonca Bull, Jasti Choudary, Edward Cox, Gerald Del Pan, Mark Goldberger, Brian Harvey, John Hyde, Sandy Kweder, Lee Lemley, Anne Pariser, Sol Sobel, Cristi Stark, Bob Temple, Keith Webber, Karen Weiss, Helen Winkle, Hong Zhao, Marlene Swider, Joyce Korvick, Mauren Dewey, Ryan Barraco, Nam Rahman, Betsy Scroggs, Eric Brodsky, Shewit Bezabeh, Susan McCune, Hari Sachs, Jean Temeck, Debbie Avant, Michelle Clark-Stuart, Kristen Everett, Nancy Snow, David Joseph, Ann Mackey, Lanh Green, Rosemary Roberts, Kay Schneider, Lolita Lopez, Susan Daugherty, Fathia Gibril, Joanna Ku, Ruyi He, Lisa Mathis, Wilson Bryan, Henry Startzman, Doug Throckmorton, Steven Galson, John Jenkins, Sandy Kweder, Steve Kozlowski, Amy Rosenberg, Barry Cherney, Gibbes Johnson, Fred Mills, Anil Rajpal, Dave Green**

A regulatory briefing for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides [redacted], was held on March 3, 2006. Attached are the handouts from the three presentations (total of 4 handouts: product slides, clinical pharmacology slides, clinical slides and clinical supplemental handout).

There were a total of three presentations given during the briefing. These presentations were given to reach consensus on the regulatory options surrounding the product issues and Pompe disease population for whom Myozyme is indicated.

Product presentation (presented by Fred Mills, Ph.D.):

Dr. Mills presented the pathway by which Alglucosidase alfa acts, the major CMC deficiencies in the original BLA submission, the sponsor's progress in addressing the potency deficiencies, and various regulatory options.

BLA STN 125141

Product: Myozyme (α glucosidase)
cleaves glycogen to release glucose
produced in CHO cells

Sponsor: Genzyme

Status of Myozyme BLA Review

- **Pre-BLA Meeting with Sponsor-May 3, 2005**
- **Original submission - July 31, 2005 (6 month review cycle) 160 L and 2000 L processes**
- **FDA CMC information request letter – November 18, 2005**
- **Genzyme Clinical/CMC major amendment-December 30, 2005: 2000 L process withdrawn**
- **Action date-April 28, 2006**

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Major CMC Deficiencies in Original Myozyme BLA Submission

- potency assay is not suitable for release testing
- No potency assay which measures

Conclusion: Potency of Myozyme cannot be assured using proposed assay

Genzyme's Progress Toward Addressing Potency Deficiencies

Developed Qualified Potency Assays:

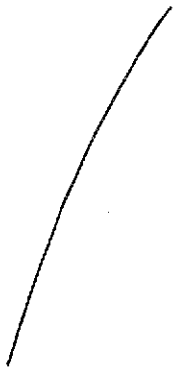
1.
2.
3.

Qualified Assay for:

4. **Amount of**

Data to be Provided using New Assays:

1. **Optimization to be completed February 24, 2006**
2. **Analysis of BLA clinical lots and commercial launch lots to be completed March 24, 2006. The BLA clinical lot data will be used to set provisional release specifications**



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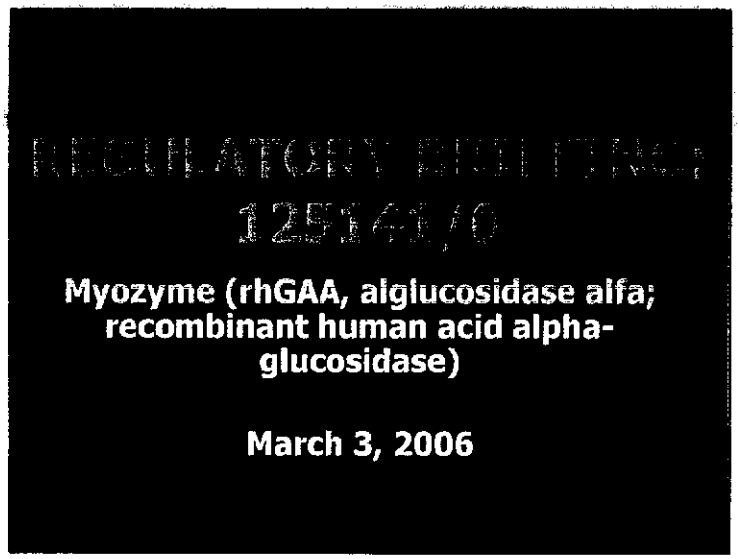
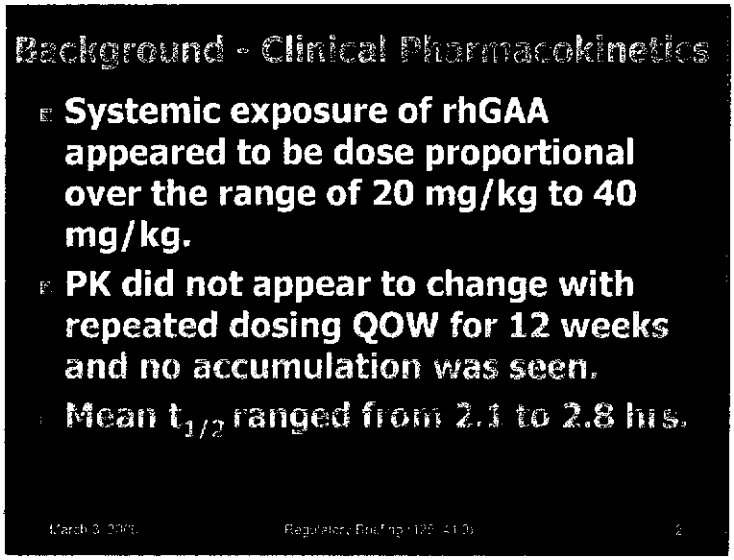
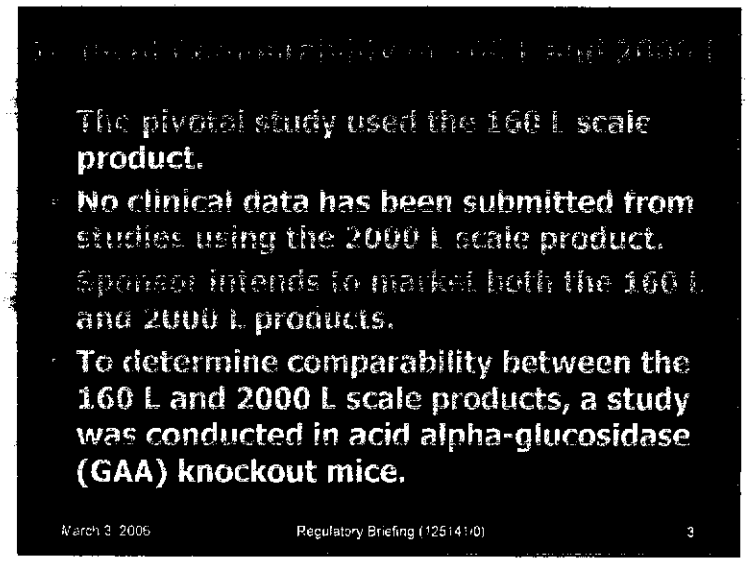
Clinical Pharmacology presentation (presented by Anil Rajpal, M.D.):

Dr. Rajpal presented the clinical pharmacokinetics and the comparability of 160 L and 2000 L scales with results.







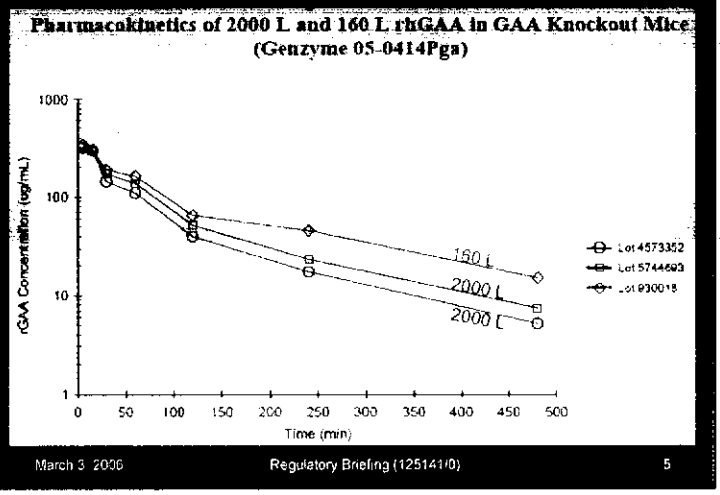
Bob Temple: Was there any thought given to a larger dose?
Anil Rajpal: This was discussed; however, with the issues surrounding the potency assay we cannot ensure the potency of the 2000 L scale.
Bob Temple: So there was no 2000 L product used in clinical trials?
Anil Rajpal: Correct.
Brian Harvey: This is something that happens in biologics. As you scale from the 160 L to the 2000 L there are changes. When the 2000 L scale is the only product on the market, the drug may have a different effect from when it started. There are now some internal questions for dosing regarding the different scales.

PK Comparability Study Design (05-1414)

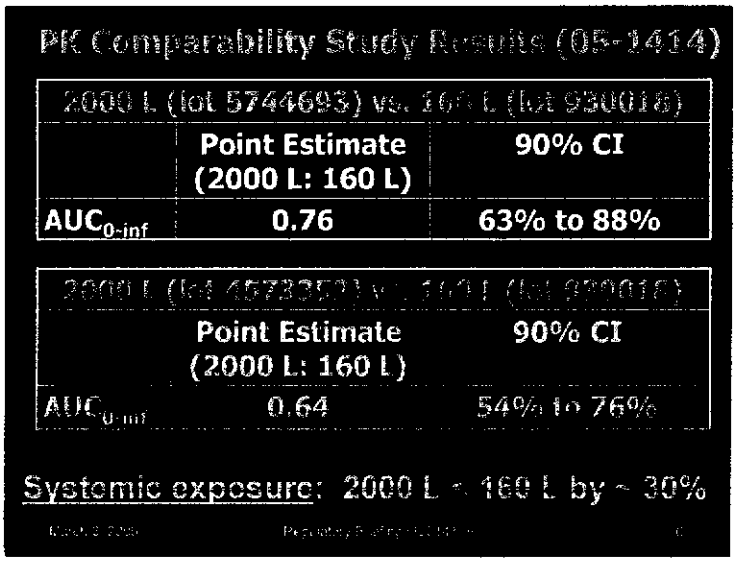
- Dose: 20 mg/kg IV X 1
  - Reference: One 160 L scale lot (930118)
  - Test: Two 2000 L scale lots (5744693, 4573352)
    (N=12 knockout mice per lot)
- Assay: Plasma GAA Activity
- Sampling: 5, 15, 30, 60, 120, 240, and 480 minutes

March 3, 2006 Regulatory Briefing (125141/0) 4

PK Comparability Study Results (05-1414)



March 3, 2006 Regulatory Briefing (125141/0) 5



Keith Webber: Since this protein functions through the liver, wouldn't that mean it works better?
Amy Rosenberg: It could have a first pass through the liver and then be gobbled up.
John Jenkins: You see PK differences through the manufacturing practice. What is the explanation? I assume it is a similar process just a larger scale.
Gibbes Johnson: Genzyme does not actually know how the difference arises. They claim physiochemistry from comparability; however, they are not sure. This was a question posed in our November 18, 2005 information request letter.
Dave Green: During scale up a cell is stressed to a larger extent. As you try to gather a larger yield from the cell, you force more metabolism which leads to variation in many things.
Brian Harvey: Also differences have been found in the manufacture of —— —— No one knows why the differences exist for two identical manufacturing processes that are located on different coasts.
Mark Goldberger: Are there antibody differences? Are there differences in antibody formation?
Brian Harvey: That is a question we are currently struggling with. In this product it has not yet been shown.
Barry Cherney: We are looking at the —— . On the 2000 L scale we are seeing —— a little higher which could account for faster binding and take-up.

John Jenkins: Do you have head-to-head data for 160 L versus 160 L scales so you know it is a consistent product?
Anil Rajpal: They did not compare the final product. Genzyme only compared the drug substance lots. The two lots did show differences. Genzyme then pooled the two drug substance lots to make the final product for clinical trials.
John Jenkins: So how do we know that pooled product is the same as what will be out there? What do we have to ensure the lots are the same?
Steve Kozlowski: This is the extra testing and validation we are asking for.

Clinical presentation (presented by Anne Pariser, M.D.):

Dr. Pariser presented the clinical data for the Pompe disease population studied and defined the Pompe disease population for whom Myozyme (rh-GAA) is indicated (please see attached handouts).

Myozyme for the Treatment of Pompe Disease

Anne Pariser, M.D.
Clinical Reviewer

Division of Gastroenterology Products

CDER Regulatory Briefing
March 3, 2006

Purpose

- Summarize clinical data for Pompe disease population studied

- Define Pompe disease population for whom Myozyme (rh GAA) is indicated

Agenda

- Rh-GAA Background
- Review Pompe disease, and Pompe disease population classifications
- Overview of Myozyme clinical program
- Summarize clinical data
  - Infantile-onset population
  - Childhood-, juvenile-, and adult-onset populations
- Questions

[illegible]

Initial BLA application for Myozyme (rh-GAA)

Enzyme replacement therapy (ERT) proposed for the long term treatment of Pompe disease (rh-GAA deficiency)

Previous formulations include transgenic rabbit milk (Pharming) and Synpac CHO-cell formulations

Pompe Disease Background

- Pompe disease
  - Aka glycogen storage disease II (GSD II) and acid maltase deficiency (AMD)
  - Rare disease (1/300,000 to 1/40,000)
  - Autosomal recessive inherited disorder of glycogen metabolism
  - Deficiency of lysosomal acid α-glucosidase (GAA)
  - Results in intralysosomal accumulation of glycogen
  - Highly heterogeneous presentation and progression
  - Wide range of genotypes, most compound heterozygotes with unique mutations
  - No approved treatment (other than supportive care)

[illegible]

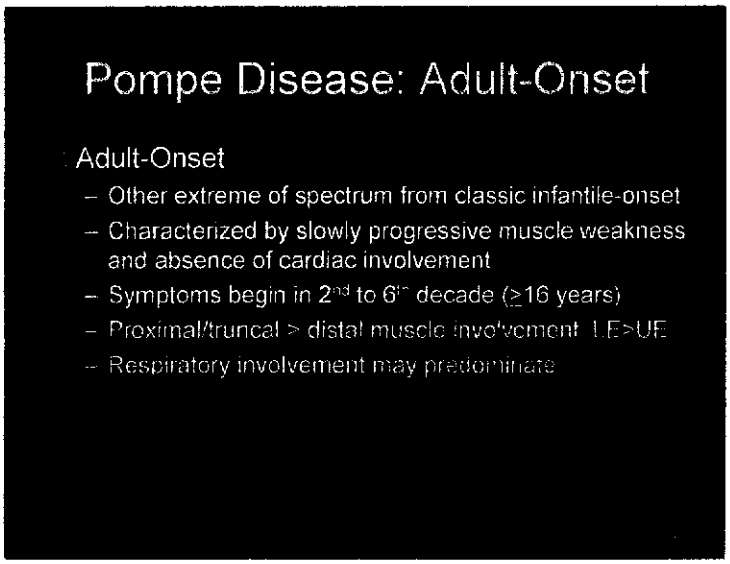
- Infantile-Onset
  - Classic infantile-onset
    - [illegible]
    - [illegible]
    - cardiomegaly, cardiorespiratory, and hepatomegaly
    - Virtual absence of GAA
    - Marked accumulation of glycogen in numerous tissues, most marked in cardiac and skeletal muscle

Pompe Disease: Infantile-Onset cont.

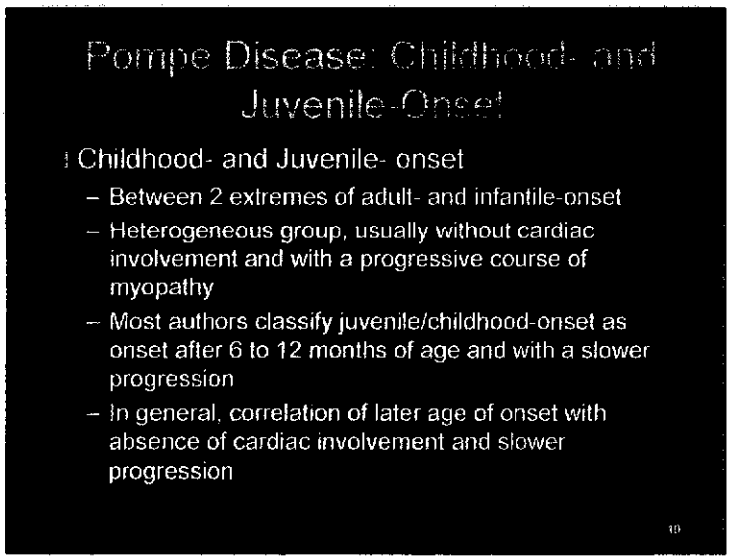
- Classic infantile-onset cont.
  - Universally fatal, usually by 18 months of age
  - Death due to respiratory and/or cardiac failure
- Infantile-onset muscular variant
  - Less common than classic infantile-onset form
  - Patients present <6 months of age
  - No cardiac involvement
  - Typically more attenuated form of disease with longer survival

Pompe Disease: Childhood-

- Childhood-, juvenile-, and adult-onset (late-onset) classifications
  - Comprises spectrum of clinical
  - Adult-onset classified
  - [illegible] of progression
  - In general, distinguished from infantile-onset by lack of cardiac involvement, older age of presentation (>6 to 12 months), attenuated progression
- Death in all forms results from respiratory failure



Bob Temple: Is the amount of naturally occurring levels of alpha glucosidase more in this population?
Anne Pariser: Relative to the infantile population (where there is no GAA) that is correct. However, the amount in the juvenile- and adult-onset is wide spread and has no correlation with disease severity.
Keith Webber: In regards to the infantile- through the late-onset disease, what is the predominance of naturally occurring GAA?
Anne Pariser: That is not known as the infantile population dies too early.



Pompe Disease Classification cont.

- The Metabolic & Molecular Bases of Inherited Disease
  - Infantile-onset
    - Classic
    - Muscular Variant
  - Childhood/Juvenile-onset
  - Adult-onset

[illegible]

SNOMED recognizes infantile-, juvenile- and adult-onset (not defined)

[illegible] recognizes "Pompe disease" with age divisions:

- [illegible]
  - Infantile-onset
    - Study 1798 (pivotal) age of symptom onset < 6 months
    - Study 1782, EAP and other open-label studies as symptom onset < 12 months
  - Late-onset: symptom onset >12 months of age

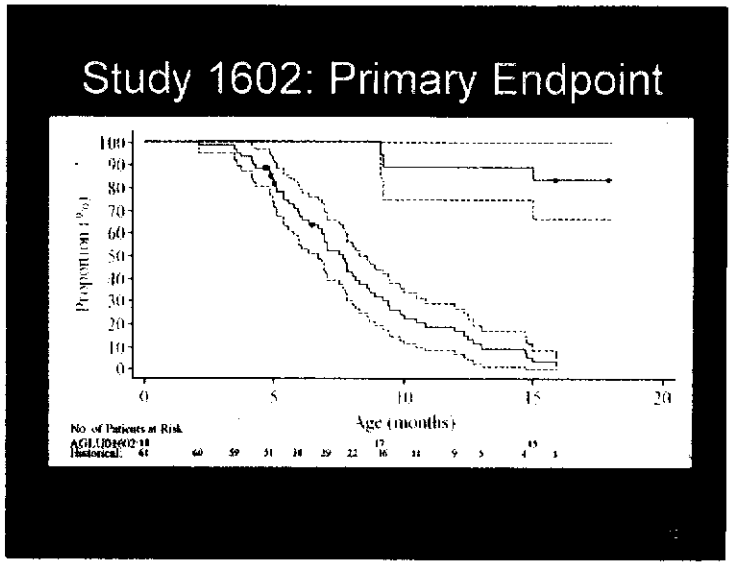
Pompe Disease Classification cont.

- Pubmed (Medline) Search
  - "late onset Pompe disease" search – "49" hits
    - No consensus as to definition
    - appears to apply to patients with onset in childhood to adulthood
    - Signs and symptoms limited to skelelal muscle and respiratory involvement

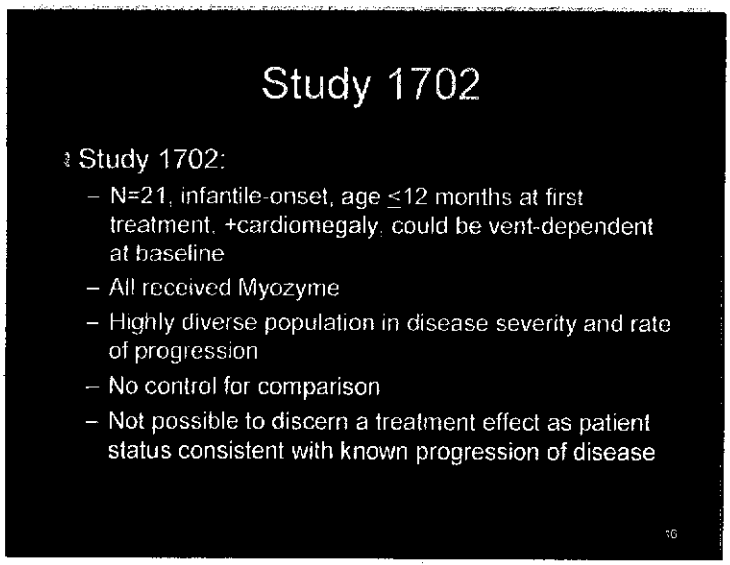
Myozyme Clinical Development Program

Study 1602, Pivotal Study

- [illegible] historically controlled study of Myozyme in [illegible]
- Primary endpoint: Invasive ventilation free survival vs. survival in historical control at age 18 months
- Results: 15 of 18 (83%) Myozyme-treated patients alive & VF at 18 months vs. 1 of 61 (2%) patients alive in historical control



Bob Temple: Was the historical control study conducted without knowing the survival results?
Anne Pariser: It was a retrospective chart review.
Steve Kozlowski: Was there any evidence that survival got better over time?
Anne Pariser: Yes, however there was selection bias. Genzyme had to have a subject survive about six months in order to be included in the study. In the historical control, even if a subject died at one month, they were included.
Bob Temple: What about looking at the historical control starting at a five month survival point?
Anne Pariser: We conducted sensitivity analyses, whereby patients who died prior to six months of age were excluded. The data still held up, and any selection bias was gone by age 18 months as virtually everyone would have died without treatment by that time. That was why the 18-month survival endpoint was selected.



Juvenile- and Adult-Onset Clinical Program

- Information on 25 juvenile-and adult-onset patients was submitted
  - Study AGLU02804 only GCP study
    - n=5 juvenile-onset patients ages 6 to 15 years at entry (median 12.7 years), first symptom onset 1 to 12 years
    - OL, uncontrolled, all patients were able to ambulate at least 10 m for 6MWT at baseline, excluded patients on invasive ventilation

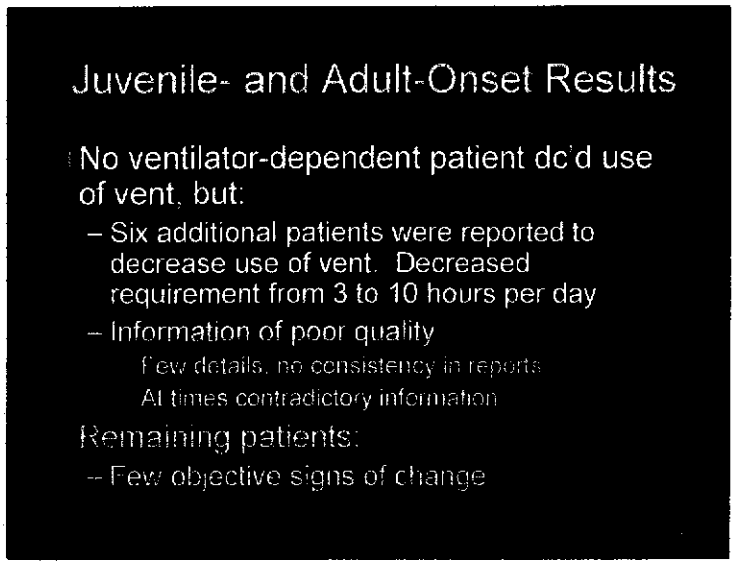
Study AGLU02804 Results

Juvenile- and Adult-Onset Results

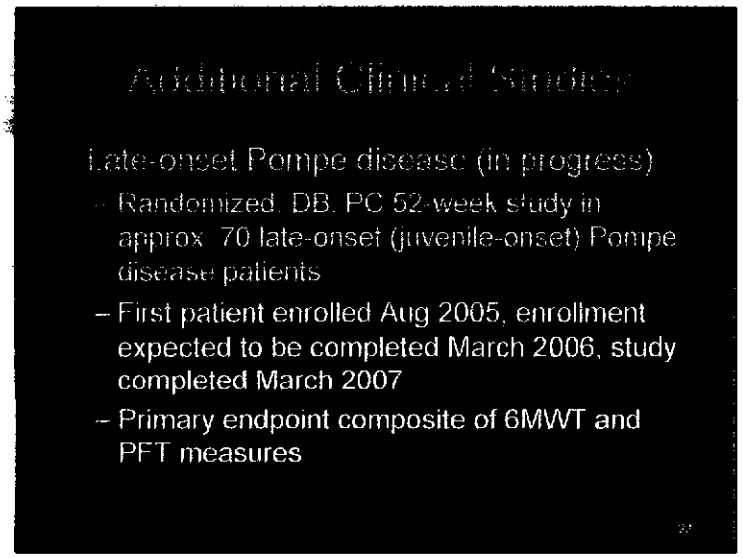
- Remaining 20 of 25 juvenile- and adult-onset Myozyme-treated patients
  - All received rh-GAA in OL, uncontrolled, non-GCP studies/EAPs
  - 19/20 vent-dependent at baseline (only Patient [redacted] not on vent) and 19/20 wheelchair dependent, c/w advanced stage of disease
  - Quality of information was very poor
    - All information as narratives

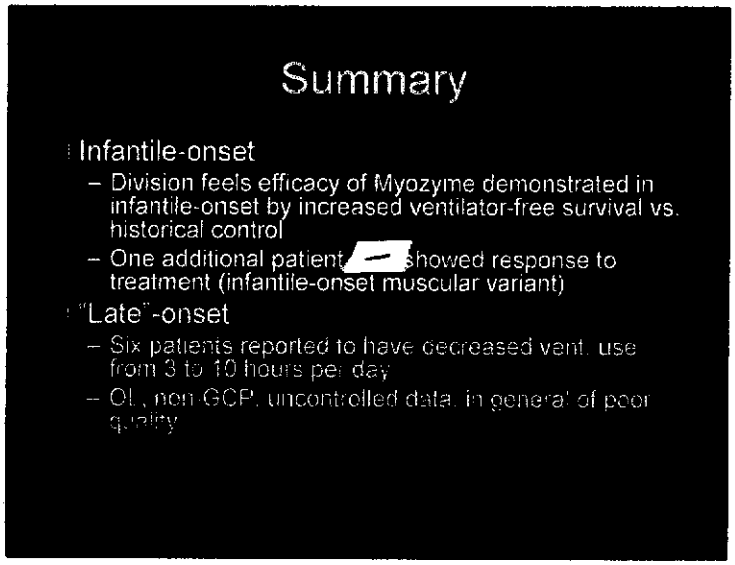
Juvenile- and Adult-Onset Results

- One definite responder: Patient [redacted]
  - Age 6 months at symptom-onset c/w infantile onset muscular variant form of disease
  - Wheelchair dependent at age 9, never on vent
  - [redacted] of treatment with Pharming rh-GAA
  - Dramatic response to treatment
    - Walked at 72 weeks (on Pharming formulation)
    - Running, biking, playing soccer w/ following years
    - Gains maintained on Myozyme
  - Total rh-GAA treatment approximately 8 years



Julie Beitz: When you look through the datasets and see the consistencies, is this something the drug is doing?
Anne Pariser: There is a different progression for each patient. We do not know if it is from the drug or not.



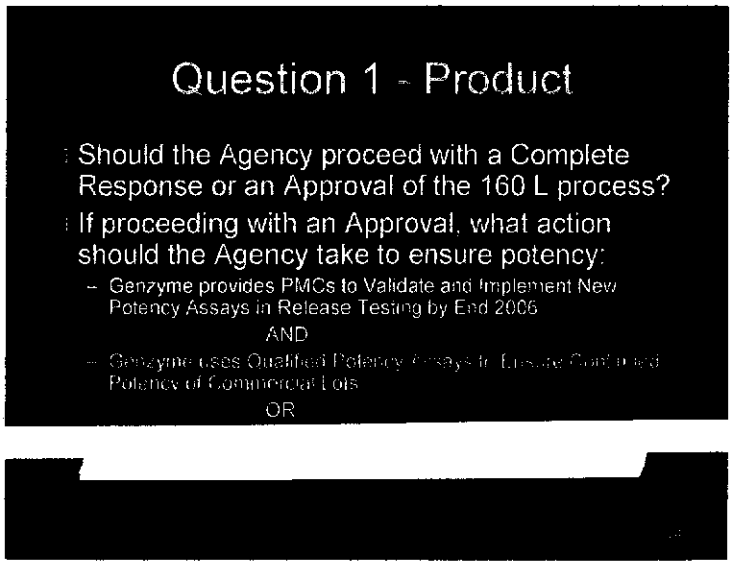


General Discussion:

John Jenkins: In the infantile studies there were still patient deaths. Is this typical of the group?
Anne Pariser: In Study 1602 there were 2 deaths due to respiratory failure. In Study 1702 there were also several deaths due to respiratory failure. For both of these studies these are typical events you expect to see in this population.
Amy Rosenberg: Were the deaths in antibody positive patients?
Anne Pariser: Yes, Myozyme is extremely antigenic.
Amy Rosenberg: This is where tolerance progression is important. Since we don't have a good potency assay we cannot measure neutralizing antibodies. In literature searches, we find that with a surge of antibodies, a sudden decrease in antibodies, and then again a spike in antibodies, usually result in death.
Anne Pariser: There is one patient that went into cardiac arrhythmia from catheter placement and died. This led to a change in procedure.
John Jenkins: How old are the infantile patients now?
Anne Pariser: Aged two and a half years.
John Jenkins: So we know that we shifted the curve to the right, but that is it.
Anne Pariser: All but 2 subjects are still alive, but with motor delays for age. We do not know that they will make it to adulthood.
John Jenkins: The shifting of the curve brings up societal questions; however we will not deal with that here. What about safety?
Anne Pariser: The adverse events are consistent with underlying disease or similar to AEs seen with other enzyme therapies, such as rash or urticaria. We have not seen any anaphylaxis.
John Jenkins: Is the entire population with the disease now getting the drug through expanded access?
Anne Pariser: We do not know. You have to head to certain centers and physicians that will administer the drug.
John Jenkins: I ask because it is easier to deny approval if patients are already receiving drug.

Steve Galson: Not all patients are getting drug.
Anne Pariser: Recently Europe approved Alglucosidase alfa for the treatment of Pompe disease.
Amy Rosenberg: With the late-onset study, did you see any antibody or infusion reactions in the safety profile?
Anne Pariser: The only data collected systematically in late-onset patients was in one good clinical practice (GCP) study in five patients. Three of the five developed rising antibody titers.
Karen Weiss: Currently we are looking at a QOW interval. The enzyme is taken up into the lysosomes and has a half life of only a few hours. Is there a tagged study to justify the dosing schedule? What about immunogenicity?
Amy Rosenberg: They did try to tolerize 1 patient by the Factor VIII protocol and the patient developed a serum sickness.
Anne Pariser: This is something that can be worked out over time.
Brian Harvey: The issue of dosing was brought up during review. Genzyme did pharm/tox studies with dosing up to 100 mg/kg; however, they did have issues of infusing smaller patients. There is very little dosing information. The current interval is based on animal data.
Anne Pariser: There are a few cases of patients (approximately 4-5) that were not doing well. The investigators did raise the dosing in these patients so that they received 40 mg/kg qweek. It appeared that these patients continued to do poorly, but they were not doing well when the dose was increased.
Steve Kozlowski: Can these patients be placed into a tolerance study? This should be done as a post marketing commitment.
Sol Sober: This is reminiscent of Genzyme's program for Cerezyme for Gaucher's disease. With that program the dosing interval is still being worked on.
Amy Rosenberg: With the Fabry experience, when the product was approved in Europe there were patients flying to Europe for treatment every two weeks for infusions. If we do not approve the late-onset population here in the US, this will create hardships for these Pompe patients and it will result in them having to go to Europe as well.
Brian Harvey: We also need to consider getting the drug shortage memo in now as they may not be enough drug for all US patients.
Julie Beitz: Currently Genzyme predicts that there is enough drug with the 160 L process for all US patients for two years.

Question 1:

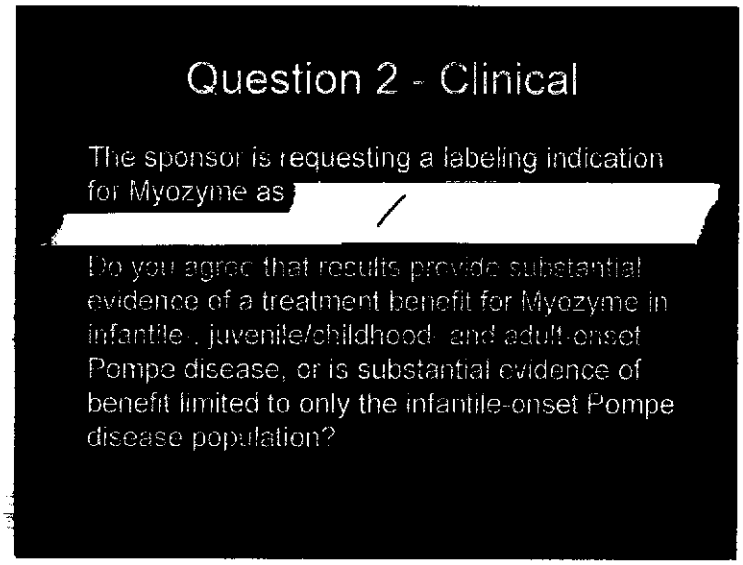


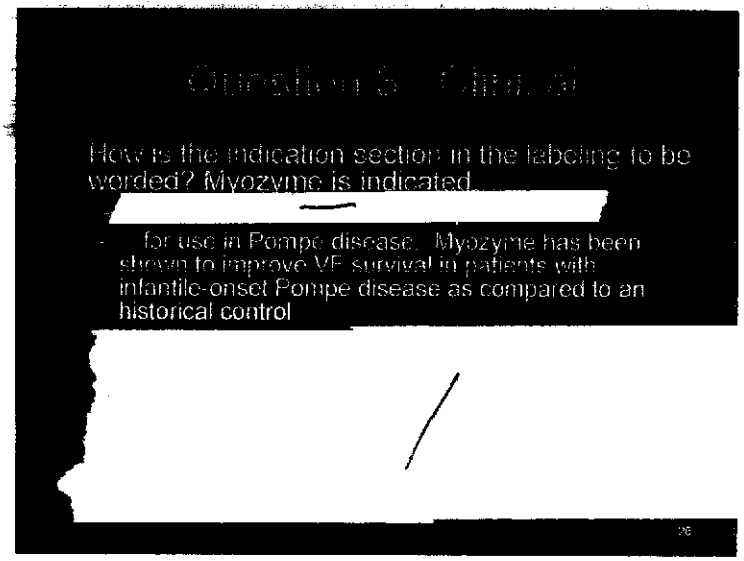
Amy Rosenberg: The sponsor is happy with the new assays. This is something that their scientific staff wanted. They are willing to work with us and complete validation.
John Jenkins: Do you feel there are precedents similar to this for approval?
Barry Cherney: For non-specified products there are similar precedents.

Steve Kozlowski: Ideally validated means that it is truly validated. Currently we do have an assay that is prospectively validated but not adequate. In the interim we are supporting that assay with other assays until it is fully validated.

Barry Cherney: Assay validations are very common in BLA approval letters. Just know that we are NOT allowing the change of manufacturing processes.

Questions 2 & 3:





John Jenkins: I assume that most people feel infantile is adequate?
Anne Pariser: Yes.

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✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Office of Drug Safety

MEMO

To: Brian Harvey, MD, PhD
Director, Division of Gastroenterology Products, ODE III (HFD-180)

From: Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety

Through: Alina Mahmud, MS, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Date: February 15, 2006

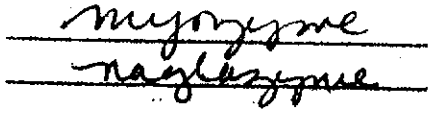
Subject: ODS Consult 05-0210-1, Myozyme (Alglucosidase Alfa), 50 mg; BLA 125141/0.

This memorandum is in response to a January 18, 2006, request from the Division of Gastroenterology Products for a re-review of the proprietary name, Myozyme. The proposed proprietary name was found acceptable by DMETS on February 11, 2004 (ODS Consult 04-0009). Additionally, DMETS conducted a review of the container labels, carton and insert labeling (see ODS Consult 05-0210 dated September 12, 2005). Revised labels and labeling were not submitted for review at this time.

Since the last name review, the Division of Medication Errors and Technical Support (DMETS) has identified one additional proprietary name, Naglazyme, that has the potential for confusion with Myozyme. Additionally, a discussion on the proposed labeling and use of the suffix "zyme" will be included below.

A. Look-alike, Sound-alike Name

Naglazyme and Myozyme have the potential to look similar when scripted. Galsulfase is indicated for patients with mucopolysaccharidosis VI. Galsulfase has been shown to improve walking and stair-climbing capacity. Myozyme and Naglazyme share a similarly scripted first letter (M vs. N), a down stroke "y" vs. "g" in the first syllable, and shared last syllable "zyme" (see below). However, the letter "a" in the prefix "Nag" and the up stroke of the letter "l" in Naglazyme help differentiate the names from one another.



Myozyme and Naglazyme have similar characteristics including route of administration (intravenous following dilution), length of infusion rate (long infusion, e.g., 4 hours), numeric similarities in strength (50 mg/vial vs. 5 mg/5 mL vial) and storage conditions (refrigerate). However, the products differ in dose such that Naglazyme is dosed 1 mg/kg and Myozyme is dosed 20 mg/kg. Most likely, prescriptions for these products will include the dose.

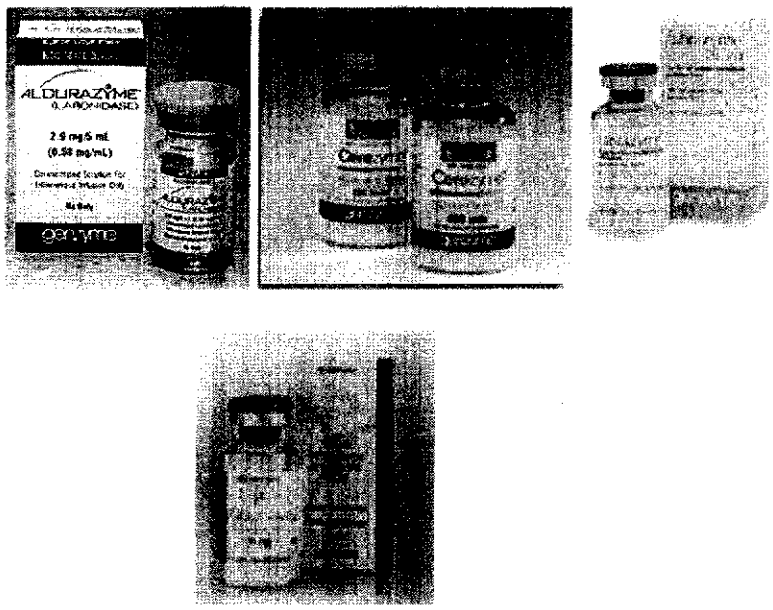
Overall, DMETS believes that the potential for confusion is minimal given a lack of convincing look-alike similarity as well as differences in dose and dosing interval.

B. Similarities between Myozyme and other products for lysosomal storage disorders may increase the risk of error

Myozyme is a member of a group of products which are indicated for the treatment of various relatively rare genetic disorders[1]. The products in this class have many similarities, including dosage form, route of administration, dosing regimens, duration of dose administration, and storage conditions. (See Appendix A for a comparison of product similarities).

1. Packaging Similarities

Lysosomal storage disorder products are manufactured/marketed by Genzyme (Myozyme, Fabrazyme and Cerezyme), BioMarin (Naglazyme), or both (Aldurazyme)[2]. We note that Genazyme has differentiated currently marketed products adequately however the proposed labels and labeling for Myzozyme are very similar in layout to Naglazyme. These two products share similar design elements, including vertical color bar and watermarked, stylized person with outstretched arms, with the labeling proposed for Myozyme (see below).



Although DMETS does not have any objections with the proposed labeling for Myozyme, the sponsor should exercise caution in using this similar layout for any future products.

[1] Soni S, Asamoah A. Current Treatment of Lysosomal Storage Disorders. *Medical Genetics Minute.* 2006; 2(1): 1-4.
[2] BioMarin and Genzyme established a 50/50 joint venture, BioMarin/Genzyme LLC, for the worldwide development and commercialization of Aldurazyme® for MPS I.

2. Nomenclature Similarities

Lysosomal storage disorder products have similar established names, ending in "ase" and similar proprietary names, ending in "zyme". Thus as more products are approved the similarity in names will also proliferate. Therefore, the potential for confusion between the names will increase also. For example, post-marketing experience has shown confusion and resulting medication errors due to proliferation of names with a common prefix or suffix. One example of such confusion has been seen with products having the prefix "APO", manufactured in Canada by Apotex (see Appendix B for list of names with prefix "APO"). Consequently, DMETS has objected to inclusion of the prefix "APO" for proprietary names proposed in this country since this practice may result in the introduction of numerous sound-alike/look-alike names. DMETS believes that the continued entrance in the marketplace of different products which include common lettering, "zyme", will lead to confusion and may result in medication errors. At this time, DMETS has no objections to the name Myozyme, however we recommend that the sponsor exercise caution with the proliferation of proprietary names with the ending "zyme" for future products.

C. Need for patient information for this product

Due to the special nature of this product in terms of dosing, e.g., length of infusion, side effects, patient registry information, and the disease state for which it is to be given, DMETS believes that the sponsor should develop patient information for this product. The product, Aldurazyme (Laronidase), has patient information which describes side effects, what other medications to take it with, disease-related information, etc. This product should have similar information since it is similar and has serious side effects as well. Alurazyme also has a web site for patient information: www.aldurazyme.com and www.MPSIdisease.com

In summary, DMETS has no objections to the use of the proprietary name Myozyme. We would be willing to meet with the Division for further discussion, if needed. DDMAC finds the name proprietary name Myozyme acceptable from a promotional perspective. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Appendix A. Lysosomal Storage Disorder Products

Product Attribute	Myozyme	Naglazyme	Cerezyme	Fabrazyme	Aldurazyme
Dosage Form	For Injection (powder)	Injection (solution)	For Injection (powder)	For Injection (powder)	Injection (solution)
Route of Administration	IV Infusion over 4 hours	IV Infusion over no less than 4 hours	IV Infusion over 2 hours	IV infusion 15 mg/hr… therefore probably greater than 4 h	IV infusion over 4 hours
Dosing	20 mg/kg every other week	1 mg/kg once a week	Varies: could be given every other week	1 mg/kg every other week	0.58 mg/kg once a week
Storage Conditions	Store under refrigeration	Store under refrigeration	Store under refrigeration	Store under refrigeration	Store under refrigeration
Similar Established Names (both use "ase" suffix)	Aglucosidase alpha	Galsulfase	Imiglucerase	Agalsidase beta	Laronidase
Strength	50 mg/vial	5 mg/5 mL	200 unit/vial 400 unit/vial	5 mg/vial 35 mg/vial	2.9 mg/vial
Manufacturer	Genzyme	BioMarin	Genzyme	Genzyme	BioMarin/ Genzyme
Indication	Pompe Disease	Maroteaux-Lamy	Gaucher	Fabry	Hurler-Scheie

Appears This Way
On Original

Appendix B. "Apo" Nomenclature for a product

INDEX D

ALPHABETICAL LIST OF PHARMACEUTICAL PRODUCT NAMES

Harper Velazquez, Tia M

From: Ferguson, Shirnette D
Sent: Thursday, February 09, 2006 9:24 AM
To: Clark-Stuart, Michelle
Cc: Harper Velazquez, Tia M; Cruz, Concepcion; Hoyt, Colleen; Merritt, Babette A
Subject: RE: 125141/0 Request for a compliance check

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the compliance check request below. There are no pending or ongoing compliance actions that would prevent approval of STN 125141/0 at this time. The inspection and compliance history of Genzyme Corporation, MA has been reviewed and found to be acceptable. The classification for Allston Landing, MA was NAI for the inspection conducted on January 11, 2006 for profile CBI. The classification for the Framingham, MA was NAI for the inspection conducted on October 28, 2005 for profile CBI. The Framingham inspection has not received a final endorsement in FACTS.

Shirnette Ferguson
Consumer Safety Officer
Investigations and Preapproval Compliance Branch
CDER/OC/DMPQ
(301) 827-9009
email: fergusons@cder.fda.gov

-----Original Message-----
From: Clark-Stuart, Michelle
Sent: Wednesday, February 08, 2006 4:45 PM
To: Ferguson, Shirnette D
Subject: 125141/0 Request for a compliance check

Hi Shirnette,

Please provide a compliance check for the following firm:

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
License #=1596
FEI # 1) 100305672, Allston Landing, Ma site &
2) 1220423, Framingham, MA site
STN = 125141/0, BLA for alglucosidase alfa product

TRFB inspected in Oct/Nov, 2005 for this BLA so please provide the compliance status for their last cGMP inspection (or Team Bio. inspection).

Thanks,

Michelle

Michelle Y. Clark-Stuart, MGA/MIS, MT, (ASCP)
FDA/CDER/OC/DMPQ
HFD-328 Rm. 1012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JAN 12 2006

Our STN: BL 125141/0

Genzyme Corporation
Attention: Alexander Kuta, PhD
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Alglucosidase alfa.

We received your December 30, 2005, amendment to this application on December 30, 2005, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to April 28, 2006, to provide time for a full review of the amendment.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

1/12/06

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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___ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125141/0

DEC 6 2005

Genzyme Corporation
Attention: Alexander Kuta, Ph.D.
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the clinical; chemistry, manufacturing, and controls (CMC); clinical pharmacology; and pharmacology/toxicology section(s) of your application dated July 29, 2005, for Myozyme and have determined that the following additional information is necessary to take a complete action on your application:

1. Regarding — Study #6354-140 (Comparison of three preparations of rhGAA: GenzrhGAA, BI2KrhGAA, BI – rhGAA), the protocol calls for retrieval and preserving a full panel of tissues, presumable for histopathology. However, no histopathology data are reported, in the face of apparent dose related gross lesions (liver enlargement that correlates with changes in liver function, stomach lesions). Provide the fate of those tissues and why the histopathology data were not reported.

2. In —— study # 6354-133 (rat tox study), gross lesions to those in study #6354-140 were not seen, nor were any effects noted for clinical chemistry parameters even though the high dose (100 mg/kg) was greater than that administered in study 140 and the regimen was the same. Please comment on these differences. Describe which process was used to produce the lot in study 133 (GW10124094)?

3. Identify the manufacturing process by which each lot of rhGAA used in all non-clinical studies was manufactured.

4. It appears, from your non-clinical toxicology studies, that the rat is a more sensitive species to rhGAA toxicities. Traditionally, reproductive toxicology studies should be performed in the most sensitive species. Justify your choice of mouse as the species in which to perform your reproductive toxicology.

5. According to the FDA guidance, ICH-S5A "Detection of Toxicity to Reproduction for Medicinal Products", embryotoxicity studies should be performed in two species, one non-

rodent (usually rabbit). BLA 125141 contains studies from mouse only. Comment on why this application does not include a study using a second species was not used to assess embryotoxiciy.

6. Regarding the Reproductive toxicology study, #6354-155 (fertility and early embryonic development), the high dose used in this study was 40 mg/kg delivered every other day to both male and female mice starting prior to mating and continuing through early gestation for females until termination. The justification for the highest dose is not clear. Provide more detailed information on how the exposures (both male and female) for study #6354-155 compare to those of other toxicology studies. In addition provide more detailed information on how the exposures of the animals (both male and female) in study #6354-155 compare to those anticipated for human use?

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

for BEH

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: **Information Request (IR)**

SS Data Check:
- **Communication**

cc: C. Stark/HFD-180
A. Pariser/HFD-180
B. Strongin/HFD-180
J. Hyde/HFD-180
B. Harvey/HFD-180
J. Korvick/HFD-180
F. Mills/HFD-122
J. Wang/HFD-122
G. Johnson/HFD-122
A. Rosenberg/HFD-122
B. Cherney/HFD-122
E. Shores/HFD-123
S. Kozlowski/HFD-123
A. Rajpal
H. Zhao
B. Wilcox
J. Choudary/HFD-180
L. Kammerman
S. Grosser
F. Houn
J. Beitz
M. Clark-Stuart
J. Li
DRMP BLA file (hard copy)

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 12, 2005

TO: Brian Harvey, MD, Director
Division of Gastrointestinal Drug Products

THROUGH: Claudia Karwoski, PharmD, Scientific Coordinator
Office of Drug Safety

FROM: Allen Brinker, M.D., M.P.H., Epidemiology Team Leader
Ann Corken Mackey, R.Ph., M.P.H., Safety Evaluator
Lanh Green, PharmD, M.P.H., Safety Evaluator Team Leader
Division of Drug Risk Evaluation

DRUG: Myozyme (Alglucosidase alfa)

BLA#: 125141/0

SPONSOR: Genzyme

SUBJECT: Pharmacovigilance Plan (PP) submitted July 29, 2005

PID #: D050475

The Office of Drug Safety performed a review of the proposed Pharmacovigilance Plan (PP) for Myozyme as submitted on July 29, 2005 and conclude that the plan appears routine but reasonable since no significant safety issues have been identified to date for Myozyme.

Myozyme is an enzyme replacement product used in patients with Pompe disease (also known as glycogen storage disease type II, acid maltase deficiency, and glycogenosis type II), a rare, genetic muscle disease resulting from an underlying deficiency of the lysosomal enzyme acid alpha-glucosidase. The submission does not identify a specific safety concern for which a Risk Minimization Action Plan (RiskMAP) to minimize risk would be associated.

Genzyme is proposing a voluntary patient registry to collect clinical data on patients with Pompe disease in order to enhance the understanding of the disease and its management.

A patient registry has already been established to enhance the understanding of Pompe disease. Patients currently receiving treatment with Myozyme are not enrolled in the patient registry; however upon approval the collection of treatment related data, including adverse event experiences will be collected in the registry. The sponsor anticipates that they will disseminate data collected from the registry to the FDA as part of the BLA annual report.

We remind the Sponsor of the final guidance to industry "Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report" at http://www.fda.gov/cder/guidance/1830fn1.pdf, states,

> "The FDA has determined, for purposes of postmarketing safety reporting under 21 CFR 310.305, 314.80, 314.98, and 600.80, that information concerning potential adverse experiences derived during planned contacts and active solicitation of information from patients (e.g., company sponsored patient support programs, disease management programs) should be handled as safety information obtained from a postmarketing study. Applicants, manufacturers, and licensed manufacturers should not report safety information obtained through these types of patient contacts unless the adverse event meets the regulatory definitions of serious and unexpected and there is a reasonable possibility that the drug or biological product caused the adverse experience (see 21 CFR 310.305(c)(1)(ii), 314.80(c)(2)(iii), 314.80(e), 600.80(c)(2)(iii), and 600.80(e))."

Under the process described above, the sponsor of Myozyme would have to report within 15 days serious, unexpected events from the registry for which they believe there is a reasonable possibility that the product caused the adverse experience, and other registry events would not be reported. If there was concern about particular events or if for some reason we wanted to see all serious unexpected events from the registry within 15 days, regardless of attribution, the sponsor could be asked to do more. The guidance doesn't specifically include "registry" in its description of planned contacts and active solicitation, but registries fit the definition and have been treated that way in the past.

If the Sponsor or the Review Division determine that a safety concern warrants consideration of a Risk Minimization Action Plan (RiskMAP), please refer to the following Guidance document: Development and Use of Risk Minimization Action Plans: http://www.fda.gov/cder/guidance/6358fnl.htm>. Should the review division want ODS to review a future RiskMAP submission please send a consult to ODS and notify the ODS-IO Project Management Officer, Mary Dempsey, at 301-796-0147.

Claudia B. Karwoski

Claudia Karwoski, PharmD, Scientific Coordinator
Office of Drug Safety

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

DEC 5 2005

Our STN: BL 125141/0

Genzyme Corporation
Attention: Alexander Kuta, Ph.D.
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the clinical; chemistry, manufacturing, and controls (CMC); clinical pharmacology; and pharmacology/toxicology section(s) of your application dated July 29, 2005, for Myozyme and have determined that the following additional information is necessary to take a complete action on your application:

1. In Study 1602, it appears that patients may have undergone at least some study-related screening procedures, especially skin biopsies, prior to the parent's signing of the study Informed Consent Form (ICF).

    a. Provide documentation of the timing of all screening and baseline procedures and the signing of the study ICF for all patients, regardless of whether patients were randomized or received treatment.

    b. In any case where a patient received any study-related procedure or test prior to the study ICF being signed, explain why the procedure or test occurred prior to obtaining study informed consent.

    c. In any case where a patient underwent a test prior to the study ICF being signed and for which Genzyme's central laboratory was used, explain why that laboratory was used.

    d. In instances where Genzyme had any involvement in a patient's care prior to study entry and prior to obtaining study informed consent, describe the nature of Genzyme's involvement, provide documentation as to why this was necessary, and explain how it related to the conduct of the study.

    e. Provide an explanation and supporting documentation for any instance where a central catheter was placed or a muscle biopsy was performed prior to obtaining

study informed consent. Not all patients have baseline catheter placement dates in the ivx_0.xpt dataset. Provide baseline catheter placement dates for patients 303, 305, 306, 308 and 314.

2. In Study 1602, patient 303 was randomized prior to the study ICF being signed. This was justified by time differences between the United States and Israel, and by concerns about a time delay through the weekend that could have resulted in patient ineligibility due to the age of the patient approaching six months. However, five days elapsed between randomization and the first infusion. Explain the necessity for the urgent randomization prior to obtaining study informed consent in light of the delay in giving treatment.

3. Provide more details on the process used to randomize subjects. Your explanation of why Subject 303 was randomized prior to the signing of the study ICF raises the question of whether the United States personnel responsible for randomizing the subjects were available on weekends. Clarify why the start of the week was problematic for the Israeli site, but not for other sites. If a subject was eligible for randomization on a Saturday or Sunday, discuss whether randomization was delayed until Monday. Provide documentation.

4. Clearly describe when the first infusion was supposed to occur, relative to the time of randomization. The study protocol suggests the start of therapy was at least 24 hours and as long as 30 days after randomization took place, as evidenced by the following:

   "Baseline must be completed within 30 days of first infusion"; see Footnote 1 to Table 9-1 "Initial Treatment Module", study protocol.

   "Placement of an indwelling catheter is at the discretion of the Investigator. Catheter placement should occur during the same episode of anesthesia as the muscle biopsy, at least 24 hours prior to the first infusion of study drug"; see Footnote 2 to Table 9-1 "Initial Treatment Module", study protocol.

5. Two patients died prior to completing screening procedures (— and — on screening log), and one patient became ineligible after study entry and before first infusion due to respiratory deterioration. We are concerned that delays in completion of screening procedures could have provided an opportunity for selection bias toward healthier patients. Please comment and discuss.

6. Information about protocol deviations and violations was not included with the datasets nor with the study report in the amendments submitted to the BLA with the updated 52-week study data. Protocol deviation and violation listings are necessary to adequately assess data integrity. Submit the protocol deviations and violations listings to the BLA.

7. Provide the screen log information in a SAS dataset.

8. Provide a dataset that contains the following dates:

   Randomization
   Birth
   First symptoms
   Diagnosis
   Informed consent
   Skin biopsy
   Shipment of cells
   Results received
   Blood draw for GAA analysis
   Shipment of blood
   Results received
   Screening procedures completed
   Baseline procedures completed
   Muscle biopsy
   Placement of catheter
   First infusion

9. Provide the following sensitivity analyses to help address the issue of selection bias:

   Using the data from Study 1602, calculate the maximum chronological age at the time of randomization.

   From the historical control cohort, select the subset of subjects who were alive at the maximum chronological age calculated from Study 1602.

   Use Kaplan-Meier analyses and graphs to compare the combined treatment groups from Study 1602 with the subset of historical controls. The analyses are based on the maximum chronological age at the time of randomization:

   a. For each subject in 1602, truncate data at age of randomization or maximum chronological age, whichever is greater. Use this as the baseline.

   b. For each subject in the historical controls, truncate data at the maximum chronological age. Use this as the baseline. If someone has not reached the maximum chronological due to death or other reasons, that person's data will not be included in this analysis.

10. Provide copies of all DSMB meeting minutes and copies of all communications between Genzyme and the DSMB.

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information

request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: **Information Request (IR)**

SS Data Check:
- **Communication**

cc: C. Stark/HFD-180
A. Pariser/HFD-180
B. Strongin/HFD-180
J. Hyde/HFD-180
B. Harvey/HFD-180
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M. Clark-Stuart
J. Li
DRMP BLA file (hard copy)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 12, 2005

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Telecon

PARTICIPANTS:

CDER:	Cristi Stark, Florence Houn, Debi Nhu Tran, Fred Mills, Gibbes Johnson, Lisa Kammerman, Jasti Choudary, Barbara Wilcox, Anil Rajpal, Anne Pariser, Hari Sachs, Jean Temech, Debi Avant, Brian Harvey, John Hyde, Marlene Swider
Genzyme:	Alison Lawton, Alexander Kuta, Betty Wiley, Mark Hayes, Jennifer Panagoulias, Edward Kaye, Jennifer Hunt, Alison McVie-Wylie, Nancy Silliman

A telecon for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides
was held on December 12, 2005.

Genzyme: Received all three information request letters (November 18, 2005, December 5, 2005, and December 6, 2005). They believe they can respond to all the questions posed in each letter to FDA with a response by December 30, 2005. In the December 30, 2005 response Genzyme will officially remove the process of the 2000 L scale. Genzyme does question the items outlined in the three information request letters. Are these data new requests? It seems that all information needed is contained in the submission.

FDA: The Agency has tried to keep the transition process smooth. The primary medical officer, medical team leader, and pharm/tox reviewer are consistent. Some of the issues we are raising in the information request letters were presented in your End of Phase 2 (EOP2) meeting and letters previous from ODE6.

Genzyme: In response to your pre-clinical requests in the information request letters we can respond to all questions. We will detail all chronic toxicology and manufacturing issues. We do agree with question #5 and the need for a second species and have plans to conduct embryo

toxicology studies early next year. In addition we can provide the exposure data asked for in the context of other studies and human studies.
In response to your clinical requests in the information request letters, we verify that skin biopsy and TMB blood draws are tools used for standard of care. We do have and will provide all the details for dates of informed consent, screening, and randomization. In addition, we did set up regional study sites due to the various patient locations of subjects which did impact time (caused delays). Also we did accept assessments done as the standard of care for the patient baselines.
We will take the 2000 L scale off the table at this time so we can deal with the indication. You have indicated that data in the infantile population are stronger. Where do you stand?

FDA: The withdrawal of the 2000 L process is helpful and will lead to a better outcome. We want you to focus on the 160 L data for CMC and clinical trials, and the infantile population. We will send you numbers to focus on for the infantile population and the 160 L process.

Genzyme: We would like to know what the FDA is defining as infants. Limiting to the 1602 trial is almost impossible. What are your thoughts of including the expanded access program (EAP) for the indication? The 1702 data and EAP data will be submitted to the agency on December 15, 2005. The responses to the information request letters will be submitted to the agency on December 30, 2005. In our December 30, 2005 response we will officially withdrawal the 2000 L process but not the late-onset indication. Is there any way from a broad medical policy, the ability to extrapolate from the infantile population to the late-onset population?

FDA: You cannot extrapolate from infantile to late-onset. The disease course for the late-onset population is very different from the infantile disease course. We are open to discussing this before an advisory committee. However, if you want this route you will receive a complete response at the end of January 2006 so we can prepare. Also note that we do have administrative options regarding your application. We can administratively split the indications so we review the infantile for approval and split the late-onset population for a complete response.

Genzyme: To what extent can you extrapolate the infant data, the 1702 data, and the EAP data to somewhere in-between?

FDA: We will need to see the data and then we can try to talk about what is possible. You will need to put in writing and argue what your position is for the indication you desire. What population are you seeking? Through age 2? 6? 16?

Genzyme: We have several options but are looking towards an indication statement of "

FDA: The indication statement you just proposed is very similar to what is currently proposed. That is highly unlikely. You still have not answered Dr. Harvey's concerns regarding

— You need to make your proposal with data justifying — — and we will get back to you.

FDA: Do you acknowledge problems with the 2000 L process and the need to focus on the 160 L process?

Genzyme: We do have data for the 2000 L process, but now what is specifically asked for.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 2, 2005

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Telecon

PARTICIPANTS:

CDER: Cristi Stark, Florence Houn, Debi Nhu Tran, Fred Mills, Gibbes Johnson, Lisa Kammerman, Jasti Choudary, Barbara Wilcox, Anil Rajpal, Anne Pariser, Hari Sachs, Jean Temech, Debi Avant, Brian Harvey, John Hyde, Marlene Swider, Amy Rosenberg, Barry Cherney, Jin Hai Wang

Genzyme: Alison Lawton, Alexander Kuta, Betty Wiley, Mark Hayes, Jennifer Panagoulias, Edward Kaye, Jennifer Hunt, Alison McVie-Wylie, Nancy Silliman

A telecon for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides
was held on December 2, 2005.

Genzyme: As per our fax, we received the November 18, 2005 information request letter and had the following questions based on the requests outlined in the letter:

Question 13a: Please note that Study 1702 remains ongoing and a final report is not expected until Q3 2006. Patients were initially treated under a 52-week treatment module and were then transitioned to a 52-week repeating maintenance module, which is currently ongoing. Accordingly, Genzyme will provide FDA with all efficacy and safety data sets on 21 patients from Study 1702 which will consist of merged data from the first 15 patients enrolled through September 3, 2004 (as submitted in the initial filing) and data through Week 52 for the remaining 6 patients. Please comment.

Question 16: For the electronic data set, should Genzyme also calculate the number of days to event? If so, please specify the "baseline" date that should be used.
Please confirm that the time to event endpoints that should be included are invasive ventilator-free survival, ventilator-free survival and survival.

Questions 17-19: We understand these questions wish to address the potential bias in the time-to-event analyses due to patients having survived for a period of time prior to receiving treatment. To address this

issue, Genzyme recently prepared an analysis of invasive ventilator-free survival, ventilator-free survival and survival for the EMEA using a Cox proportional hazards model with treatment as a time-varying covariate to compare endpoints between 1602 and the historical control, as well as for survival in 1702. Overall treatment and the effect of the different doses were analyzed. This analysis is conservative in that it credits survival in the treated patients from birth up to their first infusion to the untreated group. This analysis was done using date of diagnosis as the beginning of the risk period for each patient, although this type of analysis could be performed using date of birth as the beginning of the risk period. Would this type of anlaysis address Questions 17-19? If this analysis does not address questions 17-19, we have the following questions:
-For Question 17, should the description compare the 20 mg/kg versus 40 mg/kg groups only? If comparisons to the historical control are requested, it is unclear what date we would use for the control group for baseline as they have no date of randomization.
-For Question 19, Genzyme is unclear which analyses the Agency would like repeated by does. If it refers to Question 17, then please clarify how to compare the historical control as they have no date of randomization.

Question 36: Given that activity values are likely to vary significantly when the — Genzyme would like additional information on the potential value of using a —

Question 42: Question 42 requests a side-by-side comparison of 3 commercial 2000 L lots and a minimum of 3 160 L lots (Phase II/III clinical materials). These data were provided in the BLA in the Characterization section (3.2.S.3.1) and in the Technical Reports TR-TPR-04002 and 05GSTR009 section attached to Section 3.2.S.2.6. Does FDA want a re-representation of the data in a side-by-side format, or in a format other than what is specified in Questions 43-50, that would assist in the review of comparability? The question also asks for data from "commercial 2000 L lots." We assume this means the commerical scale 2000 L lots and not the first 3 commerical lots released.

Question 46: Question 46 requests head-to-head forced degradation studies. Degradation pathway studies were provided in Section 3.2.S.3.1.4 using rhGAA exposed to — (Appendix 3.2.s.3.1-01, Technical report TR-BD-03K06). Is FDA requesting for analysis of rhGAA from — Given that the specific modes of degradation were identified in the completed studies noted above, would the agency accept using that subset of assays to support a comparative analysis?

Question 70: Please indicate the time frame (cut off date) for which the Agency is seeking information regarding IgE testing.
Regarding infusiono-associated reactions, is tryptase and complement testing data also requested as part of this response?

Question 71: Based on the range of titers seen to date in patients who have received Myozyme, Genzyme defines "high titers" as IgG antibody titers > 10,000. Please comment.

FDA: In regards to Question 13a - The original protocol states that Study 1702 is a 52-week study. As original 52-week treatment has been completed and as last update to Study 1702 data was at the Sept-2004 cutoff, there is >1 year's worth of safety data outstanding. Please submit safety data to a more reasonable cutoff date (e.g. after all patients completed 52 weeks of study, or e.g., Sept-2005 cutoff. Please also submit primary efficacy update (any ventilation survival status) to within a reasonable cutoff (e.g., Sept-2005), and antibody data for all patients through initial 52 weeks of study.

In regards to Question 16 – Calculating the number of days to event would be very helpful. The "baseline" dates that should be used are the following:

Date of randomization
Date of birth
Date of 1st symptoms
Date of diagnosis
Date of 1st infusion

We confirm that the time to event endpoints that should be included are invasive ventilator-free survival, ventilator-free survival and survival.

In regards to Questions 17-19 - Your analysis will be helpful as a sensitivity analysis and we look forward to seeing the results. We still want the analysis that we suggested in Questions 17-19 of your November 18, 2005 letter. Please refer to our responses to your questions. Here is a rationale and clarification for Questions 17-19.

The Kaplan-Meier analysis most appropriate for Study 1602 requires the date of randomization as the baseline. In addition, as you pointed out, selection bias is an issue when making comparisons between Study 1602 and the historical controls. Questions 17-19 attempt to address these concerns.

Questions 17 and 19: Use the data from Study 1602 only. Present the Kaplan-Meier analyses and graphs using the date of randomization as the baseline. Because this was a dose-ranging study, please present the results for both treatment groups combined and separately for each treatment group. Discuss whether there is a dose response or not (calculated from the date of randomization).

Question 18: This request is an additional sensitivity analysis for the comparison with the historical controls. This analysis is limited to those subjects who survived to the age of 6 months. This age is based on Study 1602, in which the maximum age at randomization was 6 months.

For the combined treatment groups from Study 1602 and for the historical controls do Kaplan-Meier analyses and graphs that use 6 months of age as the baseline date.

Genzyme: We can do the Kaplan-Meir analyses and graphs that use 6 months of age as the baseline date but then we are disregarding the 1st five months.

FDA: These are all sensitivity analyses so you should do what you proposed and then add this as additional testing.

In addition to the requests in your November 18, 2005 information request letter we have some new requests.:

Clinical

1. In the IR, Item 15 states

   "For Study 1602, provide an electronic dataset that contains the date of randomization for each subject".

   In addition to date of randomization, please include the following dates:

   Birth
   First symptoms
   Diagnosis
   Informed consent
   Skin biopsy
   Shipment of cells
   Results received
   Blood draw for GAA analysis
   Shipment of blood
   Results received
   Screening procedures completed
   Baseline procedure completed
   Date of placement of cathedar
   Date of first infusion

   Also provide the screening log to SAS datasets (for all subjects screened).

2. In all but 1 patient for whom skin biopsy data are available (n=14), skin biopsy was done before (often months before) informed consent was signed. While it's possible that this could have been part of practice of medicine to diagnose the patient in the first place, study or no study, it says in the protocol that fibroblast analysis was done at Duke Med Ctr, which would have required informed consent. This needs to be clarified - were they using prior biopsies for study qualification, and if yes, why is Duke noted as central lab? If no, why is ICF so long after biopsy? Were other screening or baseline procedures routinely performed on patients prior to the signing of ICF? Were central labs used for these assessments as well?

3. There was 1 patient who was randomized prior to ICF being signed (Patient 303 in Israel). Explanation received from Genzyme as follows:

   "Since the site was in Israel, their work week began on a Sunday and with the time delay to the US where randomization was conducted, a randomization request sent on Sunday

would not be returned to the site until the end of the day on Monday in Israel. Keeping in mind the patient's age and the time difference between Israel and the US, it was important for the site to be able to enroll and infuse the patient as soon as the remaining screening/baseline procedures could be completed and the patient qualified for the study. As such, the randomization occurred prior to signing informed consent."

However, since 5 days elapsed between randomization and first infusion, this explanation doesn't explain why randomization had to occur prior to ICF signing. Please clarify.

4. Three patients died or were inelgibile for study based on respiratory status on screening log (+ patient 304). Were there delays in screening procedures or patient identification that led to ineligibility? Two additional patients' parents refused to consent – do we know why?

5. Protocol deviations/violations were not included in 52-week submission. Please submit ASAP.

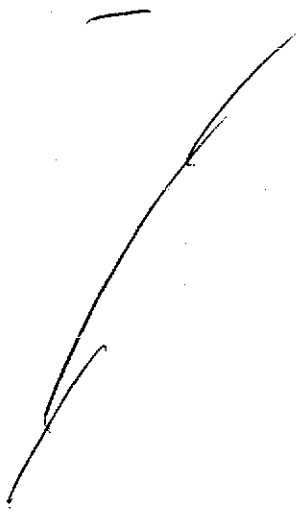
Pharm/Tox

4. Regarding — Study #6354-140 (Comparison of three preparations of rhGAA: GenzrhGAA, BI2KrhGAA, BI —rhGAA
   - The protocol calls for retrieval and preserving a full panel of tissues, presumable for histopathology. However, no histopathology data are reported, in spite of the fact that apparent dose related gross lesions were observed (liver enlargement that correlates with changes in liver function, stomach lesions).
     What was the fate of those tissues? Why was histopath not reported?
   - It appeared that the BI2KrhGAA may have had slightly higher incidence of these adverse effects. Which process was the GENZ rhGAA produced with? Was this a lot produced with the 160L (Lot #GA028)
   - In — study # 6354-133 (rat tox study), similar gross lesions were not seen, nor were any effects noted for clinical chemistry parameters even though the high dose (100 mg/kg) was greater than that administered in study 140 and the regimen was the same. Please comment. By which process was the lot used in study 133 (GW10124094) produced?

5. Regarding the Reproductive toxicology study, #6354-155, (fertility and early embryonic development)
   - The high dose used in this study was 40 mg/kg delivered every other day to both male and female mice starting prior to mating and continuing through early gestation for females and until termination.
     The justification for the high dose is not clear. How do the exposures (both male and female) to test article for this study compare to those of other tox studies that used higher doses but less frequent dosing? How do the exposures of the animals (both male and female) in this repro/tox study compare to those anticipated for human use?

All of these deficiencies will be included in another information request letter to you.

In regards to Question 36 -



In regards to Question 42 -Please refer to the Agency Comment, Bullet Point 2, provided at the May 3, 2005 pre BLA meeting.
In order to expedite review, it would be of great help if the data were presented as side by side comparisons of 160 L and 2000 L material. should include 160 L and 2000 L samples run and in general, analyses on 160 L and 2000 L samples should be performed during a similar time frame. Please note that the comparability assessment should include the data requested in questions 43-50.
Data from commercial scale 2000 L lots (not the first 3 commercial lots) is what is being requested.

In regards to Question 46 - It would be desirable to obtain 160 L and 2000 L degradation data both under conditions shown to produce significant degradation, such as Data obtained at 4 ^{0}C and 25 ^{0}C, for a single lot each from the 160 L and 2000 L process would be adequate. In general, measurements that capture previously identified modes of degradation would be sufficient, but the data should include measurements using a physiologically relevant activity assay (not the assay).

Please note that if, upon completion of the requested photostability studies, significant sensitivity to light is observed, it will be important to perform comparative photo-degradation studies on 160 L and 2000 L material.

In regards to Question 70 - Because there were no anaphylaxis episodes, we can consider validating this as a post marketing commitment.

In regards to Question 71 – Due to repeatability tests, you can be off by as much as a titer. So, 1 in 6400 should be defined as a high titer.

Please note that submission of a large amount of material for review in the last 90 days of a review cycle can trigger a major amendment which extends the clock by another 90 days. Response to your deficiencies will be considered a major amendment. You must address these deficiencies in order to obtain a positive action on your application. Due to the time constraints on a priority clock you must submit a major amendment by the close of December 2005. Otherwise, the deficiencies will warrant the division to move forward with a complete response on your application.

Genzyme: We plan to respond to all deficiencies and will do so by December 31, 2005.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 18, 2005

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Telecon

PARTICIPANTS:

CDER: **Cristi Stark, Joyce Korvick, Florence Houn, Brian Harvey, John Hyde, Anne Pariser**

Genzyme: **Alexander Kuta, Betty Wiley, Jennifer Panagoulias**

A telecon for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides
was held on November 18, 2005.

Genzyme: We submitted the late onset data to the agency. Has this information helped the agency with their review?

FDA: It has been a very short time period since the late-onset data was submitted. We do have some basics but are not willing to go into detail. The summaries were high level and not informative. The datasets were just received a few days ago so we need time to review them. The data is strongest for the youngest group. We will be sending you an information request letter shortly. When you receive your letter please let us know your preference for a complete response or a major amendment.

Genzyme: At the start of the submission we discussed accelerated approval with the possibility of using the infantile population as a surrogate endpoint for the late-onset population.

FDA: How many patients enrolled in the late-onset study? Are all of these patients to be treated with the 2000 L process product?

Genzyme: There are currently 20 patients enrolled. All patients in the late-onset study will be treated with the 2000 L process.

FDA: Your accelerated approval with surrogates is not a good option. You do not have the circumstances and data to move down that path. What is your surrogate for this? A patient population does not count. Do you have muscle biopsies, etc?

Genzyme: We do not have any other biomarkers for a surrogate. We were thinking that the results of the infantile population would serve as a surrogate as a worst case scenario.

FDA: Subpart E does not fit that definition. In addition, you are asking us to extrapolate. This is not possible. Where is your data for patients treated with 80 mg/kg?

Genzyme: We are still gathering data and will supply it to the agency when it becomes available. In our next telecon we would like to discuss the plan for additional data: the 120-day safety update is due on November 29, 2005, the 6 patients update is due on December 15, 2005, and the narratives for the EAP is due on December 15, 2005. Please fax the information request letter to Betty Wiley at: (617) 768-6419.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125141/0

NOV 18 2005

Genzyme Corporation
Attention: Alexander Kuta, Ph.D.
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the clinical; chemistry, manufacturing, and controls (CMC); clinical pharmacology; and pharmacology/toxicology section(s) of your application dated July 29, 2005, for Myozyme and have determined that the following information is necessary to take a complete action on your application:

Clinical/Statistical

1. For Study 1602, confirm whether or not the following personnel were blinded to patient and to study timepoint:
   a) central cardiologist reading ECGs and echocardiograms
   b) pathologist evaluating tissue samples for histopathological, biochemical and gene expression analyses.

2. In Study 1602, describe procedures used to "standardize" or "quality control" the performance of the pathologists and cardiologists. For example, were they also given "normal" samples as a means to quality control their performance, or were the samples all from study subjects? Describe any training they may have received.

3. In Study 1602, the AIMS assessments was performed by trained personnel at study sites and raw scores were centrally scored by a trained clinician. Were the personnel performing the AIMS test and the central scorer blinded to dose? Was the central scorer blinded to patient and sequence?

4. Describe the training given to the AIMS and Pompe PEDI evaluators and discuss procedures used to maintain consistency across study sites.

5. In Study 1602, describe blinding procedures used for the BSID-II and measures used across sites to maintain consistency.

6. Discuss the process used to translate the instruments into different languages. Describe the procedures used to validate the AIMS, Pompe PEDI and BSID-II instruments for use in the cultures and languages encountered in the studies.

7. In Study 1602, describe blinding techniques, if any, used for respiratory and radiology assessments.

8. In Study 1602, blinding for the central cardiologist was stopped after the first year of treatment. Is this also true for any other assessments after the first year?

9. For Study 1702, "single-blind interpretation" was noted for cardiology parameters - clarify exactly what blinding procedures were used (e.g., blinded to patient, to treatment, or to sequence), and what blinding procedures, if any, were used for any of the other study assessments, including motor and mental development, respiratory function, pathology, and radiology assessments.

10. For Study 1602,
    a) Clarify what happened to subjects, beginning with screening, through randomization and first infusion, i.e., provide explicit timelines for each patient from screening to randomization and then to first infusion.
    b) Describe what was supposed to occur, including a description of when the first infusion was to take place once a subject was randomized (e.g., randomized and treatment/first infusion within 24 to 48 hours).
    c) Provide explanations for subjects who started treatment after the time window specified in your answer to b.
    d) For Subject 304, who was not randomized, identify the amount of time that elapsed between the date of informed consent and the date the patient was placed on ventilation.

11. In Study 1602, it appears that there was one screening failure in addition to the one subject randomized but not treated (Subject 304). Supply screening failure information on this patient and any other screening failure patients. Were screening failures entered into any other treatment protocols?

12. For Study 1602, supply copies of medical records from all four patients entered at the Taiwan site (304, 305, 306 and 310) and the patient entered at the Cincinnati site (316), beginning with pre-screening/screening information leading to patient identification and entry into the study. Also, supply the English translation for the Taiwanese patients, if the records are not in English.

13. For Study 1702, the study was conducted March 17, 2003, through unknown (52-week treatment study). The data collected to the cut-off date of September 3, 2004, as well as the corresponding Study Report were noted to be "interim". At the time of data cut-off, efficacy data through study completion were provided on the first 15 of

21 enrolled patients and on the remaining six patients up to Week 12, and safety data to September 3, 2004, were supplied on all 21 patients. The synopsis of the protocol states "A final analysis and report will describe all data from all 21 patients who were treated in the study." As this study has been completed, submit the following:

a) All efficacy and safety datasets for all 21 subjects treated through Week 52.
b) For patients receiving ongoing treatment, provide an updated status (survival and ventilator status) on these patients current to within 3 months.

14. Provide all data on all patients treated with rhGAA at doses greater than 40 mg/kg.

15. For Study 1602, provide an electronic dataset that contains the date of randomization for each subject.

16. For Study 1602, provide an electronic dataset that contains a censoring variable (1=event, 0=censored) and date of event for each of the time to event endpoints. Calculate these variables for each subject based on the subject's last available information.

17. For Study 1602, redo the time-to-event analyses using date of randomization as the baseline.

18. Provide landmark analyses to compare the results from Study 1602 with the historical controls. Use a cutoff age of 6 months for both Study 1602 and the historical controls. Repeat the time-to-event analyses using the cutoff age as the baseline. Provide Kaplan-Meier graphs of the results.

19. Submit results summarized by treatment group based on the date of randomization. Discuss your findings.

20. For Subject 8101313:
    a) Explain why 45 days elapsed between the date of informed consent and the date of randomization
    b) Explain why 10 days elapsed between the date of randomization and the start of infusion

21. For Subject 6003315, explain why 17 days elapsed between the date of randomization and the start of infusion.

22. As shown in the following table, four of the study sites evaluated only one of the doses. Discuss how these imbalances may have affected the results and their interpretation, including the lack of a dose response finding.

	Site 10	*Site 20*	*Site 21*	*Site 52*	*Site 60*	*Site 81*	*Site 83*
20 mg/kg	1	-	1	3	1	1	2
40 mg/kg	2	3	-	-	2	2	-
	3	3	1	3	3	3	2

Clinical Pharmacology

23. For Studies 1602 and 1702, provide a plot for each individual patient after infusion on Weeks 0 and 12 of plasma GAA activity versus time that has anti-rhGAA antibody titers superimposed on each plot.

24. For Studies 1602 and 1702, provide a scatter plot of individual plasma GAA activity AUC after infusion on Week 0 versus individual anti-rhGAA antibody titers between Weeks 0 and 12, and a scatter plot of individual plasma GAA activity AUC after infusion on Week 12 versus individual anti-rhGAA antibody titers after Week 12.

25. For Study 1602, provide scatter plots (one for the 20 mg/kg group and one for the 40 mg/kg group) of individual skeletal muscle glycogen content determined by the biochemical method versus time (Baseline and Week 12). Also provide a scatter plot of change in individual skeletal muscle glycogen content determined by the biochemical method from Baseline to Week 12 versus dose (20 mg/kg and 40 mg/kg).

26. For Study 1602, provide the same plots as requested in item number 25 above for skeletal muscle glycogen content determined by the histomorphometric method.

27. For Study 1602, provide scatter plots (one for the 20 mg/kg group and one for the 40 mg/kg group) of individual plasma Hex4 levels versus time (Baseline, Week 4, Week 12, and Week 26); in addition, provide a scatter plot of individual plasma Hex4 levels versus time that has 20 mg/kg group and 40 mg/kg group data at each of the time points. Also provide plots (one for the 20 mg/kg group and one for the 40 mg/kg group) of change in individual plasma Hex4 levels from Baseline versus time (Week 4, Week 12, and Week 26); in addition, provide a scatter plot of change in individual plasma Hex4 levels from Baseline versus time that has 20 mg/kg group and 40 mg/kg group data at each of the time points.

28. For Study 1602, provide the same plots as requested in item number 27 above for urine oligosaccharide (Hex4) levels.

29. For Study 1602, provide plots that compare the results with regard to CRIM status. In particular, provide scatter plots of individual plasma GAA activity AUC, skeletal muscle GAA activity, skeletal muscle glycogen content (biochemical and

histomorphometric), plasma Hex4 levels, and urine Hex4 levels versus CRIM status. In addition, provide scatter plots of each of these parameters as change from Baseline versus CRIM status.

30. For Study 1702, provide a scatter plot of individual skeletal muscle GAA activity versus time (Baseline, Week 12, and Week 24). Also provide a plot of individual change in skeletal muscle GAA activity from Baseline versus time (Week 12 and Week 24).

31. For Study 1702, provide the same plots as requested in item number 30 above for skeletal muscle glycogen content determined by the biochemical method and for skeletal muscle glycogen content determined by the histomorphometric method.

32. For Study 05-0271Pga, provide scatter plots (one for each lot group and one for each tissue) with individual glycogen content (biochemical) in the heart, quadriceps, and triceps versus time (Baseline, and after 4 doses). In addition, provide scatter plots (one for each tissue) of glycogen content (biochemical) versus time that has that has data for individual animals in each lot group at each of the time points. Finally, provide a scatter plot of change in glycogen content (biochemical) from Baseline versus tissue (heart, quadriceps, and triceps) that has data for individual animals in each lot group by tissue.

33. For Study 05-0252Pga, provide scatter plots (one for each lot group and one for each tissue) of individual activity results in the liver, quadriceps, spleen, and triceps versus time (1 hour, 4 hours, and 8 hours). In addition, provide scatter plots (one for each tissue) of activity results versus time that has data for individual animals in each lot group at each of the time points.

34. For Study 05-0252Pga, provide plots (one for each tissue) of the percent injected dose of the 2000 liter lot divided by the percent injected dose of the 160 liter lot versus time that has data for individual animals in each of the two 2000 liter lot groups at each of the time points.

CMC

35. Implement a potency assay which reflects [redacted] This assay must be used for Drug Substance and Product lot release and in stability specifications. Include data supporting the proposed acceptance criteria.

36. An [redacted] potency assay [redacted] must be implemented for Drug Substance and Product lot release and stability specifications. Include data supporting the proposed acceptance criteria. In addition, you should evaluate the feasibility of using a [redacted]

37. The position and amount of per mole of rhGAA needs to be controlled and specified. may be responsible for the in vivo bioactivity. Provide a specification for the position and amount of per mole of rhGAA in Drug Substance and include data supporting the proposed acceptance criteria.

38. Establish a quantitative measurement of the test method used for Drug Substance release testing. Include data supporting the proposed acceptance criteria.

39. Photostability studies must be performed on Drug Substance and Product because and Drug Product is diluted in IV bags for administration.

For the 2000 liter process

40. The application did not include a method validation report for the new testing for the 2000 liter process. Submit the report including results of the validation studies.

41. Provide the data from the for the 2000 liter Bioreactor E.

Comparability (160 versus 2000 liter scales)

42. A side-by-side comparison of three (3) commercial 2000 liter lots and a minimum of three (3) lots of 160 liter Phase II/III clinical materials should be performed to demonstrate comparability of the two manufacturing processes. Provide qualitative and quantitative results.

43. The use of ms provides a much more sensitive method for evaluating subtle but important changes in product quality. Submit compartive results from an potency assay using a more should be determined in comparability studies.

44. Provide information adequate to assess the methodologies used in the assays. It is not clear if the binding is specific and high affinity. All data submitted should include clearly labeled raw data values prior to any calculations or subtractions of background.

45. Provide a comparative analysis of the position and amount of per mole of rhGAA.

46. Provide head-to-head forced degradation studies to demonstrate consistent degradative kinetics.

47. be performed on pre and post changed product. These data can support comparability.

48. The comparability study needs to include the use of a method c

49. Provide a comparative assessment of

50. A comparative pharmacokinetic analysis indicates that there are significant differences observed between the 160 and 2000 liter materials. Provide an analysis of the physicochemical basis for these differences. If a root cause is identified, describe how this physicochemical difference will be monitored and controlled. If a root cause is not identified, describe how you will proceed in establishing comparability.

Other CMC

51. Tighten the limits for in accord with manufacturing and clinical experience. Provide justification for the new limits.

52. Set a quantitative specification for the present in oligosaccharide mapping analysis. Provide data supporting the proposed changes.

53. Include a specification for for the Drug Substance.

54. Establish a limit for the amount of in Drug Substance.

55. Concerning bioburden: It is not clear what positive control was used in the determination of bioburden in rhGAA Provide clarification.

56. rhGAA Concentration: The protocol for determination of rhGAA concentration (QC-050-55) does not describe an acceptable length of sample storage period prior to analysis. Include this information in the protocol and provide data supporting this limit.

57. history. Propose revised limits and justification for these limits.

58. : Content: Submit the validation study assessing the detection/quantitation limits of this assay.

59. Mannitol: Submit data describing the limit of detection, limit of quantification and robustness. An acceptable length of time for mannitol standard storage should be described.

60.

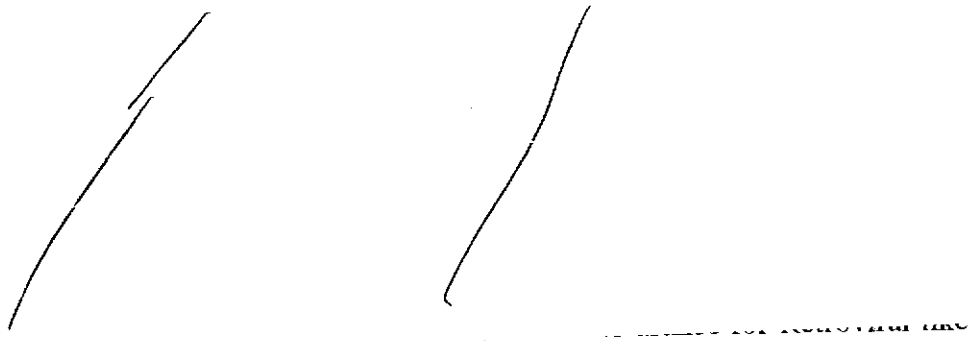
61. Polysorbate 80: Limits of quantitation and range of this assay are narrow (— % for formulated drug substance and for the drug product, respectively). The Additional studies addressed the narrow range but results were not presented. Provide these studies.

62. — Impurities (— Include validation studies assessing the . — concentration and incubation time.

63.

64.

65.



66. The Drug Product Container closure compatibility studies appear to be performed on one sample. Provide justification on this approach.

67. There are no — s data (in the context of the vehicle or product/vehicle) available for the Drug Product. Provide this information.

68. For Drug Product near the end of its reconstitution hold time, provide analyses using —

Immunogenicity

69. Regarding assessment of neutralizing antibody, no information was included in your package regarding the capacity of GAA antibody to impact the binding and entry of GAA into human muscle cells. Provide information from a neutralizing assay that assesses this potential effect of antibody, or develop and implement a neutralizing antibody to do so. Provide the validation data for your current neutralizing (enzyme activity) assay. Also provide the results from the testing of all patient samples that were positive in the binding assay, as well as samples from patients that were negative

for binding antibodies, but whose clinical outcome suggest less than optimal treatment effect, ie, loss of developmental milestones, requirement for invasive ventilation, or death.

70. Provide the validation data for your IgE assay and the results of testing sera of all patients with infusion associated reactions.

71. High titers of anti-rhGAA antibody found in many patients correlate with unfavorable clinical outcomes including loss of developmental milestones, requirement for invasive ventilation, and death. Examine this correlation to understand the impact of binding and neutralizing antibody on safety and efficacy.

72. Provide the data regarding the genetic mutations of patients corresponding to numbers 303, 305, 312, and 317.

73. Provide the methodologies and qualification data for both the typtase assays and the complement activation assays. Indicate whether β-tryptase or total tryptase was measured in patients.

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days.

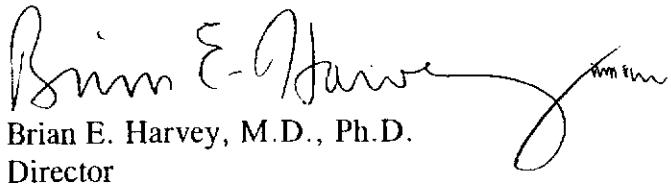
Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,



Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: **Information Request (IR)**

SS Data Check:
- **Communication**

cc: C. Stark/HFD-180
A. Pariser/HFD-180
B. Strongin/HFD-180
J. Hyde/HFD-180
B. Harvey/HFD-180
J. Korvick/HFD-180
F. Mills/HFD-122
J. Wang/HFD-122
G. Johnson/HFD-122
A. Rosenberg/HFD-122
B. Cherney/HFD-122
E. Shores/HFD-123
S. Kozlowski/HFD-123
A. Rajpal
H. Zhao
B. Wilcox
J. Choudary/HFD-180
L. Kammerman
S. Grosser
F. Houn
J. Beitz
M. Clark-Stuart
J. Li
DRMP BLA file (hard copy)

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__✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 28, 2005

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Telecon

PARTICIPANTS:

CDER: Cristi Stark, Brian Strongin, Brian Harvey, Florence Houn, Anne Pariser, Barbara Wilcox, John Hyde

Genzyme: Alison Lawton, Alexander Kuta, Betty Wiley, Edward Kaye, Deya Corzo, Jennifer Hunt, Ronald Knickerbocker, Sue Richards, Kate Melia, Nancy Mulrow, Alison McVie Wylie, Michael O'Callaghan, Richard Mosciciki

A telecon for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides
was held on October 28, 2005.

Genzyme: Believes they have demonstrated clinical benefit for the severe form of the disease and have the drug available for the entire population (including late-onset). Genzyme delivered the data on the late-onset population on 10/27/05 and reference the guidance for special cases/orphan. Currently the late-onset controlled study (LOTS) has 10% enrollment and will be full by the close of January 2006. Genzyme has successfully completed studies in Phase 4 while commercial drug is available (ex. Fabrazyme). In addition they have established a registry.

FDA: For your proposed indication we are looking carefully at your data. Making your drug available to all patients may not be the approved indication. We are currently five months out from the completion of study 1602 and have not received the full 52-week data. Regarding historical control, there are possible questions on the sensitivity analyses. A determination was made to not go to an Advisory Committee for this application. The endpoint of survival and ventilator-free survival are hard endpoints and speak for themselves. We do notice data quality issues, which makes it difficult to locate items. This may lead to additional questions that our review team may ask. In regards to manufacturing and product issues, the review is continuing and future issues may be brought to your attention.

Genzyme: We just submitted an abridged study report on 10/27/05 on the 52-week data for study 1602. This report includes the key efficacy variables and datasets along with immunogenicity, cardiac, motor, etc.

FDA: Your late-onset patients, are they treated with 160 L or 2000 L product? If 2000 L, will the entire late-onset trial finishing enrollment in 2006 receive 2000 L only? Also what will be the dose given?

Genzyme: The study finishing enrollment in 2006 (LOTS) will be all 2000 L with a 20 mg/kg dose. There currently is no efficacy difference between the 20 mg/kg and 40 mg/kg doses. The 40 mg/kg dose also had higher infusion reactions and antibody titers. There will be no dose adjusting in the late-onset population. This may be reconsidered at the end of the study when we see efficacy achieved.

FDA: Based on pharm/tox data, you can go up to 100 mg/kg in dosing. Our concern is that you may see differences in the population efficacy at a higher dose. You currently could be at the wrong dose (at the bottom of the curve).

Genzyme: We did not see any real advantage going above 20 mg/kg in the population. It is expensive to produce and going up to 100 mg/kg may not be practical in the real world. We have dosed some patients at 40 mg/kg every other week and at 80 mg/kg.

FDA: Since this is such a small population, we want you to submit ALL clinical data including 80 mg/kg. You should also submit all non-clinical data both in and outside the IND. All clinical and non-clinical data both IND and non-IND related to the product is requested. We are very accustomed to looking at expanded access; therefore, please submit this information. In addition we would like to see the information from patients in the 1702 study as the last cut-off was 9/3/04 and we expect all 21 patients to have completed the study by now.

Genzyme: We will submit the requested information. The last patient in 1702 just completed the 52 weeks. We will work with you to see what info can be submitted. Will submitting this information extend the review clock?

FDA: In reviewing, if it would result in something in your interest, we would work with you. This may result in a clock extension. We sense the urgency for a safe and effective treatment of Pompe disease. The requested information may help allay concerns with your data submission.

Genzyme: Is it possible to set up a communications channel? Also can we send you outside expert input?

FDA: We will provide an information request letter to you later this month/early next month with issues. Please let the team review the information that just arrived and get back to you for

feedback. As for the the outside expert—there is a procedure. If we need the input we will go through the executive secretary and use the appropriate channels.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 25, 2005

From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180

To: BLA 125141/0 file
Genzyme Corporation
Alglucosidase alfa (Myozyme)

Subject: Pre-clinical/Clinical Midcycle Meeting

PARTICIPANTS:

CDER: **Cristi Stark, Brian Strongin, Brian Harvey, Janet Whitley, Gibbes Johnson, Jin Hai Wang, Anne Pariser, Hong Zhao, Anil Rajpal, Peter Vaccari, Hari Sachs, Amy Rosenberg, Barbara Wilcox, Jasti Choudary, John Hyde, Florence Houn, Joyce Korvick, Catherine Gray, Jose Taverezpagan, Lisa Kammerman, Stella Grosser**

The early midcycle meeting for the Genzyme Corporation Alglucosidase alfa original BLA, STN 125141/0, which provides [redacted], was held on October 25, 2005.

Product: the team is not sure of the safety and efficacy of the product. There are significant problems. Currently there is insufficient data for comparability of the 160 L versus the 2000 L batches. In addition, Genzyme addressed very few concerns that were laid out at the pre-BLA meeting. The neutralizing antibody assay has not been validated.

Pharm/Tox: Pregnancy category [redacted]s recommended due to apparent reduction in embryo viability and reduction in sperm count at higher doses (potential fertility issue). The 40 mg/kg dose is not a high dose relative to other toxicology studies. Further toxicology studies can be a PMC (additional studies are not needed now, repro studies will be a labeling issue). All animals developed anti-drug antibodies; however, the pharmacokinetics were not affected.

Clin Pharm: The main issue is the comparability of the 160 L versus the 2000 L of the product. They are not comparable. The biochemical and histopathological skeletal muscle glycogen did not give a good read out. We need a better marker. The recommendation is to only approve the 160 L lot.

Clinical/Statistical/DSI: DSI is inspecting site 01 and 81. Problems were uncovered at site 52 (Taiwan). This is currently being discussed. Recommendation is to approve the infantile population and not the late-onset Pompe population.

See the attached handouts from the midcycle.

Midcycle Meeting: BLA 125141

STN:	125141/0
Sponsor:	Genzyme Corp
Product:	Myozyme (recombinant alglucosidase alfa, rhGAA)
Date:	25-October-2005

I. Introduction and Background

A. Introduction

This is the initial BLA application for Myozyme (alglucosidase alfa, rhGAA), under STN 125141/0, received 27-July-2005. This BLA submission has been granted priority review status as a proposed treatment for Pompe disease, an inherited disorder for which there is currently no available treatment. Myozyme has been studied under IND 10780 and was granted Orphan Drug Designation on 17-June-1997 and Fast Track Designation on 13-February-2003.

Related INDS: rhGAA derived from transgenic animal milk and Synpac rhGAA.

B. Background: Pompe Disease[1]

Pompe disease aka glycogen storage disease type II, GSDII, acid maltase deficiency:

- Autosomal recessive inherited disorder of glycogen metabolism resulting from deficient activity of acid α-glucosidase (GAA), a lysosomal hydrolase. Estimates of the incidence of Pompe disease in western nations ranges from 1/300,000 to 1/40,000, and may vary in different ethnic groups and for the different clinical forms. Heterozygous carriers are considered healthy.
- GAA catalyses the hydrolysis of α-1,4- and α-1, 6-glucosidic linkages at acid pH, leading to the complete hydrolysis of glycogen. In contrast to the other glycogen storage disorders, no defect in the glycogen degradation pathway is associated with Pompe disease (the major site of glycogen metabolism is within the cytoplasm). Presumably, intralysosomal GAA plays a role following autophagy of intracytoplasmic glycogen.
- GAA is synthesized and processed along a pathway common to many soluble lysosomal enzymes e.g., extensive posttranslational modification. There is evidence for differences in processing compared to most lysosomal enzymes and for alternative pathways with different localization in tissues, such as intestine and kidney.
- GAA deficiency results in intralysosomal accumulation of glycogen in most tissues, but the symptoms are mainly due to functional impairment of skeletal muscle. In infantile-onset form of the disease, accumulation is most marked in cardiac and skeletal muscle, but is essentially limited to skeletal muscle in the late-onset form and is of a lesser magnitude.

[1] In The Metabolic & Molecular Bases of Inherited Disease, 8th Edition, Chapter , Volume . Editors Scriver CR, Beaudet AL, Sly WS and Valle D. McGraw-Hill Medical Publishing Division, New York. 2001.

- Clinical diagnosis is made by a virtual absence (infantile-onset) or markedly reduced activity (late-onset) of GAA in muscle biopsies and in cultured fibroblasts.
- Pompe disease is genetically heterogeneous. Patients are typically compound heterozygotes for various mutations in the GAA gene, with missense, nonsense and splice-site mutations, partial deletions and insertions described.

Clinical signs and symptoms:
Wide range of clinical phenotypes, all of which include varying degrees of myopathy, but differ in the age of onset, extent of organ involvement and rate of progression to death.

- Classic infantile-onset disease is the most severe
  - Typically presents within the first few months of life with marked cardiomegaly, hypotonia ("floppy baby"), rapidly progressive weakness, macroglossia and less marked hepatomegaly.
  - There is generalized glycogen deposition predominantly in cardiac, skeletal and smooth muscle, liver, renal tubular epithelium and the CNS (mental development is grossly normal).
  - Cardiomegaly is progressive
  - Course is rapidly progressive with death usually before 1 to 2 years of life due to cardiorespiratory failure.
- Late-onset form:
  - Patients typically present in childhood (most common) or adulthood, with progressive proximal muscle weakness, usually of the pelvic girdle muscles with relative sparing of the distal musculature; however, in some patients, the first manifestations of the disease are restrictive respiratory insufficiency and respiratory failure.
  - The disease tends to follow a slowly progressive pattern of symmetrical, selective muscle weakness (lower > upper extremity) with distal sparing, later involvement of the upper extremities severe diaphragm weakness, and respiratory insufficiency.
  - Cardiac muscle is spared.
- Between the two extremes is a heterogeneous group of presentations, usually without cardiac involvement and with a progressive course of myopathy including major impairment of respiratory function. Childhood, juvenile or muscular variant generally has onset after infancy with a predominance of skeletal muscle involvement, usually without cardiac involvement and with a more slowly progressive course as compared with classic infantile-onset form.
- Death in all forms of the disease usually results from respiratory failure.

II. Review of BLA Application

A. Overview of Myozyme® Clinical Development Program

As of the date of the submission, a total of 56 patients have been exposed to Myozyme most commonly at a dose of 20 mg/kg qow (range 10 mg/kg to 40 mg/kg qweek to qow).

Efficacy data from a total of 50 (41 infantile-onset and 9 late-onset) patients are used to support the efficacy of Myozyme in this BLA application, including:

- Study 1602, n = 18 (infantile)
- Study 1702, 15 completed patients (52-week data) (out of 21 total patients in study (infantile)
- AGLU02203, first 5 patients enrolled (late)
- AGLU02003, n = 7 (infantile)
- AGLU02503, 2 patients (1 additional patient was treated, but died before any efficacy assessments could be performed; however this patient is included in the safety database) (late) , and
- AGLU02103, n = 1 (late)

Safety data from a total of 56 patients exposed to Myozyme are included:

- 50 patients in efficacy set above + 6 additional patients treated under Study 1702 + 1 patient treated under AGLU1205-02.

e 1: Myozyme Clinical Development Program

Study	Description
Infantile-Onset Studies	
AGLU-004-00	Natural History Study of 168 infantile-onset Pompe disease patients conducted between Feb-2002 and Nov-2002. **This study included data obtained using a retrospective chart review of 168 untreated patients diagnosed with** infantile-onset Pompe disease with the purpose of better characterizing the natural course of the disease. The results of this study were used as the comparator/control for Studies 1602 and 1702.
AGLU01602 (Study 1602)	Randomized (to dose), open-label (OL), multi-center, multi-national, safety, efficacy, PK, PD, and dose-ranging study of Myozyme 20 mg/kg or 40 mg/kg qow in 18 infantile-onset Pompe disease patients ages ≤6 months at the time of first infusion. Study 1602 was conducted from 26-May-2003 to ongoing (last enrolled patient completed Week 52 visit in June-2005).
AGLU01702 (Study 1702)	OL, uncontrolled, multi-center, multi-national, safety, efficacy, PK and PD study of Myozyme 20 mg/kg qow in 21 infantile-onset Pompe disease patients ages >6 to ≤18 months at time of first infusion. Study 1702 was conducted from 17-Mar-2003 to ongoing. 15 patients have completed 52 weeks of the study.
AGLU02203	OL, uncontrolled, US expanded-access, safety and efficacy study of Myozyme 20 mg/kg qow in 5 Pompe disease patients at an advanced stage of disease progression (29-Dec-2003 to ongoing). Patients had a mean age of 10.3 years at study entry.
AGLU02003	OL, extension, safety and efficacy study of Myozyme (10, 20 or 40 mg/kg qow) in 7 infantile-onset patients who had previous received treatment with a prior formulation of rhGAA (Synpac) (10-Apr-2003 to ongoing). Patients were a mean age of 22 months at Synpac rhGAA treatment entry, and 41 months at Myozyme treatment entry.
AGLU1205-02, Amendments 4 & 5	OL, extension study of Myozyme 20-40 mg/kg qweek in a single (1) infantile-onset Pompe disease patient who had previously received rhGAA for 3 years (Synpac and Pharming rhGAA) under IND [redacted] (Study AGLU1205-02 conducted from 12-June-2003 to ongoing).
Late-Onset Studies	
AGLU02503	OL, European, expanded access, safety and efficacy program of Myozyme 20 mg/kg qow in 3 patients with clinically advance late-onset Pompe disease (04-Nov-2003 to ongoing).
.U02103	OL, extension, safety and efficacy study of Myozyme 30 mg/kg qow in 1 late-onset Pompe disease patient who had

previously received 3.7 years of Pharming and Synpac rhGAA under INDs from 11-Apr-2003 to ongoing). (AGLU02103 conducted

Additional Myozyme Studies and Programs

Table 2: Myozyme Clinical Development Program

Study/Program	Description
International EAP	An expanded access program conducted outside the US providing Myozyme to patients with infantile- and late-onset Pompe disease. 54 patients have been enrolled as of 08-Mar-2005.
Pompe Disease Registry	An established database that will be used to follow and collect long-term observational data on patients with Pompe disease.
AGLU02303	12-month, prospective, multi-center, multi-national, observational study initiated Mar-2004, which intends to better characterize the clinical presentation of late-onset Pompe disease and assist in determining clinical efficacy endpoints for the planned placebo-controlled study AGLU02704.
AGLU02704	Randomized, DB, multi-center, multi-national, safety, efficacy and PK study of 52-weeks of Myozyme treatment in late-onset Pompe disease patients. Enrolled is planned to start in mid-2005.
AGLU02804	Ongoing, 26-week, OL, safety, efficacy and PK study of Myozyme 20 mg/kg qow to 5 patients with late-onset Pompe disease. Preliminary, 12-week data are expected late-2005.
AGLU02603	Ongoing, OL, expanded access study in the US for severely affected patients with late-onset Pompe disease who do not meet the clinical eligibility criteria for enrollment in an ongoing study of Myozyme. The first patient was enrolled Dec-2004.

B. Natural History Study: AGLU-004-00 and Historical Control Subgroup

1. Natural History Study: Study Design

Multi-national, multi-center historical cohort study designed to characterize the natural history of disease progression in untreated patients with infantile Pompe disease.

- Historical data were obtained from a retrospective review of patient medical records from sites in North America, Europe, Israel, and Taiwan.
- **Inclusion/Exclusion criteria:**
  - Clinical diagnosis of infantile Pompe disease for the purpose of retrieving historical data from different sources as defined by documented GAA enzyme deficiency or GAA gene mutations, AND
  - onset of symptoms by 12 months of age corrected for gestation
  - Patients were excluded if they did not meet the specific inclusion criteria.

2. Historical Control Subgroup: Study Design

Patients were selected from the historical database based on screening criteria adapted from the inclusion and exclusion criteria of Study 1602, for the purpose of 1) characterizing the natural course of infantile-onset Pompe disease; and 2) providing an historical control for Study AGLU01602. All 62 patients included in the historical control subgroup had a documented GAA enzyme deficiency or GAA gene mutation, and had onset of symptoms by 12 months of age.

- Inclusion criteria included:
  - Age at first symptoms by ≤26 weeks, corrected for gestation
  - Documented cardiomyopathy first identified by ≤26 weeks of age.
  - Age at confirmed diagnosis by ≤26 weeks
- Patients were excluded if they had:

- Endogenous GAA activity by PBMC assays ≥5% (— lab), ≥10% (— lab), or ≥8% (— lab) of the mean of the normal range, OR GAA activity level >1% of the mean of the normal range assessed by the skin fibroblast assay.
- Any known ventilator use between 0 and 6 months of age.
- Documented major congenital abnormality.
- Clinically significant disease, other than symptoms relating to Pompe disease.

3. Results

a) Patient Population

A total population of 168 patients were included in the AGLU-004-00 study, and 62 patients were selected from this group to form the Historical Control Subgroup.

Table 3: AGLU-004-00 and Historical Control Subgroup, Selected Baseline Characteristics

	AGLU-004-00	Historical Control Subgroup
Number of Patients Enrolled	168	62
Demographic Measure		
Gender		
Male	83	28
Female	85	34
Ethnicity		
Caucasian	80	31
Black	22	4
Hispanic	1	1
Asian	52	18
Other	1	1
Unknown	12	7
Year of Birth		
2000 to present	33	12
1995 to 1999	60	20
1990 to 1994	38	17
1985 to 1989	20	9
Before 1985	17	4
Age at First symptoms (mos), n =	162	62
Mean	2.7	1.9
Median	2.0	1.9
Min, max	0, 12.0	0, 5.9
Age ≤6 mos, n =	151	62
Age >6 mos, n =	15	0
Unknown, n =	2	0
Age at Diagnosis (mos), n =	165	62
Mean	6.0	3.6
Median	4.7	4.1
Min, max	-5.1, 84.2	-4.4, 6.6
Age ≤6 mos, n =	109	61
Age >6 mos, n =	56	1
Unknown, n =	2	0

b) Patient Status: AGLU-004-00

Table 4: AGLU-004-00, Patient Status

Status	Documented Symptoms		If Yes, Age at Death	
Deaths		n =	n = 163*	Months
	Died	144 →	Mean	12.6
	Known Alive	12	Median	8.7
	Unknown	12	Min, max	0.3, 73.4

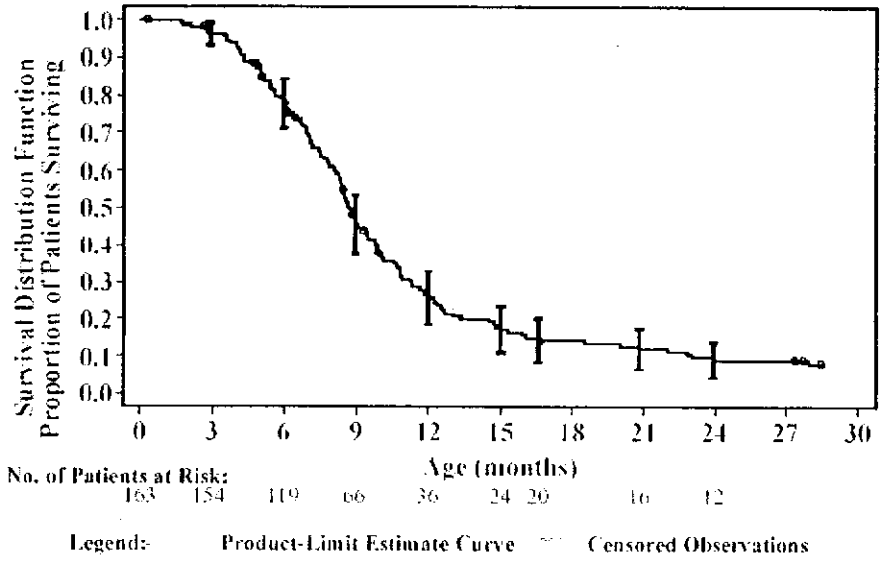
* Patients not known to have died were right-censored

Table 5: AGLU-004-00Mean Age of Death by Time Period

Mean Age of Death by Time Period		
2000 to present	n =	33
	Mean	10.9
	Median	8.9
1995 to 1999	n =	52
	Mean	10.6
	Median	8.6
1990 to 1994	n =	27
	Mean	9.4
	Median	6.9
1985 to 1989	n =	12
	Mean	7.1
	Median	5.9
Before 1985	n =	15
	Mean	9.4
	Median	9.8

Kaplan Meier analysis of survival:

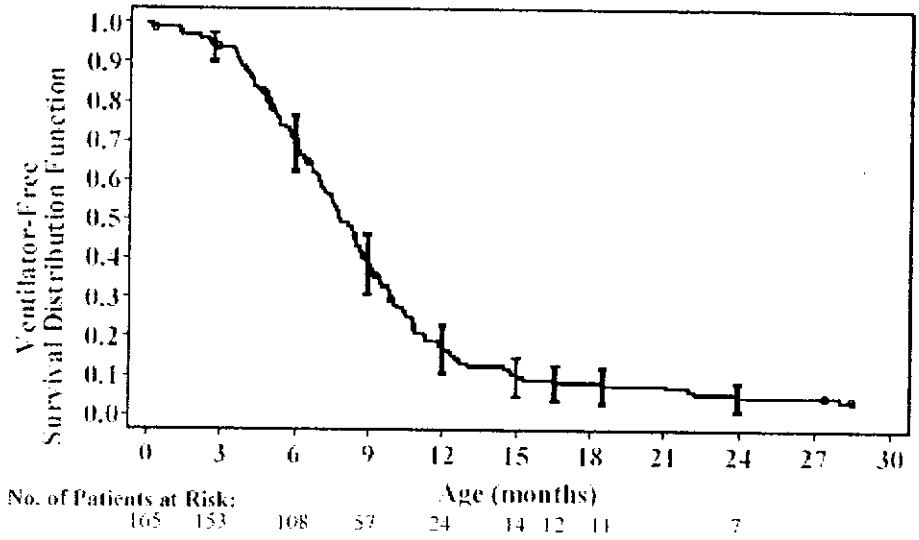
Figure 10-1 Kaplan-Meier Plot of Survival Time Since Birth



Ventilator-free survival time:

- Median ventilator-free survival 5.9 months,
- 24 of 165 infants survived beyond 1 year of life ventilator-free
- 11 of 165 survived beyond 18 months of age ventilator free.

Figure 10-2 Kaplan-Meier Plot of Ventilator-Free Survival Time Since Birth



Legend: —— Product-Limit Estimate Curve ⁰⁰⁰ Censored Observations
Bars Represent 95 % CIs

First occurrence of ventilator support data was available on approximately 2/3 of patients.

Table 6: AGLU-004-00, First Ventilator Support

Status	Documented Symptoms		If Yes, Age at Death	
Ventilator Support (1st occurrence)		n =	n = 49	Months
	Yes	49 →	Mean	7.0
	No	58	Median	5.9
	Unknown	61	Min, max	0.1, 39.1

c) Patient Status: Historical Control Subgroup

Survival time:

One (1) patient was excluded from the analysis as the date of death was unknown.

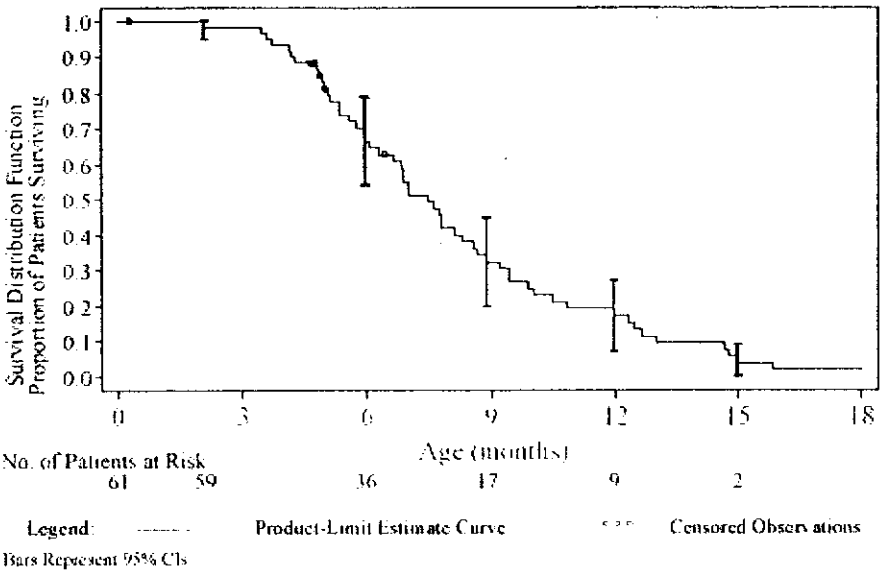
- Median age at death was 7.5 months,
- 9 of 62 infants survived beyond their first birthday, and
- 1 infant survived beyond 18 months of age.

Table 7: Historical Control Subgroup, Patient Status

Status	Documented Symptoms		If Yes, Age at Death	
Deaths		n =	n = 61*	Months
	Died	55 →	Mean	8.6
	Known Alive	1	Median	7.5
	Unknown	6	Min, max	0.3, 43.9

* Patients not known to have died were right-censored

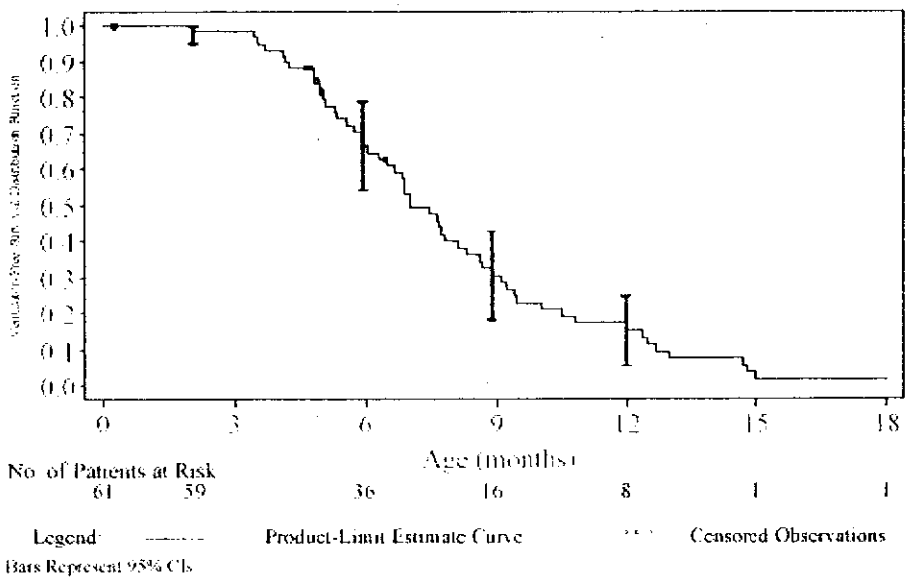
Figure 4-1 Kaplan-Meier Plot of Survival Time Since Birth



Ventilator-free survival:

- Median age from birth to first ventilatory support or death was 7.0 months.
- Eight (8) of 61 infants survived beyond 1 year of life ventilator-free and
- 1 infant survived ventilator-free beyond 18 months of age.

Figure 4-2 Kaplan-Meier Plot of Ventilator-Free Survival Time Since Birth



Ventilator support:

Data were available for 37 of 62 patients:

- history of ventilator support was reported in 6 of 62 patients, and
- no use of ventilator support at any time in 31 patients (50%).
- In the 6 patients placed on ventilator support, 3 patients had available data on the length of ventilator support. This support lasted a median of 1 day, and appeared to be a per-terminal event.

C. Study AGLU01602 (Study 1602)

1. Study Design and Plan for Study 1602

- Multicenter (n=7), multinational, open-label, randomized (to dose), dose-ranging, safety, efficacy, PD and PK study of alglucosidase (rhGAA; Myozyme) in 18 subjects with infantile-onset Pompe disease.
- Subjects were randomized 1:1 to receive IV rhGAA 20 or 40 mg/kg qow for 52 weeks
- As infantile-onset Pompe disease is a uniformly fatal disease for which there is no established treatment, no placebo treatment was administered, and an historical control subgroup was used as the control group.

The sponsor conducted an interim analysis after all patients had completed 26 weeks of treatment, which was submitted as the original submission to the BLA application. Per agreement with the sponsor, 52-week updates to the primary endpoint (ventilator-free survival) and major secondary endpoints (AIMS, Pompe PEDI, BSID-II and growth) were submitted as an amendment to the BLA in late August, 2005. Thus, the BLA submission consists of:

- Primary endpoint (ventilator-free survival, with comparison to historical control subgroup) after all patients had completed 52 weeks of treatment (to 15-June-2005 cut-off; an update was obtained with a cut-off of 15-September-2005)
- Motor and development scores (AIMS, Pompe PEDI and BSID-II scores) after 52 weeks of treatment
- Growth (weight, length and head circumference) after 52 weeks of treatment
- Interim analyses (up to 26 weeks of treatment) for all other efficacy endpoints
- Safety data up to 26 weeks of treatment (December, 2004 cut-off), with updated SAE data to 15-March-2005

2. Study Objectives

To evaluate the safety, efficacy (ventilator-free survival compared to historical control), PK and PD of 2 doses (20 and 40 mg/kg qow) of rhGAA in the treatment of patients with infantile-onset Pompe disease after 26 weeks of treatment (interim analysis) and after 52 weeks of treatment.

3. Eligibility Criteria

Inclusion criteria:

- age $\leq$6 months at the first dose of rhGAA, and
- diagnosis of infantile-onset Pompe disease defined as onset of clinical symptoms of Pompe disease at <6 months of age,
- deficient GAA activity, and
- cardiomyopathy (LVMI $\geq$65 g/m^2 by echocardiography).

Exclusion criteria:

- the presence of respiratory insufficiency (O_2 sat <90% on RA or venous pCO_2 >55 mmHg on RA or arterial PCO_2 >40 mmHg on RA, or any ventilation use (invasive or non-invasive) at the time of enrollment);

- major congenital abnormality;
- clinically significant organic disease (excluding Pompes) that would potentially decrease survival; or
- had received ERT with GAA from any source.

4. Study Visits and Procedures

NOTE: All patients required placement of a permanent, indwelling, central intravenous catheter to receive ongoing study treatments.

Table 8: Study 1602, Study Visits and Procedures, Screening through Week 26

			Day	Week												
	Screen	Baseline	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Procedure																
Informed consent	X															
Medical history	X															
Head MRI	X															
Blood for GAA activity in PBMC	X															
Skin biopsy for GAA activity	X	X														
Skin biopsy for CRIM status		X														
Blood spot collection		X														
ACE marker allele status		X														
Venous blood gas	X															
Pulse ox (RA)	X															
GAA gene mutation analysis			X													
Chest xray		X														X
tral venous catheter ement		X														
Muscle biopsy		X							X							
Plasma oligosaccharide levels		X			X				X							X
Urine oligosaccharide levels		X			X				X							X
Hearing test		X														X
Physical exam	X	X	X		X		X		X							X
Echocardiogram	X	X			X		X		X							X
ECG		X			X		X		X							X
Safety labs (heme & chem)		X			X		X		X							X
Urinalysis		X			X		X		X		X		X		X	
Nutritional analysis		X							X							X
Anti-rhGAA antibody (IgG)			X		X		X		X		X		X		X	
PK			X						X							
AIMS		X			X		X		X							X
PDMS-2		X														X
Motor development milestones assessment		X			X		X		X							X
PEDI and Pompe PEDI		X			X		X		X							X
Modified BSID-II		X							X							X
Weight		X	X		X		X		X		X		X		X	
VS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug infusion			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator use	← Continuous monitoring →															
AE assessment	← Continuous monitoring →															
Conmeds/therapy monitoring	← Continuous monitoring →															
FU contact	X															

Table 9: Study 1602, Study Visits and Procedures, Weeks 28 through 52 (end-of-study)

	Week												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Procedure													
Chest xray													X
Muscle biopsy													X
Plasma oligosaccharide levels						X							X
Urine oligosaccharide levels						X							X
Hearing test													X
Physical exam						X							X
Echocardiogram						X							X
ECG						X							X
Safety labs (heme & chem)						X							X
Urinalysis	X		X		X		X		X		X		X
Nutritional analysis						X							X
Anti-rhGAA antibody (IgG)						X							X
AIMS						X							X
Motor development milestones assessment						X							X
PEDI and Pompe PEDI						X							X
Modified BSID-II						X							X
Weight	X		X		X		X		X		X		X
VS	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator use	← Continuous monitoring →												
AE assessment	← Continuous monitoring →												
Conmeds/therapy monitoring	← Continuous monitoring →												
FU contact	X												

5. Efficacy and Endpoint Measures

Data to the cut-off date of 15-June-2005 after all subjects had received 52 weeks of rhGAA treatment was received for selected endpoints only, including: the primary endpoint (ventilator free-survival), the motor and cognitive scores (AIMS, BSID-II, Pompe PEDI), and for physical growth (length, weight and head circumference). Individual cutoff dates varied as patients were enrolled at different times and at different ages, so data was evaluated up to 52-weeks of treatment for all patients. As of the 15-June-2005 cut-off date, all but 3 subjects had reached the age of 18 months (range 13.1 to 19.3 months, median 17.5 months). For all other efficacy endpoints, interim data up to 26 weeks of treatment were submitted (individual cutoff dates varied). The safety data include all safety data collected up to the interim analysis cutoff date (16-December-2004) for each patient.

a) 52-Week Study Endpoints

Primary efficacy endpoint: proportion of patients who were alive and free of invasive ventilator support at 18 months of age, as compared to an historical control subgroup.

Secondary efficacy endpoints included:

- proportion of patients alive and free of any ventilatory support at 18 months of age, as compared to an historical cohort;
- cardiac status as measured by LVMI change from baseline to Week 52; and
- physical growth (length and weight) from baseline to Week 52.

Tertiary efficacy endpoints included:

- proportion of patients alive at 18 months of age;
- proportion of patients with signs or symptoms of cardiac failure at Week 52;
- AIMS scores change from baseline to Week 52;
- number of motor development milestones achieved change from baseline to Week 52;
- BSID-II scores change from Baseline to Week 52;
- PEDI scores change from baseline to Week 52;
- Pompe PEDI scores change from Baseline to Week 52;
- Change from baseline to Week 52 in urinary and plasma oligosaccharides; and
- Hours on ventilation from baseline to Week 52.

Exploratory variables included:

- CRIM status
- ACE marker allele status
- Gene expression
- GAA gene mutation

Safety was assessed by incidence in AEs, discontinuations due to AEs, drug-related, serious and severe AEs. Clinical and laboratory assessments included: clinical chemistry, hematology and urinalysis, changes in anti-GAA antibody IgG titers from baseline, changes in vital signs and physical exams, and ECG assessments. Other safety variables included: circulating immune complex detection (as indicated), inhibitory antibody formation in patients testing positive for IgG, GAA IgE antibodies, serum tryptase and complement activation (as indicated).

PK and PD measures: PK profile at baseline and Week 12, PD by comparing skeletal muscle GAA activity and glycogen content at baseline and Week 12

b) Interim Analysis

Endpoints analyzed and submitted to the BLA in the original submission and in Amendment 1 (submitted as of late August, 2005) include the following:

The primary efficacy endpoint: proportion of subjects alive and free of invasive ventilation at 12 months of age (interim analysis), as compared to the historical cohort. Per agreement between the sponsor and the division, an update to the primary endpoint after all patients had achieved the 18-month of age/52 weeks of treatment milestone (15-June-2005) was submitted and analyzed in addition to the 26-week milestone.

Secondary endpoints include:

- Proportion of patients who were alive and free of any ventilatory support (invasive or non-invasive) at 12 months of age (updated to 18 months of age with amendment)
- Mean LVMI change from Baseline to Week 26 (updated to Week 56);
- Physical growth
    - Length change from baseline to Week 26 (updated to Week 56)

  - Weight change from baseline to Week 26 (updated to Week 56)
  - Head circumference from baseline to Week 26 (updated to Week 56)

Tertiary endpoints include:

- Proportion of patients alive at 12 months of age (updated to 18 months of age with amendment)
- Proportion of patients with signs and/or symptoms of cardiac failure at Week 26
- Change in AIMS scores from Baseline to Week 26 (updated to Week 52)
- Changes in the number of motor development milestones achieved from Baseline to Week 26
- Changes in the MDI of the BSID-II from Baseline to Week 26 (updated to Week 52)
- Changes in Pompe PEDI scores from Baseline to Week 26 (updated to Week 52)
- Oligosaccharides
  - Changes in urine oligosaccharide concentrations from Baseline to Week 26
  - Changes in plasma oligosaccharide concentrations from baseline to Week 26 (not performed)
- Hours on ventilation from baseline to Week 26

6. Study Conduct

A Data Safety Monitoring Board (DSMB), comprised of 3 physicians (later added a fourth) knowledgeable about Pompe disease and who had no direct relationship with the study, provided medical and ethical guidance related to the conduct of the study. The DSMB assembled quarterly to review Adverse Events (AEs), Serious AEs (SAEs), laboratory listings and for other safety related reasons. An independent Allergic Reaction Review Board (ARRB) was also established, that was consulted on an ad hoc basis to review reports of moderate or severe infusion-associated reactions (IARs) and provide guidance on IAR management.

A central cardiologist read all echocardiograms and ECGs. The readings were single-blinded in the first year of treatment, and unblinded thereafter. A central physical therapist scored all motor and cognitive assessments conducted on study patients.

7. Results

The following table summarized patient ages and length of treatment at the 52-week and 26-week data cut-offs.

Table 10: Study 1602, Summary of Myozyme Administration and Cutoff Dates for Interim and Week 52 Analyses

Patient Number	Treatment Group (mg/kg)	Age at 1st Infusion* (mos)	Age at Interim Analysis Cutoff (mos)	Age at 26-Week Milestone (mos)	Age at 15-June-2005 Cutoff (mos)	Age at 52-Week Milestone (mos)
301	40	4.8	18.4	12.0	29.7	18.0
302	20	5.6	18.0	12.0	28.6	18.0
303	40	6.1	18.2	12.0	28.1	18.0
305	20	5.0	18.1	12.0	**	18.0
306	20	5.8	18.1	12.0	26.4	18.0
307	40	6.0	18.3	12.0	26.2	18.0
308	40	4.3	12.1	12.0	23.1	18.0
309	20	4.8	12.2	12.0	23.7	18.0
310	20	5.7	18.5	12.0	24.4	18.0
311	40	6.1	18.3	12.0	25.2	18.0
312	20	5.1	12.1	12.0	21.2	18.0
313	40	1.8	12.4	12.0	18.5	18.0
314	20	1.9	12.0	12.0	18.0	18.0
315	40	1.2	7.3	7.3	15.9	15.9
316	20	5.5	13.4	12.0	20.3	18.0
317	40	5.6	12.3	9.2	18.8	18.0
318	40	5.4	11.3	11.3	17.9	17.9
319	20	1.8	7.8	7.8	14.4	14.4

*Corrected for gestational age (adjusted to full-term gestational age of 40 weeks if <40 weeks of gestation)
**Patient died at age 19.8 months

a) Patient Population

Nineteen (19) patients were enrolled in Study 1602 and 18 patients were treated with rhGAA. The first dose of rhGAA was administered to the first patient on 26-May-2003 and the last patient was randomized to treatment on 03-June-2003. The last patient randomized underwent their Week 26 visit on 24-Nov-2004 and their Week 52 visit on 15-June-2005.

The 1 patient who was enrolled, but not treated with rhGAA was Patient 304, who required ventilation during the baseline period. Five (5) days after the informed consent was signed, this patient developed respiratory decompensation and requiring intubation and mechanical ventilation. This patient had undergone some screening/baseline study-related procedures, but no invasive procedures (i.e., no central line placement or muscle biopsy – personal communication with sponsor). The patient was discontinued from the study. One additional patient was excluded from the study (screen failure) due to poor respiratory status.

Patients were enrolled at 7 of 11 participating sites as follows:

Table 11: Study 1602, Enrollment by Site

Site ID #	Site (Investigator)	Number of Subjects Enrolled	Patients Enrolled at Site
01	Durham, NC, USA (Duke Univ. Med. Ctr, PI: P. Kishnani)	3	307, 309, 311
02	Lyon, France (Pediatrique Hôpital Debrousse, PI : M. Nicolino)	3	301, 308, 318
21	Cincinnati, OH, USA (Cincinnati Children's Hosp. Med. Ctr, PI: N. Leslie)	1	316
52	Taipei, Taiwan, ROC (Natl. Taiwan Univ. Hosp., PI: WL Hwu)	4	304*, 305, 306, 310
60	Haifa, Israel (Rambam Med. Ctr, PI: H. Mandel)	3	302, 303, 315
81	Gainesville, FL, USA (Shands Hosp. Univ. FL, PI: B. Byrne)	3	313, 317, 319
83	Manchester, UK (Royal Manchester Hosp, PI: JE Wraith)	2	312, 314
Total, n =	**7 sites**	**19**	

*Withdrawn prior to receiving rhGAA

b) Demographics

Table 12: Study 1602, Demographic Data

		Treatment Group	
	All	20 mg/kg	40 mg/kg
ITT Population, n =	18	9	9
Demographic			
Gender			
Male, n (%)	11 (61)	4 (44)	7 (78)
Female, n (%)	7 (39)	5 (56)	2 (22)
Race			
Caucasian, n (%)	7 (39)	3 (33)	4 (44)
Black, n (%)	4 (22)	1 (11)	3 (33)
Asian, n (%)	3 (17)	3 (33)	0
Hispanic, n (%)	2 (11)	1 (11)	1 (11)
Other, n (%)	2 (11)	1 (11)	1 (11)
Chronologic Age at 1st Infusion (mos)			
Mean	5.1	5.1	5.1
Median	5.6	5.7	5.4
Min, max	1.2, 7.3	1.9, 7	1.2, 7.3
Corrected Age at 1st Infusion (mos)			
Mean	4.6	4.6	4.6
Median	5.3	5.1	5.4
Min, max	1.2, 6.1	1.8, 5.8	1.2, 6.1
Age at First Symptoms (mos)			
Mean	1.6	1.7	1.5
Median	1.0	1.5	0.4
Min, max	0, 5.4	0, 5.4	0, 4.3
Age at Postnatal Diagnosis (mos)			
Mean	3.6	4.0	3.3
Median	4.3	4.7	4.2
Min, max	0.2, 6.8	0.7, 6.2	0.2, 6.8

By individual subject

Table 13: Study 1602, Demographic Data by Individual Subject

Patient Number	Treatment Group (mg/kg)	Gender	Race	Chronologic Age at 1st Infusion (mos)	Corrected* Age at 1st Infusion (mos)	Chronologic Age at Symptom Onset (mos)	Chronologic Age at Diagnosis (mos)
301	40	M	Caucasian	5.0	4.8	0	0.7
302	20	M	Caucasian	7.0	5.6	0	4.7
303	40	F	Caucasian	7.0	6.1	2.4	4.9
305	20	F	Asian	5.7	5.0	2.6	4.0
306	20	M	Asian	5.9	5.8	1.5	4.8
307	40	M	Black	6.9	6.0	4.2	4.2
308	40	M	Other (Turkish)	4.3	4.3	0	1.7
309	20	F	Hispanic	5.3	4.8	0.2	5.0
310	20	M	Asian	6.4	5.7	5.4	6.2
311	40	M	Hispanic	7.3	6.1	2.2	6.8
312	20	F	Caucasian	5.1	5.1	2.5	2.9
313	40	F	Black	2.3	1.8	0.4	0.7
314	20	M	Other (Ecuadorian)	1.9	1.9	0	0.7
315	40	M	Caucasian	1.2	1.2	0.2	0.2
316	20	F	Black	6.9	5.5	3	6.0
317	40	M	Black	6.2	5.6	0.1	6.0
318	40	M	Caucasian	5.4	5.4	4.3	4.5
319	20	F	Caucasian	2.1	1.8	0	1.9

rrected for gestational age

c) Primary Efficacy Endpoint

Proportion of patients alive and free of invasive ventilation using Kaplan-Meier methodology. For the primary analysis, time to event is measured from data of birth. The following are as of 15-June-2005 update:

Overall:

Table 14: Study 1602, Primary Endpoint, 52-Week Results with 15-June-2005 Information Update Included

Dose Group	Study 1602				Historical Control	
	n =	Patients Alive & VF	Patients meeting Primary Endpoint	Patients Censored	n =	Patients Alive
Overall, n =	18	13	3	2	61	1
20 mg/kg, n =	9	8	1	0	-	-
40 mg/kg, n =	9	7	2	2	-	-

By individual subject:

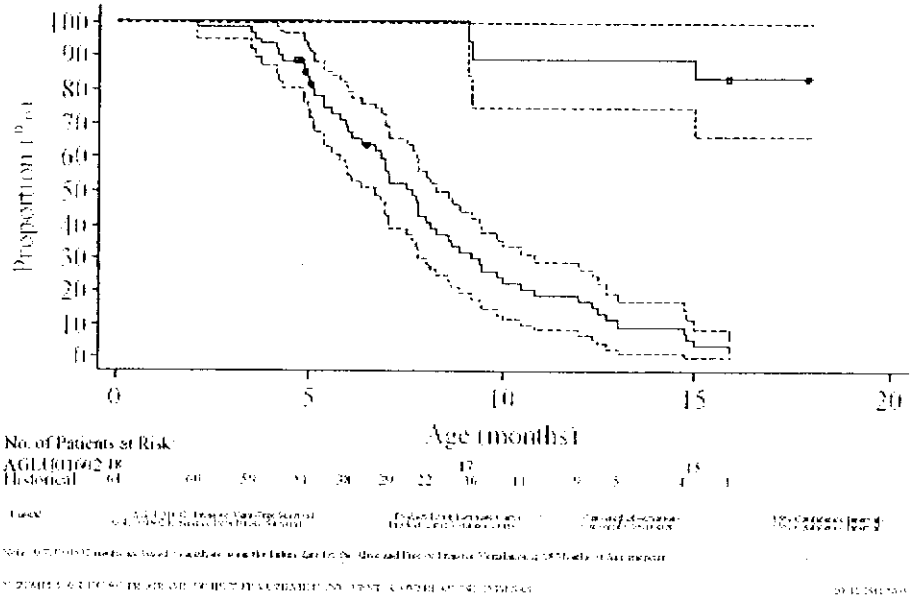
ble 15: Study 1602, Status of Individual Subjects at 52-Week Milestone, Updated with 15-June-2005 Results

atient Number	Treatment Group (mg/kg)	Age*at 1st Infusion (mos)	Age* at week milestone (mos)	Myozyme exposure at 52-week milestone (mos)	Status at 52-week milestone (mos)	Age*at start of invasive ventilation (mos)
301	40	5.0	18.0	10.0	Invasive	15.0
302	20	7.0	18.0	11.0	Alive & VF	-
303	40	7.0	18.0	11.0	Alive & VF	-
305	20	5.7	18.0	12.3	Noninvasive	(12.0)
306	20	5.9	18.0	12.1	Noninvasive	(13.7)
307	40	6.9	18.0	11.1	Alive & VF	-
308	40	4.3	18.0	7.8	Alive & VF	-
309	20	5.3	18.0	6.9	Alive & VF	-
310	20	6.4	18.0	11.6	Alive & VF	-
311	40	7.3	18.0	10.7	Alive & VF	-
312	20	5.1	18.0	7.0	Alive & VF	-
313	40	2.3	18.0	10.1	Noninvasive	(14.9)
314	20	1.9	18.0	10.1	Alive & VF	-
315	40	1.2	15.9	6.1	Censored	-
316	20	6.9	18.0	6.4	Alive & VF	-
317	40	6.2	18.0	3.0	Invasive	9.2
318	40	5.4	17.9		Censored	-
319	20	2.1	14.4	5.7	Invasive	9.1

*Age not adjusted for age at gestation
**VF = invasive ventilator-free

Kaplan-Meier Time to Invasive Ventilation or Death at 18 Month Age Milestone

Kaplan-Meier Estimate of Time to Invasive Ventilation or Death in AGLU01602 and Time to Death in the AGLU01602 Historical Control Subgroup from Date of Birth (18 Month Age Milestone)



Reference: Figure 2.7.3.6-2.
Note: AGLU01602 results are based on available data as of 15 June 2005.

Contrast to the 61 subjects (for whom an age of death is known of the 62 subjects)in the historical control subgroup:

- 8 of 61 (13%) survived ventilator-free beyond 12 months of age and 1 or 61 subjects (2%) survived ventilator-free beyond 18 months of age.
- Median age from birth to first ventilatory support or death was 7.0 months (95% CI 6.5, 8.3).

Status of all patients as of 15-June-2005

Table 16: Study 1602, Status of Individual Subjects as of 15-June-2005

Patient Number	Treatment Group (mg/kg)	Age* at 1st Infusion (mos)	Myozyme exposure at 15-Jun-05 or time of death (mos)	Age* at 15-Jun-05 (mos)	Status as of 15-Jun-05	Age* at start of invasive ventilation (mos)	Age* at death (mos)
301	40	5.0	24.7	29.7	Invasive	15.0	-
302	20	7.0	21.6	28.6	None	-	-
303	40	7.0	21.1	28.1	Invasive	24.5	-
305	20	5.7	14.0	-	Invasive/died	19.4	19.8
306	20	5.9	20.5	26.4	Invasive	19.7	-
307	40	6.9	19.2	26.2	None	-	-
308	40	4.3	18.8	23.1	None	-	-
309	20	5.3	18.4	23.7	None	-	-
310	20	6.4	17.9	24.4	None	-	-
311	40	7.3	18.0	25.2	None	-	-
312	20	5.1	16.1	21.2	None	-	-
313	40	2.3	16.2	18.5	Invasive	18.5	-
314	20	1.9	16.1	18.0	None	-	-
315	40	1.2	14.7	15.9	None	-	-
316	20	6.9	13.4	20.3	None	-	-
317	40	6.2	12.6	18.8	Invasive	9.2	-
318	40	5.4	12.5	17.9	None	-	-
319	20	2.1	12.3	14.4	Invasive	9.1	-

*Chronologic age not adjusted for age at gestation

Status as of 15-September-2005 update:

Table 17: Study 1602, Status of Individual Subjects as of 15-September-2005

Patient Number	Treatment Group (mg/kg)	Age* at 1st Infusion (mos)	Myozyme exposure at 15-Sep-05 or time of death (mos)	Age* at 15-Sep-05 (mos)	Status as of 15-Sep-05	Age* at start of invasive ventilation (mos)	Age* at death (mos)
301	40	5.0	24.7	32.7	Invasive	15.0	-
302	20	7.0	21.6	31.6	None	-	-
303	40	7.0	21.1	31.1	Invasive	24.5	**
305	20	5.7	14.0	-	Invasive/died	19.4	19.8
306	20	5.9	20.5	29.4	Invasive	19.7	-
307	40	6.9	19.2	29.2	None	-	-
308	40	4.3	18.8	26.1	None	-	-
309	20	5.3	18.4	26.7	None	-	-
310	20	6.4	17.9	27.4	None	-	-
311	40	7.3	18.0	28.2	None	-	-
312	20	5.1	16.1	24.2	None	-	-
313	40	2.3	16.2	21.5	Invasive	18.5	-
314	20	1.9	16.1	21.0	None	-	-
315	40	1.2	14.7	18.9	None	-	-
316	20	6.9	13.4	23.3	None	-	-
317	40	6.2	12.6	21.8	Invasive	9.2	-
318	40	5.4	12.5	20.9	None	-	-
319	20	2.1	12.3	17.4	Invasive	9.1	-

*Chronologic age not adjusted for age at gestation

**Personal communication with sponsor – patient died approx [redacted] after completing Study 1602. This patient did not enroll AGLU02403, but was enrolled into the expanded access program in Israel.

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Table 18: Patients by Invasive-Ventilation Status (last date noted 15-Sept-05)

Patient	Dose (mg/kg)	Age at First Symptoms (mos)	Age at Diagnosis (mos)	Age at First Infusion (mos)	Age at Start of Invasive Ventilation (mos)	Myozyme Exposure (mos)	Age at Cut-off (mos)
Patients Requiring Invasive Ventilation							
301	40	0	0.7	5.0	15.0	24.7	32.7
303	40	2.4	4.9	7.0	24.5	21.1	31.3
305	20	2.6	4.0	5.7	19.4/19.8*	14.0**	-
306	20	1.5	4.8	5.9	19.7	20.5	29.4
313	40	0.4	0.7	2.3	18.5	16.2	21.5
317	40	0.1	6.0	6.2	9.2	12.6	21.8
319	20	0	1.9	2.1	9.1	12.3	17.4
Mean	-	1.0	3.3	4.9	16.6	17.3	25.7
Median	-	0.4	4.0	5.7	18.5	16.2	25.6
Min, max	-	0, 2.6	0.7, 6.0	2.1, 7.0	9.1, 24.5	14.0, 24.7	17.4, 32.7
Patients Not Requiring Invasive Ventilation							
302	20	0	4.7	7.0	-	21.6	31.6
307	40	4.2	4.2	6.9	-	19.2	29.2
308	40	0	1.7	4.3	-	18.8	26.1
309	20	0.2	5.0	5.3	-	18.4	26.7
310	20	5.4	6.2	6.4	-	17.9	27.4
311	40	2.2	6.8	7.3	-	18.0	28.2
312	20	2.5	2.9	5.1	-	16.1	24.2
314	20	0	0.7	1.9	-	16.1	21.0
315	40	0.2	0.2	1.2	-	14.7	18.9
16	20	3.0	6.0	6.9	-	13.4	23.3
318	40	4.3	4.5	5.4	-	12.5	20.9
Mean	-	2.0	3.9	5.2	-	17.0	25.2
Median	-	2.2	4.5	5.4	-	17.9	26.1
Min, max	-	0, 5.4	0.2, 6.8	1.2, 7.0	-	12.5, 21.6	18.9, 31.6

*age at death
** exposure at time of death

d) Secondary Efficacy Endpoints

For Week 52 analysis, secondary efficacy endpoints included for Physical growth (length, weight and head circumference) from baseline to Week 52. Available data included results up to the cutoff data of 15-June-2005 (amendment 1 dated 17-August-2005).

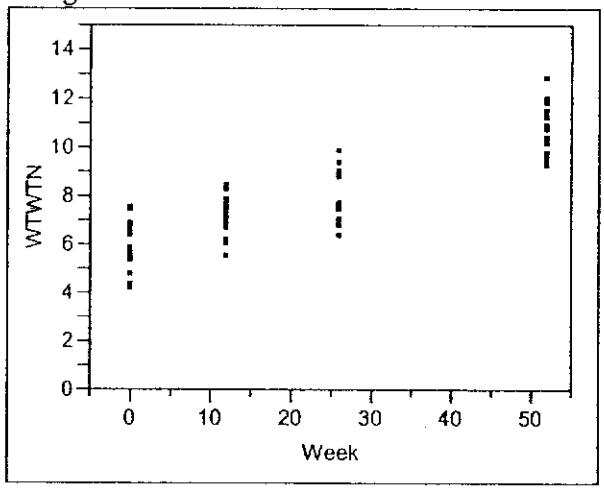
(1) Physical Growth at Week 52

Growth data were expressed as standardized age- and gender-matched percentiles and Z-scores with reference to the Center for Disease Control/National Center for Health Statistics (CDC/NCHS) growth charts (Note: CDC/NCHS charts are scaled for a US populations and patients in this study are an international cohort).

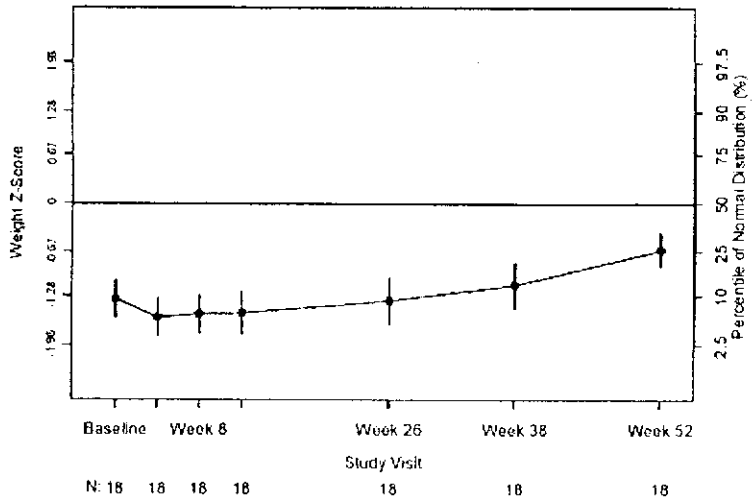
Table 19: Study 1602, Growth Parameters

	Screening	Week 12	Week 26	Week 52
Parameter				
Weight (kg), n =	18	18	18	18
Mean	5.9	7.1	8.4	10.6
Median	5.7	7.1	8.7	10.6
Range	4.1, 7.5	5.5, 8.4	6.3, 9.8	9.2, 12.8
Length (cm), n =	15	17	17	15
Mean	63	67	74	82
Median	63	69	75	82
Range	53, 76	28, 76	66, 80	74, 91
Head Circumference (cm), n =	14	17	16	15
Mean	41	42	44	46
Median	41	43	45	47
Range	36, 44	39, 46	42, 47	43, 49

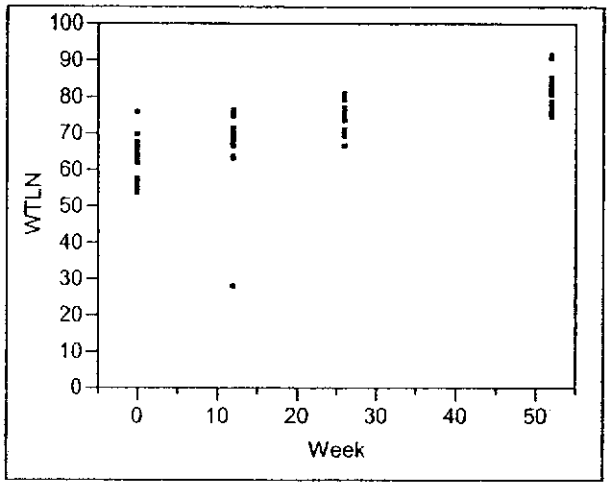
Weight over time



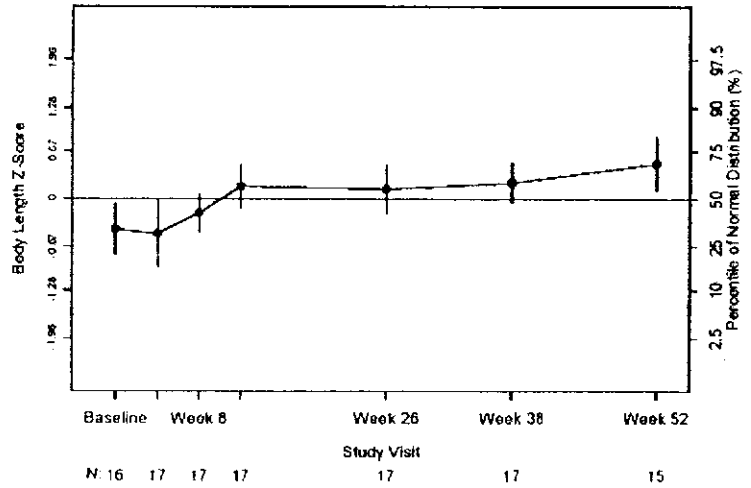
Mean weight z-scores from baseline to Week 52



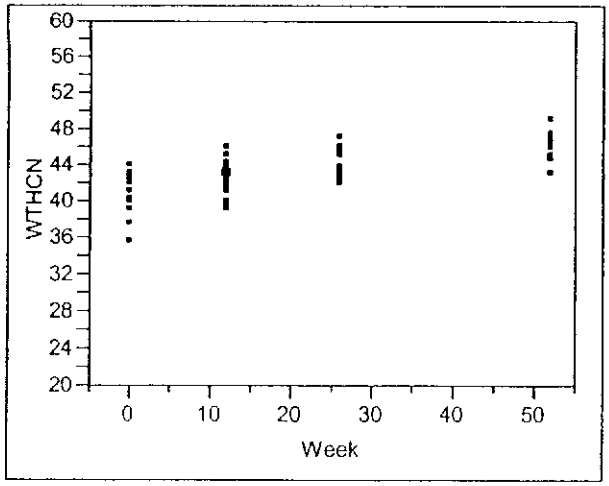
Length over time (note outlier Week 12 = patient 311, likely an error, results for patient 311: screening 69 cm, Week 12 28 cm, Week 26 75 cm, Week 52 80 cm).



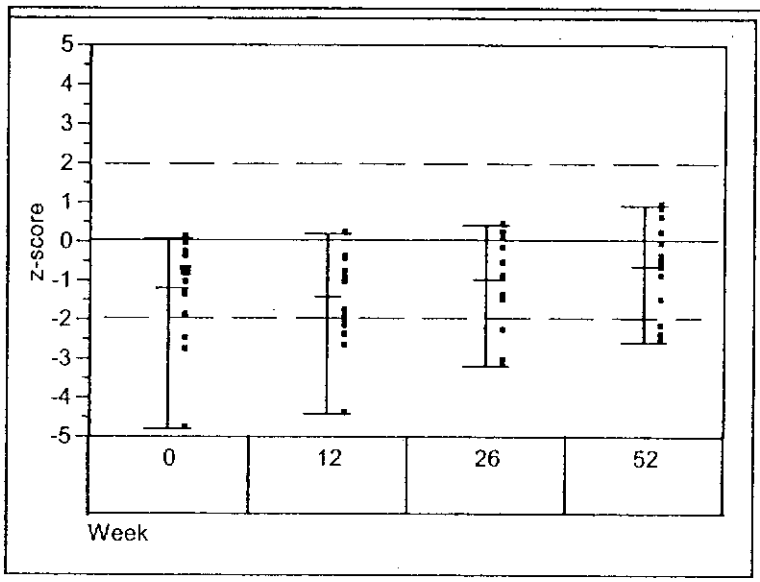
Mean length z-scores from baseline to Week 52



Head Circumference over time



Head Circumference Z-score plot



(2) Alive and Free of Ventilatory Support

For the interim analysis, the proportion of patients who were alive and free of any ventilatory support (invasive or non-invasive) at 12 months of age was evaluated, which was updated to Week 52 with available data (up to 15-September-2005). The results at the Week 52 milestone (each individual subject at Week 52) are as follows:

Table 20: 1602, Patients Alive and Free of Any Ventilatory Support at 52-Week Milestone

Treated Patients, n =	All 18	40 mg Group 9	20 mg Group 9
Parameter			
Alive and Free of Any Ventilatory Support, n =	12	6	6
Died, n =	0	0	0
On Ventilatory Support	6	3	3
Invasive	3	2	1
Non-invasive	3	1	2

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By individual subject:

Table 21: Study 1602, Status of Individual Subjects at 52-Week Milestone, Updated with 15-Sept-2005 Results

Patient Number	Treatment Group (mg/kg)	Age*at 1st Infusion (mos)	Age* at week milestone (mos)	Myozyme exposure at 52-week milestone (mos)	Status at 52-week milestone (mos)	Age*at start of invasive ventilation (mos)
301	40	5.0	18.0	10.0	Invasive	15.0
302	20	7.0	18.0	11.0	Alive & VF	-
303	40	7.0	18.0	11.0	Alive & VF	-
305	20	5.7	18.0	12.3	Noninvasive	(12.0)
306	20	5.9	18.0	12.1	Noninvasive	(13.7)
307	40	6.9	18.0	11.1	Alive & VF	-
308	40	4.3	18.0	7.8	Alive & VF	-
309	20	5.3	18.0	6.9	Alive & VF	-
310	20	6.4	18.0	11.6	Alive & VF	-
311	40	7.3	18.0	10.7	Alive & VF	-
312	20	5.1	18.0	7.0	Alive & VF	-
313	40	2.3	18.0	10.1	Noninvasive	(14.9)
314	20	1.9	18.0	10.1	Alive & VF	-
315	40	1.2	18.0	6.1	Alive & VF	-
316	20	6.9	18.0	6.4	Alive & VF	-
317	40	6.2	18.0	3.0	Invasive	9.2
318	40	5.4	18.0		Alive & VF	-
319	20	2.1	17.4	5.7	Invasive	9.1

*Age not adjusted for age at gestation
VF = invasive ventilator-free

The status of all subjects, including all ventilatory data known as of 15-Sep-2005 is as follows:

Table 22: 1602, Patients Alive and Free of Any Ventilatory Support as of 15-Sep-2005

	All	40 mg Group	20 mg Group
Treated Patients, n =	18	9	9
Parameter			
Alive and Free of Any Ventilatory Support, n =	11	5	6
Died, n =	1	0	1
On Ventilatory Support	6	4	2
Invasive	6	4	2
Non-invasive	0	0	0

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By individual subjects:

Table 23: Study 1602, Status of Individual Subjects as of 15-September-2005

Patient Number	Treatment Group (mg/kg)	Age* at 1st Infusion (mos)	Myozyme exposure at 15-Sep-05 or time of death (mos)	Age* at 15-Sep-05 (mos)	Status as of 15-Sep-05	Age* at start of invasive ventilation (mos)	Age* at death (mos)
301	40	5.0	24.7	32.7	Invasive	15.0	-
302	20	7.0	21.6	31.6	None	-	-
303	40	7.0	21.1	31.1	Invasive	24.5	-
305	20	5.7	14.0	-	Invasive/died	19.4	19.8
306	20	5.9	20.5	29.4	Invasive	19.7	-
307	40	6.9	19.2	29.2	None	-	-
308	40	4.3	18.8	26.1	None	-	-
309	20	5.3	18.4	26.7	None	-	-
310	20	6.4	17.9	27.4	None	-	-
311	40	7.3	18.0	28.2	None	-	-
312	20	5.1	16.1	24.2	None	-	-
313	40	2.3	16.2	21.5	Invasive	18.5	-
314	20	1.9	16.1	21.0	None	-	-
315	40	1.2	14.7	18.9	None	-	-
316	20	6.9	13.4	23.3	None	-	-
317	40	6.2	12.6	21.8	Invasive	9.2	-
318	40	5.4	12.5	20.9	None	-	-
319	20	2.1	12.3	17.4	Invasive	9.1	-

*Chronologic age not adjusted for age at gestation

(3) Cardiac Parameters at Week 26

Cardiac parameters were assessed by echocardiography at baseline, and Weeks 4, 8, 12 and 26. Cardiac hypertrophy was defined as an LVM >2 SDs from the normal mean. All patients had cardiomyopathy at baseline (entry criteria for the study). Fifteen (15) of 18 patients had LVMI and LVM Z-scores at baseline (missing patients 302, 303 and 318).

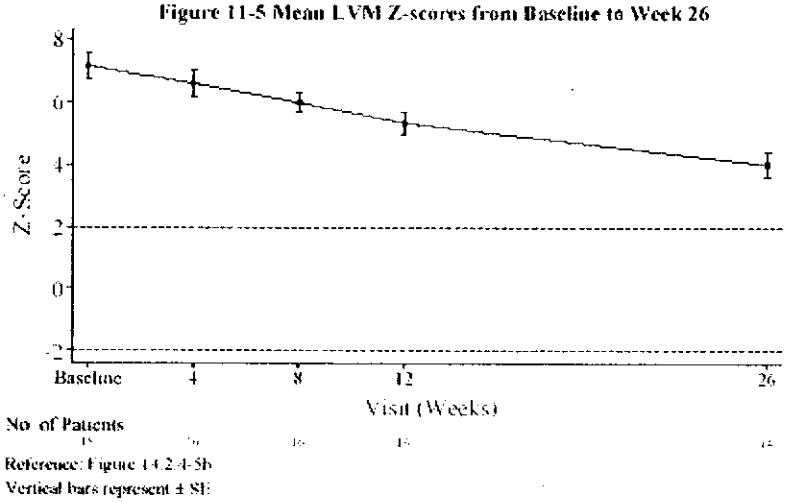
Table 24: Study 1602, Cardiac Parameters, Interim Data (26 Weeks)

	Screening	Week 4	Week 8	Week 12	Week 26
Parameter					
LVMI, n =	15	16	16	16	14
Mean	193	172	147	130	98
Median	202	180	140	126	92
Range	59, 302	73, 302	83, 217	72, 205	56, 158
ΔLVMI from Screening, n =	-	14	13	13	12
Mean	-	-26	-59	-70	-110
Median	-	-27	-55	-78	-102
Range	-	-75, +44	-120, 0	-116, -26	-178, -43
Ejection Fraction, n =	16	16	17	16	15
Mean	51	44	42	44	55
Median	50	43	42	44	57
Range	25, 76	27, 64	22, 69	27, 60	21, 74
ΔEF from Screening, n =	-	15	15	14	13
Mean	-	-7	-11	-7	+1
Median	-	-3	-9	-8	-8
Range	-	-24, +11	-38, +10	-30, +10	-14, +26
LVMI Z-Score, n =	15	16	16	16	14

Mean	6.0	5.5	4.8	4.3	3.0
Median	6.4	5.8	4.9	4.3	2.9
Range	1.7, 8.0	2.1, 8.0	2.8, 6.6	2.0, 6.3	1.2, 5.3
ΔZ-Score from Screening, n =	-	14	13	13	12
Mean	-	-0.7	-1.5	-1.9	-3.4
Median	-	-0.6	-1.7	-1.8	-3.5
Range	-	-2.2, +0.8	-2.9, -0.1	-3.0, -0.8	-5.1, -1.1

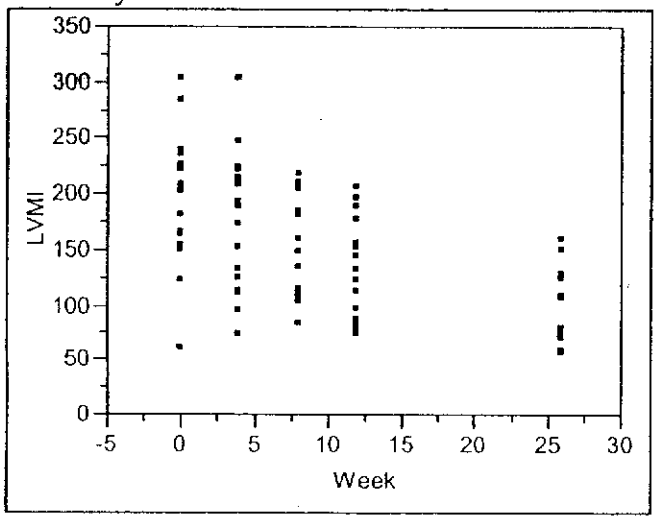
Mean LVM Z-scores from Baseline to Week 26

Figure 11-5 Mean LVM Z-scores from Baseline to Week 26

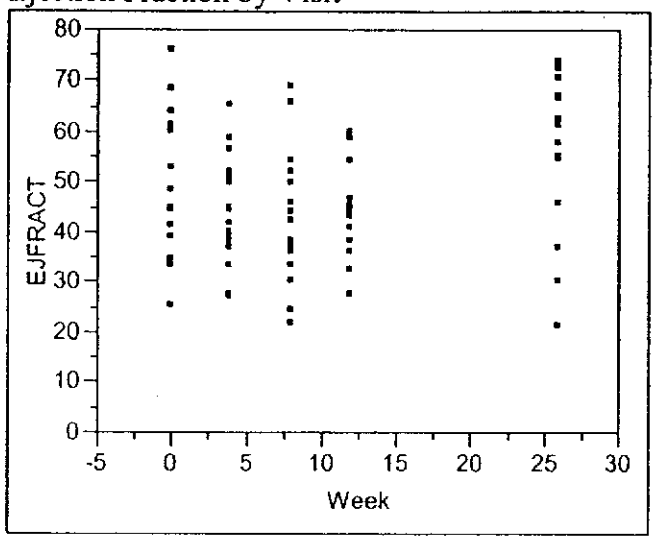


Reference: Figure 14.2.4-5b
Vertical bars represent ± SE

LVMI by Visit



Ejection Fraction by Visit



e) Tertiary Efficacy Endpoints

(1) Alberta Infant Motor Scale (AIMS) Performance Scores at Week 52

AIMS is a validated, widely used observational measure of infant motor performance that assesses motor maturation of the infant from term (40 weeks gestational age) through the age of independent walking (approximately 18 months of age). AIMS describes the motor development sequence according to the development of postural control relative to the various postural positions: prone, supine, sitting and standing (maximum scores prone 21, supine 9, sit 12 and stand 16). Observations are scored (maximum 58 points for raw score), and the raw score is converted into an age-equivalent score (the age at which 50% of healthy peers achieved such score, indicating the developmental age at which the patient is performing.

AIMS Motor Development Milestones

Positions		Milestone Description
Supine Or Supported Supine		Turns Head Side To Side To Look At Parent
		Grasps Small Object
		Reaches Up Or Out To Grasp Small Object
		Brings Hands Together In Midline
		Transfers Small Object Hand To Hand
Floor Mobility		Rolls Prone To Supine Position
		Rolls Supine To Prone Position
Sitting	Supported Sitting	Holds Head Upright With Body Supported In Chair Or By Person
		Holds Head Steady While Attending To An Activity-trunk Supported
		Grasps Small Object
		Reaches Up Or Out To Grasp Small Object
		Brings Hands Together In Midline-supported Sitting
		Transfers Small Object Hand To Hand
	Independent Sitting	Sits Independently-propped Without Independent Head Control
		Sits Independently-holds Head Steady To Attend To Activity
		Grasps Small Object
		Reaches Up Or Out To Grasp Small Object
		Brings Hands Together In Midline-independent Sitting
		Transfers Small Object Hand To Hand
	Sitting Transitions	Pulls To Sit Without Head Lag
		Transitions From Floor Into Sitting Independently
Standing and Walking		Bears Weight Through Lower Extremities
		Walks With Hands Held
		Pulls To Stand Independently
		Walks Independently
		Walks While Carrying Object
		Goes Up Stairs With Assistance (rail, hand[s] held, assistive device)
		Goes Up Stairs Independently

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AIMS Motor Performance Scores

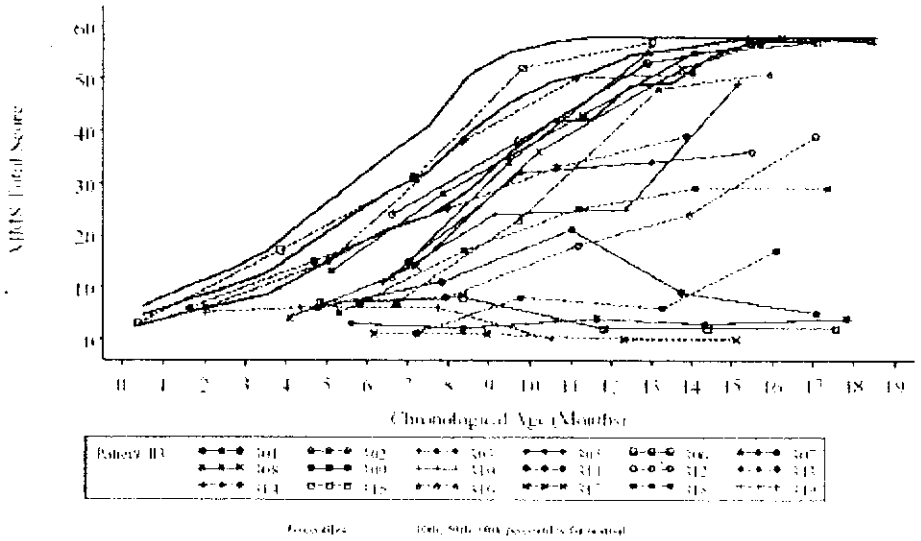
Table 25: Study 1602, AIMS Motor Performance Scores from Baseline to Week 52

Patient	Study Week	Chronologic Age (mos)	Raw Score (58)	Age Equivalent Score (mos)	Percentile Score	Status
301	Baseline	4.8	6	1.1	<1	
	52	17.1	5	0.8	<1	Invasive
302	Baseline	6.6	24	6.0	66	
	52	18.9	58	≥14	≥50	A & VF
303	Baseline	7.0	15	4.0	2	
	52	19.4	55	13	≥50	A & VF
305	Baseline	5.6	3	<0.5	<1	
	52	17.8	4	<0.5	<1	Noninvasive
306	Baseline	5.8	7	1.4	<1	
	52	17.6	2	<0.5	<1	Noninvasive
307	Baseline	6.6	12	3.3	1	
	52	18.9	58	≥14	≥50	A & VF
308	Baseline	4.1	4	<1	<1	
	52	16.2	58	≥14	≥50	A & VF
309	Baseline	5.1	13	3.6	7	
	52	17.1	57	≥14	≥50	A & VF
310	Baseline	6.4	11	3.0	<1	
	52	18.4	47	9.9	<1	A & VF
311	Baseline	7.2	1	<0.5	<1	
	52	19.2	16	4.2	<1	A & VF
312	Baseline	4.8	1	1.3	<1	
	52	17.0	1	8.4	<1	A & VF
313	Baseline	2.0	2	1.0	16	
	52	14.0	9	11.4	9	Noninvasive
314	Baseline	1.6	1	1.0	25	
	52	13.8	7	8.4	<1	A & VF
315	Baseline	0.4	1	0.5	14	
	52	13.0	15	≥14	65	A & VF
316	Baseline	6.7	0	1.4	<1	
	52	18.9	15	≥14	≥50	A & VF
317	Baseline	6.2	0	0.5	<1	
	52	18.7	0	<0.5	<1	Invasive
318	Baseline	5.3	0	0.8	<1	
	52	17.3	1	6.7	<1	A & VF
319	Baseline	2.0	1	0.8	7	
	26	7.7	6	1.0	<1	Invasive
	52	Not available	Not available	Not available	Not available	

Results represented graphically (electronically copied and reproduced from sponsor's submission):

AIMS Motor Performance Age-Equivalent Scores from Baseline to Week 52

Figure 3-1 AIMS Motor Performance Age-Equivalent Scores from Baseline to Week 52



Reference: Figure 14.2.3-1a

Note: The 13 patients who made gains on the AIMS (Patients 302, 303, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, and 318) are indicated in blue. The 5 patients who did not make gains in the AIMS assessment (Patients 301, 305, 306, 317, and 319) are indicated in black. The shaded area indicates the normal range of AIMS scores.

(2) Pediatric Evaluation of Disability Inventory: PEDI and Pompe PEDI

Pediatric Evaluation of Disability Inventory (PEDI)[2]

- Standardized instrument developed to assess the functional capabilities of children 6 months to 7.5 years of age administered as a parental report questionnaire
- Functional skills (performed independently) and Caregiver assistance skills (performed with assistance) are assessed in 3 contents domains: self-care (e.g., feeding, grooming bathing, dressing), mobility (e.g., chair or bed transfer, locomotion), and social function (e.g., comprehension, expression).
- Higher scores indicate better performance and increased independence. Raw scores are transformed to normative and scaled scores.
    - Normative scores available for children up to 7 years of age, describe how a child is performing compared to same-aged peers without a disability.
    - Scaled scores, 0-100 continuum, based on a model of item difficulty used to represent the functional skills of children older than 7 years.

[2] Feldman AB, Haley SM, Coryell J. Concurrent and Construct Validity of the Pediatric Evaluation of Disability Inventory. Phys Ther 1990;70:602-610.

Pompe PEDI[3]

- standardized, modified version of the PEDI specifically designed for patients with Pompe disease.
- Since Pompe disease primarily impacts motor function, the PEDI self-care and mobility functional skills scales were modified by adding items that reflected the types of functional skills and deficits noted in children with Pompe disease. New items were added to the original PEDI to increase the ceiling level, decrease the basal level, create smaller skill increments between items to improve scoring precision and potential sensitivity to change and to include assistive technology items (e.g., use of wheelchair).

The following average Pompe PEDI scores were seen in the original Pompe PEDI study group (n = 30; mean age 7.7 ± 5.5 years, range 0.4-22.1 years), grouped by gross motor function classification level groups.

Table 26: Average Pompe PEDI Scores by Gross Motor Function Classification Level Groups

Pompe-PEDI Scales	Group 1: self-mobility severely limited (n=8)	Group 2: self-mobility limitations; use of powered mobility (n=11)	Group 3: Walks with or without restrictions or devices (n=8)
Self-care functional skills scores	33.6	52.5	74.1
Mobility functional skills scores	21.6	40.3	68.8

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[3] Haley SM, Fragala MA, Aseltine R, Ni P, Skrinar AM. Development of a disease-specific disability instrument for Pompe disease. Pediatr Rehabil 2003;6(2):77-84.

Pompe PEDI Mobility Scores

Table 27: Study 1602, Pompe PEDI Scores, Mobility Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Mobility Scores			Status
			Raw	Scaled (SE)	Normative Std Score	
301	Baseline	4.8	2	8.1 (3.0)	34	
40 mg	52	17.1	1	4.5 (3.6)	<10	Invasive
302	Baseline	6.6	15	26.7 (1.5)	62	
20 mg	52	18.9	86	54.8 (1.0)	51	A & VF
303	Baseline	7.0	9	21.0 (1.9)	16	
40 mg	52	19.4	65	48.7 (0.9)	37	A & VF
305	Baseline	5.6	6	16.8 (2.2)	47	
20 mg	52	17.6	6	16.8 (2.2)	<10	Noninvasive
306	Baseline	5.8	9	21 (1.9)	54	
20 mg	52	17.6	3	10.8 (2.7)	<10	Noninvasive
307	Baseline	6.6	9	21.0 (1.9)	54	
40 mg	52	18.9	72	50.7 (0.9)	41	A & VF
308	Baseline	4.1	3	10.8 (2.7)	38	
40 mg	52	16.2	53	44.9 (1.0)	45	A & VF
309	Baseline	5.1	9	21.0 (1.9)	54	
20 mg	52	17.1	64	48.4 (0.9)	52	A & VF
310	Baseline	6.4	12	24.2 (1.7)	23	
20 mg	52	18.4	51	44.2 (1.0)	26	A & VF
311	Baseline	7.2	4	13.1 (2.5)	42	
40 mg	52	19.2	18	28.8 (1.4)	<10	A & VF
312	Baseline	4.8	6	16.8 (2.2)	47	
20 mg	52	17.0	27	34.0 (1.3)	23	A & VF
313	Baseline	2.0	2	8.1 (3)	34	
40 mg	52	14.0	42	40.9 (1.1)	37	Noninvasive
314	Baseline	1.6	1	4.5 (3.6)	29	
20 mg	52	13.8	28	34.6 (1.2)	24	A & VF
315	Baseline	0.4	0	0 (5.8)	22	
40 mg	52	13.0	60	47.2 (1.0)	49	A & VF
316	Baseline	6.7	8	19.8 (2.0)	52	
20 mg	52	18.9	80	53.0 (0.9)	47	A & VF
317	Baseline	6.2	2	8.1 (3)	<10	
40 mg	52	18.7	3	10.8 (2.7)	<10	Invasive
318	Baseline	5.3	3	10.8 (2.7)	38	
40 mg	52	17.3	29	35.1 (1.2)	25	A & VF
319	Baseline	2.0	0	0 (5.6)	22	
20 mg	52	14.4	6	16.8 (2.2)	<10	Invasive

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Pompe PEDI Self-Care Scores

Table 28: Study 1602, Pompe PEDI Scores, Self-Care Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Self-Care			Status
			Raw	Scaled (SE)	Normative Std Score	
301	Baseline	4.8	5	18.8 (2.8)	58	
40 mg	52	17.1	7	23.1 (2.5)	11	Invasive
302	Baseline	6.6	8	25.0 (2.5)	71	
20 mg	52	18.9	46	53.0 (1.2)	54	A & VF
303	Baseline	7.0	10	28.7 (2.4)	31	
40 mg	52	19.4	25	42.4 (1.4)	30	A & VF
305	Baseline	5.6	5	18.8 (2.8)	58	
20 mg	52	17.6	6	21.0 (2.6)	<10	Noninvasive
306	Baseline	5.8	3	12.7 (3.5)	46	
20 mg	52	17.6	3	12.7 (3.5)	<10	Noninvasive
307	Baseline	6.6	10	26.7 (2.4)	79	
40 mg	52	18.9	33	46.7 (1.3)	40	A & VF
308	Baseline	4.1	1	4.9 (4.0)	30	
40 mg	52	16.2	35	47.7 (1.3)	58	A & VF
309	Baseline	5.1	6	21.0 (2.6)	63	
20 mg	52	17.1	30	45.2 (1.3)	53	A & VF
310	Baseline	6.4	8	25.0 (2.5)	21	
20 mg	52	18.4	31	45.7 (1.3)	38	A & VF
311	Baseline	7.2	9	26.8 (2.5)	75	
40 mg	52	19.2	25	42.4 (1.4)	30	A & VF
312	Baseline	4.8	6	21.0 (2.6)	63	
20 mg	52	17.0	32	46.2 (1.3)	55	A & VF
313	Baseline	2.0	6	21.0 (2.6)	63	
40 mg	52	14.0	23	41.2 (1.4)	46	Noninvasive
314	Baseline	1.6	2	9.0 (3.5)	38	
20 mg	52	13.8	19	38.6 (1.5)	41	A & VF
315	Baseline	0.4	0	0 (6.3)	19	
40 mg	52	13.0	25	42.4 (1.4)	48	A & VF
316	Baseline	6.7	10	28.7 (2.4)	79	
20 mg	52	18.9	48	53.9 (1.2)	56	A & VF
317	Baseline	6.2	3	12.7 (3.5)	<10	
40 mg	52	18.7	7	23.1 (2.5)	<10	Invasive
318	Baseline	5.3	6	21.0 (2.6)	63	
40 mg	52	17.3	23	41.2 (1.4)	46	A & VF
319	Baseline	2.0	2	9.0 (3.5)	38	
20 mg	52	Not avail	11	30.3 (2.3)	25	Invasive

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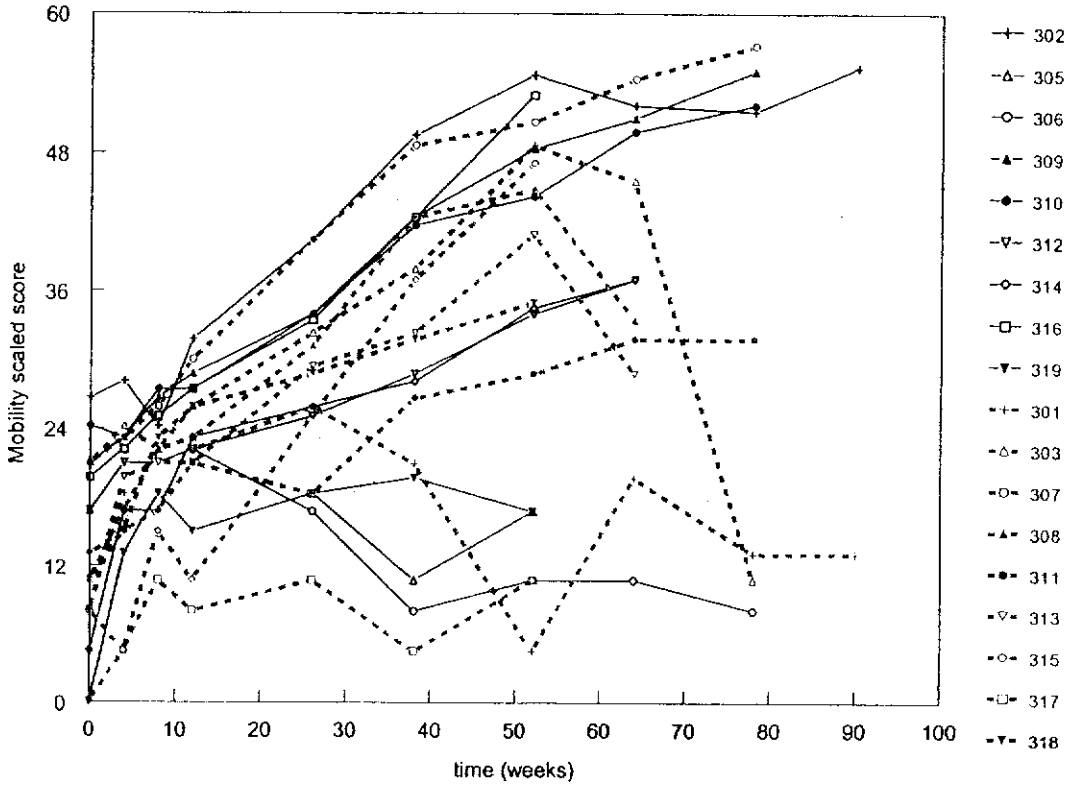
Pompe PEDI Social Function Scores

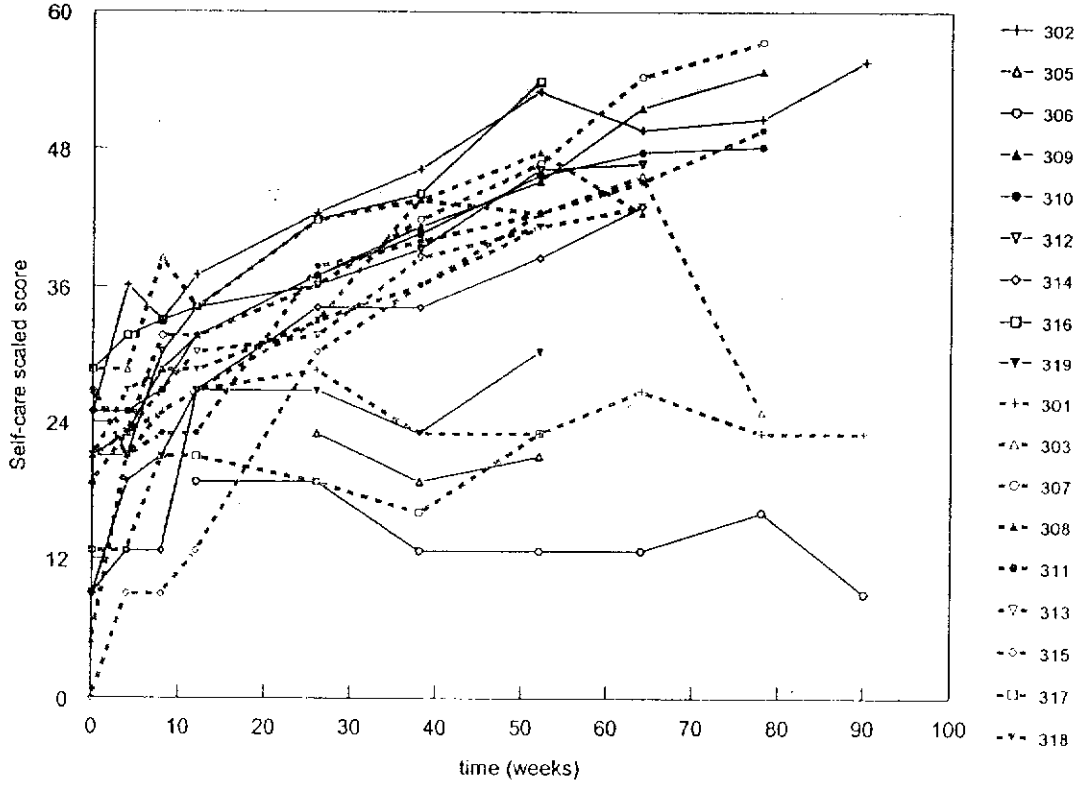
Table 29: Study 1602, Pompe PEDI Scores, Social Function Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Social Function Scores			Status
			Raw	Scaled (SE)	Normative Std Score	
301	Baseline	4.8	4	14.7 (3.2)	NA	
40 mg	52	17.1	12	36.1 (1.5)	45	Invasive
302	Baseline	6.6	5	21.6 (5.5)	NA	
20 mg	52	18.9	20	42.5 (1.3)	37	A & VF
303	Baseline	7.0	3	10.5 (3.2)	29	
40 mg	52	19.4	16	39.6 (1.4)	29	A & VF
305	Baseline	5.6	5	21.6 (5.5)	NA	
20 mg	52	17.6	9	32.9 (1.7)	41	Noninvasive
306	Baseline	5.8	7	30.0 (2.1)	NA	
20 mg	52	17.6	10	34.0 (1.6)	43	Noninvasive
307	Baseline	6.6	3	10.5 (3.2)	NA	
40 mg	52	18.9	15	38.8 (1.4)	27	A & VF
308	Baseline	4.1	2	6.6 (2.9)	NA	
40 mg	52	16.2	19	41.8 (1.3)	53	A & VF
309	Baseline	5.1	3	10.5 (3.2)	NA	
20 mg	52	17.1	16	39.6 (1.4)	50	A & VF
310	Baseline	6.4	5	21.6 (5.5)	43	
20 mg	52	18.4	17	40.4 (1.3)	31	A & VF
311	Baseline	7.2	2	6.6 (2.9)	NA	
40 mg	52	19.2	15	38.8 (1.4)	27	A & VF
312	Baseline	4.8	2	6.6 (2.9)	NA	
20 mg	52	17.0	18	41.1 (1.3)	53	A & VF
313	Baseline	2.0	1	3.1 (3.1)	NA	
40 mg	52	14.0	12	36.1 (1.5)	45	Noninvasive
314	Baseline	1.6	0	0 (NA)	NA	
20 mg	52	13.8	8	31.6 (1.8)	39	A & VF
315	Baseline	0.4	0	0 (NA)	NA	
40 mg	52	13.0	14	37.9 (1.5)	48	A & VF
316	Baseline	6.7	3	10.5 (3.2)	NA	
20 mg	52	18.9	22	43.8 (1.2)	41	A & VF
317	Baseline	6.2	2	6.6 (2.9)	24	
40 mg	52	18.7	10	34 (1.6)	13	Invasive
318	Baseline	5.3	4	14.7 (3.2)	NA	
40 mg	52	17.3	17	40.4 (1.3)	51	A & VF
319	Baseline	2.0	2	6.6 (2.9)	NA	
20 mg	52	Not avail	12	36.1 (1.5)	45	Invasive

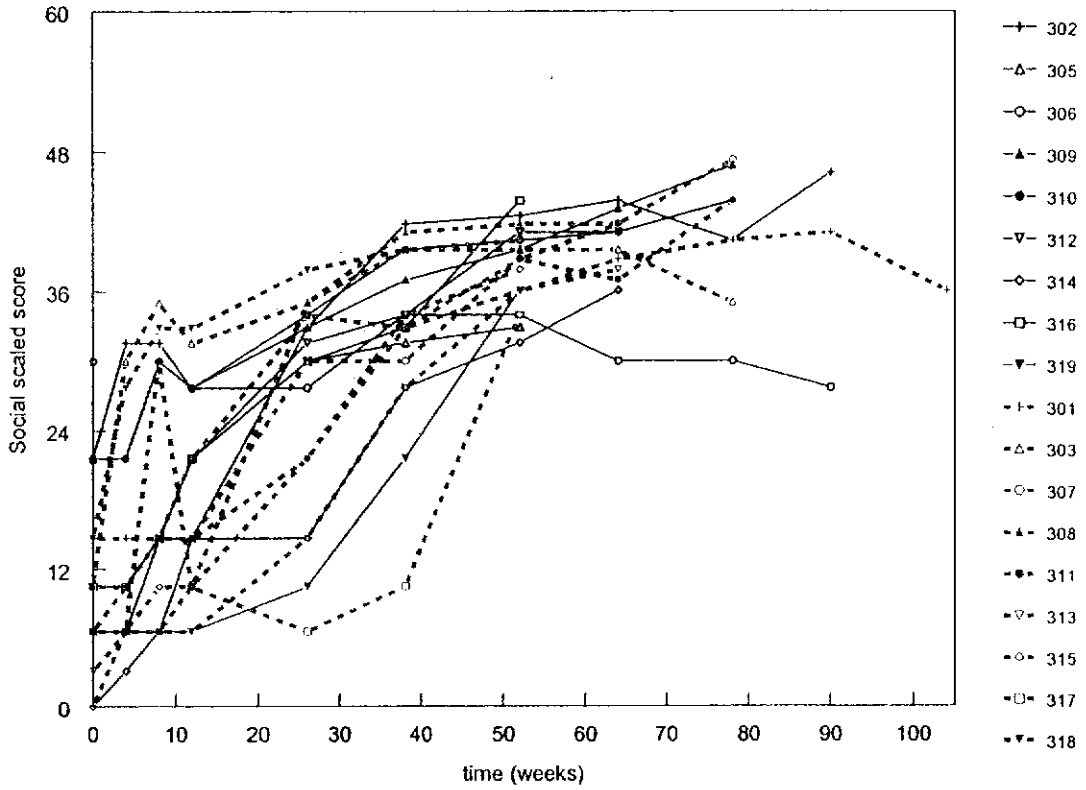
Pompe PEDI Mobility Scores (slide design credit: Ellis Unger, M.D.)



Pompe PEDI Self-Care Scores (slide design credit: Ellis Unger, M.D.)



Pompe PEDI Self-Care Scores (slide design credit: Ellis Unger, M.D.)



(3) Bayley Scales of Infant Development II (BSID-II)

The Modified Bayley Scales of Infant Development (BSID-II) was used to assess cognitive, language, and personal/social development in children from 1 through 42 months of age. The mental age-equivalent score is used to determine the age level at which a child is functioning, regardless of chronological age, while the mental development index (MDI) score is used to compare a child's performance to that of same-age normally developing peers.

MDIs within normal limits (WNL) range from 85-114, mildly delayed performance 70-84, and significantly delayed ≤69.

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Table 30: Study 1602, BSID-II Scores

Patient/ Dose Group	Week	Total Raw Score	Chron Age (Mos)	Age Equiv (Mos)	MDI	Status
301	Baseline	38	4.8	3	65	
40 mg	52	82	17.1	11	56	Invasive
302	Baseline	59	6.6	6	107	
20 mg	52	109	18.9	17	85	A & VF
303	Baseline	62	7.0	6	98	
40 mg	52	101	19.4	15	77	A & VF
305	Baseline	11	5.6	<1	<50	
20 mg	52	76	17.8	9	52	Noninvasive
306	Baseline	34	5.8	3	<50	
20 mg	52	Not available				
	64	25	20.3	2	<50	Noninvasive
307	Baseline	58	6.6	5	90	
40 mg	52	106	18.9	16	79	A & VF
308	Baseline	38	4.1	3	87	
40 mg	52	96	16.2	14	86	A & VF
309	Baseline	57	5.1	5	103	
20 mg	52	107	17.1	17	107	A & VF
310	Baseline	41	6.4	4	56	
20 mg	52	101	18.4	15	77	A & VF
311	Baseline	60	7.2	5	94	
40 mg	52	104	19.2	16	83	A & VF
312	Baseline	45	4.8	4	101	
20 mg	52	102	17	16	88	A & VF
313	Baseline	17	2.0	1	78	
40 mg	52	96	14	14	103	Noninvasive
314	Baseline	8	1.6	<1	87	
20 mg	52	78	13.8	10	65	A & VF
315	Baseline	0	0.4	<1	Not done	
40 mg	52	93	13	13	105	A & VF
316	Baseline	56	6.7	5	101	
20 mg	52	109	18.9	17	102	A & VF
317	Baseline	53	6.2	5	80	
40 mg	52	76	18.7	9	<50	Invasive
318	Baseline	47	5.3	4	83	
40 mg	52	101	17.3	15	86	A & VF
319	Baseline	9	2.0	<1	62	
20 mg	52	96	14.4	14	103	Invasive

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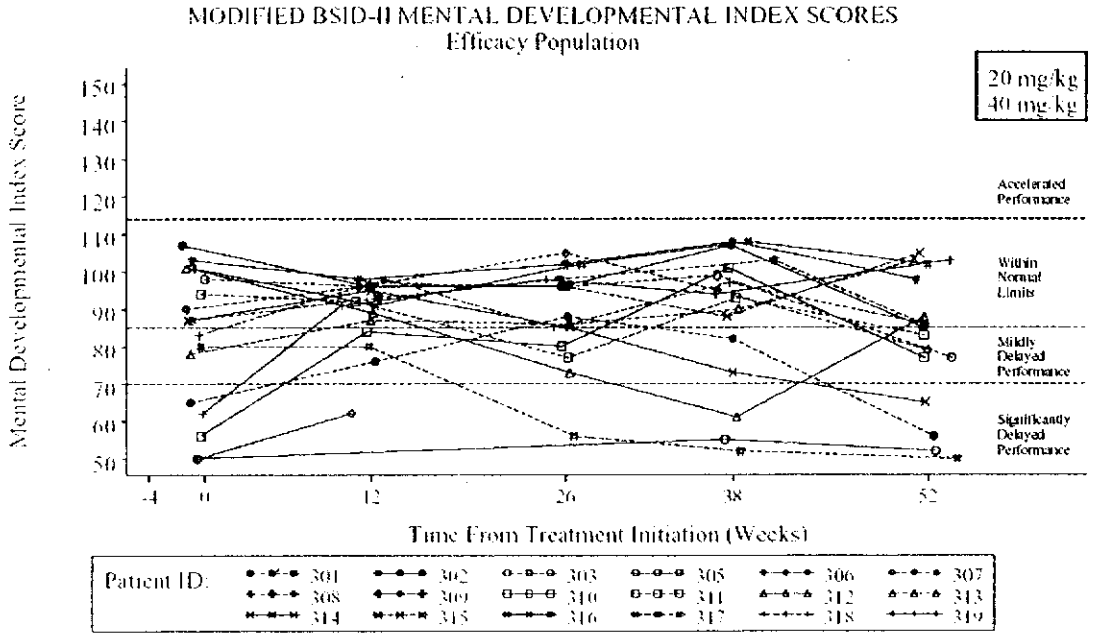
BSID at Week 52



Note: Fewer than 0.1% of the infants in the standardization sample obtained MDI scores that were more than 3 SD above or below the mean (below 55 or above 145). Therefore, the norms for the MDI do not extend below 50 or above 150 (Black MM and Matula K. Essentials of Bayley Scales of Infant Development-II Assessment. New York: John Wiley & Sons, Inc., 2004).

f) Other Secondary Endpoints: Week 26 Interim Analyses

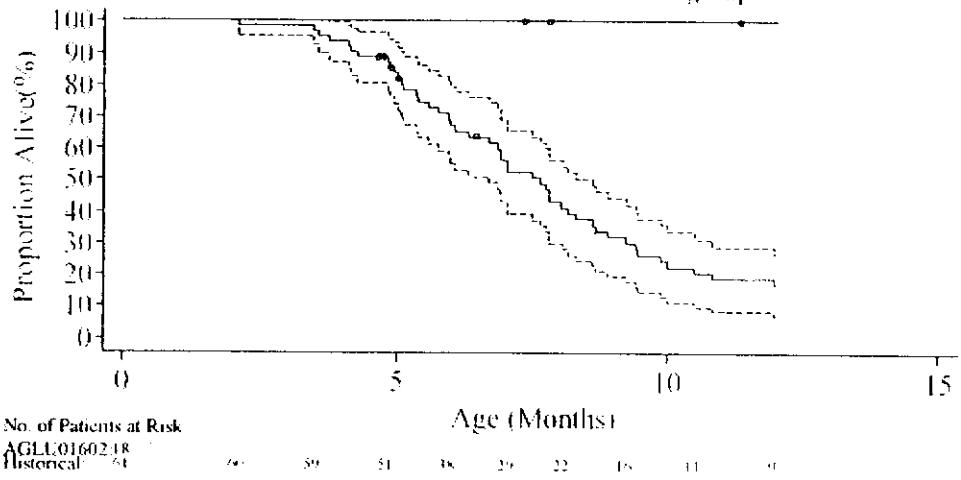
(1) Survival at 12 Months of Age and at 18 Months of Age

The proportion of patients alive at 12 months of age was estimated and compared to survival probability in the historical control subgroup, and survival to 18 months was available with updated results.

- 18 of 18 subjects survived to 12 months of age, and 18 of 18 subjects survived to 18 months of age.
- Median age of death in the Study 1602 population has not been reached (2 patients had died as of late-Sept 2005: Subject 305 age 19.8 months and Subject 303 age approx. 32 months)
- In the historical control subgroup 9 of 61 (15%) survived beyond 12 months of age and 1 of 61 (2%) survived beyond 18 months of age.
- Median age at death was 7.5 months in the historical control subgroup

KM-Survival Curve to Age 12 Months only (data cutoff 15-Dec-2004, 3 patients censored [315, 318, and 319] as had not yet reached 12 months of age)

Figure 11-4 Kaplan-Meier Estimate of Time to Death from Date of Birth as Compared Survival in the Historical Control Subgroup



Reference: Figure 14.2.3-5b

The blue solid line shows the Kaplan-Meier estimate of the proportion of patients in Study AGLU01602 alive as a function of age. The purple solid line shows the Kaplan-Meier estimate of the proportion of patients in the historical control subgroup alive as a function of age. The dashed purple line shows the 95% CI for this estimate. Circles indicate censored observations.

(2) Cardiac Failure at Week 26

An analysis through Week 26 showed that there were patients 2 patients (309 and 314) who had signs and/or symptoms compatible with cardiac failure at baseline (although overlap with respiratory failure was difficult in this population), and by Week 26, no patient had findings compatible with cardiac failure. There were no other reports of cardiac failure noted.

(3) Hours on Ventilation

Hours on ventilation (both invasive and non-invasive) from baseline to Week 26 was not a meaningful analysis. As of the Week 26 milestone, a total of 4 subjects required ventilatory support, including:

- 2 subjects (317 and 319) were receiving invasive ventilatory support (317 and 319) beginning at 9.2 and 9.1 months of age. Both of these subjects were unable to discontinue ventilatory support, and were continued on invasive ventilation for the duration of the study.
- Subject 305 had 19 days for invasive and non-invasive ventilation in 3 separate time periods between 6-8 months of age (twice for invasive procedures and once for infection), but did not require ongoing invasive ventilation until 19.4 months of age (died age 19.8 months).
- Subject 311 required 15 days of non-invasive ventilation (BIPAP) at age 7.5 months for influenza, and did not require ventilatory support thereafter.

In contrast, in the historical control subgroup, a history of any ventilator support was reported in 6 of 62 patients (10%), and no use of ventilator support at any time was reported in 31 patients (50%) and unknown in 25 patients (40%). The median age at

which ventilator support was first instituted was 7.7 months. In the 6 patients who required ventilatory support (a total of 9 ventilator episodes), which was required primarily for "advancement of the disease". The reasons for stopping support were not documented. In the 3 patients in whom data were available, first ventilator support lasted a median of 1 day and was likely a peri-terminal event. In a separate analysis of the original historical control population (AGLU-004-00), there was no statistically significant difference in the survival distribution between 47 patients in whom ventilator use was documented compared to 58 patients in whom ventilatory support was not used (log-rank test p-value = 0.434).

g) Exploratory Variables

(1) Gene expression GAA Gene Mutational Analysis

Lower limit of quantification of assay (3.0 nmol/hr/g wet tissue).

Table 31: Study 1602, GAA Mutational Analysis

Patient	Maternal Allele	Maternal Allele: Class of Mutation	Paternal Allele	Paternal Allele : Class of Mutation	Baseline GAA Activity
301	(Del exon 18) c.2481+102_2646+31del p.Gly828_Asn882del	Inframe deletion	c.437delT p.Met146ArgfsX7	Frameshift	<3.0
302	c.1064T>C p.Leu355Pro	Missense	c.1064T>C p.Leu355Pro	Missense	8.8
[illegible]	N/A	N/A	N/A	N/A	<3.0
	N/A	N/A	N/A	N/A	<3.0
[illegible]	c.872T>C p.Leu291Pro	Missense	c.872T>C p.Leu291Pro	Missense	8.5
307	c.1710C>G p.Asn570Lys	Missense	c.2560C>T p.Arg854X	Nonsense	<3.0
308	c.1465G>A p.Asp489Asn	Missense	c.40_47delGCCGTCTG p.Ala14ArgfsX18	frameshift	<3.0
309	c.1802C>T p.Ser601Leu; c.1726G>A p.Gly726Ser; c.2065G>A p.Glu689Lys	Missense	c.1099T>C p.Trp367Arg	Missense	4.6
310	c.1935C>A p.Asp645Glu; c.1726G>A p.Gly726Ser; c.2065G>A p.Glu689Lys	Missense	c.1194(IVS7)+2T>C	Splice site mutation	<3.0
311	c.2297A>C p.Tyr766Ser	Missense	c.2297A>C p.Tyr766Ser	Missense	<3.0
312	N/A	N/A	N/A	N/A	<3.0
313	c.2560C>T p.Arg854X	Nonsense	c.2560C>T p.Arg854X	Nonsense	<3.0
314	c.2741_2742delAG; c.2743_2746dupCAGG p.Gln914ProfsX30	Frameshift	c.2741_2742delAG; c.2743_2746dupCAGG p.Gln914ProfsX30	Frameshift	<3.0
315	c.1210G>A p.Asp404Asn	Missense	c.1064T>C p.Leu355Pro	Missense	<3.0
316	c.2560C>T p.Arg854X	Nonsense	c.1979G>A p.Arg660His	Missense	<3.0
317	N/A	N/A	N/A	N/A	<3.0
318	(Del exon 18) c.2481+102_2646+31del p.Gly828_Asn882del	Inframe deletion	(Del exon 18) c.2481+102_2646+31del p.Gly828_Asn882del	Inframe deletion	<3.0
319	c.1754(IVS12)+1G>A	Splice site mutation	c.722_723delTT p.Phe241CysfsX88	frameshift	<3.0

h) Pharmacokinetic (PK) Measures

Plasma rhGAA PK parameters were calculated for each patient at baseline and Week 12. Pharmacodynamic (PD) measures were evaluated by comparing skeletal muscle GAA activity and skeletal muscle glycogen content (by biochemical and histomorphometric methods) at baseline and Week 12. Other than differences in AUC (1.9 times higher in 40 mg/kg group than 20 mg/kg) and C_{max} (1.5 times higher in 40 mg/kg than 20 mg/kg group), which are related to concentration of rhGAA present in plasma, there were no other notable differences in PK characteristics between the 2 dose groups. The PK Parameters are summarized as follows:

Table 32: Study 1602, Plasma PK Parameters

Parameter	Day 0	Week 12
C_{max}, ng/mL		
20 mg/kg	160910 ±27598	195540 ±73190
40 mg/kg	271253 ±61251	256096 ±50920
AUC, ng*h/mL		
20 mg/kg	937896 ±199381	1017118 ± 262278
40 mg/kg	1883581 ±407002	1861479 ± 407002
α-half-life, hrs	0.57 ± .081	0.59 ± .065
β-half-life, hrs	2.71 ± .58	2.80 ± .57
Clearance,		
mL/hr	133 ± 41	154 ± 51
mL/hr/kg	22.1 ± 4.2	21.8 ± 5.4
V1		
mL	264 ± 87	308 ± 91
mL/kg	43.5 ± 8.4	43.5 ± 8.4
Vss		
mL	404 ± 116	469 ± 100
mL/kg	66.9 ± 10.3	67.0 ± 9.8

i) Safety

In general, AEs reflected underlying disease. AEs most commonly reported in the Infections and Infestations SOC, followed by Respiratory, Thoracic and Mediastinal. All patients reported at least 1 AE. Most commonly reported AEs (up to 26-week safety cutoff date 16-Dec-2004):

c) Secondary Efficacy Endpoint: Subjects Alive and Ventilator-Free

Table 39: Study 1702, Ventilator Use of First 15 Treated Patients

Patient	Ventilator Status at Baseline	Ventilator Status at Week 52	Age at 1st Infusion (mos)	Age at Invasive Ventilator Dependence (mos)	Age at Death (mos)
402	None	None	17.0	-	
403	Invasive	Invasive	37.3	32.3 (prior to study entry)	
404	None	None	8.2	-	
405	Invasive	Died	13.0	11.7 (prior to study entry)	
406	Invasive	Invasive	16.2	8.8 (prior to study entry)	17.3
407	None	Died	8.2	11.6	11.7
408	None	None	43.1	-	
409	None	Died	6.3	-	7.7
410	Invasive	Invasive	36.6	26.6 (prior to study entry)	
411	Noninvasive	Invasive	9.8	16.2	
412	None	Died	8.0	-	14.4
413	None	Invasive	7.0	18.2	
414	None	None	24.1	-	
415	None	None	15.0	-	
416	Invasive	Invasive	18.1	13.0 (prior to study entry)	

III. Summary and Conclusions

A. Infantile-Onset Pompe Disease

- Primary endpoint (ventilator-free survival): clear treatment effect
  - Median ventilator-free survival not yet reached vs. historical control median survival of 7.5 months (mean 8.6 months)
  - At 52-week milestone (all patients 18 months of age), 18 of 18 patient living, and 3 of 18 requiring invasive ventilation
  - As of 15-Sept-2005 (age range 17.4 to 32.7 months), 1 of 18 patients died, 7 of 18 patients required invasive ventilation (including patient who died)
  - No obvious effect of dose (20 mg/kg vs. 40 mg/kg)
- Secondary and tertiary endpoints:
  - Motor development: Majority of patients show delays in motor milestones vs. age-matched peers; however, many patients appear to show within-patient progress (albeit delayed)
  - Cognitive development: appears to be WNL for majority of patients
  - Growth: length WNL, weight and head circumference below mean
  - Cardiac parameters: progressive declines in LVMI with treatment; however, means were $\geq$2 SD from age-matched norms at Week 26 cutoff. Unclear if this results in a clinical benefit to patients (CHF, EF)
- Safety: acceptable risk/benefit (given severity of underlying disease)
  - AEs and SAEs most commonly infections and respiratory, and most commonly appear to be due to underlying disease

B. Late-Onset Pompe Disease

- Sponsor has submitted open-label, uncontrolled, case-report data using all 3 (Synpac, Pharming and Myozyme) formulations of rhGAA in approximately 9 subjects
- Late-onset randomized, placebo-controlled, 52-week study (AGLU02704) in approximately 60 patients was initiated August-2005
- 1-year natural history (observational) study in late-onset patients has been completed in anticipation of Study (AGLU02303) to better characterize late-onset Pompe disease

C. Recommendations

- Recommend approval of Myozyme for the treatment of infantile-onset patient population
- Recommend against giving a broad indication for Pompe disease pending results of late-onset study already underway. In-house data insufficient to make any assessment of Myozyme treatment in late-onset Pompe disease
- Recommend black box warning for catheter placement and general anesthesia associated with Myozyme use
- Recommend dose- and dose-interval-exploration studies be performed as condition of approval (PMC).

07

19 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125141/0

OCT 6 2005

Genzyme Corporation
Attention: Alexander Kuta, PhD
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

Please refer to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated September 23, 2005. While conducting our filing review we identified the following potential review issue:

You are requesting an indication for the [redacted] It does not appear that you have provided sufficient data from clinical trials on the effects of Myozyme in patient populations other than infantile-onset Pompe disease. If you intend to pursue an indication for a broad range of patients, we recommend that you consider what additional clinical data you can provide as evidence of the safety and efficacy of Myozyme in Pompe disease other than infantile-onset disease.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

Brian Strongin, R.Ph, M.B.A.

Brian Strongin, R.Ph, M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Deficiencies Identified (DI)

SS Data Check:
- **Communication**
- **Milestone: Confirm Deficiencies Identified Entry & Closed Date**

cc: HFD-180/C. Stark
HFD-180/B. Strongin
HFD-180/A. Pariser
HFD-180/J. Hyde
HFD-180/J. Korvick
HFD-180/B. Harvey
HFD-122/R. Bernstein
HFD-122/I. Markovic
HFD-122/E. Max
HFD-122/F. Mills
HFD-122/N. Spiridonov
HFD-122/G. Johnson
HFD-122/B. Cherney
HFD-122/A. Rosenberg
HFD-120/B. Wilcox
HFD-328/M. Clark-Stuart
HFD-328/J. Li
HFD-328/M. Smedley
L. Kammerman
S. Grosser
C. Gray
HFD-005/Mike Jones
HFD-40/Office of Medical Policy/R. Temple if application or clinical issues
HFD-123/OBP Director/Keith Webber if application or product issues
HFD-320/DMPQ Director if application or facility issues
HFD-328/Mike Smedley if application or facility issues
DRMP BLA file (hard copy)
HFD-020/ Immediate Office (hard copy)

V

38 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Office of Drug Safety

MEMO

To: Marc Walton, MD
Medical Division Director, Division of Review Management and Policy, ODE VI (HFD-109)

From: Nora Roselle, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety

Through: Alina Mahmud, MS, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Date: September 12, 2005

Re: ODS Consult 05-0210, Myozyme (Alglucosidase Alfa), 50 mg; BLA 125141/0.

This memorandum is in response to an August 5, 2005 request from the Division of Review Management and Policy for a review of container label, carton and insert labeling of Myozyme.

In the review of the labels and labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

DMETS notes the use of trailing zeros when expressing product strength (e.g., 5.0 mg/mL) throughout the carton and package insert labeling. The use of terminal zeroes may result in error as decimals are often overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs....the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list. Revise the labeling so that strengths, etc. are expressed without the use of a terminal zero (e.g., 5 mg rather than 5.0 mg).

B. CONTAINER LABEL (VIAL)

1. The proprietary name is difficult to read as it currently appears in a — against a — background. This color combination does not provide sufficient color contrast for maximum readability. In addition, the established name is difficult to read in the blue font against the white background for the same reason. Revise accordingly so that the proprietary and established names have sufficient contrast and increased readability so that they are the most prominent information on the label.

2. The font size of the established name is small and difficult to read. Please ensure that the information is prominent and legible and meets 21 CFR 201.10(g)(2).

3. The graphic design of the distracts from the most important information on the label (proprietary and established names). DMETS recommends removing the graphic design from the label.

4. The statement "For Intravenous Infusion Only" is not prominent on the label and blends in with other information written in black font. Increase the prominence of these statements by bolding and/or change the font color to . In addition, include the statement. " on the principal display panel following the statement "For Intravenous Infusion Only."

5. Currently, the product strength is labeled as "50 mg". The strength should be revised to include the total drug content per vial (e.g., 50 mg/vial). Revise accordingly.

6. In addition, the resultant concentration (5 mg/mL) following reconstitution with 10.3 mL Sterile Water for Injection should be included if space permits.

7. Since not all the drug may be administered following reconstitution, a statement should be included on the labels stating "For Single Use Only to avoid confusion and potential error. In addition, the statement ' ' should be included in conjunction with the above warnings.

8. Injectable drug products are required to list the quantitative and qualitative inactive ingredients as per 21 CFR 201.100(b)(5). The vial label should be revised accordingly, if space permits.

C. CARTON LABELING

1. See comments B1 – B5, B7 – B8.

2. The statement "Package contains one vial of" should be relocated to the front display panel and revised to read for example

3. The carton labeling currently reads, "Following reconstitution with 10.3 mL … a total extractable volume of 10 mL and 5.0 mg/mL." Please revise to read, "Following reconstitution with 10.3 mL Sterile Water for Injection, USP, the resultant solution contains 5 mg/mL". Likewise, all trailing zeros should be deleted from the labeling (e.g., 5.0 mg/mL should read as 5 mg/mL).

4. Numerous steps are required to prepare this product prior to patient administration. The labeling should include the

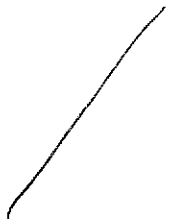
D. PACKAGE INSERT

1. DMETS notes that the DOSAGE AND ADMINISTRATION section of the package insert is confusing and may lead to error among prescribers. DMETS would like to meet with the Division regarding possible ways to improve this section of the package insert for clarity. We have included some of our concerns below.

2. According to the DOSAGE AND ADMINISTRATION section of the package insert, the total volume of infusion is determined by the patient's body weight and should be administered over 4 hours for the

20 mg/kg dose ——— The infusion is initiated at a rate of 1 mg/kg/hr and may be increased to 3 mg/kg/hr after 30 minutes if the patient's vital signs are normal and they are tolerating the infusion rate. Subsequent increases to the infusion rate may be achieved every 30 minutes until a maximum rate of 7 mg/kg/hr is achieved. The sponsor has provided a table labeled "Recommended Administration of MYOZYME" which may lead to confusion and error as some may believe that the drug should be administered over 30 minutes from the way that the table currently reads. We suggest revising the table as follows:

Recommended Administration of Myozyme



3. In the "Instructions for Use: Reconstitution, dilution, and administration" section of the package insert, please delete the sentence "Round up to the nearest whole — from step 1 (line 417). In addition, the calculations for patient dose and the number of vials to reconstitute (lines 422 and 423) should be relocated to follow the —

4. In the "Instructions for Use: Reconstitution, dilution, and administration" section of the package insert, step 1 and step 4 include the symbol "÷" (lines 424, 430, and 460) which can look like a plus sign "+" in some instances when printed. Revise so the "÷" symbol is clearly identifiable or written out as "divided by".

5. In the "Instructions for Use: Reconstitution, dilution, and administration" section of the package insert, step 2 should be revised so that the statements "Each vial will yield 5 mg/mL" and "The total extractable dose per vial is 50 mg per 10 mL" appear directly following sentence one of step 2. In addition, please revise the third sentence of step 2 to read as follows: "This is done by slow drop-wise addition of the water for injection down the inside wall of the vial and not directly onto the lyophilized cake.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-3242.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: Katherine Needleman, M.S. KN

To: File: STN 125141/0

Subject: Filing Meeting

Sponsor: Genzyme

Product: Alglucosidase alfa

Indication: Treatment of Pompe disease

Date, Location, & Time of Meeting: September 7, 2005
WOC-2, Conference Room G
3:00 - 4:30 p.m.

FDA Representatives: Katherine Needleman, Marc Walton, John Hyde, Anne Pariser, Bo Zhen, Anil Rajpal, Barbara Wilcox, Joyce Korvick, Brian Harvey, Cristi Stark, Jasti Choudary, Ralph Bernstein, Nikolay Spiridonov, Michelle Clark-Stuart

Summary:

Updates on Product/CMC, DMPQ, Pharmacology/Toxicology, and Statistical/Clinical disciplines were discussed.

No filing issues were raised by any of the committee members. The committee recommended that this application be filed in accordance with 21 CFR 601.2(a).

Issues for the 74 day letter were discussed which will currently include clinical issues.

DMPQ informed the committee that the PAI will be scheduled for October 24, 2005 through November 4, 2005.

DGP asked for regularly scheduled meetings for the remainder of the review cycle, including the midcycle (following the inspection) and a clinical pre-midcycle meeting. Cristi Stark will begin to schedule these meetings.

A need for an Advisory meeting was discussed. Further discussion with the ODE director is needed to make this decision.

There being no further business, the filing meeting was adjourned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: Katherine Needleman, M.S. KN

To: File: STN 125141/0

Date: August 17, 2005

Subject: First Committee Meeting

Sponsor: Genzyme

Product: Alglucosidase alfa

Attendees:

Marc Walton	Michelle Clark-Stuart
Wilson Bryan	Jianming Li
Anne Pariser	Barbara Wilcox
Brian Harvey	Amy Rosenberg
Joyce Korvick	Fred Mills
Katherine Needleman	Andrea Slavin
Bo Zhen	Jasti Choudary
Gibbes Johnson	

Summary:

1. Milestones
   - Filing Due Date: **Monday, September 26, 2005**
   - Mid-Cycle: **End of October 2005 – not scheduled**
   - First Action Due Date: **Friday, January 27, 2006**

2. **Filing procedures/Filing Memo/RTF guidance**
   - Each discipline needs to fill out the appropriate section of the filing memo.

3. **Meeting planning (Filing and Mid-cycle)**
   - Filing meeting: September 7, 2005
   - Mid cycle: ~ end of October. Kathy Needleman will speak with Cristi Stark and Division of Gastroenterology Products (DGP) about scheduling this meeting. Other requested meetings by DGP are monthly meetings starting from the filing meeting through the end of the review cycle. These will be scheduled.

4. **Inspection schedules (DMPQ and DSI)**
   - DSI
     - Selection of the sites and scheduling is in progress. Two domestic sites chosen.
   - DMPQ
     - PAI will be scheduled for October 24, 2005 through November 4, 2005. This timeframe was chosen based on production schedules obtained from Genzyme. This is the time when the purification suite (a new area never licensed) is in operation and Myozyme is being produced.

5. **Advisory Committee need**
   - A top-line overview was presented by Anne Pariser and a brief history of this project was explained by Marc Walton. At this time, an advisory meeting may look necessary but further evaluation is needed. Further discussions will take place at the filing meeting.

6. **Administrative procedures (memos, telecons, reviews)**
   - This BLA will continue to use BLA procedures (use of CBER EDR and RMS-BLA) and memos, reviews and telecons will be given to the RPM in paper for inclusion in the BLA file (i.e., no DFS, no COMIS).

7. **EDR issues**
   - Please see Kathy Needleman with any issues. There are no issues identified at this time. Kathy Needleman will check on the status of getting DGP access to the CBER EDR and CBER databases.

8. **Transition Issues**
   - Cristi Stark will be the RPM following the reorganization (currently September 16, 2005). Bo Zhen may or may not continue as the statistical reviewer. Barbara Wilcox will remain as the Pharm/Tox reviewer. A clinical pharmacology reviewer will be needed to be reassigned after the reorganization where currently Ed Bashaw and Anil Rajpal are assigned.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

AUG 04 2005

Genzyme Corporation
Attention: Alexander Kuta, Ph.D.
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): **BL 125141/0**

Name of Biological Product: Alglucosidase alfa

Indication: —

Date of Application: July 28, 2005

Date of Receipt: July 28, 2005

User Fee Goal Date: January 27, 2006

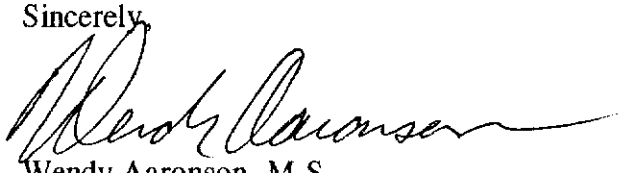
We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

If you have any questions, please contact the Regulatory Project Manager, Katherine Needleman, M.S., at (301) 827-4358.

Sincerely,



Wendy Aaronson, M.S.
Acting Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: August 1, 2005

FROM: Marc Walton, M.D., Ph.D. 8/1/05
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status
Sponsor: Genzyme
Product: Alglucosidase alfa
Indication: —

TO: BLA file STN 125141/0

The review status of this file submitted as a BLA application is designated to be:

☐ Standard ☒ Priority

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125141/0

SEP 2 3 2005

Genzyme Corporation
Attention: Alexander Kuta, PhD
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated July 29, 2005 for Alglucosidase alfa to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The user fee goal date is January 27, 2006. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before October 10, 2005.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-2120.

Sincerely,

Brian Strongin, R.Ph, M.B.A.

Brian Strongin, R.Ph, M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date:

From: **Florence O. Moore, M.S., DRMP, HFD-109**

To: **Genzyme Corp**

Subject: **IND 10780 Pre-BLA Meeting Summary**

Meeting Date: June 1, 2005 **Time: 2:30 - 4:00 p.m.**

Location: WOC-2, Conference Room I

Meeting Requestor/Sponsor: Genzyme

Product: Alpha-Glucosidase (human, recombinant, CHO cells, Genzyme)

Proposed Use: Treatment of infantile Pompe's disease.

Type of Meeting: Pre-BLA (IND 10780)

Meeting Purpose: To discuss clinical and preclinical data and submission content related to the submission of a BLA.

Note: ***FDA provided draft responses to the questions submitted in the meeting package by Genzyme by facsimile transmission on June 1, 2005.***

Meeting Summary

At the beginning of the meeting, Genzyme acknowledged receiving the FDA's responses to the submitted questions and gave a brief overview of the BLA content for electronic submission. What follows is a summary of specific discussions and clarifications sought by Genzyme regarding our responses.

1. *Genzyme plans to submit a BLA in Q3 2005 using 26-week interim data from the pivotal Study AGLU01602 and 52-week supportive data from Study. AGLUOI702. Does CDER agree that the available clinical data support a BLA filing for Myozyme?*

FDA Response (by facsimile): FDA finds the preliminary interim primary endpoint results encouraging. However, there will be substantially more data at the time of the proposed BLA filing in July 2005. FDA will expect the submission of validated primary endpoint results with a data cutoff one month prior to submission of the BLA. A final decision on the adequacy of the BLA for filing can only be made after initial review of submission.

Discussion During the Meeting: Genzyme indicated they plan to submit the BLA in the third quarter of 2005 using 26-week interim data from the pivotal study AGLU01602 and 52-week data from Study AGLU01702, and asked if the available clinical data will support the BLA filing. Genzyme stated the last patient's 52-week visit in AGLU01602 is early June 2005, and Genzyme will be able to provide updated data and analysis of only the primary endpoint as of June 2005. Genzyme stated that it will not be possible for them to include in the submission anything other than the primary endpoint to Week 52, as there is not adequate time prior to July 29, 2005 to monitor, enter, clean and analyze the data for the safety and secondary endpoints. All data other than for the primary endpoint will be through December 8, 2004 (26-week interim data).

FDA reiterated it is essential to have up-to-date the ventilator and survival information (primary endpoint). A lag of more than six months is not acceptable for key secondary endpoints, especially motor and development scores, and FDA proposed a cut-off date of March 8, 2005. Genzyme stated that a cut-off of March 8, 2005 would pose significant logistical difficulties for them and that they would discuss this internally and follow-up with the Agency in the near future.

2. *In addition to the data outlined in Question 1, Genzyme plans to include supportive data from other studies which provide data on long-term treatment of Pompe's disease with enzyme replacement therapy. Does CDER have any comment with respect to the supportive clinical data to be provided as part of the BLA filing (specifically, Studies AGLUOI702, AGLU02203, AGLU02003 AGLU 1205-02 A4-5, AGLU02103 and expanded access program AGLU02503)?*

FDA Response (by facsimile): From the pre-BLA meeting materials, it is not clear if Genzyme plans to provide clinical data from trial AGLU02603, the expanded-access experience for late-onset patients. Information from all subjects treated with rhGAA is relevant to the review of the BLA. Please plan to include data from the subjects in AGLU02603 study in the BLA.

FDA will need to review the AGLU-004-00 historical review report, including the report of Genzyme's selected comparator patients, and associated data. Please ensure that the following issues, as raised in the February 2004 pre-phase 3 meeting, are addressed:

a. Please plan to submit in the BLA the number of patients that were screened out of AGLU01602 due to poor ventilatory parameters, as well as other causes of screening exclusion.

b. For analyses where comparability of the populations is unclear (for example, the presence of congenital abnormality, clinically significant disease, or poor ventilatory parameters), please perform exploratory analyses, perhaps including screened-out subjects in the analysis of AGLU01602 and excluding patients who died before the age of six months in the historical control subgroup.

c. Please clarify the rule for imputing ages for the comparator group. The data set still appears to use an imputed age that is biased downward (if month only is given, it is likely to be lower than an actual age).

Discussion During the Meeting:

a. Genzyme indicated the late onset study was recently initiated and 2 patients were enrolled. Safety data and screening log will be included in the BLA submission. Genzyme noted the historical data for the study was previously submitted as an amendment to IND 10780.

b. Genzyme expressed an understanding of the comments made in the facsimile regarding sensitivity analyses for unclear comparability.

3. *The proposed indication for Myozyme is as follows:*

Please comment on the proposed indication.

FDA Response (by facsimile): Detailed discussion of the indication statement is premature prior to review of the data. The evidence of effectiveness in the proposed BLA would come only from infantile-onset Pompe disease patients. In the course of the review FDA will consider what extent of extrapolation beyond the clinical study population is appropriate.

Discussion During the Meeting: Regarding the indication statement, Genzyme indicated they would
and would like the FDA to consider the data submitted for a broader indication. FDA stated they will consider all data submitted for review.

4. *Given the small number of patients treated in the clinical program for Myozyme Genzyme proposes to summarize all safety and efficacy data in Module 2, Section 7.3, Summary of Clinical Efficacy, and Section 2.7.4, Summary of Clinical Safety, of the CTD. Separate Integrated Summaries of Safety and Efficacy will not be provided, as Genzyme believes that all elements required per 21 CFR 314.50 can be met with the content provided in Module 2. Please comment on this approach.*

FDA Response (by facsimile): FDA is uncertain whether Genzyme is proposing to submit the BLA without an integrated summary of efficacy and an integrated summary of safety, or if the question concerns the location for that information.
The BLA submission must contain these integrated summaries, in addition to whatever individual trial report summaries are provided.

Discussion During the Meeting: Genzyme stated that given the small number of patients treated in the clinical program for Myozyme, they proposed to summarize all safety and efficacy data in Module 2. Genzyme does not plan to provide separate integrated summaries of safety and efficacy (ISS and ISE respectively) because Genzyme believes that all elements required per 21 CFR 314.50 can be met with the information provided in Module 2.

FDA stated that the ISS and ISE need to be included in the submission and the ICH guidelines specify this should be included in Module 5. FDA cannot comment if there will be a technical problem to have it located in a different Module, but would stress to at least link the information to Module 5.

5. *Does CDER have any comment with respect to the preclinical data package for the BLA filing?*

FDA Response (by facsimile): Please provide a summary of preclinical data for PK studies for the different lots.

Discussion During the Meeting: Genzyme acknowledged FDA's response regarding the preclinical data and agreed to include results of all preclinical PK studies of the manufacturing changes with the BLA submission. FDA stated that submission of these results (particularly from Study 04-0424Pga and Study 05-0414Pga) before submission of the BLA would be preferable because this would alleviate any potential concerns relating to comparability issues. Genzyme stated that the earliest possible time that they would be able to submit the results of the preclinical PK studies would be only a few weeks before the BLA submission date. Genzyme further stated that they will discuss internally the possibility of submitting the results earlier than the BLA submission date, and will get back to the FDA.

6. *Genzyme is proposing to file a BLA for Myozyme using the CTD format. A paper copy will be submitted as the official archival copy, however an electronic reviewer aid will be provided following the eCTD format. It is anticipated that Genzyme would convert the paper application to an electronic application at a later point in time. The paper archival copy will be prepared from the same source files as those used for the eCTD reviewer aid. Please comment on the acceptability of this approach.*

FDA Response (by facsimile):

a. CDER does not accept the submission of a marketing application together in both paper and electronic form. FDA encourages an electronic submission.

b. Data files should be linked to clear and comprehensive define files. If data are submitted in CDISC format, Genzyme should also provide horizontal (one line per patient) analysis data files.

c. Does Genzyme plan to submit the BLA package in the format that was used for the submission for Fabrazyme?

Discussion During the Meeting: Genzyme sought clarification regarding the eCTD format for the BLA. Genzyme stated they are new users of the eCTD tool and are not fully comfortable yet with the use of it. Genzyme stated they propose to submit the official copy in paper and include an eCTD reviewer aid to enhance navigability of the submission. Genzyme plans to submit the standard CRTs in SAS XPORT format and will not be using the hybrid MAA/BLA format that was used in the Fabrazyme submission.

FDA stated the submission can only be sent in one format (i.e., paper or electronic). The reviewers will review the archive submission. FDA recommended the electronic format as it eases the review process and stated that all links should be operational. FDA suggested Genzyme send a list of the technical issues they are concerned about and FDA is willing to review the concerns and provide feedback. Genzyme indicated they would discuss this issue further internally and provide FDA a response.

7. *Does CDER have any comments or questions regarding the proposed content and format of the BLA filing for Myozyme?*

FDA Response (by facsimile): At the April 2004 meeting FDA recommended that Genzyme develop information on the concordance between the skin fibroblast assay and the PBMC assay, in order to help FDA consider how to characterize the intended population in labeling, and to determine whether one or both assays might be useful to assess the ongoing need for dosing.

Discussion During the Meeting: Genzyme explained that all patients in the AGLU01602 study were analyzed for endogenous GAA activity via fibroblast assay and had activity less than 1%. A subset of patients was also screened via a PBMC assay and the data will be included in the clinical study report (CSR) for FDA review. Genzyme stated that clinically, both assays are used for confirmation of GAA deficiency. Genzyme further explained that they are aware the amount of residual GAA activity is not the only determinant of clinical phenotype, a range from less than 1% to 40% has been reported in available literature in late-onset patients. Genzyme stated that the amount of residual enzyme activity is not factored into dosing decisions in other LSDs.

FDA inquired if Genzyme can get information from the three sites where the studies are being conducted because it will be useful to have some of the information on patients to evaluate assay validation in the BLA. Genzyme acknowledged this and indicated they will provide the data.

8. *In support of the BLA, Genzyme plans to include cross-references to prior clinical studies of rhGAA enzyme replacement therapy (ERT) conducted under BB- – Synpac rhGAA) and BB-IN – Pharming rhGAA). Clinical study reports from these previous ERT trials will not be included in the Myozyme BLA. Does the Agency agree with this proposal for cross-referencing?*

FDA Response (by facsimile): Safety data from trials of Pompe disease subjects conducted under IND – and IND –are relevant to the review of the proposed product. FDA request that Genzyme include safety data from prior clinical trials under INDs — and – in the BLA submission.

Discussion During the Meeting: Regarding the safety data, Genzyme stated that it will be difficult to extrapolate safety analysis because there are differences between Myozyme, Pharming and Synpac rhGAA since differences in — may result in differences in immunogenicity profiles. Genzyme agreed to include final study reports for all the IND studies in the BLA submission.

Genzyme proposed not to pool data, but submit narrative summaries of SAEs and safety data sets with adverse events related to the products with the CSR.

9. *Please comment on the potential for an Advisory Panel meeting relative to the review of the Myozyme BLA.*

FDA Response (by facsimile): The decision about the use of an Advisory Panel has not been made. However, FDA judges that there are some issues that might be gainfully discussed at an Advisory Panel meeting, including, but not necessarily limited to, the adequacy and appropriateness of the historical control group for the AGLU01602 trial, and the indicated patient subgroup.

Discussion During the Meeting: Genzyme asked if there were any outstanding concerns from the April 2004 meeting for the need for an Advisory Panel meeting relative to the review of the Myozyme BLA. FDA stated there were no additional concerns, but there are unique issues in this application where we may want to seek an Advisory Committee's input.

Genzyme indicated the target date for submitting the BLA is July 29, 2005. Genzyme plans to submit data up to subject age of 18 months in December 2005. FDA stated that these data could be reviewed prior to preparation for the Advisory Committee however; this will be discussed with the Division of Therapeutic Biologics Internal Medicine (DTBIMP) Division Director when the BLA is received.

FDA Attendees:
Office of Drug Evaluation VI
Division of Review Management and Policy
Florence Moore, M.S.
Katherine Needleman, M.S.

Office of Drug Evaluation VI
Division of Therapeutic Biological Internal Medicine Products
Ellis Unger, M.D.
John Hyde, M.D.
James Kaiser, M.D.
Anne Pariser, M.D.
Anil Rajpal, Ph.D.
Boguang Zhen, Ph.D.
Barbara Wilcox, Ph.D.

Office of the Commissioner
Office of Orphan Product Development
Paul Maher, M.D., M.P.H.

Sponsor Attendees:
Betty Wiley, RAC, Regulatory Affairs
Jennifer Panagoulias, RAC, Regulatory Affairs
Deya Corzo, MD, Clinical Affairs
Edward Kaye, MD, Clinical Affairs
Jennifer Hunt, MS, Clinical Affairs
Bruce Belanger, Ph.D., Biostatistics
Ronald Knickerbocker, Ph.D., Biostatistics
Alison McVie Wylie, Ph.D, Preclinical Biology

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date:

From: Katherine Needleman, M.S., DRMP, HFD-109

To: Genzyme Corp

Subject: IND 10780 CMC Pre-BLA Meeting Summary

Meeting Date: May 3, 2005 **Time: 1:00 - 2:30 p.m.**

Location: WOC-2, Conference Room C

Meeting Requestor/Sponsor: Genzyme

Product: Alpha-Glucosidase (human, recombinant, CHO cells, Genzyme)

Proposed Use: Treatment of infantile Pompe's disease.

Type of Meeting: CMC Pre-BLA

Meeting Purpose: To discuss Chemistry, Manufacturing and Controls (CMC) issues and submission content related to the filing of a BLA, particularly the requirements necessary for filing two manufacturing scale processes (160 and 2000 L).

Note: *FDA provided draft responses to the questions submitted in the meeting package by Genzyme by facsimile transmission on May 3, 2005. These are provided as Appendix A and are considered part of this meeting summary.*

Meeting Summary

At the beginning of the meeting, Genzyme acknowledged receiving the FDA's responses to the submitted questions. What follows is a summary of specific discussions and clarifications sought by Genzyme regarding our responses.

There was no discussion on question 1 bullet points 1, 2 subbullets 3, 5, 6, 7, 8, question 2 bullet 1, 2 subbullets 4 and 6, and question 4b bullet 3.

Regarding question 1, bullet 2 sub-bullet 1, Genzyme asked for clarification of the context of the assay that FDA proposed that Genzyme consider developing and if it was for lot release or comparability. FDA stated this was for lot release purposes and will consider a package from Genzyme to determine the adequacy of the assay.

Regarding question 1, bullet 2 sub-bullet 2, Genzyme agreed.

Regarding question 1, bullet 2 sub-bullet 4, Genzyme stated that they had no direct evidence that affected thGAA activity or stability. Genzyme agreed to either demonstrate that this modification does not affect activity or to control for the presence of

Regarding question 2, bullet 2 sub-bullet 1, Genzyme agreed to try to develop the data.

Regarding question 2, bullet 2 sub-bullet 2, Genzyme stated this data on the 2000 L process material will not be available for the BLA submission, and there would be only very limited clinical data using this material available for the submission (data from approximately 3-5 patients from the late-onset study). FDA stated that the extent of comparability data in the context of only minimal clinical exposure data has not been considered internally, and may constitute a significant problem. FDA expressed a need to discuss the issue internally further.

FDA noted that the concentration is another area of concern. Genzyme stated that concentrations were not measured in the patients who have received product from the 2000L process. FDA will further internally discuss this issue.

Regarding question 2, bullet 2 sub-bullet 3, Genzyme agreed to submit this data.

Regarding question 2, bullet 2 sub-bullet 4, Genzyme will provide data defining the positions(s) of the group on the rhGAA molecule.

Regarding question 2, bullet 2 sub-bullet 5, Genzyme agreed to submit this data for characterization purposes.

Regarding question 2, bullet 2 sub-bullet 7, Genzyme asked for clarification on the kind of information FDA wanted. FDA stated that as much characterization as possible will be useful and FDA is aware of the limited number of methods. FDA requests a more comprehensive characterization. . FDA requested this section be complete to ease review. Genzyme agreed.

Regarding question 2, bullets 3 and 4, Genzyme clarified these points and agreed to address the concerns.

Regarding question 3, Genzyme agreed but stated it was unlikely to be a degradation pathway. FDA recommended trying degradation by various methods in relative pathways. Genzyme agreed.

Regarding question 4a, bullet 1, Genzyme agreed to revisit clearance factors.

Regarding question 4a, bullet 2, Genzyme agreed. FDA stated that — concentration may be an issue and we will need to be conservative.

Regarding question 4a, bullet 3, 4, 5 and 6, Genzyme agreed.

Regarding question 4b, bullet 1, Genzyme agreed to clarify in the BLA submission.

Regarding question 4b, bullet 2, Genzyme stated this data will not be available at the time of the BLA submission.

Regarding the rest of question 4, Genzyme acknowledged FDA's responses and there was no need for clarification.

FDA Attendees: James Kaiser, Anil Rajpal, Fred Mills, Gibbes Johnson, Barry Cherney, Amy Rosenberg, John Hyde, Earl Dye, Ellis Unger, Martin Green, Carolyn Renshaw, Michelle Clark-Stuart, Michael Smedley, Katherine Needleman

Sponsor Attendees: Betty Wiley, Bob Mattaliano, Karen Lee, Alison McVie-Wylie, Carolyn Trott, Christopher Hwang, Leslie Rhubin, Mark Hayes

Appendix A

Meeting Date: May 3, 2005 **Time: 1:00 PM - 2:30 PM**

Sponsor: Genzyme

Product: Alpha-Glucosidase (human, recombinant, CHO cells, Genzyme)

Proposed Use: Treatment of Pompe's disease

Introductory Comment: This material consists of the reviewers' preliminary notes in preparation for the discussion at the May 3, 2005 meeting between Genzyme and FDA's Review Team. This material may not have been fully vetted internally and should not be considered as an official position of the FDA. This material is shared with the Sponsor solely to promote a collaborative and successful discussion at the meeting. You have the option of canceling the meeting (or changing it to a telecon) if these answers are clear to you. Please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to reach agreement on such changes during the teleconference. Any modifications to the development plan or additional questions for which you would like FDA feedback should be submitted as a new meeting request. The minutes for the meeting will reflect agreements and discussion at the meeting and may not be consistent with these reviewers' preliminary notes.

Sponsor questions and FDA response:

1. *Please comment on the adequacy and completeness of the data package proposed to support licensure of the 160 L scale manufacturing process.*

- Appendix A Facilities: Please include waste flow diagrams.

- The proposed Format and Organization of the CM&C section of the BLA appears to be generally complete and satisfactory. It is your plan to discuss both 160 L and 2000 L manufacturing processes side by side, which is logical since licensing is requested for both processes. FDA requests that all information on comparability between the processes be brought together in one section. Regarding the Drug Substance/ Drug Product Lot Release specifications, FDA has a number of specific requests, some of which also pertain to the comparability protocol for the 160 L and 2000 L processes-Attachment 5

    - FDA recommends development of another potency assay in addition to —. Such an assay should reflect the important physiological functions of rhGAA; i.e. —

    - Please consider development of quantitative specifications for —

- Please describe the criteria for a positive identity test.

- The [redacted] Please describe the effect that [redacted] nas on rhGAA cellular uptake and enzymatic activity. Please consider development of an assay to assess the levels of this modification.

- [redacted]

- FDA recommends developing quantitative specifications for the [redacted] present in oligosaccharide mapping.

- Please describe the methodology used to detect [redacted]

- Please consider lowering the specification for [redacted] The specification for [redacted] appears generous relative to the existing manufacturing history. In this regard, what is the disposition of Lot XGA180, for which the [redacted] was out of specification, at a level o [redacted] (Table A5-5)?

2. *Please comment on the adequacy and completeness of the data package proposed to support licensure of the 2000 L scale manufacturing process.*

- Appendix A Facilities: Please include waste flow diagrams.

- See above Question 1 bullet 2. In addition:

  - Please clarify how [redacted]

  - Please provide a tabulation of patient exposure to the 2000 L process material, including lot numbers, dosage, and chronology of administration.

  - [redacted]

- Please provide data defining the positions(s) of the group on the rhGAA molecule.

- In order to demonstrate consistency between 160 and 2000 L process materials, it is recommended that be performed. This data can support comparability.

- It is recommended that the of 2000 L process material be demonstrated to be consistent with 160 L process material.

-

Process Validation

For additional discussion of process validation, please see the comments below on Question 4 e (Bulk Manufacture).

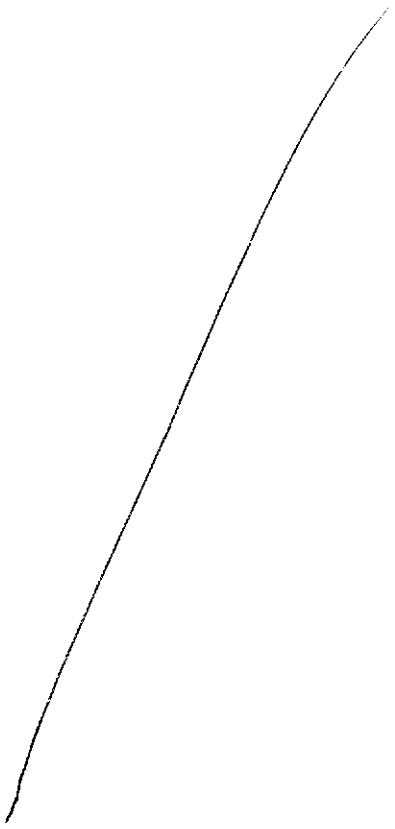
3. Please comment on the adequacy of the proposed stability package to be submitted to support proposed expiry of 24 months for product derived from drug substance manufactured at either scale.

- It is difficult to provide specific guidance on the proposed stability package without detailed information on product degradation following stress conditions. However, there is a concern that product quality attributes may not be adequately monitored for Drug product release and stability. Specifically, it is recommended that you consider adding to the release and stability program, assays which monitor , as well as tests bearing on , such as We note that a large number of the stability tests (including discussion of Attachment 6, below) are "For Stability Information Only", without limits. Actual data from these tests should be provided in the BLA, and specifications will need to be set for at least some of the tests.

Regarding the amount of stability information; there are Drug Product lots manufactured from two 160L process lots (930018 and 608341) for which real time stability data extends at least to 24 months, and data extending to — months for Drug Product manufactured from two additional 160 L process lots (608345 and 75129). The data from these additional 160 L lots should extend to at least 24 months during the BLA review cycle. Thus it appears that Genzyme could have data adequate to support 24 month expiry for Drug Product derived from the 160 L process. Subject to implementation of appropriate stability tests and satisfactory demonstration of comparability between the 160 L and 2000 L process material, 24 month expiry can also be granted to Drug Product from the 2000 L process, on the basis of the 160 L stability data, and the existing data from the 2000 L process.

4.

Bulk Manufacture Questions:



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3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Question #9: *Does the Agency agree with the proposed abbreviated Statistical Analysis Plan?*

- See statistical analysis plan comments above (discussion point 5).

X

8 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

2/11/04

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: Jan. 8, 2004 **DOCUMENT DATE:** April 8, 2003	**DESIRED COMPLETION DATE:** March 8, 2004	**ODS CONSULT #:** 04-0009

TO: Earl Dye
Director, Division of Review Management and Policy
HFM-585

THROUGH: Katherine Needleman
Project Manager
HFM-588

PRODUCT NAME: **Myozyme™** (Acid Alpha-Glucosidase Injection) 50 mg/20 mL **BB-IND #:** 10780	**SPONSOR:** Genzyme Corporation

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Myozyme™. This is considered a tentative decision, and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the BLA. A re-review of the name prior to BLA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS requests submission of the container labels, as well as carton and package insert labeling for review when available.

3. DDMAC finds the proprietary name Myozyme™ acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
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Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 11, 2004

BB-IND: 10780

NAME OF DRUG: **Myozyme™**
(Acid Alpha-Glucosidase Injection)
50 mg/20 mL

BB-IND SPONSOR: Genzyme Corporation

I. INTRODUCTION

This consult was written in response to a request from the Division of Review Management and Policy, for an assessment of the proprietary name "Myozyme" regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were not provided for review and comment at this time.

PRODUCT INFORMATION

Myozyme is the proposed name for acid alpha-glucosidase injection, a replacement for the human enzyme, acid alpha-glucosidase (GAA). Myozyme is indicated for the treatment of Pompe Disease, a rare autosomal recessive disease caused by the deficiency of GAA, which is needed to break down glycogen, a stored form of sugar used for energy. The build-up of glycogen causes progressive muscle weakness throughout the body, and affects various body tissues, particularly in the heart, skeletal muscles, liver, and nervous system. Children have a one in four chance of inheriting the disease when both parents carry the abnormal gene, and it is estimated that Pompe disease occurs in about one in 40,000 births. The recommended dose of Myozyme is 20 mg/kg every other week administered via intravenous infusion. Myozyme will be supplied in individually-boxed 20 mL single use vials containing [redacted]mg of acid alpha-glucosidase per vial. Myozyme should be stored under refrigeration, at temperatures ranging from two to eight degrees Celsius. Myozyme contains no preservatives. Therefore, each vial is intended for single administration only.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound-alike or look-alike to "Myozyme" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[v] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Myozyme. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed name Myozyme.

2. The Expert Panel identified three proprietary names that have potential for confusion with Myozyme. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

[i] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2004, and the electronic online version of the FDA Orange Book.

[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	**Dosage form(s), Established name**	**Usual adult Dose***	**Other****
Myozyme (Rx)	**Acid Alpha-Glucosidase Injection 50 mg/20 mL**	**Infants 20 mg/kg every other week.**	
Mycocide NS (OTC)	Benzalkonium Chloride Solution	Apply 2 to 3 drops twice daily around the entire nail, under the free edge, over the cuticle, and over all other affected areas.	**S/A
Megazyme (OTC)	Pancreatic Enzyme Complex Tablets 266 mg	Take 1 to 3 tablets before each meal.	**L/A, S/A
Myoview (Rx)	Kit for the Preparation of Technetium Tc99m Tetrofosmin for Injection	Myocardial imaging 5 millicuries to 33 millicuries. Imaging may being 15 minutes following administration. Stress and rest imaging When rest and stress injections are administered on the same day, the first dose should be 5 millicuries to 12 millicuries, followed by the second dose of 15 millicuries to 33 millicuries given approximately 1 to 4 hours later.	**L/A, S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs though the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA that were not discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Myozyme with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Myozyme (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Myozyme 3 vials To be given in clinic today.	Myozyme, dispense three vials that will be given in clinic today.
Inpatient RX: Myozyme IV 100 mg by IV infusion today	

2. Results:

   None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Myozyme", the primary concerns raised were related to three look-alike and/or sound-alike names currently marketed in the United States. The products considered to have potential for name confusion with Myozyme were: Mycocide NS, Megazyme, and Myoview.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Myozyme and Mycocide NS, Megazyme, or Myoview. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. The majority of incorrect interpretations from the written and verbal studies were misspelled/phonetic variations of the proposed name, Myozyme.

1. Mycocide NS was identified to have sound-alike similarity to the proposed name, Myozyme, when the modifier "NS" is omitted. Mycocide is a non-prescription topical solution containing benzalkonium chloride. It is indicated for the treatment of microbial infections affecting the finger or toe areas, skin around the nails, and under the free edge. Mycocide and Myozyme sound similar in that both names contain three syllables, with the first two syllables differing by only one letter ("Myco" vs. "Myo"). In addition, the letter combinations "ci" (in Mycocide) and "zy" (in Myozyme) sound similar when pronounced. There are, however, differences, which help to distinguish these two products from one another. Mycocide and Myozyme differ in route of administration (topical vs. intravenous), dosage form (injection vs. topical solution), dosing regimen (twice daily vs. every other week), and packaging (20 mL vials vs. 30 mL bottle with dropper). Also, because the dose of Myozyme is determined by the patient's weight, there is no overlap in dosing quantity as well. Lastly, Myozyme will be stored under refrigeration, and administered in a clinical setting where dosage preparation and administration is performed by

healthcare professionals who are familiar with its use. Despite the sound-alike similarities between the names, DMETS believes that the differences in route of administration, dosage form, dosing regimen, packaging, storage conditions, and context of use, will minimize the risk of confusion and error between Mycocide and Myozyme.

2. Megazyme was identified to have sound-alike and look-alike similarity to the proposed name, Myozyme (see below). Megazyme is an over-the-counter herbal product that contains a high potency pancreatic enzyme complex, indicated to promote the break down of fats and carbohydrates in the small intestine. The recommended dose of Megazyme is one to three tablets before each meal. Both names contain three syllables, begin with the letter "M", and have letters with a down stroke at the beginning of the names ("g" in Megazyme, and "y" in Myozyme). With the exception of one letter ("a" vs. "o"), which can also look similar when scripted, the remainder of the names are identical ("zyme"). The products differ in route of administration (oral vs. intravenous), dosage form (tablet vs. injection), dosing regimen (three times a day vs. every other week), and packaging (bottles of 100 tablets vs. 20 mL vials). Also, because the dose of Myozyme is determined by the patient's weight, there is no overlap in dosing quantity. Lastly, Myozyme is stored under refrigeration, and will be administered in a clinical setting where dosage preparation and administration is performed by healthcare professionals who are familiar with its use. Megazyme, on the other hand; is an over-the-counter medication, which does not require refrigeration, and therefore, will not be stored near Myozyme on pharmacy shelves. Despite the sound-alike similarities, DMETS believes that the differences in route of administration, dosage form, dosing regimen, packaging, storage conditions, and context of use, makes it unlikely that Megazyme and Myozyme will be confused for one another.

Megazyme **Myozyme**

Megazyme Myozyme

MEGAZYME
MYOZYME

3. Myoview was identified to have sound-alike and look-alike similarities to the proposed name, Myozyme (see page 7). Myoview contains Technetium Tc99m tetrofosmin for injection. It is indicated for scintigrphnic imaging of the myocardium following separate administrations under exercise and/or resting conditions. It is also used in the delineation of regions of reversible myocardial ischemia in the presence or absence of infracted myocardium, imaging of the myocardium to identify changes in perfusion, and for assessment of left ventricular function in patients being evaluated for heart disease. Myoview and Myozyme have sound-alike and look-alike similarities in that each name contains seven letters, three syllables, and begin with the same letter combination ("Myo"). The remainder of the names ("view" vs. "zyme") sound different due to the strong sound of the letter "z", and look different due to the downstroke letters "z" and "y" in Myozyme. Myoview and Myozyme overlap in dosage form (injection), route of administration (intravenous), and storage conditions (refrigeration). However, the products differ in dosing regimen (15 min prior to procedure vs. every other week). Because the dose of Myozyme is determined by the patient's weight, the products do not overlap in dosing strength or dosing quantity. Myoview is a radiopharmaceutical that is prepared under specific conditions, including proper shielding, in order to ensure radiochemical purity of the final drug product,

unlike Myozyme. DMETS believes that the difference in the sound-alike and look-alike characteristics of the names, in addition to the differences dosing regimen, dosing strength, and product preparation, decreases the risk for confusion and errors between Myoview and Myozyme. Furthermore, both Myoview and Myozyme are administered by clinically trained healthcare professionals who are familiar with their use, further decreasing the risk of errors between the two products.

Myoview	**Myozyme**
Myoview	Myozyme

III. RECOMMENDATIONS

A. DMETS has no objections to the use of the proprietary name, Myozyme. This is considered a tentative decision, and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the BLA. A re-review of the name prior to BLA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

B. DMETS requests submission of the container labels, as well as carton and package insert labeling for review when available.

C. DDMAC finds the proprietary name Myozyme acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. DMETS prescription study results.

Outpatient	Inpatient	Voicemail
Myozyme	Mycozyme	Miazarm
Myozyme	Myczyme	Miazyme
Myozyme	Myczyme	Miotin
Myozyme	Myczyme	Miozyme
Myozyme	Myczyme	Myazar
Myozyme	Myczyme	Myazide
Myozyme	Myczyme	Myazyme
Myozyme	Myczyme	Myazyme
Myozyme	Myczyme	Myodon
Myozyme	Myczyme	Myozon
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	Myozyme
Myozyme	Myczyme	viozyme
Myozyme	Myczyme	Viozyme
Myozzme	Myczyme	
Myozzme	Myczyml	
Myozzyme	Myozime	
Myozzyme	Myozyme	
	Myozyme	
	Myozyme	
	Myozyme	
	Myozyme	
	Myozyme	
	Myozyme	
	Myozyme	

BLA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

BLA 125141/0	Efficacy Supplement Type	Supplement Number	
Drug: Alglucosidase alfa		Applicant: Genzyme Corporation	
RPM: Cristi Stark		HFD-180	Phone # (301)796-1007

Application Type: ( ) 505(b)(1) ( ) 505(b)(2) N/A (BLA's are under the PHS Act) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	() Standard (**X**) Priority
• Chem class (NDAs only)	N/A
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	April 28, 2006
❖ Special programs (indicate all that apply)	(**X**) None Subpart E ( ) 21 CFR 601.41 (accelerated approval) ( ) 21 CFR 601.42 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number ____
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	(**X**) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (**X**) No

• This application is on the AIP	( ) Yes (**X**) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	Compliance check complete
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(**X**) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	( ) Verified (N/A under PHS Act)
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified (N/A under PHS Act) 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) (N/A under PHS Act)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	(N/A under PHS Act)
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(**X**) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	(N/A under PHS Act)
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No (N/A under PHS Act)
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No (N/A under PHS Act)
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	(N/A under PHS Act)
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No (N/A under PHS Act)
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No (N/A under PHS Act)
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A – only orphan exclusivity under the PHS Act
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Project Manager, 8/11/05 (committee assignment) Project Manager, 9/7/05 (filing

	meeting)
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA ( ) CR
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release (X) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	4/25/06
• Original applicant-proposed labeling	7/28/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	ODS/PP review – 12/12/05 ODS/DMETS reviews – 2/15/06, 9/12/05, 2/11/04 DDMAC review – 3/16/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Naglazyme, Aldurazyme, Cerezyme, Fabrazyme
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	7/28/05
• Reviews	ODS/DMETS reviews – 2/15/06, 9/12/05, 1/8/04 DDMAC review – 3/16/06 Project manager review – see project management tab reviews – 3/31/06, 4/25/06
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See AP letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	ACK letter, combined 60-day letter, 74-day letter, IR letter #1, IR letter #2, IR letter #3, Major Amendment letter
❖ Memoranda and Telecons	10/28/05 tcon, 11/18/05 tcon, 12/2/05 tcon, 12/12/05 tcon, 4/24/06 tcon, 4/25/06 tcon
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	4/28/05

• Pre-BLA meeting (indicate date)	6/1/05 – clinical and non-clinical 5/3/05 – CMC
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	Type A – 2/2/06 Reg Briefing – 3/3/06
❖ Advisory Committee Meeting	N/A
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical Team Leader – 4/27/06 Supervisory Pharmacologist – 4/14/06 Pharm/Tox Office Director – 4/20/06 Compliance Office Director – 4/21/06 Product Office Director - see executive summary with CMC reviews – 4/27/06 Division Director – 4/28/06 Office Director – 4/28/06
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Clinical review – 4/27/06 Pediatric consult – 3/20/06 DNP consult – 12/16/05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Incorporated in clinical review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	ODS/PP – 12/12/05
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A – orphan product
❖ Demographic Worksheet *(NME approvals only)*	Not required yet
❖ Statistical review(s) *(indicate date for each review)*	4/27/06
❖ Biopharmaceutical review(s) *(indicate date for each review)*	3/23/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	12/23/05
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Executive Summary – 4/27/06 Drug Substance – 4/27/06 Drug Product – 4/27/06 Immunogenicity – 4/27/06 Analytical Methods – 4/26/06 Cell Line – 4/27/06
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Incorporated in facility review
• Review & FONSI *(indicate date of review)*	Incorporated in CMC & facility

	reviews
• Review & Environmental Impact Statement *(indicate date of each review)*	Incorporated in CMC & facility reviews
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	3/10/06
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed - under facility review **( )** Requested **( )** Not yet requested
[redacted]	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4/13/06
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: 125141/0

☒ Initial Assignment
☐ Change

Applicant: Genzyme Corp

Product: Alglucosidase alfa

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Katherine Needleman	Reg. Project Manager	Admin/Regulatory	Kay Schneider	7/28/05
	Reviewer	Admin/Regulatory		
Fred Mills	Reviewer	Product*	Gibbes Johnson	8/2/05
	Reviewer	Product*		
	Reviewer	Product		
Anne Pariser	Chairperson	Clinical	John Hyde	7/28/05
	Reviewer	Clinical		
Anil Rajpal	Reviewer	Clinical Pharmacology	Dave Green	8/3/05
Barbara Wilcox	Reviewer	Pharm/Tox	Dave Green	8/3/05
Bo Zhen	Reviewer	Biostatistics	Bo Zhen	8/1/05
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
Jianming Li	Reviewer	CMC, Facility*	Michael Smedley	8/11/05
		Labeling		
		Other		
Michelle Clark-Stuart	Reviewer	Facility, CMC	Michael Smedley	8/1/05
Catherine Gray	Reviewer	Labeling consult	Marci Kiester	8/5/05
Edward Bashaw	Reviewer	Clinical Pharmacology	Edward Bashaw	8/3/05

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Katherine Needleman — Name Printed

Katherine Needleman — Signature

8/11/05 — Date

Memo entered in RMS by: DCS Date: 8/22/05 QC by: 8/29/05 Date: LB

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125141/0 Product: Alglucosidase alfa Applicant: Genzyme

Final Review Designation (circle one): Standard (Priority)

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date 9/7/05 Committee Recommendation (circle one): (File) RTF

RPM: _____
(signature/date)

Attachments:

- [x] Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - [x] Part A – RPM
  - [x] Part B – Product/CMC/Facility Reviewer(s): M Clark-Stuart, Fred Mills
  - [x] Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): B. Wilcox
  - [x] Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers A Parker, B. Zhen, A Rajpal
- [x] Memo of Filing Meeting

STN 125141/0 Product Alglucosidase alfa

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Yes?		If not, justification, action & status
Cover Letter	(Y)	N	
Form 356h completed	(Y)	N	
❑ including list of all establishment sites and their registration numbers	(Y)	N	
❑ If foreign applicant, US Agent signature.	Y	N	N/A
Comprehensive Table of Contents	(Y)	N	
Debarment Certification with correct wording (see * below)	(Y)	N	
User Fee Cover Sheet	(Y)	N	
User Fee payment received	Y	N	N/A orphan
Financial certification &/or disclosure information	(Y)	N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	(Y)	N	
Pediatric rule: study, waiver, or deferral	Y	N	N/A
Labeling:	(Y)	N	
❑ PI –non-annotated	(Y)	N	
❑ PI –annotated	(Y)	N	
❑ PI (electronic)	(Y)	N	
❑ Medication Guide	Y	N	N/A
❑ Patient Insert	Y	N	
❑ package and container	(Y)	N	
❑ diluent	Y	N	
❑ other components	Y	N	N/A
❑ established name (e.g. USAN)	(Y)	N	
❑ proprietary name (for review)	(Y)	N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?		If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y)	N	
❑ legible	(Y)	N	
❑ English (or translated into English)	(Y)	N	
❑ compatible file formats	(Y)	N	
❑ navigable hyper-links	(Y)	N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y)	N	
❑ summary reports reference the location of individual data and records	(Y)	N	

Examples of filing issues			Comments/Clarification & Action & Status
❑ protocols for clinical trials present	(Y)	N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	(Y)	N	
companion application received if a shared or divided manufacturing arrangement	Y	N	N/A
if CMC supplement:			
❑ description and results of studies performed to evaluate the change	(Y)	N	
❑ relevant validation protocols	(Y)	N	
❑ list of relevant SOPs	(Y)	N	
if clinical supplement:			
❑ changes in labeling clearly highlighted	(Y)	N	
❑ data to support all label changes	(Y)	N	
❑ all required electronic components, including electronic datasets (e.g. SAS)	(Y)	N	
if electronic submission:			
❑ required paper documents (e.g. forms and certifications) submitted	(Y)	N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo). None

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? NO

Does this submission relate to an outstanding PMC? NO

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:
- Dates:

Recommendation (circle one): (File) RTF

RPM Signature: [signature] Branch Chief concurrence: Schneider

STN 125141/0 Product Myozyme

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Quality overall summary [2.3]	(Y)	N	
❑ Drug Substance	(Y)	N	
❑ Drug Product	(Y)	N	
❑ Facilities and Equipment	(Y)	N	
❑ Adventitious Agents Safety Evaluation	(Y)	N	
❑ Novel Excipients	(Y)	N	
❑ Executed Batch Records	(Y)	N	
❑ Method Validation Package	(Y)	N	
❑ Comparability Protocols	(Y)	N	

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	(Y)	N	
Drug Substance [3.2.S]			
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	(Y)	N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	(Y)	N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	(Y)	N	
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	(Y)	N	
❑ process validation (prospective plan, results, analysis, and	(Y)	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	(Y) N	
❑ characterization of drug substance	(Y) N	
❑ control of drug substance	(Y) N	
○ specification		
○ justification of specs.		
○ analytical procedures		
○ analytical method validation		
○ batch analyses		
○ consistency (3 consecutive lots)		
○ justification of specs.		
❑ reference standards	(Y) N	
❑ container closure system	(Y) N	
❑ stability	(Y) N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P]		
❑ description and composition	(Y) N	
❑ pharmaceutical development	(Y) N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
❑ batch formula	(Y) N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
❑ controls of critical steps and intermediates	(Y) N	
❑ process validation including aseptic processing & sterility assurance:	(Y) N	
○ 3 consecutive lots		
○ other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of	(Y) N	

CTD Module 3 Contents			Reviewer comments, justification for action & status
human/animal origin)			
❑ control of drug product (justification of specifications; analytical method validation)	(Y)	N	
❑ container closure system [3.2.P.7]	(Y)	N	
○ specifications (vial, elastomer, drawings)			
○ availability of DMF			
○ closure integrity			
○ administration device(s)			
❑ stability	(Y)	N	
❑ summary			
❑ post-approval protocol and commitment			
❑ pre-approval			
○ protocol			
○ results			
○ method validation			
Diluent (vials or filled syringes) [3.2P']			Not applicable diluted with sterile water USP
❑ description and composition of diluent	(Y)	N	
❑ pharmaceutical development	Y	N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	N	
❑ batch formula	Y	N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	N	
❑ controls of critical steps and intermediates	Y	N	
❑ process validation including aseptic processing & sterility assurance:	Y	N	
○ 3 consecutive lots			
○ other needed validation data			
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y	N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y	N	
❑ reference standards	Y	N	

CTD Module 3 Criteria			Reviewer Notes/Comments & Status
☐ container closure system ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity	Y	N	
☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval ○ protocol ○ results	Y	N	
Other components to be marketed (full description and supporting data, as listed above):			Not Applicable
☐ other devices	Y	N	
☐ other marketed chemicals (e.g. part of kit)	Y	N	
Appendices for Biotech Products [3.2.A]			
☐ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination	(Y)	N	
☐ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production	(Y)	N	
☐ novel excipients	(Y)	N	
USA Regional Information [3.2.R]			
☐ executed batch records	(Y)	N	
☐ method validation package	(Y)	N	
☐ comparability protocols	(Y)	N	

CTD Module 3 Contents			Deficiency, information, action & status
Literature references and copies [3.3]	(Y)	N	

Examples of Filing Issues			Deficiency, information, action & status
content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
▫ legible	(Y)	N	
▫ English (or translated into English)	(Y)	N	
▫ compatible file formats	(Y)	N	
▫ navigable hyper-links	(Y)	N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y)	N	
▫ summary reports reference the location of individual data and records	(Y)	N	
▫ all electronic submission components usable	(Y)	N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y)	N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	(Y)	N	
includes data demonstrating consistency of manufacture	(Y)	N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y)	N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y)	N	
certification that all facilities are ready for inspection	(Y)	N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y)	N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	(Y)	N	

☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	(Y) N (Y) N (Y) N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	(Y) N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	(Y) N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	(Y) N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	(Y) N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	(Y) N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): (File) RTF

Reviewer: Frederick C. Mills Type (circle one): Product (Chair) Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: 9-14-05
(signature/ date)

Division. Director:
(signature/ date)

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Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Quality overall summary [2.3]	(Y)	N	
☑ Drug Substance	(Y)	N	
☑ Drug Product	(Y)	N	
☑ Facilities and Equipment	(Y)	N	
☑ Adventitious Agents Safety Evaluation	(Y)	N	
☑ Novel Excipients	Y	(N)	N/R
☑ Executed Batch Records	(Y)	N	
☑ Method Validation Package	(Y)	N	
☑ Comparability Protocols	Y	(N)	N/R

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	(Y)	N	
Drug Substance [3.2.S]			
☑ general info	(Y)	N	
○ nomenclature			
○ structure (e.g. sequence, glycosylation sites)			
○ properties			
☑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
☑ description of manufacturing process	(Y)	N	
○ batch numbering and pooling scheme			
○ cell culture and harvest			
○ purification			
○ filling, storage and shipping			
☑ control of materials	(Y)	N	
○ raw materials and reagents			
○ biological source and starting materials			
○ cell substrate: source, history, and generation			
○ cell banking system, characterization, and testing			
☑ control of critical steps and intermediates	(Y)	N	
○ justification of specifications			
○ analytical method validation			
○ reference standards			
○ stability			
☑ process validation (prospective plan, results, analysis, and	(Y)	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
☑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	(Y) N	
☑ characterization of drug substance	(Y) N	
☑ control of drug substance	(Y) N	
○ specification		
○ justification of specs.		
○ analytical procedures		
○ analytical method validation		
○ batch analyses		
○ consistency (3 consecutive lots)		
○ justification of specs.		
☑ reference standards	(Y) N	
☑ container closure system	(Y) N	
☑ stability	(Y) N	Deferred to Prod. Ofc.
☐ summary		
☐ post-approval protocol and commitment		
☐ pre-approval		
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P]		
☑ description and composition	(Y) N	
☑ pharmaceutical development	(Y) N	
☑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
☑ batch formula	(Y) N	
☑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
☑ controls of critical steps and intermediates	(Y) N	
☑ process validation including aseptic processing & sterility assurance:	(Y) N	
○ 3 consecutive lots		
○ other needed validation data		
☑ control of excipients (justification of specifications; analytical method validation; excipients of	Y (N)	N/R

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin)		
☑ control of drug product (justification of specifications; analytical method validation)	(Y) N	
☑ container closure system [3.2.P.7]	(Y) N	
○ specifications (vial, elastomer, drawings)		
○ availability of DMF		
○ closure integrity		
○ administration device(s)		
☑ stability	(Y) N	Deferred to Prod. Ofc.
☐ summary		
☐ post-approval protocol and commitment		
☐ pre-approval		
○ protocol		
○ results		
○ method validation		
Diluent (vials or filled syringes) [3.2P']		
☑ description and composition of diluent	Y (N)	N/R, — . D.P. vials
☑ pharmaceutical development	(Y) N	
☑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
☑ batch formula	(Y) N	
☑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
☑ controls of critical steps and intermediates	(Y) N	
☑ process validation including aseptic processing & sterility assurance:	(Y) N	
○ 3 consecutive lots		
○ other needed validation data		
☑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	(Y) (N)	N/R for human/animal or novel
☐ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y (N)	N/R
☑ reference standards	(Y) N	

CTD Module 3 Contents	Y/N	If not, justification/action & status
☑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity	(Y) N	
☑ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval o protocol o results	(Y) N	Defer to Prod. Ofc.
Other components to be marketed (full description and supporting data, as listed above):		
☐ other devices	Y (N)	N/R
☐ other marketed chemicals (e.g. part of kit)	Y (N)	
Appendices for Biotech Products [3.2.A]		
☑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination	(Y) N	
☑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production	(Y) N	
☑ novel excipients	Y (N)	N/R, none used
USA Regional Information [3.2.R]		
☑ executed batch records	(Y) N	
☑ method validation package	(Y) N	
☑ comparability protocols	Y (N)	N/R, none used

CTD Module 4 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	(Y) N	
☑ legible	(Y) N	
☑ English (or translated into English)	(Y) N	
☑ compatible file formats	(Y) N	
☑ navigable hyper-links	(Y) N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
☑ summary reports reference the location of individual data and records	(Y) N	
☑ all electronic submission components usable	(Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	(Y) N	
includes data demonstrating consistency of manufacture	(Y) N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
certification that all facilities are ready for inspection	(Y) N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	Prod. Ofc.
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y N	

Examples of Filing Issues	Yes?	If Not, Justification/Location & Status
☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	Y N Y N Y N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	(Y) N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	(Y) N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	(Y) N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	(Y) N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): (File) RTF

Reviewer: Michelle Y. Blackstuart Type (circle one): Product (Chair) (Facility (DMPQ))
(signature/ date) 9/14/05

Concurrence:
Branch/Lab Chief: _____ Division. Director: _____
(signature/ date) (signature/ date)
9/16/05

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Non-clinical overview [2.4]	(Y) N	
Non-clinical summary [2.6]	(Y) N	
❑ Pharmacology	(Y) N	
❑ Pharmacokinetics	(Y) N	
❑ Toxicology	(Y) N	

CTD Module 4 Contents	Present?	If not, justification, action & status
Module Table of Contents [4.1]	(Y) N	
Study Reports and related info. [4.2]	(Y) N	
❑ Pharmacology	(Y) N	
❑ Pharmacokinetics	(Y) N	
❑ Toxicology	(Y) N	
Literature references and copies [4.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or translated into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	(Y) N	
❑ all electronic submission components usable	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
for each non-clinical laboratory study, either a statement that the study was conducted in compliance with the good laboratory practice requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance	(Y) N	

Reasons to File			Comments/Notes
animal reproduction studies included, if the biological product is to be administered to people with reproductive potential, unless an explanation of why such studies are not applicable	Y	N	
includes carcinogenicity and/or reproductive and developmental toxicology studies deemed necessary by well established agency interpretation or communication during the IND review process	Y	N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): (File) RTF

Pharm/Tox reviewer: Barbara J. Wilcox 8/13/05
(signature/ date)

Branch Chief concurrence: Mattia DeGreen 8/15/05
(signature/ date)

Division. Director concurrence: _____
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y)	N	
❑ Biopharmaceutics and associated analytical methods	Y	N	NA (not applicable for stat review)
❑ Clinical pharmacology [includes immunogenicity]	Y	N	NA
❑ Clinical Efficacy [for each indication]	(Y)	N	
❑ Clinical Safety	(Y)	N	
❑ Synopses of individual studies	(Y)	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	
Study Reports and related information [5.3]	(Y)	N	
❑ Biopharmaceutic	Y	N	NA
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	NA
❑ Pharmacokinetics (PK)	Y	N	NA
❑ Pharmacodynamic (PD)	Y	N	NA
❑ Efficacy and Safety	Y	N	NA
❑ Postmarketing experience	Y	N	NA
❑ Case report forms	(Y)	N	
❑ Individual patient listings (indexed by study)	(Y)	N	
o electronic datasets (e.g. SAS)	(Y)	N	
Literature references and copies [5.4]	Y	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
❑ legible	(Y)	N	
❑ English (or certified translation into English)	(Y)	N	
❑ compatible file formats	(Y)	N	
❑ navigable hyper-links	(Y)	N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y)	N	

Examples of Filing Issues			Information & Notes
☐ summary reports reference the location of individual data and records	(Y)	N	
☐ protocols for clinical trials present	(Y)	N	
☐ all electronic submission components usable	(Y)	N	
statement for each clinical investigation:			
☐ conducted in compliance with IRB requirements	Y	N	N/A
☐ conducted in compliance with requirements for informed consent	Y	N	NA
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y)	N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y)	N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y)	N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	(Y)	N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y)	N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y)	N	
drug interaction studies communicated as during IND review as necessary are included	(Y)	N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y)	N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y)	N	

Is/Are adequate and well-controlled studies of:			Identification of Study
data supporting the proposed dose and dose interval	(Y)	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y)	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	(Y)	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Signed and dated case report forms for all subjects submitted?			SAS & other electronic datasets provided, complete & usable?		FDA sites identified?		
AGLU01602	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	(NR) MA
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

STN 125141 Product Myozyme

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

NO

Is clinical site(s) inspection (BiMo) needed?

Yes

Is an Advisory Committee needed?

NO

Recommendation (circle one): File RTF

Reviewer: [signature] 9/30/05 Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)

Concurrence:

Team Leader: [signature] 9/30/05 Division. Director: Alaka Chakravarty 8/6/05
~~Branch Chief~~: (signature/ date) (signature/ date)

STN 125141/0 Product Alglucosidase alfa

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y)	N	
❑ Biopharmaceutics and associated analytical methods	(Y)	N	
❑ Clinical pharmacology [includes immunogenicity]	(Y)	N	
❑ Clinical Efficacy [for each indication]	(Y)	N	
❑ Clinical Safety	(Y)	N	
❑ Synopses of individual studies	(Y)	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	
Study Reports and related information [5.3]	(Y)	N	
❑ Biopharmaceutic	(Y)	N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y)	N	
❑ Pharmacokinetics (PK)	(Y)	N	
❑ Pharmacodynamic (PD)	(Y)	N	
❑ Efficacy and Safety	(Y)	N	
❑ Postmarketing experience	Y	N	N/A
❑ Case report forms	(Y)	N	
❑ Individual patient listings (indexed by study)	(Y)	N	
○ electronic datasets (e.g. SAS)	(Y)	N	
Literature references and copies [5.4]	(Y)	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
❑ legible	(Y)	N	
❑ English (or certified translation into English)	(Y)	N	
❑ compatible file formats	(Y)	N	
❑ navigable hyper-links	(Y)	N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y)	N	

STN 125141/0 Product Alglucosidase alfa

Examples of Filing Issues	ESI	Filing Decision & Status
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	(Y) N	
❑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?	If not, default status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y) N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BIMo sites identified?		
AGLU01602	(Y)[a]	N	(Y)	N	NR	(Y)	N	Y	N	(NR)
AGLU01702	(Y)[b]	N	(Y)	N	NR	(Y)	N	Y	N	(NR)
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

a 26-week clinical study report

b 52-week clinical study report

STN 125141/0 Product Alglucosidase alfa

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

N/A

Is clinical site(s) inspection (BiMo) needed? No

Is an Advisory Committee needed? No

Recommendation (circle one): (File) RTF

Reviewer: [signature] 9/7/05 Type (circle one): Clinical (Clin/Pharm) Statistical
(signature/ date)

Concurrence:

Branch Chief: Martin Dree 9/12/05 Division. Director: _____
(signature/ date) (signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		Comments (location, section & status)
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
❑ Biopharmaceutics and associated analytical methods	Y	N	
❑ Clinical pharmacology [includes immunogenicity]	Y	N	
❑ Clinical Efficacy [for each indication]	Y	N	
❑ Clinical Safety	Y	N	
❑ Synopses of individual studies	Y	N	

CTD Module 5 Contents	Present?		Comments (location, section & status)
Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	Y	N	
Study Reports and related information [5.3]	Y	N	
❑ Biopharmaceutic	Y	N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	
❑ Pharmacokinetics (PK)	Y	N	
❑ Pharmacodynamic (PD)	Y	N	
❑ Efficacy and Safety	Y	N	
❑ Postmarketing experience	Y	N	N/A
❑ Case report forms	Y	N	
❑ Individual patient listings (indexed by study)	Y	N	
○ electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	

Examples of Filing Issues	Yes		Comments (location, section & status)
Content, presentation, and organization sufficient to permit substantive review?	Y	N	
❑ legible	Y	N	
❑ English (or certified translation into English)	Y	N	
❑ compatible file formats	Y	N	
❑ navigable hyper-links	Y	N	
❑ interpretable data tabulations (line listings) & graphical displays	Y	N	

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
❑ Biopharmaceutics and associated analytical methods	Y	N	
☒ ~~Clinical pharmacology~~ [includes immunogenicity]	Y	N	
❑ ~~Clinical Efficacy~~ [for each indication]	Y	N	
❑ Clinical Safety	Y	N	
❑ Synopses of individual studies	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	Y	N	
Study Reports and related information [5.3]	Y	N	
❑ Biopharmaceutic	Y	N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	
❑ Pharmacokinetics (PK)	Y	N	
❑ Pharmacodynamic (PD)	Y	N	
❑ Efficacy and Safety	Y	N	
❑ Postmarketing experience	Y	N	
❑ Case report forms	Y	N	
❑ Individual patient listings (indexed by study)	Y	N	
○ electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	

Examples of Filing Issues	Present?		If not, justification & status
Content, presentation, and organization sufficient to permit substantive review?	Y	N	
❑ legible	Y	N	
❑ English (or certified translation into English)	Y	N	
❑ compatible file formats	Y	N	
❑ navigable hyper-links	Y	N	
❑ interpretable data tabulations (line listings) & graphical displays	Y	N	

Examples of Filing Issues			Reviewer Comments
❑ summary reports reference the location of individual data and records ❑ protocols for clinical trials present ❑ all electronic submission components usable	(Y) N (Y) N (Y) N		
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements ❑ conducted in compliance with requirements for informed consent	(Y) N (Y) N		
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y N		Uncontrolled pivotal study by agreement · Rare disease, universally fatal.
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N		
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N		
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N		N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y N		n=18 for pivotal study by agreement · Rare disease.
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N		
drug interaction studies communicated as during IND review as necessary are included	Y N		N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N		
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N		

Examples of Filing Issues			Comments/Issues
data supporting the proposed dose and dose interval	(Y)	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	N	N/A
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	N/A
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Protocols adequate and adhered to?			Statistical analyses adequate and adequately described?		Deviations identified?		
1602	(Y)	N	(Y)	N	NR	(Y)	N	(Y)	N	NR
1702	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	(NR)
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Yes

Is an Advisory Committee needed?

Yes

Recommendation (circle one) (File) RTF

Reviewer: [signature] 9/7/05 Type (circle one) (Clinical) Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [signature] 9-7-05 Division. Director: _____
(signature/ date) (signature/ date)