

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022458Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22458

SUPPL #

HFD # 180

Trade Name Eleyso

Generic Name taliglucerase alfa

Applicant Name Protalix Ltd. (US Agent: Target Health)

Approval Date, If Known May 1, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form:

Title:

Date:

Name of Office/Division Director signing form:

Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

CARLA L EPPS
04/27/2012
NDA 22458- Exclusivity Summary

LYNNE P YAO
04/27/2012

JULIE G BEITZ
04/27/2012

Debarment Certification

Protalix Ltd. hereby certifies that it 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 this application.

Einat Almon
Einat Almon
VP Product Development
Protalix Ltd.

17.5.20
Date

Glen Park
Glen Park
Senior Director, Clinical and Regulatory Affairs
Target Health Inc.

17 May 2010
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22458 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Eleyso Established/Proper Name: taliglucerase alfa Dosage Form: for injection		Applicant: Protalix Ltd. Agent for Applicant (if applicable): Target Health Inc.
RPM: Jessica M. Benjamin		Division: Division of Gastroenterology and Inborn Errors Products
<p><u>NDA's:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>May 1, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR 2/24/2011

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other HHS Info Advisory</p>

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(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).

- (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)?

Yes No

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 the rest of the patent questions.

If "No," continue with question (3).

- (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 (b)(2) 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.

- (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)?

Yes No

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 section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	5/1/12
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	AP dated 5/1/12 CR dated 2/24/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4/12/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	8/1/2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	VPRIV 2/2010 and Cerezyme 11/2002

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	2/10/12
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	2/9/12; 12/6/11; 11/28/11; 2/1/11; 1/21/11; 12/14/10; 7/22/10; 6/4/10
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 7/19/10 <input checked="" type="checkbox"/> DMEPA 9/15/10 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 4/18/12 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews SEALD 4/30/2012
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁴/Memo of Filing Meeting) (<i>indicate date of each review</i>) 	7/1/10
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan drug designation • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	4/13/12; 4/12/12; 1/17/12; 12/01/11; 11/10/11; 10/31/11;

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

	9/23/11; 9/15/11; 1/24/11; 12/22/10; 11/23/10; 11/19/10(2); 10/28/10; 9/8/10; 8/13/10; 8/11/10; 7/9/10; 6/11/10; 5/7/10; 4/28/10; 3/3/10; 1/28/10; 1/7/10; 1/5/10
❖ Internal memoranda, telecons, etc.	3/22/12; 8/17/11; 11/17/10; 6/2/10
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 5/21/09
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	5/3/11; 4/14/08; 2/21/07; 11/29/06; 6/30/04
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/24/11; 5/1/12
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/24/11; 5/1/12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	See CDTL Memo/Review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	2/22/11; 5/1/12
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical review dated 2/22/11 , pages 16-17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

Version: 8/25/10

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 1/21/11
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/5/12; 2/24/11
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 4/19/12; 4/12/12; 4/02/12; 1/13/11
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 2/18/11
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 12/3/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/26/12; 3/30/12; 2/24/11
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 4/26/12; 3/29/12; 2/24/11
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 4/19/12; 12/21/11; 2/10/11
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review) Immunogenicity / Statistics	<input type="checkbox"/> None 12/23/11; 2/8/11; 6/22/11

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See CMC review dated 4/26/12, page 6
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Version: 8/25/10

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

JESSICA M BENJAMIN
05/03/2012



NDA 022458

LABELING PMR/PMC DISCUSSION COMMENTS

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm D.
Senior Director, Clinical/Regulatory Affairs

Dear Dr. Park:

Please refer to your April 26, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elelyso (taliglucerase alfa) for injection.

We also refer to our December 1, 2011, letter in which we notified you of our target date of April 5, 2012, for communicating labeling changes and/or postmarketing requirements/commitments (PMR/PMCs) in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

We have your application and are providing you with our proposed postmarketing requirement/commitment studies. We request that you review our proposal and submit a response to NDA 022458 by close of business April 19, 2012.

Postmarketing Requirement Studies

1. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ELELYSO that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

Final Protocol Submission: [insert proposed date]
Study Completion Date: [insert proposed date]
Final Report Submission: [insert proposed date]

2. To develop a validated, sensitive, and accurate assay for the assessment of cellular uptake inhibition by cell surface mannose receptor due to presence of neutralizing antibodies to ELELYSO that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the

development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

Final Protocol Submission: [insert proposed date]
Study Completion Date: [insert proposed date]
Final Report Submission: [insert proposed date]

3. To develop a validated, sensitive, and accurate assay for the detection of antibodies to plant sugar in ELELYSO that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

Final Protocol Submission: [insert proposed date]
Study Completion Date: [insert proposed date]
Final Report Submission: [insert proposed date]

4. To conduct an assessment of neutralizing ADA response and antibodies against plant-specific sugars to ELELYSO with validated assays (required under PMR 1, PMR 2 and PMR 3) capable of sensitively detecting neutralizing ADA responses and the plant sugar antibodies that are expected to be present at the time of patient sampling. The neutralizing ADA response, cellular uptake inhibition and plant-sugar antibodies will be evaluated in all archived sampling time points available from all patients in Phase 3 trials (PB-06-001, PB-06-002, PB-06-003, and PB-06-005). Analysis will evaluate immunogenicity rates and individual patient titers to assess the impact of neutralizing antibody levels, cellular uptake inhibition, and plant-sugar antibodies on safety as well as PK, PD, and efficacy of taliglucerase.

Final Protocol Submission: [insert proposed date]
Study Completion Date: [insert proposed date]
Final Report Submission: [insert proposed date]

5. To complete the ongoing trial PB-06-005, entitled “A Multicenter, Double-blind, Randomized Safety and Efficacy Study of Two Dose Levels of Taliglucerase Alfa in Pediatric Subjects with Gaucher Disease”. This study will obtain safety, PK, PD, and additional efficacy data in pediatric patients with Gaucher disease. The trial was initiated in the U.S. on [insert date].

Study Completion Date: [insert proposed date]
Final Report Submission: [insert proposed date]

Postmarketing Commitment Studies

1. To perform a randomized, double-blind, active-controlled trial to evaluate the safety and effectiveness of taliglucerase compared to other approved ERT for Gaucher disease in adult and pediatric patients with Type 1 Gaucher disease.

Final protocol Submission Date:
Study/Clinical trial Completion Date:
Final Report Submission Date:

2. To evaluate the long-term safety and efficacy data in a registry of patients being treated with taliglucerase. Detailed clinical status information will be collected at study entry and on an annual basis for at least 15 years.

Final protocol Submission Date:
Study/Clinical trial Completion Date:
Final Report Submission Date:

3. To evaluate the effect of taliglucerase on pregnancy and fetal outcomes and to collect detailed clinical status information on newborns and infants whose mothers are treated with taliglucerase during lactation. This study may be completed as a sub-study within the registry.

Final protocol Submission Date:
Study/Clinical trial Completion Date:
Final Report Submission Date:

4. To revise the cellular uptake potency assay release and stability acceptance criteria after [insert number] lots of drug product have been manufactured.

Final Report Submission Date:

5. To revise Experion automated electrophoresis release and stability acceptance criteria after [insert number] lots of drug product have been manufactured.

Final Report Submission Date:

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JESSICA M BENJAMIN
04/13/2012



NDA 022458

LABELING PMR/PMC DISCUSSION COMMENTS

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm D.
Senior Director, Clinical/Regulatory Affairs

Dear Dr. Park:

Please refer to your April 26, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elelyso (taliglucerase alfa) for injection.

We also refer to our December 1, 2011, letter in which we notified you of our target date of April 5, 2012, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On August 1, 2011, we received your July 31, 2011 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JESSICA M BENJAMIN
04/12/2012

NDA 22458: taliglucerase alfa
Tcon with Protalix re: CMC issues and warning letter for facilities
March 21, 2012

Tcon participants: FDA

Vicky Kusiak, Deputy Director, ODE 3
Guiseppe Randazzo, Regulatory Scientist, ODE 3
Julie Beitz, Director, ODE 3
Jessica Benjamin, RPM, DGIEP
Lynne Yao, CDTL, DGIEP
Vinny Pawar, Micro reviewer
Zhong Li, OMPQ, OC
Tara Gooden, OC
Gibbes Johnson, Product Team Leader, DTP
Richard Ledwidge, Product Reviewer, DTP

Tcon participants: Sponsor

Glenn Park, US Agent Target Health
David Aviezar, Protalix
Yoseph Shaaltiel, Protalix
Einat Almon, Protalix
Sharon Hashmueli, Protalix
Michal Kahana, Protalix
Tzvi Palash, Protalix
Yaron Naos, Protalix
Danni Bartfeld, Protalix
Dudi Meraro, Protalix
Clarice Hutchens, Pfizer

Discussion:

DTP discussed deficiency #12 from Complete Response letter issued XXXXX. DTP still has an issue with the (b) (4) moisture content level since there is no data to support drug product with (b) (4) moisture content. FDA requested the sponsor to tighten the acceptance criteria. Protalix agreed to provide the info on lower moisture content level

DTP discussed deficiency #17 from CR letter. FDA requested that the sponsor identify the structural identity of (b) (4) impurities) in IEF. The sponsor agreed to submit this information.

DTP discussed deficiency #11 from CR letter. FDA discussed the MALDI-TOF and told the sponsor to take into consideration current manufacturing process and develop acceptance criterion around that – should be narrowed. The sponsor agreed to submit this information.

DTP discussed deficiency #27 from CR letter. There are no limits for (b) (4). The sponsor needs to define action limit (quantity and color) of drug substance in lot Protalix commented that the (b) (4). The FDA still needs the sponsor to develop something or compare it to something to define action limit. The sponsor agreed to do so.

DTP discussed deficiency #6 from CR letter.
DTP explained that the sponsor needs to determine if there are system suitability criteria there are independent of test sample? Is there a min amount of (b) (4)? Protalix agreed to provide this information.

Protalix explained that they are aware of the Warning letter that was issued to (b) (4) but they do not have a timeline for reinspection yet. Dr. Yao explained that this has a direct affect on approvability of the NDA.
Protalix explained that (b) (4) are other contractors that have performed sterility and that endotoxin testing is being performed at Protalix. The method is validated and Protalix will submit this information.
The FDA needs ASAP a statement that Protalix is moving endo and sterility testing to Protalix and validation from that site as well as a withdrawal of (b) (4). Also submit any recent inspections from other agencies.

Protalix will email clarification questions of any CMC issues that we discussed.

Protalix plans to respond to these requests in a few days.

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

/s/

JESSICA M BENJAMIN
03/22/2012

From: [Benjamin, Jessica](#)
To: "Glen Park"
Cc: [Benjamin, Jessica](#)
Subject: NDA 22458 information request
Date: Tuesday, January 17, 2012 8:53:17 AM

Good morning Glen,

Please refer to NDA 22458 for taliglucerase alfa. As a result of our on-going review of this application, we have the following information request.

Submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations described in the population pharmacokinetic-pharmacodynamic report submitted November 15, 2011 :

- All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- NONMEM model codes or control streams and output listings should be provided for the (1) final population PK model, (2) final dose-effect model for spleen volume (3) final PK-PD model for spleen volume, (4) final dose-effect model for platelet count and (3) final PK-PD model for platelet count. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Please let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3924. Thank you.

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

/s/

JESSICA M BENJAMIN
01/17/2012



NDA 022458

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm D.
Senior Director, Clinical/Regulatory Affairs

Dear Dr. Park:

Please refer to your April 26, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elelyso (taliglucerase alfa) for injection.

We also refer to your Class 2 resubmission dated August 1, 2011.

On November 15, 2011, we received your November 15, 2011, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 1, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 5, 2012.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Manager Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

RICHARD W ISHIHARA
12/01/2011

From: [Benjamin, Jessica](#)
To: ["Glen Park";](#)
cc: [Benjamin, Jessica;](#)
Subject: NDA 22458 - Information Request
Date: Thursday, November 10, 2011 8:05:49 AM

Hi Glen,

Please refer to NDA 22458 for taliglucerase alfa. As a result of our ongoing review of this application, we have the following information request:

Provide reviewable datasets with a define.xml file that include anti-taliglucerase IgG, IgE, and neutralizing antibody titer results by study visit for all patients in Studies PB--06-001, PB-06-002, and PB-06-003. Include a column that identifies all patients who are defined as anti-taliglucerase IgG positive based on the revised cutpoint for the assay.

Thank you for your prompt attention to this request. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3924. Thank you.

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

/s/

JESSICA M BENJAMIN
11/10/2011



NDA 022458

GENERAL ADVICE

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm D.
Senior Director, Clinical/Regulatory Affairs

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elelyso (taliglucerase alfa) for injection.

We also refer to your October 7, 2011, submission, containing a response to our information requests regarding your immunogenicity confirmatory assays.

We have reviewed the referenced material and have the following comments:

1. Your risk-based approach for excluding results from the healthy, drug-naïve donor population who appear to have pre-existing antibodies that bind taliglucerase alfa due to the exposure to natural plant glycans (Bardor et al, Glycobiology vol. 13 no. 6 pp. 427±434, 2003) is appropriate and acceptable.
2. The proposed studies to assess the specificity of anti-taliglucerase antibody responses should provide information that is supportive of your hypothesis that these antibodies are likely to react with plant glycans. We acknowledge that your proposed studies will not be completed during this review cycle and we will not require submission of completed studies during this review cycle. However, submission of the results of these studies post-approval may be required.
3. Regarding sensitivity of the neutralizing antibody assay and the cell-based assay, your approach to estimating the sensitivity of the positive control assays may be acceptable if supported by the PK/PD model of your proposal. These data should be submitted to the agency for our review.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

DONNA J GRIEBEL
10/31/2011

From: [Benjamin, Jessica](#)
To: ["Glen Park";](#)
cc: [Benjamin, Jessica;](#)
Subject: NDA 22458 - Information Request
Date: Friday, September 23, 2011 4:16:20 PM

Hi Glen,

Please refer to NDA 22458 for taliglucerase alfa. As a result of our on-going review of this application, we request the following information:

- 1. We note that of the 25 patients who completed Study PB-06-002, 18 patients enrolled into Study PB-006-03. Provide the disposition of the remaining seven patients who did not enroll into Study PB-006-03.**

- 2. Submit the ADSL and ADSPLEEN analysis datasets for the PB-06-002 study. For the requested ADSL dataset, include each patient's Screening number, Subject Identifier for the Study, and Elelyso dose.**

- 3. Refer to your August 17, 2011 telephone conversation with Doris J. Bates, Ph.D., of the Office of Surveillance and Epidemiology (OSE). In this discussion, Dr. Bates conveyed a request for the following information, to be submitted as an amendment to your NDA:**
 - A statement confirming that product characteristics have not changed (to support our re-review of your proposed proprietary name, Elelyso)**
 - An explanation of how Pfizer and Protalix will distribute the product in the US (this information may be provided by cross-reference, if it has been previously submitted in the NDA as a Quality or other amendment).**
 - If only Pfizer will handle US distribution, that needs to be clearly stated, with an explanation of who packages and labels the product carrying the Pfizer corporate name.**
 - A full set of both Protalix and Pfizer labeling, including immediate container, carton, and PI (i.e., current mockups for all items).**

Please submit the information in request #3 within 30 days from the date of this email, or submit it as part of your overall response to this Information Request, whichever is earlier.

Thank you for your prompt attention to these requests. Feel free to contact me with any questions or concerns.

Regards,
Jessica

Jessica Mongrain-Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3924. Thank you.

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

/s/

JESSICA M BENJAMIN
09/23/2011



NDA 022458

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, Pharm D.
Senior Director, Clinical/Regulatory Affairs
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elelyso (taliglucerase alfa) for injection.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Giuseppe Randazzo, M.S., Regulatory Scientist, at (301) 796-3277.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

GIUSEPPE RANDAZZO

09/15/2011

Signed for Dr. Donna Griebel

MEMORANDUM

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

DATE/TIME: August 17, 2011, 2:44 P.M. EDT

TO: File for NDA 022458

FROM: Doris J. Bates, Ph.D., Team Leader, OSE Project Management

SUBJECT: Teleconference (Container Labels, Tradename Pre-Action Review)

APPLICATION/DRUG: NDA 022458 Elelyso (taliglucerase alfa)

MEETING PARTICIPANTS:

FDA: Office of Surveillance and Epidemiology – Project Management

Bates, Doris (TL for Patel, Nitin)

Target (US Agent for Protalix): Glen Park, Senior Director, Clinical and Regulatory Affairs

Background: *Initial Submission and CR action.* This NDA is managed by Target as US Agent for Protalix; the first component of a rolling submission was submitted and received on September 15, 2009, with the NDA being completed on April 26, 2010 and the first proposed tradename submitted and received on April 30, 2010. DGIEP issued a CR letter on February 24, 2011 citing Clinical, Clinical Pharmacology, Product Quality, Immunogenicity, and Microbiology issues. In the circumstances, labeling comments were deferred.

Proprietary Name Review and Status. The initially proposed tradename, (b) (4) was rejected by DMEPA on July 22, 2010, resubmitted on September 27, 2010, and withdrawn on December 3, 2010. A second proposed name, Elelyso, was received on December 10, 2010, and conditionally granted on February 1, 2011.

- Re-review (pre-action review) of this name is necessary prior to approval of the NDA.

DMEPA Labeling Review and Status; Co-Marketing Protalix / Pfizer. The original submission included container labeling for Protalix alone. In late 2009, a co-marketing agreement was reached between Protalix and Pfizer, and on December 23, 2010, dual labeling sets were submitted to the NDA: one set displaying only manufacturer/packager/distributor information for Protalix and one displaying only Pfizer (as the distributor).

OSE/DMEPA reviewed the original submitted labeling on September 15, 2010. The December 2010 labeling submission was not reviewed prior to the CR action, but the OPS Labeling reviewer (K. Rains) noted its submission, as did the OSE PM (N. Patel).

- Review of the December 2010 labeling submission, or amendments as appropriate, will be needed prior to approval of the NDA.

NDA Resubmission. Target resubmitted the NDA in response to the CR letter, on July 31, 2011, with receipt on August 1. The Class 2 resubmission has a six month clock, with the OND

PDUFA falling on February 1, 2012.

- The resubmission did not include confirmation that none of the product characteristics have changed; this is needed for re-review of the proprietary name.
- The resubmission included only a single carton label, displaying Protalix. The Pfizer labeling and the remaining Protalix labeling were not submitted.

Discussion: In response to a 2 PM voicemail, Mr. Park contacted me at 2:44 PM on August 17, 2011. I explained the need for a pre-action review of the proprietary name, indicated that we would also need to better understand the reason for the existence of dual labeling (Protalix and Pfizer), and reviewed the following requests with him over the phone:

In order to complete our review, OSE/DMEPA needs the following information submitted as an NDA amendment:

- a statement confirming that product characteristics have not changed (to support re-review of the tradename)
- an explanation of how Pfizer and Protalix will distribute the product in the US (with cross-references, if this has been previously submitted in the NDA as a Quality or other amendment).
 - if only Pfizer will handle US distribution, that needs to be clearly stated, with an explanation of who packages and labels the product carrying the Pfizer corporate name.
- a full set of both Protalix and Pfizer labeling, including immediate container, carton, and PI (i.e., current mockups for all items).
- I confirmed that Target will submit electronically, and asked for an e-copy by e-mail.

Mr. Park explained that the fine details of the distribution agreement were not fully arranged; I thanked him for the information. Target will provide labels for each firm to assure all contingencies are covered.

Mr. Park thanked me, and we agreed that the submission should be in house within two weeks of the date of this call. The call ended cordially.

Attachment: Excerpt of biorunup.com article documenting distribution agreement between Protalix and Pfizer. Information about stock prices, etc. has been removed as not relevant.

COPYRIGHT MATERIAL

2 Page(s) of Copyright Material have been Withheld in Full
immediately following this page

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

/s/

DORIS J BATES
08/26/2011



NDA 022458

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm D.
Senior Director, Clinical/Regulatory Affairs

Dear Dr. Park:

We acknowledge receipt on August 1, 2011, of your July 31, 2011, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elelyso (taliglucerase alfa) for injection.

We consider this a complete, class 2 response to our February 24, 2011 action letter. Therefore, the user fee goal date is February 1, 2012.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JESSICA M BENJAMIN

08/11/2011



NDA 022458

MEETING MINUTES

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm D.
Senior Director, Clinical/Regulatory Affairs

Dear Dr. Park:

Please refer to your New Drug Application (NDA) dated April 26, 2010, received April 26, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elelyso (taliglucerase alfa) for injection.

We also refer to the meeting between representatives of your firm and the FDA on May 3, 2011. The purpose of the meeting was to obtain clarification on how to respond to deficiencies identified in the Complete Response letter issued February 24, 2011.

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

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 3, 2011

TIME: 2:00 PM – 3:00 PM (EDT)

LOCATION: White Oak, Building 22, Room 1315

APPLICATION: NDA 022458

PRODUCT: taliglucerase alfa

INDICATION: Treatment of Gaucher disease

SPONSOR: Protalix Ltd. (US Agent: Target Health)

TYPE OF MEETING: Type A

MEETING CHAIR: Lynne Yao, M.D.

MEETING RECORDER: Jessica M. Benjamin

FDA Attendees	Title
Julie Beitz M.D.	Director, Office of Drug Evaluation III (ODE3)
Andrew E. Mulberg, M.D., FAAP, CP	Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Lynne Yao, M.D.	Clinical Team Leader, DGIEP
Carla Epps, M.D.	Clinical Reviewer, DGIEP
Sushanta Chakder, Ph.D.	Pharmacology Team Leader, DGIEP
Tamal Chakraborti, Ph.D.	Pharmacology Reviewer, DGIEP
Yeruk Mulugeta, Ph.D.	Clinical Pharmacology Reviewer
Yow-Ming Wang, Ph.D.	Clinical Pharmacology Team Leader
Gibbes Johnson, Ph.D.	Product Quality Team Leader
Richard Ledwidge, Ph.D.	Product Quality Reviewer
Anne Pariser, M.D.	Office of Rare Diseases
Larry Bauer, R.N., M.A.	Office of Rare Diseases
Guiseppe Randazzo, M.S.	Regulatory Scientist, ODE 3
Behrang Vali, M.S.	Biostatistics Reviewer
Jessica M. Benjamin	Regulatory Health Project Manager, DGP
Protalix Ltd.	Title
David Aviezer, Ph.D.	CEO
Yoseph Shaaltiel, Ph.D.	VP, R&D

Einat Almon, Ph.D.	VP, Product Development
Yoram Tekoah, Ph.D.	Director of Glycobiology
Raul Chertkoff, M.D.	Medical Director
(b) (4)	Consultant
Glen Park, Pharm.D.	Consultant
(b) (4)	Consultant
Laura McKinley	Regulatory Affairs, Pfizer
(b) (4)	Consultant

BACKGROUND:

The Agency issued a Complete Response letter on February 24, 2011 for NDA 022458, taliglucerase alfa, for the treatment of Gaucher disease. On April 19, 2011, Protalix Ltd. submitted a Type A meeting package requesting clarification on how to respond to deficiencies identified in the Complete Response letter. Each of Protalix's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided preliminary written responses to the sponsor on May 2, 2011.

MEETING OBJECTIVES:

The main objective of this meeting was to discuss the deficiencies identified in the Complete Response letter issued on February 24, 2011.

DISCUSSION POINTS:

Question 1. FDA CRL Item 6: A potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells is required since internalization is a critical component of taliglucerase alfa's mechanism of action and it is not fully assessed in your current potency assay. The assay should use multiple taliglucerase alfa concentrations to generate a complete dose-response curve in order to calculate the half-maximal effective concentration (b) (4). Develop and implement this assay for use in release and stability testing.

The Sponsor intends to further develop and validate the current high affinity cellular uptake assay with the (b) (4), and to use multiple taliglucerase alfa concentrations to generate a complete dose-response curve in order to calculate the half-maximal effective concentration (b) (4)

Is the proposed strategy acceptable to the Agency?

FDA Response:

No. (b) (4). A validation report and implementation information in the resubmission is required. Results from three lots of taliglucerase alfa that have been manufactured (b) (4) should also be provided at the time of resubmission.

Discussion:

The sponsor clarified (b) (4) that they will provide the validation report and implementation information for the high affinity cellular uptake assay using the (b) (4) in the resubmission. They also plan to include data from 3 lots manufactured in both (b) (4). The agency agrees with the proposal.

Question 2. FDA CRL Item 11: The mannose content specification is based on a MALDI-TOF analysis of taliglucerase alfa. However, the property that is being measured in the MALDI-TOF analysis is mass to charge ratio, not mannose content. Thus, the acceptance criterion should be set around the mass to charge ratio and the mannose content acceptance criterion should be removed from the MALDI-TOF specification. Provide the new specification together with supporting data

The sponsor wishes to clarify if it is the intent of the Agency that the Sponsor replace the mannose content criteria with the molecular weight criteria in the release specifications, or add it in addition to the mannose content criteria?

FDA Response:

The mass spectrometry test method acceptance criteria should be replaced and reported as a mass to charge ratio.

Discussion:

There was no further discussion on this point.

Question 3. FDA CRL Item 13: Monosaccharide content and glycan structure analysis submitted in the characterization section of the NDA contained inconsistent results. Monosaccharide content analysis on two batches indicated that the (b) (4) whereas the glycan analysis data determined that (b) (4) of the glycan structures have a (b) (4). Provide an explanation for these results or submit data that identify the more accurate analysis using batches made (b) (4)

The Sponsor wishes to clarify that the initial monosaccharide content analysis was performed on two early experimental batches only, one of which was used for preclinical studies. The determination of the total glycan content using this method varies due to sensitivity of different

glycan linkages to hydrolysis. Therefore this method is not sufficiently robust for routine use.

As a result, the sponsor developed an alternative, robust method of glycan profiling which is used currently for DS release testing. Both the updated validated method, together with additional characterization using peptide sequencing, confirms that the initial monosaccharide content analysis data is not quantitative.

The NDA sections will be updated and reference to the initial monosaccharide content analysis will be removed to avoid confusion.

Does the Agency agree that this clarification resolves the request?

FDA Response:
The proposed strategy is acceptable.

Discussion:

There was no further discussion on this point.

Question 4. FDA CRL Item 20: The peptide map specification calls for (b) (4). Justify the use of this acceptance criterion in light of the potential amounts of impurities and contaminants that would be acceptable, or revise the criteria for countable peaks. Also, include a revision of the acceptance criteria such that relative peak areas on several selected peptides are specified. Provide the new specification together with supporting data.

In the current NDA submission, the peptide mapping is used as an identity test only. Impurities are quantified and controlled by other release assays. Peptide mapping may assist in identifying and characterizing certain impurities, particularly product related impurities (as discussed below), but this method is not used for quantitative assessment of impurities.

The peptide mapping method allows accurate detection of peaks with (b) (4), as described in the validation report (b) (4).

Regarding identification of impurities, the samples are routinely run with reference standard and compared to the profile of the reference standard. In cases that other "impurity peaks" are observed, above 5%, the profile is considered not similar to reference. Although this assay is not used for quantification of impurities, it should be noted that impurities arising in

DS samples under accelerated stability conditions or following forced degradation can be observed with this approach, if present.

To clarify the acceptance criteria the Sponsor intends to set specifications for [REDACTED] (b) (4) which will be added to the release monograph at the time of submission of the response to the CRL.

Does the Agency agree that this modified specification addresses the issue?

FDA Response:

The proposed strategy appears to be acceptable. However, a final determination will be made after review.

Discussion:

There was no further discussion on this point.

Question 5. FDA CRL Item 26: Process validation reports indicate that vials containing drug product were put on [REDACTED] (b) (4) lyophilizer shelves. Validation of the lyophilization process should include assessment of vials placed on [REDACTED] (b) (4) to confirm consistency of the lyophilization process. Provide a revised validation protocol and report including the results for moisture content testing.

The validation study performed at [REDACTED] (b) (4)

An interim report summarizing the results of those two batches is provided with the briefing document. In this study, samples at [REDACTED] (b) (4) in the lyophilizer were sampled and tested for water content.

Does the Agency agree that the data provided with the revised validation study report is adequate?

FDA Response:
This proposal is acceptable for the resubmission.

Discussion:

There was no further discussion on this point.

Question 6. The CRL includes several requests for analysis of drug substance and drug product manufactured using only (b) (4) for comparison to (b) (4) (CRL Items 9, 22 and 24).

The manufacturing process using (b) (4)

The sponsor proposes to use only (b) (4) for the comparability exercises requested in the CRL (Items 9, 22 and 24), (b) (4)

Does the Agency agree with this proposal?

FDA Response:
The proposed strategy is acceptable.

Discussion:

There was no further discussion on this point.

Question 7. FDA CRL Item 2: There are insufficient data provided to assess the efficacy and safety of taliglucerase alfa in patients switched from other enzyme replacement therapies. Submit the final study report from PB-06-002, and a minimum of 12 months of efficacy and safety data from PB-06-003 for patients switched from other enzyme replacement therapies to taliglucerase alfa.

The Sponsor seeks clarification on this question and will address the data requests from the two studies, PB-06-002 and PB-06-003, separately.

PB-06-002 - efficacy and safety in patients switched from other enzyme replacement therapies

The first patient was enrolled in the switchover study (Protocol PB-06-002) in December 2008 and initiated treatment in March 2009. The

original protocol as submitted to the IND was planned for the enrolment of 15 adult patients. The protocol was amended as follows:

- 1. 7 May 2009: to allow inclusion of patients off Cerezyme or on reduced dose due to the Cerezyme shortage conditions, and to increase the number of patients to a total sample size of 30 with a planned interim analysis after the first 15 patients completed the study.*
- 2. 19 January 2010: enrolment of five (5) pediatric patients 2 years of age and older (out of the 30) in response to a PDCO/EMA request.*

The planned interim analysis for safety and efficacy of the first 15 patients completing the study was performed and reported in the clinical study report dated 20 October 2010. This report also included safety data for all enrolled adult patients (n=25) with a data cut-off date of 15 August 2010. This interim report was not submitted in the original NDA because of late availability.

The status of PB-06-002 switchover study as of 28 February 2011 (proposed interim analysis data cut-off date) is as follows:

- 1. Thirty (30) patients signed informed consent and were eligible for treatment. Of these 30, twenty eight (28) patients received taliglucerase alfa infusions. Of the 28 patients:*
 - Twenty-six (26) adults were enrolled and treated, and 25 of these adult patients completed 9 months of the study.*
 - Two (2) of the above 28, are pediatric patients, which were enrolled in October 2010 and are currently under treatment.*
 - Two (2) patients of the above 30 who signed inform consent, did not start treatment following eligibility approval due to personal reasons.*
- 2. Enrollment remains open only for inclusion of an additional 3 pediatric patients based on a commitment to the PDCO/EMA in a Pediatric Investigational Plan.*

A final report for PB-06-002 will not be available until after completion of enrolment and treatment of the pediatric subjects. At this time the Sponsor is not seeking a pediatric indication for taliglucerase alfa in the NDA and as such considers the data from adult patients of most relevance to the Agency. Therefore, the sponsor proposes to submit an interim report of final data on all 26 adult patients switched from imiglucerase for safety and 25 adult patients for efficacy who have completed the 9 month protocol with monitored efficacy and safety data. Does the Agency agree?

FDA Response:

We agree with your plan to submit 12 months of efficacy and safety data (9 months from study PB-06-002 and 3 months of interim data from PB-06-003) on the 18 adult patients; we are not requiring you to submit an additional 12 months of data from PB-06-003 for these patients. However, please clarify when you plan to submit your complete response as we will also review all available data on pediatric patients that you have enrolled. Your complete response should include efficacy and safety data for all patients enrolled in PB-06-002, including pediatric patients, to within three months of the date of your complete response.

Discussion:

There was no further discussion on this point.

Question 8. PB-06-003 - extended treatment data for patients switched from other enzyme replacement therapies in the switch over study (PB-06-002) and are now treated in the extension study (PB-06-003)

The current status as of 28 February 2011 for patients switched from other enzyme replacement therapy and enrolled in the extension study, PB-06-003, is as follows:

- Twenty six (26) adult patients have completed PB-06-002.*
- Eighteen (18) adult patients of the above 26 have continued treatment with taliglucerase alfa from the switchover study (PB- 06-002) to the extension study (PB-06-003).*
- All 18 patients have completed at least Month 3 in the extension study, thus presenting at least 12 months of total treatment following switching from Cerezyme to taliglucerase alfa.*
- Two (2) patients of the above 26, opted to not continue treatment under Protocol PB-06-003 for personal reasons*
- Five (5) patients of the above 26, continued treatment with taliglucerase alfa under foreign compassionate use programs.*
- The extension study is ongoing.*

With regards to submitting data from PB-06-003 for patients switched from other enzyme replacement, the Sponsor proposes to submit an interim report that will include all available efficacy data representing a minimum total duration of 12 months of treatment with taliglucerase alfa in the 18 adult patients switched from previous enzyme replacement therapies in PB-06-002 and continuing in PB-06-003. This represents 9 months treatment in PB-06-002 and at least an additional 3 months treatment in PB-06-003 extension study.

In addition, all available safety data with a cut-off date of 28 February 2011 will be included in this interim report, which will also include safety data for treatment-naïve patients from the pivotal study, PB-06-001 (see

below – Response to CRL #3). Does the Agency agree with this proposal?

FDA Response:

Please clarify how many patients have received treatment with taliglucerase and for how long. Your proposal to submit a minimum of 12 months of safety and efficacy data (9 months of treatment in PB-06-002 and 3 months of treatment in PB-06-003) for patients switched from previous ERTs is acceptable; however, you should also submit data from all patients enrolled in PB-06-002 regardless of the length of treatment with taliglucerase. The appropriate cut-off date for available safety data to be included in your complete response will depend on the date that you submit your complete responses. You should plan to submit all available safety data from your clinical trials to within three months of the date of your complete response (see response to Question 7).

Discussion:

There was no further discussion on this point.

Question 9. FDA CRL Item 3: Longer-term safety data were insufficient to evaluate the chronic immune-mediated adverse events that are typically associated with enzyme replacement therapies, and Gaucher disease-specific bone events. Provide additional long-term safety data from PB-06-003.

As of 28 February 2011 safety data is available for patients currently being treated in the extension study PB-06-003 as follows:

- *A total of 44 patients have enrolled in PB-06-003 extension study.*
 - *Of the above 44 patients, 26 are treatment-naïve patients who have continued treatment from the pivotal study (PB-06-001). These 26 patients have all completed at least 24 months of total treatment (9 months in PB-06-001 pivotal and 15 months in PB-06-003 extension study).*
 - *Of the above 44 patients, 18 patients switched from other enzyme replacement therapy have continued treatment from the switchover study (PB-06-002). They have been treated for at least 12 months, 9 months in PB-06-002 switchover study and 3 months in PB-06-003 extension study.*
 - *All the above 44 patients have completed at least 12 months of total treatment (9 months in PB-06-001 or PB-06-002, (Naive or Switchover respectively) and 3 months in PB-06-003 extension study).*
1. *Please clarify what adverse events should be considered “chronic immune-mediated adverse events” and if any special analysis is requested.*

2. *The Sponsor proposes to submit an interim report for PB-06-003 extension study with all available safety data from 44 patients as of 28 February 2011, including the data for the 26 adult enzyme treatment-naïve patients treated for at least 24 months in total.*
3. *In addition, as part of the overall safety update, the Sponsor plans to provide an updated analysis of all immune-related adverse events as performed in previous submissions, including the analyses requested by the Agency.*

Does the Agency agree with this proposal?

FDA Response:

The Division is defining “chronic immune-mediated adverse events” broadly as events caused by the development of anti-product antibody formation (e.g., type II-IV hypersensitivity reactions). Your analysis of safety data should include an analysis of adverse events that could be considered to be related to types II, III, and IV hypersensitivity reactions. Case report forms should be included for all patients who may have sustained a hypersensitivity reaction during treatment with your product.

Your proposal to provide at least 24 months of safety data for the 26 treatment-naïve patients enrolled in PB-06-003 is acceptable. We also request that you provide additional data on all pediatric patients enrolled in clinical trials (see response to Question 7).

As stated in the Complete Response letter, you should submit a re-analysis of the impact of anti-product antibody development on PK and PD parameters, efficacy, and safety in patients treated with taliglucerase alfa, using an acceptable cut-point for your confirmatory anti-product IgG antibody assay. In addition, you should develop an acceptable neutralizing antibody assay for both enzyme activity and enzyme uptake and submit a re-analysis of the impact of both types of neutralizing antibody development on PK and PD parameters, efficacy, and safety in patients treated with taliglucerase alfa.

Discussion:

Protalix stated that the cut-point is being established according to the 2009 FDA Draft Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins. The cut-point calculation is being performed according to the Shankar et al. (2008) paper referenced in the guidance using logarithmic transformation from 100 serum samples in healthy individuals. The cut-point will be confirmed with target population serum samples. The Division agrees with this proposal.

Question 10.

(b) (4)

(b) (4)



Is this plan acceptable?

FDA Response:

No, your proposal (b) (4) is not acceptable. Your complete response should include all of the data you have regarding neutralizing assay development and validation. An analysis of the impact of neutralizing antibody development on the safety and efficacy of taliglucerase alfa will be required at the time of the complete response.

Discussion:

The sponsor will be able to submit results from two independent assays measuring neutralizing antibody activity. The first assay is an *in vitro* assay based on enzyme activity with a positive control of anti-taliglucerase antibody that inhibits the enzyme activity. The second is a cell-based assay that combines both cellular uptake and intracellular enzymatic activity. The Division concurs with this proposal. The sponsor further clarified that the positive control for the cellular uptake is the same anti-taliglucerase antibody used for the *in vitro* neutralizing antibody assay.

Action Items:

Protalix estimates a complete response submission in early third quarter 2011. The Agency strongly recommended that the complete response submission include thorough responses to all of the deficiencies. This would include complete clinical study reports, clinical data sets, analysis data sets and the accompanying meta data for PB-06-002 and PB-06-003. The format used in the original submission is acceptable.

Regarding complete response deficiency #25, the sponsor will submit a proposal to address this deficiency for agency review prior to the resubmission of the complete response.

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

/s/

JESSICA M BENJAMIN
05/12/2011



NDA 022458

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

ATTENTION: Glen D. Park, Pharm.D.
Senior Director, Clinical and Regulatory Affairs
Target Health Inc.

Dear Dr. Park:

Please refer to your New Drug Application (NDA) dated April 26, 2010, received April 26, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taliglucerase Alfa for Injection, 200 units per vial.

We also refer to your December 10, 2010 correspondence, received December 10, 2010, requesting review of your proposed proprietary name, Elelyso. We have completed our review of the proposed proprietary name, Elelyso and have concluded that it is acceptable.

The proposed proprietary name, Elelyso, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 10, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412.

For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jessica Benjamin, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
02/01/2011

From: [Benjamin, Jessica](#)
To: ["Glen Park";](#)
cc: [Benjamin, Jessica;](#)
Subject: NDA 22458 - clarifying PK information request
Date: Wednesday, December 22, 2010 10:22:45 AM

Hi Glenn,

Please refer to NDA 22458 for taliglucerase alfa. We received your submission dated December 21, 2010, which responded to our PK information requests from November 23rd. We have the following information requests regarding your recent submission.

For request #1: Submit concentration-time data, not derived pharmacokinetic parameter values.

For request #3: Submit statistical summaries for all patients, in addition to immunogenicity positive and negative patients.

For request #4 and 5: Provide the statistical power (1-beta) in each bioequivalence test.

Thank you for your prompt attention to these requests. Feel free to contact me with any questions or concerns.

Regards,
Jessica

Jessica M. Benjamin
Regulatory Project Manager
Division of Gastroenterology Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

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

/s/

JESSICA M BENJAMIN
12/23/2010

From: Patel, Nitin M. (CDER/OSE)
To: "Glen Park"; gpark@targethealth.com
cc: Patel, Nitin M. (CDER/OSE);

Subject: FW: N 22458 Proprietary name submission - Incomplete submission (DMEPA)
Date: Monday, December 13, 2010 9:43:55 PM

Dear Glen,

Thank you for submitting a new proprietary name and a clarification to withdraw the name (b) (4) DMEPA has reviewed your submission and in order for this submission to be a complete submission please address the following:

Please submit all labels as an amendment to this request for name review submission OR
Submit a cover letter as an amendment to the request for name review submission referencing which previous submission contains the labels and labeling that DMEPA should use for this name review.

Also you have a NDA in house and so should not list the IND on the cover page.

Thank You Kindly

Nitin

Nitin M. Patel OSE-RPM covering DGP White Oak Bldg. #22, Room 4475

Tel: (301) 796-5412 Email: nitin.patel2@fda.hhs.gov

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.

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

/s/

NITIN M PATEL
12/21/2010



NDA 022458

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

ATTENTION: Glen D. Park, Pharm.D.
Senior Director, Clinical and Regulatory Affairs
Target Health Inc.

Dear Dr. Park:

Please refer to your New Drug Application (NDA) dated April 26, 2010, received April 26, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taliglucerase Alfa for Injection, 200 units per vial.

We acknowledge receipt of your December 3 and 10, 2010 correspondence, on December 3 and 10, 2010 respectively, notifying us that you are withdrawing your request for reconsideration of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of December 3, 2010.

We also acknowledge that your December 10, 2010 submission contained a new request for proprietary name review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jessica Benjamin, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
12/14/2010

From: [Benjamin, Jessica](#)
To: ["Glen Park";](#)
cc: [Benjamin, Jessica;](#)
Subject: NDA 22458 - PK request for information
Date: Tuesday, November 23, 2010 1:45:09 PM

Hi Glen,

Please refer to NDA 22458 for taliglucerase alfa. For an adequate pharmacokinetic (PK) characterization of taliglucerase alfa, we request the following information:

1. Provide taliglucerase alfa concentration-time data for each subject in each visit and each dose level collected from Study PB-06-001 in a format (e.g., SAS transport or excel file) that an FDA reviewer can reproduce derived PK parameter values that you estimated and draw concentration-time curves.
2. Provide each derived PK parameter value for each subject in each visit and dose level including dose-adjusted AUC_{∞} , AUC_{last} and C_{max} in a table format.
3. Provide the summary statistics of each PK parameter value in each visit and each dose level with and without stratified by immunogenicity status (Note: use the new immunogenicity cut-point requested in the FDA letter dated on November 19, 2010).
4. Statistically (i.e, two one-sided t-test or bioequivalence test) assess the impact of immunogenicity on the PK by comparing the mean PK parameter values including dose-adjusted AUC_{∞} and C_{max} in each visit and dose level.
5. Statistically (i.e, two one-sided t-test or bioequivalence test) assess the impact of immunogenicity on the efficacy by comparing the primary and secondary clinical endpoints in each visit and dose level.
6. Statistically (i.e., two one-sided t-test or bioequivalence test) compare the mean PK parameter values including dose-adjusted AUC_{∞} and C_{max} between Day 1 and Week 38 with

and without stratified by immunogenicity status in dose level.

7. Provide spaghetti plots of taliglucerase alfa concentration-time data for each visit and each dose level with and without stratified by the immunogenicity status.

8. Provide mean \pm SD plots to compare between Day 1 and Week 38 time-concentration data with and without stratified by the immunogenicity status.

9. Provide the exposure (i.e., dose and dose-adjusted AUC_{∞}) - efficacy response (primary and secondary clinical endpoints) relationship analyses with and without stratified by the immunogenicity status.

Thank you for your prompt attention to these requests. Feel free to contact me with any questions or concerns.

Regards,
Jessica

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

/s/

JESSICA M BENJAMIN
11/23/2010

From: [Benjamin, Jessica](#)
To: ["Glen Park";](#)
cc: [Benjamin, Jessica;](#)
Subject: NDA 22458 - additional information request
Date: Friday, November 19, 2010 5:13:20 PM

Hi Glen,

Please refer to NDA 22458 for taliglucerase alfa. As a result of our on-going review of your application, we have the following information requests. Please note that these are in addition to the Information Request letter that was issued today, November 19, 2010.

1. Evaluate the cross-reactivity of anti-taliglucerase alfa with cerezyme and VPRIV.
2. Taliglucerase alfa has plant specific peptide sequence and ^{(b) (4)} [REDACTED]. Establish an assay(s) to assess for antibodies to plant components of taliglucerase alfa in antibody positive samples.
3. Provide plots of the %inhibition in the confirmatory assay over time for each patient serum sample that tested positive in the screening assay.

Thank you for your prompt attention to these requests. Feel free to contact me with any questions or concerns.

Regards,
Jessica

Jessica M. Benjamin
Regulatory Project Manager
Division of Gastroenterology Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

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

/s/

JESSICA M BENJAMIN
11/19/2010



NDA 022458

INFORMATION REQUEST

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, PharmD.
261 Madison Avenue
24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for taliglucerase alfa.

We are reviewing the chemistry, manufacturing, and controls section of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, we request a prompt written response to the following:

For the immunodepletion assay, which you use to confirm the antibody status of patients, you set the cut-point at (b) (4). The FDA recommends that the confirmatory cut-point be set based on assay precision. Re-establishing the immunodepletion assay cut-point may increase the number of patients who confirm positive. Further, the FDA considers a patient to be positive if they test positive at any point during the assessment period. Actions necessary to address these issues are provided below.

1. Re-establish the immunodepletion assay cut-point based on assay precision.
2. Based on the new cut-point, report any patient who confirmed positive at any time point during the study as positive.

Additionally, we request a prompt written response to the following clinical information requests:

For study PB-06-001, provide an additional column in the AE.xpt dataset that describes the timing of onset of each adverse event. The terms used in this column should define the timing of each AE in the AE.xpt dataset as follows:

1. Occurring during the infusion or within 2 hours after the completion of the infusion
2. Occurring within 2 hours and 24 hours after the completion of the infusion
3. Occurring at least 24 hours after the completion of the infusion

For study PB-06-002, provide an updated ADAE.xpt dataset that includes data to October 1, 2010. Provide an additional column in the dataset that describes the timing of onset of each adverse event as described for study PB-06-001.

For study PB-06-003, provide an updated ADAE.xpt dataset that includes data to October 1, 2010. Provide an additional column in the dataset that describes the timing of onset of each adverse event as described for study PB-06-001.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

RICHARD W ISHIHARA
11/19/2010

MEMORANDUM OF TELECON

MEETING DATE: November 17, 2010
APPLICATION: NDA 022458
DRUG NAME: taliglucerase alfa

FDA ATTENDEES:

Carla Epps, MD, Medical Reviewer
Lynne Yao, MD, Medical Team Leader
Richard Ledwidge, PhD, Product Reviewer
Gibbes Johnson, PhD, Product Team Leader
Jessica Benjamin, Project Manager

Protalix ATTENDEES:

Glen Park, US Agent
David Aviezer, Protalix CEO
Yoseph Shaaltiel, Protalix EVP, R&D
Eina Almon, Protalix SVP, Product Development

BACKGROUND:

Protalix provided genomic sequencing data of the master cell bank (MCB) in the NDA. Only (b) (4) of the genomic clones had the expected wild type sequence. These results suggest that the gene sequences in the master cell bank are not identical to the expression construct gene sequence, inconsistent with ICHQ5B. The CMC team sent an information request to Protalix asking for genomic sequencing data on (b) (4) each from a MCB vial and (b) (4) bioreactor bags (b) (4). Protalix requested a teleconference to discuss the information request.

SUMMARY:

- 1) Information provided by Protalix on 11/10/10 did not satisfactorily address the IR letter.
- 2) The proposed (b) (4) in lieu of genomic sequencing would not satisfactorily address the IR letter (sequencing data must be genomic).
- 3) The genomic data required to address the IR letter is required to complete the review.
- 4) The results of the genomic sequencing study in addition to the information provided in the NDA will define the manufacturing limits for end of production in either days (or doubling times). The time limit for the manufacturing process cannot be defined in cycles (b) (4).

From: [Glen Park](#)
To: [Benjamin, Jessica](#)
Subject: Request for teleconference
Date: Monday, November 08, 2010 11:02:51 PM
Attachments: [emfalert.txt](#)

Dear Jessica,

I would like to provide an update on the status of our response to the recent request for CMC information and see whether we could have a teleconference with the quality reviewer(s) to discuss the timing of the full response. I understand from the information request letter that we need only provide information on the timing of the response by November 12, but would like to make sure that the timing we will propose will meet the review requirements to meet the PDUFA date, February 25 2011.

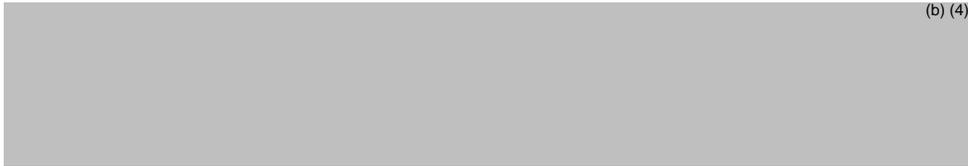
Protalix is working very hard to provide all requested CMC information before November 24, 2010. However, there is one piece of information that we cannot provide by that date as described in Item 3 below

On November 12 we propose to submit the first piece of information which will include the following:

1. Full length sequencing data derived from RNA from several early production and end of production batches. The results show that the full length sequence is identical to the expected sequence.
2. Evaluation of the presence of the potential mutation raised by the CMC reviewer during the GMP audit [- ATG (1,019-1,021)-CTC] that can result (b) (4) Two approaches were taken to resolve this question - one at the cDNA level and one at the protein level:

(b) (4)

(b) (4)



The information below as requested in the last Information request dated 28 October 2010 cannot be provide by November 2010:

3. Sequencing data from (b) (4) clones derived from Genome sequencing results. We would like to clarify that this analysis can be based (b) (4). In addition, we would like to propose a commitment for submitting this information post-approval. (b) (4)



The Sponsor believes that the data which will be provided by Novembers 12 support the notion that stability of (b) (4)



Please let me know if this teleconference is possible by Wednesday of this week (November 10).

Best regards,

Glen

EDC Made Simple Since 1999	
Glen Park, PharmD <i>Sr Director, Clinical/Regulatory Affairs</i> gpark@targethealth.com	Target Health Inc. 261 Madison Avenue, 24th Floor New York, NY 10016 tel: 212-681-2100 fax: 212-681-2105 mobile: 212-945-8512 Skype ID: glenpark6
Want to always have my latest info?	Want a signature like this?

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

/s/

JESSICA M BENJAMIN
02/12/2011



NDA 022458

INFORMATION REQUEST

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, PharmD.
261 Madison Avenue
24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (taliglucerase alfa) for Injection.

We are reviewing the chemistry, manufacturing, and controls section of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, we request a prompt written response to the following:

- 1) According to the *International Conference on Harmonisation, "Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products"* (ICH Q5B), the purpose of analyzing the expression construct is to establish that the correct coding sequence of the product has been incorporated into the host cell and is maintained during culture to the end of production. You have provided nucleic acid sequencing data indicating that only (b) (4) of the sequenced clones had the expected deoxyribonucleic acid (DNA) sequence, with some of the changes in DNA sequence altering the protein sequence. You attributed this result to matrix effects and polymerase chain reaction (PCR) artifacts but provided no data to support this conclusion. Additionally, no information was provided demonstrating that the protein coding sequence is maintained during culture to the end of production. Please submit the following information to the NDA:
 - i. Genome sequencing results for the master cell bank (MCB) and for end-of-production cells. To determine the potential extent of any genetic variation, we propose that you sequence (b) (4) clones from the MCB and (b) (4) bioreactor bags (b) (4). Do not pool harvests together. All unexpected sequences should be confirmed by a suitable method. In addition, data regarding the (b) (4) cells used in this study should be provided. Please provide data with appropriate controls to support the suitability of all methodologies used. The results of this study will define the limit for end-of-production cells in terms of population doublings or time in days as per *International Conference on Harmonisation, "Derivation and*

*Characterization of Cell Substrates Used for Production of
Biotechnological/Biological Products; Availability” (ICH Q5D).*

- 2) We refer to your submission dated September 30, 2010, which contained your response to an Agency correspondence dated August 11, 2010, requesting your comment(s) on apparent differences in the rate of [REDACTED] (b) (4) for drug product lots manufactured from drug substance batches made in [REDACTED] (b) (4). To aid in the review of your September 30, 2010 submission, provide all drug product SEC-HPLC stability data with the percentage of [REDACTED] (b) (4) reported separately.
- 3) Please provide information (or the location in your NDA) which defines the number of sample vials and replicates used from a drug product batch to perform all drug product release testing. In addition, provide a risk assessment of the sampling plan that takes into consideration the number of vials used for release testing, the total number of vials in a drug product batch, and the amount of variability introduced in drug product manufacturing from sources such as the lyophilization process and container closure system.

Please provide the Agency with an estimated date for submission of this information to your NDA no later than **November 12, 2010**.

If you have any questions, call Hee (Sheila) Lianos, Regulatory Project Manager, at (301) 796 - 4147.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

RICHARD W ISHIHARA
10/28/2010



NDA 22-458

INFORMATION REQUEST

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, Pharm D.
261 Madison Avenue
24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (taliglucerase alfa) for injection.

We are reviewing the proposed labeling section of your submission. The following issues/deficiencies have been identified in your proposed labeling:

HIGHLIGHTS

Dosage and Administration

- Please remove or rephrase the following statement:

(b) (4)

This statement is vague and the use of the terms (b) (4), are suggestive and not supported by substantial evidence.

Warnings and Precautions

- In the following statement:

(b) (4)

Remove the word (b) (4) and use command language. For example:

Treat patients with hypersensitivity to (b) (4) or other glucocerebrosidase enzymes with caution.

Adverse Reactions

- [REDACTED] (b) (4)
Only the name of the manufacturer, manufacturer's phone number, and FDA contact information belongs in this statement.

[REDACTED] (b) (4)

[REDACTED]

TABLE OF CONTENTS

Full Prescribing Information: Contents

- Please indent all subsection headings.
- Please include Section 17, Patient Counseling Information.

FULL PRESCRIBING INFORMATION

- Throughout the label, please reformat the proprietary name with established name and dosage form as follows:
[REDACTED] (b) (4) (taliglucerase alfa) for Injection
- Provide white space between all bolded section headings and paragraphs.
- Remove all use of the words [REDACTED] (b) (4), throughout the label and replace with command language.
- The preferred presentation of cross-references in the full prescribing information is the section heading followed by the numerical identifier. The cross-reference should be in brackets and the text in italics. For example, [*see Use in Specific Populations (8.4)*].

Please apply the correct format in all of your references throughout the label.

Boxed Warning

- Heading and summary of warning must be contained within a box and bolded.

Dosage and Administration

2.1 Dosage

- Remove the use of the word [REDACTED] (b) (4), in the following sentence
[REDACTED] (b) (4)

Warnings and Precautions

5.1 Antibody Response

- The following statement is vague. Please revise or remove:
[REDACTED] (b) (4)
- Remove the use of the word [REDACTED] (b) (4) in the following statement:
[REDACTED] (b) (4)

Adverse Reactions

- In the second paragraph, last sentence, [REDACTED] (b) (4) is written twice. Please remove.

Patient Counseling Information

- You have not provided a Section 17 Patient Counseling Information in your label. Please include the required information in this section.

Manufacture Information

Manufacture information is required in labeling (see 21 CFR 201.1 and 201.100(e)) and should be located after the Patient Counseling Information section, at the end of labeling. You have not provided this information. Please add to the label.

Please address the identified deficiencies/issues and re-submit labeling by October 1, 2010. We also request that you submit a Word version of the label in your submission. This updated version of labeling will be used for further labeling discussions.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2269.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

BRIAN K STRONGIN
08/13/2010



NDA 22-458

INFORMATION REQUEST

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, Pharm D.
261 Madison Avenue
24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (taliglucerase alfa) for injection.

We are reviewing the Quality section of your submission and have the following comments and information requests.

- 1) Please provide the storage age (in months) for each drug substance batch that was used to manufacture clinical and commercial batches of drug product.
- 2) For each patient in the Phase III clinical trial (Study PB-06-001), please provide the drug product batch number and the age of the drug product (in months) at the time of the drug administration. Make sure to include the patient identification number.
- 3) It appears that drug product manufactured using (b) (4) than drug product manufactured for the Phase III trial (b) (4) at the proposed storage condition (5 ± 3 °C). All drug product lots on stability that were made in (b) (4) that have been tested out to at least three months (n=4, PR2003, PR2005, PR2006, WA004268) (b) (4) by month 3.

Conversely, phase III trial material (b) (4).
The following table summarizes information provided in the NDA:

Phase III DP Lots	Time at which (b) (4) are detected by SEC-HPLC	Comment
K38743	(b) (4)	
K39065		
K40306		
PR2001		
PR2002		

Please comment on the apparent difference in (b) (4) detected by SEC-HPLC upon a change to (b) (4)

In order to continue our review of your NDA, please provide a response to this Information Request letter by October 1, 2010.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2269.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

BRIAN K STRONGIN
09/08/2010



NDA 22-458

INFORMATION REQUEST

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, Pharm D.
261 Madison Avenue
24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (taliglucerase alfa) for injection.

We are reviewing the Statistical and Quality sections of your submission and have the following comments and information requests.

1. For parenteral drug products in solution, the ability to measure and control particulate matter from extraneous substances within specific size ranges is essential towards maintaining product quality. The standard test for particulate analysis for injections is USP <788> Light obscuration test which specifies and limits particulate sizes >10 μm to 6000 particles/container and particulate sizes >25 μm to 600 particles/container. Therefore, please provide the following:
 - a) Incorporate USP <788> light obscuration test into your drug product release and stability protocols.
 - b) Provide data on particulate levels in drug product lots that were used to support your NDA including validation and stability studies.
2. Large protein aggregates have the potential to elicit immune responses to the active moiety and therefore should be appropriately characterized and controlled. Although there is a gap in current analytical technology for quantitation of sub-visible particulates between 0.1 and 2.0 μm , suitable techniques such as light obscuration, Coulter counter and microfluidic devices can quantitate particles in the 2.0 to 100 μm range and should be employed in your assessment of product quality. We recommend the following:
 - a) Provide a protocol describing your plans to conduct a robust characterization of the sub visible particulate content of the drug product. This characterization should include the use of orthogonal techniques to quantitate the particle content and studies designed to identify the nature of the particles and the type of

interaction, if proteinaceous (e.g. covalent or non covalent, reversibility, conformational status).

- b) We also recommend the use of multiple stress conditions to assess the potential pathways for sub visible particulate formation. This information should be used in a risk assessment and design of an appropriate control strategy for sub visible protein aggregate content.

3. You have provided the validation report 70-60-016 for SEC-HPLC to determine the levels of taliglucerase alfa [REDACTED] ^{(b) (4)}. Accuracy, the closeness in agreement between the value and the conventionally true value, is one of the critical components of analytical procedure validation. [REDACTED] ^{(b) (4)}
[REDACTED]

4. Clarify the randomization methodology administered (i.e. simple or adaptive, stratified or non-stratified, blocks utilized or not utilized, etc.) for the PB-06-001 study.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2269.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22458	----- ORIG-1	----- PROTALIX LTD	----- PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

BRIAN K STRONGIN
08/11/2010



NDA 022458

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

ATTENTION: Glen D. Park, Pharm.D.
Senior Director, Clinical and Regulatory Affairs
Target Health Inc.

Dear Dr. Park:

Please refer to your New Drug Application (NDA) dated April 26, 2010, received April 26, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taliglucerase Alfa for Injection, 200 units per vial.

We also refer to your April 30, 2010, correspondence, received April 30, 2010, requesting review of your proposed proprietary name, (b) (4). Your submission indicates that the proposed product characteristics for Taliglucerase Alfa for Injection have changed as compared to those submitted under your IND. Your current proposal is to market this product in a single strength (b) (4)

We found the proposed proprietary name (b) (4) acceptable during the IND review. This decision was based on (b) (4)

Therefore, we conclude (b) (4) is unacceptable. Our rationale follows.

(b) (4)

(b) (4)



(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M.Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Chantal Phillips at (301) 796-2259

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

CAROL A HOLQUIST
07/22/2010



NDA 22-458

FILING COMMUNICATION

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, Pharm D.
261 Madison Avenue
24th Floor
New York, NY 10016

Dear Mr. Park:

Please refer to your new drug application (NDA) dated April 26, 2010, received April 26, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (taliglucerase alfa) for injection, 200 units.

We also refer to your submissions dated April 30, 2010; May 4, 2010; and June 4, 7, 11, 18, & 29, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is February 25, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 8, 2011.

During our filing review of your application, review issues were identified that must be addressed to allow for complete review of the application. Assays designed to assess immunogenicity need to be validated for specificity, repeatability, linearity of response, limits of detection (Cutpoint) and quantitation, inter-analyst and inter-day precision, background of normal serum samples, robustness, and stability of critical reagents. Currently, the Agency

cannot interpret the assay validation data in a meaningful way because information currently provided in the application are lacking in several areas. Therefore, we request the following:

Information regarding the antibody screening assay:

1. You report the sensitivity of your assay as (b) (4) based on a standard curve generated by spiking rabbit polyclonal antibody in human serum. Please clarify how this limit was established and provide the data that support it in a tabular form.
2. Establish quality controls (QC) for your assay to ensure reproducible sensitivity and range. A LOW positive quality control (LQC) should have an antibody concentration close to the LOD (limit of detection). The LQC should be set to fail the assay 1% of the time.
3. Provide data to establish that the assay is specific for antibodies to your product or its endogenous counterpart. Please provide any available information regarding the potential cross-reactivity of antibodies to pr-GCD and currently licensed products for the same indication.
4. Provide a clear explanation of how the cut point was derived along with the raw data utilized to determine it. A sample size of 50 – 100 subjects from the target population (treatment-naïve) is generally recommended for establishing the cut-point. The Agency recognizes that these samples may not be available and there are alternative approaches that may be acceptable.

Information regarding the IgE assay:

5. For the assay for detection of anti- prGCD IgE please provide the following information:
 - Data to demonstrate the sensitivity and specificity of the assay in the presence of other antibody subtypes, including human IgG.
 - The serum concentration used in your assay and demonstrate lack of interference from serum matrix components in your assay.
 - Quality controls (QC; low, medium and high) and relevant standards for your assay and establish their acceptance criteria for your assay. Please ensure a low positive control that is set to fail the assay 1% of the time to help monitor assay performance.
 - Results of patient sample analyses.

Information regarding the confirmatory assay:

6. Provide data to support the proposed cut point of (b) (4) reduction as an acceptance criterion for the presence of anti- prGCD antibodies in confirmatory test. Cut-points for confirmatory assays should be established statistically based on assay variability rather than on the results of displacement studies.

7. Provide data that establishes the linearity of the assay and justifies the selection of (b) (4) of product as optimal for this assay.
8. Establish the accuracy and precision of the assay using samples of LOW, MED and HIGH antibody concentration that are within the linear range of the assay. Include data to demonstrate that the study samples are insensitive to the position in the plate wells.
9. Establish the robustness of your assay showing the assay quality remains unaffected with small variations in the method parameters.

Information regarding the neutralizing antibody assay:

10. Develop an assay that will measure the ability of patient antibodies to block the uptake of *prGCD* into target cells.
11. Regarding the neutralization of enzymatic activity assay:
 - Develop a suitable positive control neutralizing anti-prGCD antibody to use in your assay.
 - Submit data regarding the sensitivity of this assay. The sensitivity of the assay should be provided in mass units if at all possible.
 - Verify the cut-point you determined for this assay using sera from the target patient population and establish appropriate quality controls.
 - Establish the linearity of your assay and provide data showing that the method is optimized to detect the presence of neutralizing antibodies.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Because this drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

DONNA J GRIEBEL
07/09/2010

Phillips, Chantal

From: Phillips, Chantal
Sent: Friday, June 11, 2010 2:18 PM
To: 'Glen Park'
Subject: NDA 22-458

Hi Glen,

I am following up with you regarding the recent submissions for NDA 22-458. You have not provided any data definition files (define.pdf or define.xml) for the analysis datasets submitted on June 4 & 7, 2010. In addition, please submit SAS program code for each analysis dataset created and submitted on June 4 & 7, 2010. You must provide this material before June 18, 2010. Please verify the date that you intend to submit the requested data definition files and SAS programs as soon as possible.

Thank you,

Chantal Phillips, M.S.H.S.
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Food and Drug Administration
Division of Gastroenterology Products
BLDG 22, Room 5128

chantal.phillips@fda.hhs.gov
(301) 796-2259 Phone
(301) 796-9905 Fax

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

CHANTAL N PHILLIPS
06/11/2010

MEMORANDUM OF TELECON

DATE: 02 JUN 2010

APPLICATION NUMBER: NDA 22-458

BETWEEN:

Name: David Aviezer, PhD, CEO, Protalix Inc.
Yoseph Shaaltiel, PhD, SVP, R&D, Protalix Inc.
Einat Almon, PhD, VP, Product Development, Protalix Inc.
Raul Chertkoff, MD, Medical Director, Protalix Inc.
James Balun, MS, Regulatory Affairs, Pfizer Inc.
Glen Park, PharmD, Regulatory Consultant, Target Health Inc.

Phone: Provided by sponsor
Representing: Target Health, U.S. Agent for Protalix

AND

Name: Division of Gastroenterology Products, HFD-180
Lynne Yao, M.D., Acting Medical Team Leader
Carla Epps, M.D., M.P.H., Medical Reviewer
Chantal Phillips, CDR, M.S.H.S., Regulatory Project Manager

Division of Biometrics III
Behrang Vali, Ph.D., Statistical Reviewer

SUBJECT: Data required to File NDA 22-458

BACKGROUND:

The purpose of this teleconference is to discuss the data still required from the Sponsor to file the application by June 25, 2010. This NDA is a rolling review, with final module being submitted on April 26, 2010. An IR letter was sent to the Sponsor on March 3, 2010, requesting information to support both Clinical and Statistical review. The Sponsor provided response to the IR letter on May 4, 2010. An email was sent to the Sponsor on May 7, 2010, reiterating that the requested and still missing data is required for review of the application.

Filing meeting was held on May 26, 2010. The missing data is considered a filing issue and the team agreed to hold a tcon with the sponsor to obtain more information on the status of the missing items.

SUMMARY:

The Sponsor was referred to FDA communications dated March 3, 2010 and May 7, 2010; and their response dated May 4, 2010. Prior to the Tcon, the Sponsor provided updates in an email dated June 1, 2010 (see attached).

FDA informed the Sponsor that items 1-6 listed in their email are required for review and must be submitted by close of business on June 11, 2010. If the Sponsor is unable to submit these items by this date, the FDA will restart the review clock.

The Sponsor stated that they may be able to submit some of the items by June 11, 2010, but others may come after that date. FDA asked the Sponsor to provide the Project Manager with a timeline of their expected dates of submission for items 1-6 and we will re-evaluate at that time.

The Sponsor referred to the pre NDA meeting minutes from May 21, 2009, and stated their understanding was they only needed to submit data from PB-06-001 to file their application. FDA clarified that the pre NDA meeting minutes do state, in our response to question 12, that although PB-06-002 and PB-06-003 are supportive studies, we requested interim safety data.

In addition, FDA reiterated that PB-06-001 is the basis for their efficacy claim and therefore the analysis datasets for this study are required. Therefore, since the Sponsor has not provided these datasets, the data for PB-06-001 is incomplete. FDA emphasized that these missing datasets are refuse to file issues; however, because they have a rolling review, we can adjust the review clock as needed.

The Sponsor confirmed that they will provide FDA with a timeline of submission for the missing items and that they plan to have the majority in by June 11, 2010.

Chantal Phillips, CDR, M.S.H.S.
Regulatory Project Manager

Phillips, Chantal

From: Glen Park [gpark@targethealth.com]
Sent: Tuesday, June 01, 2010 9:09 AM
To: Phillips, Chantal
Subject: NDA 22-458: Teleconference regarding clinical request for information
Attachments: emfalert.txt

Hi Chantal,

In anticipation of our teleconference for tomorrow, we provide the following information that should help address any questions the FDA team may have:

We provided in NDA 22-458 clinical and biostatistical data consistent with the agreements reached at the preNDA meeting held on 21 May 2009.

As stated in the preamble to Question 8 of the preNDA meeting briefing document:

“Protocol No. PB-06-001 was the subject of several discussions with the Division, including meetings on 30 June 2004, 21 February 2007 and 14 April 2008. At the pre-IND meeting the Division agreed that a study in 30 patients would provide sufficient evidence of effectiveness of prGCD if the results were sufficiently robust and statistically significant. A Special Protocol Assessment was conducted with final agreements on the design of the trial obtained in response to questions for a Type A meeting scheduled with the Division on 24 July 2007. Therefore, this pivotal study is meant to provide the primary evidence of the safety and effectiveness of prGCD as enzyme replacement therapy for patients with Gaucher disease.”

Study PB-06-001 was submitted as a complete and final clinical study report and accompanied by SAS data sets. In addition, available data for two ongoing studies, PB-06-002 and PB-06-003, was provided as agreed with the Division at the preNDA meeting (see Question 12 of the preNDA meeting minutes).

With the background of these understandings and agreements with the Division, we will provide additional information as requested in the letter from Dr Re on 03 March 2010.

Our commitment is to submit on or before 25 June 2010 all requested information as clarified in our Submission on 4 May 2010 and correspondence with Ms Phillips, which included her final response on 7 May 2010.

This submission will include:

1. Analysis datasets in SAS transport format for studies PB-06-001, PB-06-002, and PB-06-002.
2. Abbreviated CSR for study PB-06-002 that will include 6-month efficacy data for 13 patients and adverse event data for all enrolled subjects with a cutoff date of 30 April 2010.
3. Abbreviated CSR for study PB-06-003 that will include a summary of efficacy data, including organ volumes following a total of 12 months of treatment with taliglucerase alfa, and all available safety data.
4. CRFs for patients with reported serious adverse events in studies PB-06-002 and PB-06-003. Neither event was considered related to the investigational product and reportable as an IND safety report.
5. An integrated summary of safety for studies PB-06-001, PB-06-002, and PB-06-003.
6. Analysis of taliglucerase alfa efficacy and safety information in the context of a historical review of Ceredase® and Cerezyme® data from the literature.

We are happy to have the opportunity to discuss any of the particulars of this information.

The dialin number is [REDACTED] (b) (4)

Best regards,

Glen

<p>Glen Park, PharmD <i>Sr Director, Clinical/Regulatory Affairs</i></p> <p>gpark@targethealth.com</p>	<p>EDC Made Simple Since 1999</p> <p>Target Health Inc. 261 Madison Avenue, 24th Floor New York, NY 10016</p> <p>tel: 212-681-2100 fax: 212-681-2105 mobile: 212-945-8512 Skype ID: glenpark6</p>
---	--

[Want to always have my latest info?](#)

[Want a signature like this?](#)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22458

ORIG-1

PROTALIX LTD

PLANT CELL EXPRESSED
RECOMBINANT HUMAN G

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

/s/

CHANTAL N PHILLIPS

06/04/2010

Phillips, Chantal

From: Phillips, Chantal
Sent: Friday, May 07, 2010 9:54 AM
To: 'Glen Park'
Subject: NDA 22-458: Response to May 4, 2010 submission

Hi Glen,

Please see our comments below in response to your May 4, 2010, submission for NDA 22-458:

1. The electronic analysis data sets are being prepared as SAS transport files and will be submitted as soon as they are available.

FDA: Please provide us with a more specific timeline, as your NDA is currently on a review clock, not a rolling submission.

2. We will prepare abbreviated CSRs that will present interim data for the two studies by the end of June 2010, reporting safety and efficacy data as follows:

PB-06-002: We will present efficacy data on 13 patients who have completed at least 6 months of treatment and safety data on all treated patients. The primary endpoint of this study is assessment of clinical deterioration as defined by the protocol.

PB-06-003: We will present efficacy data on 26 patients who have completed organ volume assessments (spleen and liver volume by MRI) at 3 months. The efficacy data for these patients will represent treatment for 12 months. These patients enrolled in PB-06-003 after completing 9 months of treatment in the pivotal study PB-06-001.

We also plan to submit an integrated safety analysis of adverse events for PB-06-001, PB-06-002 and PB-06-003.

FDA: We remind you that you submitted your April 26, 2010 submission as the final piece to stop the rolling review, and initiate the PDUFA review clock. This information is required for review.

3. Please see the [regulatory history presented in Module 1.11.3](#).

FDA: No comment.

4. A thorough literature review will be presented with the submission of abbreviated CSRs by the end of June 2010.

FDA: No comment.

5. Historical control data will be submitted by the end of June 2010.

FDA: Please see response to item 2.

6. i) We will submit electronic datasets and eCRFs, but the datasets do not fully comply with SDTM standards.

FDA: No comment.

ii) We will submit analysis datasets and DEFINE.pdf files, but the datasets do not fully comply with ADaM standards.

FDA: Please provide us with a more specific timeline, as your NDA is currently on a review clock, not a rolling submission.

iii) These will be provided.

FDA: Please provide us with a more specific timeline, as your NDA is currently on a review clock, not a rolling submission.

iv) descriptions will be submitted for each study (PB-06-001, PB-06-002 and PB-06-003).

FDA: Please provide us with a more specific timeline, as your NDA is currently on a review clock, not a rolling submission.

7. These will be provided with the abbreviated study reports.

FDA: Please see response to item 2.

8. This analysis will be included in the safety summary to be submitted by the end of June 2010.

FDA: Please see response to item 2.

9. This will be submitted by day 120 based on the filing date of the NDA.

FDA: No comment.

Thank you,

Chantal Phillips, M.S.H.S.
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Food and Drug Administration
Division of Gastroenterology Products
BLDG 22, Room 5128

chantal.phillips@fda.hhs.gov
(301) 796-2259 Phone
(301) 796-9905 Fax

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

CHANTAL N PHILLIPS
05/07/2010



NDA 22-458

NDA ACKNOWLEDGMENT

Protalix Ltd.
c/o Target Health Inc.
Attention: Glen D. Park, Pharm D.
261 Madison Avenue
24th Floor
New York, NY 10016

Dear Dr. Park:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (taliglucerase alfa) for injection, 200 units

Date of Application: April 26, 2010

Date of Receipt: April 26, 2010

Our Reference Number: NDA 22-458

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 25, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Chantal Phillips, M.S.H.S.
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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

/s/

CHANTAL N PHILLIPS
04/28/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 69,703

Target Health Inc.
Attention: Glen Park
261 Madison Ave
24th Floor
New York, NY 10016

Dear Mr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase).

We also refer to the type C meeting between representatives of Protalix Biotherapeutics and the FDA on April 14, 2008. The purpose of the meeting was to discuss the toxicology and clinical programs be developed by Protalix Biotherapeutics.

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

If you have any questions, call me at (301) 796-4147.

Sincerely,

{See appended electronic signature page}

Hee K. Lianos, RPh, PharmD.
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 14, 2008
TIME: 8:30 AM – 9:30 AM
LOCATION: FDA/CDER
White Oak, Bldg 22
Silver Spring MD 20993
APPLICATION: 69,703
DRUG NAME: prGCD (Plant Cell Expressed Recombinant Human
Glucocerebrosidase)
TYPE OF MEETING: type C
MEETING CHAIR: Anne Pariser
MEETING RECORDER: Hee Lianos

FDA ATTENDEES (Division of Gastroenterology Products/ ODE III):

Anne Pariser, M.D., Medical Team Leader
Joanna Ku, M.D., Medical Officer
Sonia Castillo, PhD, Biostatistics Reviewer
Sushanta Chakder, PhD., Acting Pharmacology Team Leader
Tamal Chakraborti, PhD., Pharmacology Reviewer
Gibbes Johnson, Chief, Laboratory of Chemistry, Division of Therapeutic Proteins
Emanuela Lacana, Chemistry and Quality Reviewer, Division of Therapeutic Proteins
Julieann DuBeau, M.S.N., R.N., Chief, Project Management Staff
Hee Kyung Lianos, RPh., PharmD., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

David Aviezer, PhD, Chief Executive Officer, Protalix Biotherapeutics
Yoseph Shaaltiel, PhD, Vice President, Research and Development, Protalix Biotherapeutics
Einat Almon, PhD, Vice President Product Development, Protalix Biotherapeutics
Sigal Aviel, Senior Director of Research, Protalix Biotherapeutics
Sharon Hashmeuli, PhD, Project Leader, Protalix Biotherapeutics
Raul Chertkoff, MD, Medical Director, Protalix Biotherapeutics

(b) (4)

Glen Park, PharmD, Regulatory Affairs, Target Health, Inc.
Jules Mitchel, PhD, MBA, Regulatory Affairs, Target Health, Inc.

(b) (4)

BACKGROUND:

Protalix Biotherapeutics is developing prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase) with a proposed indication for long-term enzyme replacement therapy for

the treatment of Gaucher's disease. Protalix Biotherapeutics is requesting a type C / Advice Meeting.

IND 69,703 was originally submitted on June 15, 2005. A partial clinical hold was lifted on April 16, 2007 (after an advice meeting was held on February 21, 2007) and complete response to clinical hold amendments were made January 12, 2007 and March 22, 2007. A Special Protocol Assessment (SPA) procedure was conducted for a Phase 3 study (Protocol No. PB-006~01) and this protocol was initiated in August 2007 at a site in Israel. Additional sites have been initiated in Stoutly, Africa and the United States.

Protalix Biotherapeutics is currently seeking guidance on chemistry, manufacturing and controls, toxicology, and clinical development programs for support of a future NDA. Also present at the meeting were representatives from Target Health, Inc., as the regulatory agent for Protalix Biotherapeutics.

MEETING OBJECTIVES:

Protalix's objective for this meeting are to obtain guidance on several CMC issues, on the design of proposed reproductive toxicology studies, and on the design of a clinical study to evaluate the safety of switching patients from Cerezyme® to prGCD.

DISCUSSION POINTS:

Following introductions, Protalix's questions from the March 14, 2008, background information package were used as the basis for further discussion regarding their clinical studies, pediatric plan, and nonclinical toxicology plan.

The format of these minutes provides for (b) (4) questions in regular typeface, followed by the Agency's responses in **bolded** print, followed by the March 17, 2008 meeting discussion in *italic and bolded* print.

DISCUSSION:

Question 1:

Protalix has made significant progress in the development of their release test methods, assay development and validation, and the specifications of Drug Substance and Drug Product. The specifications of prGCD have been set based upon the analytical data of batches manufactured and released at Protalix by the current manufacturing process, and based on batches used in preclinical and clinical studies.

Does the Agency agree that the proposed release testing and specifications for the drug substance and drug product adequate to support the NDA?

Agency Response:

No. A final determination of acceptable release testing and specifications will result from the complete review of the NDA, and all data available at that time will be used to make that determination. In regards to your proposed drug substance and drug product release testing and specifications, we have the following comments and recommendations for the future NDA submission:

1. Include glycan analysis and monosaccharide content, including mannose, in your release testing and stability programs.

Additional Discussion:

The sponsor (Protalix) referred to previous meeting minutes from the 29-November-2006 Type C meeting held between the Division and Protalix, and the CMC comments given at that time. The Sponsor stated that they are currently checking release stability testing on every fifth batch and not every batch, and intend to report these results in the Annual Report. Would this be acceptable to the Agency?

The Agency stated that the responses to Question 1 are standard comments that would be applicable any NDA. In general, with progression of the clinical development program from an IND through to an NDA, increased stringency for release stability testing is expected and would be required for an NDA submission. The previous comments from the November 2006 meeting were intended for an IND program. Thus, the Agency's comments applicable to an NDA are unchanged. The Agency additionally clarified that glycosylation is important for potency and potential efficacy; therefore, it is important to control for this. The decision whether to do this with drug substance (DS) or drug product (DP) is the sponsor's decision, and will depend on the magnitude of changes in DS to DP during manufacturing.

2. *Measure prGCD potency by the determination of the kinetic parameters K_m and k_{cat} using a physiologically relevant substrate. This potency assay should be used in your release and stability protocols.*
3. *Establish upper and lower limits acceptance criteria of all relevant release and stability tests.*
4. *Include biological activity assays that measure binding to the mannose receptor and cellular uptake of prGCD in both release and stability tests.*
5. *Limits for Host Cell protein content, endotoxin and DNA content should be set based on process capability, and manufacturing and clinical experience. Please revise the limits for these tests accordingly.*
6. *In regards to the SDS-PAGE analysis, set acceptance criteria for the major band and additional bands present in the gel.*

Additional Discussion:

The sponsor clarified that the SDS page analysis is an assay for purity and they only (b) (4) The Agency stated that the sponsor will still need to set acceptance criteria for this analysis. (b) (4)

7. *In regards to the RP-HPLC method, establish acceptance criteria for the (b) (4) observed in the chromatogram.*

Additional Discussion:

The sponsor proposed establishing RP-HPLC acceptance criteria based on a range of AUCs for each peak. The Agency stated this is acceptable, and you should set criteria based on your manufacturing experience. The sponsor proposed protein sequencing and Western blot analysis for each band. The Agency stated that the proposed characterization is acceptable as long as specifications are set, and based on manufacturing experience.

8. *You have stated that (b) (4) are separated by IEF. These (b) (4) should be characterized, and acceptance criteria should be established for (b) (4).*
9. *A clear description of acceptance criteria is recommended for all release and stability tests. For example, the acceptance criteria for peptide mapping state that "incompatibility with the standard profile will not be considered as unacceptable criteria". This acceptance criterion is confusing and may not be correct in its intent.*

Question 2:

Protalix conducted forced degradation studies according to the procedure presented in Section 7.3. (b) (4)

Does the Agency agree that the design and analysis proposed for the forced degradation studies is appropriate for prGCD?

Agency Response:

No. The studies you have submitted have not adequately characterized all of the potential degradation pathways of prGCD. Your studies should include a variety of stressed condition (to allow aggregate formation, proteolysis, deamidation, oxidation or other means of protein degradation). The drug substance should then be characterized by the complete series of physical, chemical and functional assays used for characterization and release. The results of these analyses may demonstrate that additional validated assays will be required in the drug substance and product release, and stability testing programs.

Additional Discussion:

The sponsor clarified that stability testing with increased temperature, high and low pH and oxidation have been performed; however, deamination has not been assessed, but the sponsor plans to perform this testing. In general, the results show that the product is stable and has only been affected by pH (bicarbonate) and temperature, (b) (4)

(b) (4) The Agency stated that we would expect to see some denaturation at (b) (4) and recommend looking at lower temperatures, i.e. 37°C. The sponsor should also look at several time points at these temperatures. The Agency would also like to see degradation testing at multiple time points using all available analytical techniques. Please provide the results for all of the characterization and degradation studies in the NDA submission.

Question 3:

Protalix plans to conduct a Segment I Fertility and Early Embryonic Development to Implantation study in rats and Segment II Teratogenicity studies in rats and rabbits. prGCD is administered intravenously every two weeks in the clinic. However, to assure adequate exposure per ICH S6 guidance, Protalix proposes an exaggerated dosing schedule of twice per week for the Segment I study and on Gestation Days 6, 9, 12, and 15 for the Segment II studies.

Does the Agency agree with the proposed dosing schedules?

Agency Response:

Yes.

Additional Discussion:

The sponsor requested confirmation that the proposed dosing (1x and 5x the clinical dose) are acceptable, since these were accepted for the toxicology studies. The Division stated yes, the proposed dosing is acceptable.

Question 4:

Patient 10-003 experienced an immediate hypersensitivity reaction to prGCD within the first minutes of the first infusion, receiving only a few units of the investigational product. In addition, this patient subsequently experienced a hypersensitivity reaction when administered Cerezyme (see Appendix 1). Because of the extremely small portion of the dose actually received by the patient, Protalix proposes to exclude this patient from the Intent-To-Treat (ITT) population, which is defined as (b) (4)

Does the Agency agree with excluding this patient from the ITT population for analysis of efficacy?

Agency Response:

We agree that it would be unlikely that this patient, who received an “extremely small portion of the dose” of the study drug, would be evaluable for efficacy. Although it may be reasonable to exclude this patient from the primary efficacy analysis, the patient still needs to be considered in sensitivity analyses, such as the ones you have proposed in the Statistical Analysis Plan (SAP) on page 77 of the meeting package.

We additionally note that another patient, Patient 10-002 (CK), was withdrawn for safety reasons after the eleventh infusion. This patient will need to be included in the ITT analysis.

For the proposed definition of the Intent-to-treat (ITT) population as (b) (4) stated above (and in the SAP, Section 4 Analysis Populations, page 77 of the meeting package), please clarify whether (b) (4). Per previous correspondence for the Special Protocol Assessment (SPA) for Protocol PB-06-001 (dated 22 August 2007), the ITT population is to be defined as patients who are randomized and received at least one dose of study medication.

Question 5:

The Statistical Analysis Plan for Study PB-06-001 is attached as Appendix 2.

Does the Agency agree with the proposed analysis plan for Study PB-06-001?

Agency Response:

No. We cannot agree with the proposed statistical analysis plan (SAP) until the following issues are addressed:

1. **Include in the SAP a description of the MRI blinded evaluation, number of blinded readers, situation when the organ volumes differ by more than 5% between the two primary blinded readers, and definition of unevaluable images.**
2. **Include in the SAP a description of the derivation of the spleen and liver volumes from the MRI images.**
3. **Define the ITT population as subjects who received at least one dose of study medication and have at least the Screening/Baseline MRI evaluation.**
4. **Specify the ITT LOCF analysis as the primary efficacy analysis.**
5. **Clarify and state formulas for the null and alternative hypotheses that are stated in Section 7.1 (page 79 of the meeting packet).** (b) (4)

(b) (4) which is not consistent with your sample size calculations. Your current alternative hypothesis should be that the percent change is not equal to zero. If your alternative hypothesis is that percent change

- is not equal to zero, then the point estimate needs to be at least a 20% change in spleen volume. In addition, Section 3.1.1 should be consistent with your answer.
6. Since there may be “unevaluable” MRI images during the blinded read, describe how they will be handled in the data analysis. The definition of “unevaluable” image should also be described.
 7. We recommend that you test all four endpoints for each dose (primary efficacy and three secondary efficacy) using the following step-down procedure, which should be incorporated into the protocol as an amendment to the protocol, and the statistical analysis plan:
 - (a) First, test spleen volume at each dose with adjustment for the overall 0.05 alpha-level (Bonferroni adjustment as stated in statistical analysis plan is acceptable).
 - (b) If spleen volume is shown to be significant for either one or both doses, then proceed with testing the three secondary efficacy endpoints for that dose or doses with adjustment for the overall 0.05 alpha-level (Bonferroni adjustment as stated in statistical analysis plan is acceptable).
 - (c) Please clarify your understanding of the agreed upon efficacy endpoints for study PB-06-001.

Additional Discussion:

The sponsor stated that they intend to have change in spleen volume as the primary endpoint and the other three parameters as secondary endpoints, (b) (4)

(b) (4) The Division stated that all procedures for testing must be clearly stated in the SAP, and we must see the framework for all of the endpoints. What is missing from the current SAP is the overall testing procedure.

8. Perform the testing of the three secondary efficacy endpoints (percent change in liver volume, percent change in hemoglobin, and percent change in platelet count) for each dose separately and not for the combined sample across both doses (see Section 7.2).

Additional Discussion:

The sponsor stated that based on the anticipated enrolled patient population, patients are likely to have splenomegaly and low platelet counts, but may have normal liver size and no anemia. Thus, they are concerned that testing by dose would be too rigid. The Division stated that if you are to use different testing procedures for change in spleen volume and platelet counts than for hemoglobin and liver volume, (b) (4).

9. Sections 3.1.2 and 7.2 should be consistent in the nomenclature for the three secondary efficacy endpoints.
10. Present the MRI results by individual reader separately as a secondary analysis. Statistics describing reader agreement should be presented in the analysis.

11. All raw data from the three blinded readers, and a flag for those subjects who required an assessment by the third blinded reader need to be retained and submitted with the application.

Additional Discussion:

The sponsor stated that the MRI charter will be a separate document and will be referenced in the SAP. The Division requested that in addition to referencing the MRI charter in the SAP that the sponsor include a brief summary of the necessary MRI procedures and how the primary efficacy endpoint is derived from the MRI information in the SAP.

The sponsor stated that the Agency Response numbers 2, 3, and 4 (above) will be clarified in the SAP.

For Response #5, the Division clarified that for the null and alternative hypotheses typically these would be defined as, for example, the null would be less than or equal to zero and the alternative would be greater than zero, or if the null is less than or equal to 20%, then the alternative would be greater than 20%. The sponsor stated that their statistician could not attend the meeting and requested an additional discussion with the FDA statistician after preparation and submission of the MRI charter, and revision and submission of the SAP. The Division stated that a separate conversation will need to be arranged through the project manager, and any agreements reached during the discussion will need to be captured in writing.

Question 6:

Protalix has established a central MRI reading center for spleen and liver volume with (b) (4) The procedure for reading MRI has been validated (see Appendix 3).

Does the Agency agree that the MRI reading procedure is appropriately validated for the primary endpoint of change in spleen volume for Study PB-06-001?

Agency Response:

No. As previously communication in the Type B meeting on 21 February 2007, the MRI acquisition and read charter should be a separate document for each study (PB-06-001 and PB-06-002). We recommend additional documentation of the MRI reading procedures in the "Image processing and centralized analysis" section of the charter to address the following issues:

1. The number and timing of MRIs per subject.
2. The total number of independent, blinded readers (radiologists). We recommend no more than three blinded readers evaluate all study images.
3. That Baseline and treatment MRIs be evaluated using the same procedures.
4. That the same blinded readers evaluate all images.
5. At what point in time the MRIs are presented for evaluation.

6. How the images are blinded and presented to the readers (e.g. batch sizes, randomized presentation of images, when Baseline and treatment images are evaluated, etc.).
7. Description of the situation when the image results of the two independent blinded readers are not within the protocol specified 5% error margin for volume that they will be evaluated by a third blinded reader.
8. Include screen shots of the electronic Case Report Forms (eCRFs) that will be used. We also request that screen shots of the eCRFs that will be used be submitted for review.
9. Clarification that the independent radiologists who give final approval for the resulting liver and spleen contours are the same ones who will evaluate the images for volume calculation.
10. Clarify whether the same MRI reading procedures will be used for Study PB-06-002.

Additional Discussion:

The sponsor stated that they will submit the MRI charter with the revised SAP. The sponsor additionally stated that they will submit a validation report for the MRI procedures that they feel addresses all of the Agency's concerns.

Question 7:

Protalix proposes to conduct a clinical study to evaluate the safety of switching Gaucher disease patients from Cerezyme® to prGCD (Study PB-06-002, Appendix 3).

Does the Agency agree with the proposed endpoints?

Agency Response:

You propose to study the safety of prGCD after patients have switched from Cerezyme; however, this has little clinical meaning without some assessment of efficacy as well. Specifically, you will need to assess whether there is "deterioration" from Baseline (maintenance values on Cerezyme) in the patients' laboratory parameters (hemoglobin and platelet count) and liver and spleen size over the duration of the trial. Please propose pre-specified margins of change in these clinical parameters as representing meaningful deteriorations while on treatment with prGCD.

In addition, we recommend that this study be a head-to-head comparison of prGCD and Cerezyme to assist in interpretation of the results. We recommend that the study be a randomized, double-blind, active-controlled (with Cerezyme) study, where half of the patients will be randomized to continued treatment with Cerezyme, and the other half to treatment with prGCD. We recommend that you include at least 12 evaluate patients in each study arm.

Additional Discussion:

The sponsor stated that performance of Study PB-06-002 as proposed by the Division (above) would be logistically difficult. The Division stated that the study design proposed above is a recommendation, not a requirement, since an active comparator may make interpretation of the study results easier, particularly if there is any deterioration in any of the endpoints after transition to prGCD treatment.

Additional Comments:

1. Please submit a preliminary report on the Adverse Event (AE) results of patients who have been studied in Study PB-06-001. We are particularly interested in the number, types, and severity of hypersensitivity reactions that have occurred in patients treated with prGCD to date.
2. Clarify how many patients in Study-PB-06-001 have been treated; give a listing of each patient's total time on treatment in the study, and the number of infusions received.

Additional Discussion:

The sponsor stated that seven patients have been enrolled to date and treated for up to six months. Two patients have experienced allergic reactions (as described in the briefing package). There have been no other notable safety signals. The sponsor will submit to the IND a listing of Adverse Events (AEs) experienced by patients so far. The sponsor additionally stated that they plan to submit a protocol amendment in the near future to allow for: 1) infusion rate adjustment flexibility for hypersensitivity or infusion reactions; and 2) a revised hypersensitivity treatment algorithm for pre-treatment at the investigators' discretion. The sponsor will also submit a revised Investigator Brochure as requested.

3. It is stated in the Meeting Minutes of the Protalix Data Monitoring Committee (DMC) (on page 128 of the meeting package) that the DMC recommends updating the Informed Consent Form (ICF) to include the allergic reactions experienced with prGCD treatment. Please submit to us a copy of the updated ICF, and Investigator Brochure if applicable, when available.
4. Clarify that for Study PB-06-002 blood platelet count and hematology samples will be obtained at the same visits. For example, in the Study Flow Chart on page 111, it appears that even though you have made separate rows for platelet count and hematology, you plan to collect both of these laboratory parameters at the same visits; but on page 97 (Section 12.5. Visits 8 – 12), only samples for hematology, but not platelet count, are noted for collection.
5. Please include in the inclusion criteria of Study PB-06-002 that patients must have stable platelet counts and hematology levels, and liver and spleen size prior to study entry. Please propose acceptable ranges for these parameters to ensure that patients are clinically stable on Cerezyme treatment at study entry.

6. **For the secondary endpoints in the SAP for Study PB-06-001 (Section 3.1.2 Secondary Analyses, page 74), your proposal of the change in liver percent of 8%, change in hemoglobin percent of 12%, and change in platelet count percent of 33% are noted as acceptable.**
7. **Your recalculation of the sample size based on the 20% change in spleen volume is noted.**
8. **We have the following additional comments and recommendations for your future NDA submission:**
 - a. **The drug substance must be extensively characterized. We recommend that a large battery of physicochemical tests be utilized in addition to release tests. For example, orthogonal methods for the detection of aggregates should be used. Process-related impurities, and product-related impurities and substances should be characterized and controlled.**
 - b. **Real-time, real temperature stability data should be provided to support expiry for drug substance and drug product. For guidance, please refer to ICH Q5C "Stability testing of biotechnological/biologic products".**

Linked Applications

Sponsor Name

Drug Name

IND 69703

PROTALIX
BIOTHERAPEUTICS

PRGCD (PLANT EXPRESSED H
GLUCOCEREBROSID

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

/s/

HEE K LIANOS
05/07/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,703

Protalix Biotherapeutics
Attention: Glen Park, Pharm.D.
Senior Director, Clinical &
Regulatory Affairs
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase).

We also refer to the meeting between representatives of your firm and the FDA on February 21, 2007. The purpose of the meeting was to obtain guidance on the toxicology and clinical development program for prGCD.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Ryan Barraco
Regulatory Project Manager
Division of Gastroenterology
Office of Drug Evaluation III
Center for Drug Evaluation and
Research

Enclosure

Meeting Minutes

Meeting Type: B
Meeting Category: Other
Meeting Date and Time: February 21, 2007; 10:00 – 11:00 AM
Meeting Location: White Oak, Building 22
Application Number: IND 69,703
Product Name: prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase)
Received Briefing Package: January 22, 2007
Sponsor Name: Protalix Biotherapeutics
Meeting Requestor: Dr. Glen Park
Meeting Chair: Dr. Anne Pariser
Meeting Recorder: Mr. Ryan Barraco

FDA Attendees

Brian E. Harvey, M.D., Ph.D., Director, Division of Gastroenterology Products (DGP)
Anne Pariser, M.D., Medical Team Leader, DGP
Joanna Ku, M.D., Medical Officer, DGP
Ethan Hausman, M.D., Medical Officer, DGP
Ryan Barraco, Regulatory Project Manager, DGP
Sushanta Chakder, Ph.D., Acting Supervisory Pharmacologist, DGP
Tamal Chakraborti, Ph.D., Pharmacology Reviewer, DGP
Emanuela Lacana, Ph.D., Biologist, Division of Therapeutic Proteins (DTP)
David Jacobson-Kram, Ph.D., D.A.B.T., Associate Director for Pharmacology and Toxicology, Office of New Drugs
Mike Welch, Ph.D., Statistics Team Leader, Division of Biometrics V

Sponsor Attendees (Protalix Biotherapeutics)

David Aviezer, Ph.D., Chief Executive Officer
Yoseph Shaaltiel, Ph.D., Executive Vice President Research and Development
Einat Almon, Ph.D., Vice President Product Development

(b) (4)

Jules Mitchel, Ph.D., M.B.A., Regulatory Affairs, Target Health Inc.
Glen Park, Pharm.D., Regulatory Affairs, Target Health Inc.

1.0 BACKGROUND

Protalix Biotherapeutics submitted IND 69,703/ prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase) on June 15, 2005, and the IND was placed on clinical hold on July 15, 2005. PrGCD is being evaluated as a treatment for Gaucher disease. The sponsor is seeking guidance regarding the toxicology and clinical development program for prGCD to support a future NDA filing. The projected meeting outcome was for the FDA to provide comprehensive and meaningful responses to Protalix's questions.

2.0 DISCUSSION

1. Based on the previous communications with the Agency, the Sponsor understands that if the results of the 28-day and 3 month in life data of the 9-month Cynomolgus studies demonstrate a toxicological profile similar to the reference listed product Cerezyme, they will have met all toxicology requirements for the NDA.

Does the Agency agree that following submission of the final reports of the 28-day and 9-month Cynomolgus monkey studies no further toxicology studies will be required to support the NDA?

Response:

No. The similarity of the toxicity profile of prGCD to that of Cerezyme could not be established due to following reasons:

1. **There are wide differences in the tested doses used in the prGCD and Cerezyme studies. In the 13-week study conducted in Cynomolgus monkeys, Cerezyme was tested at 8-, 27- and 81-fold clinical dose (60 U/kg), whereas in the 9-month (39-week) study conducted in Cynomolgus monkeys, prGCD was tested at 1- and 5-fold the clinical dose (60U/kg). In addition, the dosing schedules were different. Cerezyme was administered once weekly, whereas prGCD was administered once every two weeks.**
2. **Your 13-week interim report of the 9-month (39-week) study in Cynomolgus monkeys does not contain gross pathology, organ weight, or histopathology data, which precludes any comparison of these parameters with Cerezyme. This report contains only the in-life data, and therefore cannot be considered adequate to fully describe the toxicity profile of prGCD during a 13-week treatment period.**
3. **The absence of a Cerezyme treatment group in the prGCD 28-day or the 9-month (39-week) study in Cynomolgus monkeys precludes a direct head-to-head comparison of the toxicity profile of your product to that of Cerezyme.**
4. **Cerezyme induced significant dose-related anti-drug antibody formation in all treated monkeys in the 13-week study. In contrast, there was no significant anti-prGCD antibody formation in Cynomolgus monkeys following 13 week treatment with prGCD (interim data from the 39-week study).**

Therefore, as previously recommended by the Division of Metabolic and Endocrine Products, you will need to conduct the following studies to support the marketing approval of prGCD:

- 1. Submit the full report of the 39-week (9-month) study in Cynomolgus monkeys with prGCD for our review and evaluation.**
- 2. Conduct a 9-month study in a rodent species.**
- 3. Conduct a Segment I Fertility and Early Embryonic Development to Implantation study in rats, and Segment II Teratogenicity studies in rats and rabbits.**

Summary of Discussion:

At the beginning of the meeting, the Sponsor provided the Division with a handout detailing their concerns with the responses to question 1. During the meeting, the Sponsor provided another handout with their rationale for dose selection for prGCD in Cynomolgus Monkeys. See attached.

We agree that the submission of the final report of the 39-week monkey study as part of a complete response to clinical hold will be reviewed, and the regulatory action will be based upon the data submitted. The ability to remove the clinical hold from this IND is not dependent upon the issue of similarity to the Cerezyme product. We commit to continue dialogue to move this development program forward, which will include internal FDA discussions on relevant pharmacology/toxicology issues.

2. Protalix met with the Division of Metabolism and Endocrinology Products (DMEP) for a pre-IND meeting 30 June 2004 and discussed the design of the pivotal clinical trial. Protalix proposed to conduct one pivotal trial with 30 patients. The Division agreed that this could be sufficient clinical experience to support the NDA if the results were sufficiently robust, statistically significant and the safety profile is adequate.

Protalix is submitting for the Division's review a Phase III protocol in which issues raised previously by the DMEP are addressed. Protalix is planning to initiate this study following agreement by the Division to lift the partial clinical hold and agreement on the currently submitted protocol. This will be a multi-center, randomized, double-blind, parallel group trial to assess the safety and efficacy of prGCD at two dose levels in 30 untreated patients with Gaucher disease. Patients will receive IV infusion of prGCD, either 30 or 60 units/kg, every two weeks. The duration of the study will be nine months. At the end of the 9-month treatment period (21 visits, 38 weeks) eligible patients will be offered enrollment in an open-label extension study.

Does the Agency agree that the proposed study design is adequate to evaluate the safety and efficacy of prGCD for the NDA?

Response:

In general, your proposed study design appears to be adequate; however, the labeling indication for prGCD will be limited to the patient population included in your clinical development program and submitted to the NDA (please see responses to Question 6 and Additional Comments for additional discussion of this issue).

We have the following additional comments and recommendations regarding your proposed study protocol:

1. Inclusion/Exclusion Criteria

- a. Inclusion criterion #2 states that patients must have (b) (4), Please clarify what is meant by (b) (4).”
- b. Clarify whether you will be performing genotypic analyses on all enrolled patients at Screening/Baseline.
- c. Clarify that you intend to limit study participation to patients with Gaucher disease type 1. Exclusion criteria should state the exclusion of patients with neurologic manifestations of Gaucher disease (i.e., Gaucher disease type 2 and 3 patients) from study participation.
- d. Patients who have experienced severe hypersensitivity reactions while receiving Cerezyme® or Ceredase®, or who were discontinued from previous treatment with Cerezyme® or Ceredase® for safety reasons should be excluded from participation in this study.

2. Study Procedures

- a. As this is the first-in-disease-state administration of prGCD to Gaucher patients, the first three patients should receive their first doses of prGCD on a staggered schedule. For example, the first patient is to be treated, followed by an interval of at least several days prior to treatment of the second patient, and then an interval of at least several days is to occur prior to the treatment of the third patient. Should these three patients appear to tolerate treatment reasonably well, other patients may be treated at unspecified intervals thereafter.

ODE III/Division of Gastroenterology Products
IND 69,703

Confidential
3/22/2007
Type B Meeting

- b. In order to minimize the risks to patients of hypersensitivity/infusion reactions, we recommend that prGCD administration occur at a slower infusion rate for the first few administrations of the product to the first few patients. We suggest that you lower the initial infusion rates, with plans to increase the infusion rates in a step-wise manner. Should prGCD be demonstrated to be tolerated at higher infusion rates (based on available data), a higher infusion rate may be considered for later infusions, and in subsequent patients.
- c. Perform more frequent vital signs checks (e.g., at 15-minute intervals) during the first hour of each infusion, then at less frequent intervals (e.g., 30-minute intervals) after the first hour if patients tolerate the infusion.
- d. We recommend that you conduct follow-up phone calls the day after infusion for the first few infusions in at least the first few patients to ensure adequate monitoring for possible delayed-hypersensitivity or other delayed adverse reactions.
- e. Screen patients for other causes of anemia at Screening (e.g., hypothyroidism, B12/folate deficiency, and iron deficiency) in order to avoid confounding variables for anemia.
- f. Clarify whether follow-up skeletal x-ray evaluations will be performed during the study (e.g., at study conclusion). If not, please clarify how the Baseline x-ray information will be used.
- g. You are currently proposing monitoring for anti-prGCD IgG antibody formation at Screening/Baseline, (b) (4). We recommend that you collect earlier and more frequent samples to assess immunogenicity. We suggest that you perform IgG antibody monitoring at Baseline/Day 0 in all patients (regardless of previous glucocerebrosidase-exposure status), at Week 2, and at monthly intervals thereafter.

3. Safety Monitoring

- a. Include a clear algorithm for the diagnosis and treatment of hypersensitivity/anaphylactic/anaphylactoid reactions in the study protocol. This should include signs and symptoms of hypersensitivity reactions (such as upper limits of normal for vital signs, rash, etc.), and a stepwise series of measures to be taken should patients develop these reactions.

ODE III/Division of Gastroenterology Products
IND 69,703

Type B Meeting

Confidential
3/22/2007

Anti-prGCD IgE antibody collections should also be performed in patients experiencing severe or recurrent hypersensitivity reactions, for whom IgE antibody formation is suspected.

- b. Expected concomitant medications (such as medications used to treat hypersensitivity reactions), and prohibited concomitant medications (such as imiglucerase or other enzyme replacement therapies) should be listed in the study protocol.**
- c. Define stop criteria for the overall study and for individual patients. Stop criteria for the overall study could include wording such as:**

“The study will be stopped and a safety review conducted if any of the following events occur:

- WHO Grade 3 toxicity is experienced by two or more patients;**
- WHO Grade 4 toxicity is experienced by one or more patient(s).”**

4. Study Endpoints and Study Design

- a. We recommend that two independent readers read all the images in a totally randomized fashion, and that their results be analyzed separately. The central readers for the MRI volumetric analyses should be blinded to study drug, treatment group, image sequencing (i.e., visit number and patient identification), and patient clinical history and response.**
- b. Safety concerns of particular interest to this study should be included in the safety (or other, such as exploratory) analysis, such as IgG antibody results, hypersensitivity reactions, and bone events.**
- c. Specify how many study centers and how many patients will be included in QCSI monitoring.**
- e. The primary outcome is stated as mean change from Baseline in spleen volume; however, the power analysis is presented in terms of percent change from Baseline volume. Please clarify the primary endpoint, and justify the anticipated effect size both in absolute and relative scales.**
- f. We recommend that the primary statistical analysis evaluate each dose group separately. To increase precision, an**

ODE III/Division of Gastroenterology Products
IND 69,703

Type B Meeting

Confidential
3/22/2007

ANCOVA procedure can be used with Baseline spleen volume as covariate. The Type I error rate should be controlled for the multiple comparisons. Secondary analysis will be considered exploratory.

- g. If confirmatory efficacy is intended for secondary endpoints, you will need to include in your statistical analysis plan a proposal for evaluating these endpoints in a statistically rigorous manner that accounts for multiplicity.**
- h. Use of LOCF to impute missing data may be problematic. You should conduct several sensitivity analyses to show that the study results are not sensitive to the imputation method and that the LOCF assumptions are supported. LOCF may not be appropriate, for example, in the case where a reduction in the efficacy endpoint is obtained early but the study subject has dropped out of the study due to adverse events; in such case, penalty for the patient's early drop out would not be accounted for by the LOCF method. We recommend assigning a no-change value to early drop-outs.**
- i Interim analyses procedures need to be clarified; interim efficacy analyses that may impact study operations or could compromise unblinding of study data would require appropriate control of type I error spending.**

Clarify how the DSMB will be performing the interim safety analysis, (e.g., how the DSMB will be chartered and composed, how the blind will be maintained, what data will be reviewed, and how recommendations to the Sponsor will be made).

We refer you to the Agency's Guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees for additional information on DSMBs.¹

- j. You plan to collect hematology blood work at Screening and at Baseline. An inclusion criterion for the study is the presence of thrombocytopenia and/or anemia. Please clarify whether or not the Baseline value for platelets or hemoglobin could disqualify patients from continued study participation if the latter value does not continue to meet the inclusion criterion for the hematology parameters. It would be our preference that all randomized patients remain in the study (unless there**

¹ U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER). Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees. March 27, 2006. <www.fda.gov/cder/guidance/3626fn1.pdf>.

ODE III/Division of Gastroenterology Products
IND 69,703

Type B Meeting

Confidential
3/22/2007

is a safety issue that precludes their continued participation), and be included in the intent-to-treat (ITT) analysis.

- k. Your current protocol states that the ITT population is defined as patients [REDACTED] (b)(4). We request that instead you define ITT population as all patients who are randomized.

- l. Submit a statistical analysis plan for the study.

5. Other

At the time of submission of your revised study protocol, please also submit copies of the sample Informed Consent form, and copies of the Case Report Forms (CRFs) you intend to use in the study for the Division's review.

3. Does the Agency agree that administration of two dose levels of prGCD (30 and 60 units/kg) in a double-blind, randomized, parallel design will provide useful dosing information for labeling?

Response:

Yes.

4. Does the Agency agree that evaluation of reduction in spleen volume using Magnetic Resonance Imaging (MRI) read by a blinded reader(s) following a validated protocol from Baseline is an appropriate primary endpoint?

Response:

Please clarify the proposed MRI method for measuring changes in spleen volume, and justify the use of MRI with regard to both precision and accuracy as compared to other modalities. You should include a description of the measuring procedure used (e.g., manual placement of templates and/or automation methods), imaging sequences applied, anticipated use of contrast media, and inter- and intra-reader variability anticipated on measurement outcomes.

Experience with other glucocerebrosidase products has shown that enzyme replacement therapy (ERT) with glucocerebrosidase would be expected to increase hemoglobin levels and platelet counts, and to decrease liver and spleen size. Based on this experience, we would expect to see clinically meaningful changes in these parameters with treatment of Gaucher disease type 1 patients with prGCD. Therefore, you should designate an appropriate primary endpoint and major secondary endpoints for this study to ensure

ODE III/Division of Gastroenterology Products
IND 69,703

Type B Meeting

Confidential
3/22/2007

appropriate labeling of your product (see answers to Question #2: Study Endpoints and Study Design).

5. Protalix plans to conduct an interim analysis of safety after ten patients have completed 3 months of treatment with prGCD in the pivotal study. Based on the results of this analysis, Protalix plans to seek the Division's guidance on the design of a protocol for an open label extension study for continued therapy with prGCD following completion of the pivotal study. Protalix proposes to design the extension study to allow home therapy based on an acceptable ongoing safety profile in the pivotal study.

Does the Agency agree that, in principle, this would be appropriate at that stage of development?

Response:

Yes, in principle, home therapy could be considered for ongoing, open-label treatment in the extension study based on an acceptable safety profile for prGCD in the proposed Phase 3 study. You will need to establish pre-specified criteria to qualify individual patients for prGCD home therapy based on objective safety criteria, and to develop a safety and efficacy monitoring plan for these patients during home therapy in the extension study.

6. Based on an acceptable ongoing safety profile in the pivotal study, under what conditions would the Agency consider reducing the lower age limit below 18 years?

Response:

It is likely that your product will be used in Gaucher disease patients of any age post-approval; therefore, we encourage you to include pediatric Gaucher disease patients in your clinical development program. However, as there is currently no safety and efficacy information for prGCD in the Gaucher disease population, the exposure of pediatric patients to prGCD should not occur until after a reasonable amount of safety and efficacy information with prGCD has been obtained in adult Gaucher disease patients (≥ 18 years of age).

Our main safety concern at this time with the administration of prGCD to Gaucher disease patients is the potential immunogenicity of this product. There would need to be sufficient immunogenicity and safety data (such as anti-prGCD antibody formation and hypersensitivity reactions) obtained and evaluated in the adult patient population prior to proceeding with administration of prGCD to the pediatric patient population. Once there is enough evidence to suggest that prGCD is reasonably safe for use in adult Gaucher disease patients, it would be reasonable to proceed with pediatric enrollment, either in the proposed study or in a separate study.

We suggest that you develop an overall pediatric clinical development plan. We remind you that all pediatric studies will need to include a plan for monitoring and assessing growth and development as part of the study protocol. Pediatric studies need not be completed at the time of initial NDA submission; however, under PREA it is likely that pediatric studies will be required as post-marketing commitments as a condition of approval.

Additional Comments:

1. To as great an extent as possible, your overall clinical development program for prGCD should reflect the expected post-approval use of prGCD. If you plan to conduct only one study in ERT-treatment naïve patients with Gaucher disease type 1 in support of an NDA submission, then the labeling indication for your product will likely be limited to this patient population. Therefore, we recommend that you develop an overall clinical development program for prGCD, and that you plan to perform additional clinical studies that would broaden your labeling indication for prGCD, including:
 - Patients previously exposed to Cerezyme® or Ceredase®, or on maintenance therapy with Cerezyme® (or Ceredase®). These patients should be included in this study regardless of their anti-glucocerebrosidase IgG antibody status at Baseline. Should prGCD receive NDA approval, it is likely that patients failing or intolerant of Cerezyme® treatment may be switched to treatment with prGCD in clinical practice; therefore, the pre-marketing evaluation of prGCD for this anticipated situation is recommended.
 - Pediatric patients should be included in clinical studies with prGCD (see response to Question #6).
2. Twelve months of study medication administration is typically required for a long-term treatment indication for a chronic disease. Ongoing, longer-term, open-label safety studies are also typically in progress at the time of NDA submission for products intended for chronic, possibly life-long administration. Long-term evaluation is of particular interest for protein products, such as prGCD, for which antibody formation is expected, as an assessment of maintenance of treatment effect despite antibody formation may need to be demonstrated. Plans to evaluate bone disease in all age groups, and growth and development in pediatric patients over the long-term will also need to be developed
3. As prGCD will likely be used in female patients of child-bearing potential, we recommend that you design and implement a pregnancy registry as early as

ODE III/Division of Gastroenterology Products
IND 69,703 Type B Meeting

Confidential
3/22/2007

possible in your clinical development program (see FDA Guidance: Guidance for Industry: Establishing Pregnancy Exposure Registries²).

4. Provide a complete description of your immunogenicity assays. Such assays must be developed to be specific, sensitive and reproducible. The assay should be able to detect all classes of immunoglobulins, particularly IgM and IgG. If clinical issues pertaining to hypersensitivity are observed, it will be important to develop an IgE specific assay. For the current thinking on immunoassay development, please see the following references:
 - Mire-Sluis AR, Barret, YC, Devanarayan V, et al. "Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology products." J Immunol Methods. 2004; 289(1-2): 1-16.
 - Shankar G, Shores, E, Wagner C, Mire-Sluis, A. "Scientific and regulatory considerations on the immunogenicity of biologics." Trends Biotechnol. 2006; 24(6): 274-80.
5. You are currently using an inhibitor compound of prGCD as a positive control for your neutralizing assay. By using this control, you will not be able to quantify the sensitivity of the assay in terms of mass units of neutralizing antibody. In addition, this inhibitor is unlikely to be subject to the same modifying influences as that of antibody, and the robustness of the assay cannot be evaluated. Please develop a neutralizing antibody as an appropriate positive control for the neutralization assay.

Additional Discussion:

The Sponsor stated that they have reviewed the Division's clinical responses, the responses are clear, and they have no questions regarding these responses. The Sponsor intends to revise the clinical protocol for the proposed phase 3 study, and to submit this study for the Division's review as a Special Protocol Assessment.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Not Applicable

² US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry, Establishing Pregnancy Exposure Registries. August 2002. <www.fda.gov/cder/guidance/3626fnl.pdf>

ODE III/Division of Gastroenterology Products
IND 69,703 Type B Meeting

Confidential
3/22/2007

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Not Applicable		

5.0 ATTACHMENTS AND HANDOUTS

Points for Discussion
Protalix/FDA Meeting
prGCD (IND 69,703)
February 21, 2007

1. It was our clear understanding that the 28-day study in Cynomolgus monkeys with daily dosing was the pivotal study to get off clinical hold for chronic dosing in humans.
2. It was also our clear understanding that the dose level and frequency of dosing in the toxicology studies was in complete agreement with the Agency in all of our communications since our pre-IND discussion in 2004, including extensive discussion following the filing of the IND and the notification of the Partial Clinical Hold.
3. The multiples of the clinical dose cited by the Agency for the Cerezyme 13-week Cynomolgus monkey study are not understandable to us and we would like to obtain clarification on the actual doses administered (in U/kg or mg/kg).
4. In the Agency's response, you have commented on the lack of immunogenic response in the data submitted so far. We will be submitting the full report of the 9-month study by the middle of March. In recently obtained data from this study we have observed an antibody response over the course of the 9-month study, consistent with that observed in the 28-day Marmoset study. We believe that, to the best of our knowledge, this study demonstrates similarity to Cerezyme and will allow the Agency to bridge to the previous determination of safety.
5. Based on all discussions with the Agency, standard toxicological practices with regard to study design, and the study results in two primate species, we see no reason why we should remain on clinical hold.

ODE III/Division of Gastroenterology Products
IND 69,703 Type B Meeting

Confidential
3/22/2007

Rationale for dose selection for prGCD in Cynomolgus Monkeys

Dose (U/kg)	Cerezyme* (U/kg)	prGCD (U/kg)	prGCD (mg/kg)
Low Dose	60 (1 times HTD)	180 (1 times clinical dose)**	5.6
High Dose	300 (5 times HTD)	900 (5 times clinical dose)**	27.8

*Cerezyme NDA Pharmacology Review (single dose study)

**Adjusted for body surface area

FDA Pharmacology Reviewer Cerezyme Doses

Dose (U/kg)	Cerezyme	Estimated Delivered Volume (mL/kg)
Low	480	3
Mid	1620	10
High	4860	30

Maximum estimated solubility = 165 U/mL

Maximum volume (Cyno) per dose = 10 mL/kg

Maximum dose per day (Cyno) = 1650 U/kg

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

/s/

Ryan Barraco
3/22/2007 11:07:10 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,703

Protalix Biotherapeutics
Attention: Glen Park, Pharm.D.
Senior Director, Clinical &
Regulatory Affairs
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase).

We also refer to the meeting between representatives of your firm and the FDA on November 29, 2006. The purpose of the meeting was to obtain guidance with regards to the appropriate chemistry, manufacturing, and controls (CMC) to support a Phase 3 clinical study and a future NDA filing.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Ryan Barraco
Regulatory Project Manager
Division of Gastroenterology
Office of Drug Evaluation III
Center for Drug Evaluation and
Research

Enclosure

Meeting Minutes

Meeting Type: C
Meeting Category: Chemistry, Manufacturing and Controls
Meeting Date and Time: November 29, 2006; 2:30 – 3:30 PM
Meeting Location: White Oak, Building 22
Application Number: IND 69,703
Product Name: prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase)
Received Briefing Package: October 26, 2006
Sponsor Name: Protalix Biotherapeutics
Meeting Requestor: Dr. Glen Park
Meeting Chair: Dr. Anne Pariser
Meeting Recorder: Mr. Ryan Barraco

FDA Attendees

Joyce Korvick, M.D., M.P.H., Deputy Director, Division of Gastroenterology Products (DGP)
Anne Pariser, M.D., Medical Team Leader, DGP
Joanna Ku, M.D., Medical Officer, DGP
Ryan Barraco, Regulatory Project Manager, DGP
Emanuela Lacana, Ph.D., Biologist, Division of Therapeutic Products (DTP)
Gibbes Johnson, Ph.D., Chief, Lab of Chemistry, DTP

Sponsor Attendees (Protalix Biotherapeutics)

David Aviezer, Ph.D., Chief Executive Officer
Yoseph Shaaltiel, Ph.D., Executive Vice President Research and Development
Einat Almon, Ph.D., Vice President Product Development
Daniel Bartfeld, Ph.D., Director Protein Chemistry
Sharon Hashmueli, Ph.D., Project Leader
Raul Chertkoff, M.D., Medical Director

(b) (4)

Jules Mitchel, Ph.D., M.B.A., Regulatory Affairs, Target Health Inc.
Glen Park, Pharm.D., Regulatory Affairs, Target Health Inc.

1.0 BACKGROUND

Protalix Biotherapeutics submitted IND 69,703/ prGCD (Plant Cell Expressed Recombinant Human Glucocerebrosidase) on June 15, 2005, and the IND was placed on clinical hold on July 15, 2005. prGCD is being evaluated as a treatment for Gaucher disease. The sponsor is seeking guidance regarding the appropriate chemistry, manufacturing, and controls (CMC) to support a Phase 3 clinical study and a future NDA filing. The projected meeting outcome was for the FDA to provide comprehensive and meaningful responses to Protalix's questions.

2.0 DISCUSSION

Protalix is continuously working to improve the production process of prGCD drug substance and drug product. (b) (4)

(b) (4)

(b) (4)

Protalix is seeking Agency guidance on which changes would require FDA consultation prior to implementation?

Response:

You will not require our consultation to make changes that improve the quality of your product. However, when clinical data are submitted in support of an NDA using product manufactured by different processes, the NDA must include a study comparing the drug substance (DS) and product (DP) obtained with the improved manufacturing process to the DS/DP manufactured with the previous process(es). Such studies should contain all the characterization and release tests in use for the DS as well as head-to-head forced degradation studies to demonstrate consistent product degradation kinetics.

Summary of Discussion:

For the degradation studies, we prefer gradual degradation studies and that these studies are not limited to elevated temperature studies only.

2. Protalix has established a functional Master Cell Bank but has not yet established a Working Cell Bank which meets Protalix's requirements (see Appendix I). (b) (4);

(b) (4)

. Does the FDA agree that this is an acceptable strategy?

Response:

No. [REDACTED] (b) (4)
[REDACTED] **It is therefore our recommendation that a Working Cell Bank (WCB) fully characterized and representative of the Master Cell Bank (MCB) should be developed immediately.** [REDACTED] (b) (4)
[REDACTED]

Summary of Discussion:

The FDA and sponsor are in agreement with the sponsor's proposal to use the Master Cell Bank.

3. A formal validation plan for the drug substance and drug product release and stability methods has been developed and formal validation is being performed using an in-house reference standard. It is the sponsor's proposal to initiate the Phase III clinical study and concurrently complete validation of the test methods. Does the Agency agree with this proposal?

Response:

Yes. At this time, qualified test methods are acceptable. All assays submitted in support of an NDA must be fully validated.

4. The FDA requested that the sponsor analyze mannose content and glycan structure. Therefore, Protalix has performed analyses on prGCD batches of the drug substance using the M-scan methods (FAB-MS, MALDI-TOF MS, DE-MALDI-TOF MS) for both glycan structure and monosaccharide content, including mannose, and in addition glycan structure analysis was performed by [REDACTED] (b) (4) [REDACTED] (b) (4) using sequential digestion followed by HPLC and MALDI-MS (see Appendix II). Protalix plans to periodically analyze future batches and include the results in the IND annual report. Does the Agency agree with this proposal?

Response:

Yes. However a quantitative assay which assesses carbohydrate structure should be included in release testing and in stability studies.

Summary of Discussion:

The "Yes" answer was clarified to mean that the sponsor can periodically submit analyses of future batches to the IND annual report.

5. The FDA requested that the sponsor add Silver Stain Analysis of SDS-PAGE gels to the stability protocol for the drug product, however Protalix has experienced difficulties validating the test method, as it is very sensitive. Therefore Protalix proposes RP-HPLC as an alternative stability test method, which is adequate and specific for monitoring the stability of the drug product, as it can trace peptides that appear via unstable product degradation (see Appendix III). Does the Agency agree with this proposal?

Response:

Yes. In addition, Coomassie staining of SDS-PAGE is often successfully validated.

6.

the Agency agree with this proposal?

Response:

No. Protein content should be measured for release of DS and DP, and used to determine dose. prGCD potency must be measured by the determination of the kinetic parameters K_m and k_{cat} using a physiologically relevant substrate. This potency assay must be used in your release and stability protocols. We encourage you to seek FDA guidance prior to submitting your marketing application. Guidance on manufacturing of biologics can be found on the International Conference on Harmonization website, <http://www.ICH.org> (Q2,5, 6, 7, and 8) and on the FDA website, <http://www.fda.gov/cder/guidance/index.htm>

Additional Comments:

- **Regarding DS and DP release specifications, we find that you do not have adequate tests to determine product quality. Specifically, you should add the following tests:**
 - a. **Determination of biological activity of prGCD should be assessed for both release and stability. We recommend that assays measuring receptor binding and cellular uptake of prGCD be developed and implemented.**

Summary of Discussion:

The Agency stated that it is extremely important to demonstrate biological activity for each lot of prGCD.

- b. **Your release specifications for DS and DP do not include tests for the presence of aggregates. Please indicate which tests have been performed for prGCD aggregates. If the test is SE-HPLC, indicate how the test was**

determined appropriate for the detection of aggregates. Orthogonal methods for aggregate detection and quantification should be used for SE-HPLC validation.

- c. SDS-PAGE and IEF cannot serve as identity assays. An alternative assay that uniquely identifies this protein must be included for DS and DP release (e.g., Western blotting, peptide mapping, etc.)
- d. SDS-PAGE, IEF and RP-HPLC along with a test for aggregates, should be used to determine product purity.

- Regarding DS and DP stability:

- a. Storage/hold times for [REDACTED] (b) (4) need to be validated prior to NDA submission. (b) (4)
- b. All tests used to characterize the prGCD DS should be evaluated for stability indicating potential.
- c. The design of the study to evaluate the stability of the reconstituted drug product in either the vial or the infusion bag should be reflective of the intended clinical use.
- d. Please refer to ICH Q5C for guidance on stability studies for biotechnology products.

- Regarding cell banks characterization:

- a. More detailed information as to which cell line was selected, and how the master cell bank was created and characterized needs to be provided. For guidance, please refer to ICH Q5B.
- b. Detailed information as to the exact method(s) used and the specific adventitious agents, pathogens, molds and fungi that were tested should be provided.

- Please clarify your overall clinical development plan for prGCD. In particular, please comment on the following:

- When do you intend to submit a response to the partial clinical hold?
- When do you plan to initiate additional human studies?
- How do you plan to resolve the clinical issues that were raised in previous meetings with the Division of Metabolic and Endocrine Products (DMEP)?

Summary of Discussion:

- The sponsor stated that they plan to submit a Complete Response to Clinical Hold approximately January 2007.
- The sponsor plans to submit an End-of-Phase 2 meeting request in the near future. The briefing package will include a proposed Phase 3 protocol, and the issues raised in the DMEP meeting are addressed in the protocol.

To assist you in resolving these issues, we recommend that you request an additional meeting to discuss the design of any planned clinical studies prior to their initiation.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Not Applicable

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit a Complete Response to the Clinical Hold	Protalix Biotherapeutics	Approximately January 2007
Submit an End-of-Phase 2 meeting request	Protalix Biotherapeutics	No Due Date

5.0 ATTACHMENTS AND HANDOUTS

Not Applicable

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

/s/

Ryan Barraco
12/21/2006 11:57:44 AM

Ethan Hausman
12/21/2006 12:34:55 PM
Signing for Anne Pariser, MD, Medical Team Leader



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 69,703

Target Health, Inc.
Attention: Jules T. Mitchel, Ph.D.
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Mitchel:

Please refer to your Pre-Investigational New Drug Application (PIND) file for prGCD (plant expressed human recombinant glucocerebrosidase) Injection.

We also refer to the meeting between representatives of your firm and the FDA on June 30, 2004. The purpose of the meeting was to obtain Agency guidance regarding the chemistry, non-clinical, and clinical requirements needed to support an IND submission for prGCD.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Pat Madara, regulatory project manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Deputy Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 30, 2004
TIME: 1:30 PM
LOCATION: Parklawn Building, Potomac Conference Room
APPLICATION: PIND 69,703
DRUG NAME: prGCD (plant expressed human recombinant glucocerebrosidase)
TYPE OF MEETING: Type b (pre-IND)

MEETING CHAIR: Mary Parks, M.D.

MEETING RECORDER: Pat Madara

FDA ATTENDEES:

Division of Metabolic and Endocrine Drug Products (DMEDP)

- | | |
|--------------------------------|------------------------------------|
| 1. Mary Parks, M.D.; | Deputy Director |
| 2. William Lubas, M.D., Ph.D.; | Medical Officer |
| 3. Karen Davis-Bruno, Ph.D.; | Pharmacology/Toxicology Supervisor |
| 4. Todd Sahlroot, Ph.D.; | Biometrics Team Leader |
| 5. Pat Madara, M.S.; | Regulatory Project Manager |

Office of New Drug Chemistry, Division of New Drug Chemistry

- | | |
|-----------------------------|----------------------------------|
| 1. Blair Fraser, Ph.D.; | Supervisory Chemist |
| 2. Stephen K. Moore, Ph.D.; | Chemistry Team Leader I in DMEDP |

EXTERNAL CONSTITUENT ATTENDEES:

Protalix Biotherapeutics

- | | |
|-----------------------------|-----------------------------|
| 1. David Aviezer, Ph.D.; | Chief Executive Officer |
| 2. Yoseph Shaaltiel, Ph.D.; | VP R&D |
| 3. Daniel Bartfeld, Ph.D.; | Director, Protein Chemistry |
| 4. Sharon Hashmueli, Ph.D.; | Project Leader |

Consultant

[Redacted] (b) (4)

[Redacted] (b) (4)

Target Health, Inc.

[Redacted] (b) (4)

- 2. Amy Lau, MPH; Director of Biostatistics and Data management
- 3. Jules T. Mitchel, Ph.D.; Regulatory Affairs

BACKGROUND:

The sponsor is currently developing human recombinant glucocerebrosidase, expressed in carrot root cells (prGCD) grown in a bioreactor. This is an intravenous (IV) product for treatment or prevention of Gaucher disease. The purpose of this meeting was to obtain Agency guidance regarding the chemistry, non-clinical and clinical requirements needed to support submission of an IND. The sponsor submitted specific questions for discussion. In addition, discussion of these questions led to further questions, comments and exchanges.

DISCUSSION POINTS:

Question #1:

[Redacted] (b) (4)

Agency Response:

[Redacted] (b) (4)

(b) (4) *The Agency emphasized the need for consistency and reproducibility in all stages of the manufacturing process.*

Related Sponsor Comments:

- The sponsor does have a master cell bank [Redacted] (b) (4)

[Redacted] (b) (4)

Question #2:

It is the intention of the sponsor to use the single-dose and 28 day repeated dose studies to support the IND. Does the FDA agree?

Agency Response:

The proposal to use single dose and one month repeated daily dose studies to support the initial single dose clinical trial appears to be an acceptable approach. The animal dosing of 1X and 5X clinical should be based on exposure multiples (not mg/kg/day); the minimal numbers of monkeys evaluated should be 4/sex/group with full toxicology assessments (i.e. including histopathology). The toxicology studies should be designed to establish frank toxicity in addition to a no effect level. An assessment of immunogenicity is needed which includes antibody characterization if detected.

Questions #3:

It is the intention of the sponsor to initiate the Phase III clinical trial at the 3-month point of the 9-month monkey study. Does the FDA agree?

Agency Response:

Generally the toxicology data should support the dose and duration you plan for your clinical study. Clinical development should not proceed beyond the supporting toxicity data. The sponsor plans to submit 3 month interim data of the in-life portion of the chronic monkey toxicology study (with dosing every 2 weeks) which would be equivalent to 6 clinical doses but would not include histopathology. The adequacy of this plan depends on outcome of the one month monkey toxicity study with daily dosing. The 3 month interim data from the definitive 9 month monkey toxicity study should be provided before initiation of a Phase III clinical trial. Immunogenicity testing should continue throughout the toxicology program.

Question #4:

It is the intention of the sponsor to propose one pivotal clinical trial with 30 patients to support the NDA. Does FDA agree?

Agency Response:

There may be no problem using 30 patients as long as the results are sufficiently robust, statistically significant and there is an adequate safety profile.

For the Phase I trial, the Agency has no problem with the design as long as the Pharm/Tox results support the doses.

For the pivotal trial, the primary endpoint is not adequate. The sponsor must use clinically relevant endpoints. (examples include hemoglobin, platelet count or organ volume) All endpoints will be evaluated separately and changes in these endpoints should overall be supportive of a clinical benefit associated with product use.

If decreases in organ volume are selected, the radiographs must be read by a radiologist who is blinded to patient ID, treatment group and time sequence of radiographs.

Patients must be at least 18 yrs or older.

The Agency asked if the sponsor had considered the possibility of dosing once per month as another potential treatment arm.

Also, the Agency asked what differences the sponsor expected to see between the treatment groups.

The Agency asked if the enzyme contained plant derived sugars, not found in humans, since these may be immunogenic.

Sponsor Response and Comments:

(b) (4)

- With regard to the treatment groups, the sponsor expects a high clinical success rate as measured by 10% organ volume decrease from baseline. The low dose may be as effective as the high dose.

(b) (4)

- The sponsor noted that there was the possibility that some plant specific sugars may be present, but they were planning to do a more thorough analysis of the sugars to better characterize them.

Agency Responses and Comments:

To do an interim analysis, would require that a statistical penalty be applied. However, statistical significance at the interim analysis based on data from (b) (4); would not be sufficient for regulatory approval. Final regulatory approval will be based on the totality of efficacy and safety data from the 30 randomized patients.

The Agency questioned the need for a placebo group and recommended a Cerezyme arm. The purpose of the Cerezyme arm would be to collect descriptive data. The arm would not be used for statistical inference. Examples justifying no placebo included the Zavesca trials (Zavesca arm/Cerezyme arm/combination arm).

The Agency questioned possible utility in doing a maintenance study in which patients were switched from Cerezyme to prGCD.

The Agency reminded the sponsor that how the study was conducted would dictate how the product would be labeled. It was pointed out that the response obtained in this trial, in an drug naïve, severely effected study population, may not be indicative of the response which would be seen in the general population of patients with Gaucher Disease.

Sponsor Responses and Comments:

- The sponsor questioned the possibility of using data from other clinical trials involving Cerezyme.
- The sponsor pointed out that randomizing naïve patients to Cerezyme was not required in other trials. Also, they reiterated the difficulty in finding patients with severe disease (which was not done for the Zavesca trials). They are looking for patients with disease severity comparable to those in the Genzyme trials 10 years ago.
- The sponsor suggested that a maintenance type of trial would have to wait until the results of the initial trials were analyzed.

Agency Comments:

The Agency pointed out that the Cerezyme trials were compared to Ceredase. If there was no control, the study design would be similar to that of Ceredase. Also, there may be a problem determining the clinical relevance of decreases in organ volume. For example, Zavesca saw decreases in organ volume but did not see a benefit in terms of hematological parameters. The Agency asked how the data would be analyzed.

Sponsor Responses and Comments:

- The sponsor suggested they could analyze hematological parameters, in addition to organ volume. They will initially combine the groups to look at efficacy, then follow this analysis by comparing the groups for the purpose of analyzing dose response. The goal of the combined-group analysis strategy for the organ volume endpoint is to show that the upper bound of the 2-sided 95% confidence interval for the mean percent change from baseline in organ volume excludes zero. The rationale for using zero is that untreated patients, absent other confounding diseases, don't experience a decrease in organ volume as part of the natural history of their disease progression.

Agency Comments:

The sponsor was told to justify, in greater detail using historical data, the use of zero as an appropriate value to exclude in the analysis of percent change in organ volume for the combined-group data.

The Agency recommended calculating % change measurements. When analyzing data from the clinical trial, the sponsor should have a single primary endpoint, a combined endpoint and then look at all other parameters individually. To show efficacy, the trial must show statistical significance for the primary endpoint. If the trial includes patients with moderate to severe disease, improvement would be expected. Spontaneous improvement is not expected.

All statistical tests should be two-sided.

A Cerezyme control group is our recommendation but not a requirement. While it is the sponsor's intention to target treatment-naïve patients, should this product be approved it should be assumed that patients will switch from Cerezyme to this product. It would be important to evaluate whether patients with stable disease on Cerezyme therapy will maintain their efficacy when switched to this product.

With regard to the pivotal trial, it is possible to obtain Agency input by submitting specific questions with the heading "Response to questions requested".

Additional Agency Comments:

The Agency has concerns about the immunogenicity and purity of the prGCD product. Photographs in the meeting package suggest the prGCD [REDACTED] (b) (4). We suggest that you screen for antibodies post injection, ascertain if any antibodies are neutralizing, and characterize them to determine if they are against carrot proteins, prGCD or some other proteins. In addition, you should screen prospective patients and ensure they are negative for antibodies to glucocerebrosidase before enrolling them in the trials.

The sponsor should include a detailed protocol in the study design outlining specific parameters to be monitored in order to identify potential anaphylactic reactions and a step by step response to changes in these parameters which should include which medications are to be given and under what conditions is the infusion to be slowed down, interrupted or discontinued.

You should establish your own reference standards and fully characterize them rather than using Cerezyme as a reference standard. However, you may include a comparison to Cerezyme as described.

You should continue to characterize impurities and determine differences in the impurities from batch to batch. It is very important to obtain batch to batch consistency. Whatever batch is used for human trials must be equal to or purer than those used for animal studies.

A drug substance specification is needed.

Continue to characterize and monitor all glycosylation forms. You need to develop a sensitive assay for host cell proteins from carrots and agrobacterium. A response in humans to these proteins may cause a boost in the response to prGCD.

Continue to sequence constructs and characterize amino acids. Determine the sequence at the N-terminal and C-terminal and ensure that the reading frame is correct.

Become familiar with the relevant ICH guidances.

The Agency asked for a comparison of the specific activity of prGCD to Cerezyme.

Sponsor Response:

- Depending upon the assay used, the specific activity of prGCD [REDACTED] (b) (4) Cerezyme. [REDACTED] (b) (4)
- The sponsor noted their intent to submit an IND within 6 to 9 months.

The sponsor thanked the Agency for their guidance and the meeting ended.

PIND 69,703

Unresolved Issues: None

Action Items: None

Minutes Preparer:

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Chair Concurrence: July 27, 2004

Mary Parks, M.D.
Deputy Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Eric Colman
7/28/04 05:19:13 PM
Eric Colman for Mary Parks