

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761047Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761047	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Mepsevii Established/Proper Name: vestronidase alfa-vjbk Dosage Form: 10mg/5mL Injection for Intravenous Use		Applicant: Ultragenyx Pharmaceutical Agent for Applicant (if applicable):
RPM: Jenny Doan		Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☒ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: 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.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>November 16, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ 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 _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ 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.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☒ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☒ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☒ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)	☒ Included; Nov. 1, 2017
Documentation of consent/non-consent by officers/employees (link)	☒ Included;

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	BLA Approval- November 15, 2017
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included November 14, 2017
Original applicant-proposed labeling	☒ Included 03/16/2017
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	None
Original applicant-proposed labeling	None
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included August 22, 2017
❖ Proprietary Name	
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	Nonproprietary Name Suffix: Aug. 3, 2017 Proprietary Name Acceptable Letter: June 06, 2017 Review Memo: May 24, 2017
❖ Labeling reviews (indicate dates of reviews)	RPM: May 4, 2017 DMEPA: August 3, 2017 DMPP/PLT (DRISK): None OPDP: November 8, 2017 SEALD: None CSS: None Product Quality: Aug. 25, 2017 Other: DPMH (Peds): Aug. 14, 2017 DPMH (MH): Aug. 18, 2017
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	May 4, 2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - 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>)	☐ Yes ☒ No N/A N/A
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC : If PeRC review not necessary, explain: Orphan Drug Designation	None
❖ Breakthrough Therapy Designation	None
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	None
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	None
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	None
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Fast Track Granted Letter: July 15, 2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Memorandum of EMA Telecon: Oct. 19, 2017 Rare Ped Disease Priority Review Voucher Checklist: Sept. 25, 2017
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	N/A
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	Pre-BLA meeting minutes: Oct. 14, 2016 Pre-BLA meeting date: Oct. 5, 2016
EOP2 meeting (<i>indicate date of mtg</i>)	No meeting
Mid-cycle Communication (<i>indicate date of mtg</i>)	Mid-Cycle Communication: June 14, 2017 Mid-Cycle meeting date: June 14, 2017
Late-cycle Meeting (<i>indicate date of mtg</i>)	Late Cycle Meeting Minutes: Sept. 20, 2017 Late Cycle Meeting Date: Sept. 20, 2017 Late Cycle Meeting Background Package: Sept. 15, 2017
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	CMC meeting: Sept. 8, 2016

❖ Advisory Committee Meeting(s)	No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	Combined with Unified Clinical Review: November 14, 2017
Division Director Summary Review (<i>indicate date for each review</i>)	Combined with Unified Clinical Review: November 14, 2017
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	Combined with Unified Clinical Review: November 14, 2017
PMR/PMC Development Templates (<i>indicate total number</i>)	Reportable: 2 PMRs, 2 PMCs Non-reportable (OBP)- 4 PMCs Date: November 15, 2017
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	Unified Clinical Review: November 14, 2017
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Included in Unified Clinical Review: November 14, 2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	Epidemiology ARIA Sufficiency Template: Nov. 6, 2017 Clinical Outcome Assessment: Oct. 22, 2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	None
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	None
• 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>)	DRISK Review: November 13, 2017
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	Addendum Clinical Inspection Summary. Aug. 15, 2017 Inspection Letter: Aug. 11, 2017 Inspection Letter: Aug. 11, 2017 Inspection Letter: July 21, 2017 Clinical Inspection Summary: July 21, 2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	None
Biostatistics	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	Addendum: Nov. 2, 2017 Statistical Review: Sept. 29, 2017
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	Addendum Clinical Pharmacology: November 14, 2017 Clinical Pharmacology Review: Sept. 13, 2017
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	Inspection Summary of (b) (4) : Sep. 28, 2017 Inspection Summary of (b) (4) : Aug. 18, 2017
Nonclinical	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Aug. 28, 2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested

Product Quality	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	Addendum: Nov. 8, 2017 IQA Executive Summary: Oct. 26, 2017 Addendum Quality Microbiology Assessment: October 20, 2017 Addendum Product Quality Review: Sept. 12, 2017 Product Quality Review: Aug. 14, 2017 Quality Microbiology Assessment: July 28, 2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See page 4-5 of the Summary of Quality Assessments dated Aug. 14, 2017
☐ Review & FONSI (<i>indicate date of review</i>)	None
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	None
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable- Sept 5, 2017 ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
• Finalize 505(b)(2) assessment	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

JENNY N DOAN
11/17/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 5, 2017

Application Number: BLA 761047

Product Name: Mepsevii (Vestronidase alfa/recombinant human beta-glucuronidase)

Indication: Mucopolysaccharidosis type 7 (MPS VII) – Sly Syndrome

Sponsor Name: Ultragenyx Pharmaceutical, Inc.

Subject: Post-marketing study plan discussion (b) (4)

FDA Participants

Dragos Roman, MD, Associate Director, Division of Gastroenterology and Inborn Error Products (DGEIP)

Katie Donohue, MD, Clinical Team Leader, DGIEP

Dina Zand, MD, Medical Officer, DGIEP

Joyce Korvick, MD, Deputy Director for Safety, DGIEP

Preeti Venkataraman, MD, Safety Medical Officer

Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)

Christine Hon, PharmD, Clinical Pharmacology Reviewer, OCP

Cristina Ausin, PhD, Product Quality Team Leader, Office of Biostatistics (OBP)

Sushanta Chakder, PhD, Pharmacology/Toxicology Team Leader, DGIEP

Joel Weissfeld, MD, Medical Officer, Office of Pharmacovigilance and Epidemiology (OPE)

Michelle Iannacone, MD, Medical Officer, OPE

Susan McCune, MD, Director, Office of Pediatric Therapeutics (OPT)

Robert Nelson, MD, PhD, Deputy Director, OPT

Jean Temeck, MD, Director of International Programs, OPT

Suzanne Malli, BA, BSN, Health Science Administrator, OPT

Lucas Kempf, MD, Medical Officer, Rare Diseases Program

Tracy Cutler, MPH, Health Science Administrator, Rare Diseases Program

(b) (4)

1.0 BACKGROUND

The biologics licensing application (BLA) for vestronidase alfa was submitted to FDA on March 16, 2017, with a goal date of November 16, 2017. This product is also currently under review at EMA. (b) (4)

The following documents were provided to all participants in advance of the teleconference:

- FDA Late Cycle meeting minutes (dated September 20, 2017)
- (b) (4)

2.0 DISCUSSION

- FDA is concerned with the anaphylaxis safety signal and would like to propose a post-marketing requirement (PMR) to the Sponsor.
 - (b) (4) The Sponsor's response will most likely effect labeling.
 - FDA noted that this safety signal has also been identified with other enzyme replacement therapies. A black box warning was added to the labeling for such products.
- FDA noted that the goal date is approaching (~ November 2017), in which they are leaning towards an approval of the product. FDA concurs with (b) (4) and that robust data for efficacy is lacking. FDA acknowledged that there are limitations. However, the application does show modest efficacy with long-term exposure to the product. FDA is also using expanded access data and reviewing improvement in the 6 minute walk test to aid in their application decision.
 - (b) (4)
- FDA provided a brief summary of the potential clinical post-marketing requirement/commitments (PMRs/PMCs) to be proposed to the Sponsor.
 - PMR: 3-year immunogenicity/hypersensitivity reactions study
 - 20 participants (including 6 new participants less than 1 year of age)
 - Collect information on genotype/phenotype
 - Treatment to be provided. Collect safety and efficacy data
 - PMC: 10-year registry/observational study
 - Collect safety and efficacy data at annual visits
 - Collect clinical outcome information regarding liver & spleen size, pulmonary function, motor function, and neurocognitive function.
- (b) (4)

- (b) (4)
- FDA also noted that the Sponsor recently submitted an amendment to protocol 401, which is intended to serve as the registry/observational study. FDA is looking to include additional endpoints (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)

3.0 ACTION ITEMS

1. FDA will (b) (4) the proposed post-marketing study plan, summarizing potential PMRs/PMCs to be completed by the Sponsor. This plan includes one clinical PMR to analyze the long-term immunogenicity and hypersensitivity reactions and one clinical PMC to create a 10-year registry of patients with MPS VII.
2. FDA will (b) (4) the UX003-CL401 protocol amendment (dated July 24, 2017).
3. (b) (4)

Update following the teleconference:

As requested, Tracy Cutler emailed redacted versions of the Late Cycle Meeting background package (dated September 15, 2017), detailing the post-marketing study plan, as well as the protocol amendment (b) (4) on October 6, 2017. It was requested that (b) (4) to FDA **no later than October 20, 2017**.

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/s/

TRACY L CUTLER
10/19/2017

Rare Pediatric Disease Priority Review Voucher eligibility checklist

Under section 529 of the Food, Drug, and Cosmetic Act, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act) for a rare pediatric disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product.

This checklist is intended to help determine if an NDA or BLA is eligible for a **Rare Pediatric Disease Priority Review Voucher**. **An application that does not meet all of these criteria is not eligible for a voucher.**

BLA 761047 (vestronidase alfa (recombinant human beta-glucuronidase, rhGUS, UX003)	Review Division: DGIEP
Requirement	Meets? (yes/no)
For prevention or treatment of a <i>rare pediatric disease</i> ? (<i>OOPD makes determination</i>)	Yes (consult #2017-7), review completed 8/21/2017
Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act?	Yes
FDA deems eligible for priority review?	Yes
Submitted under section 505(b)(1) (includes 505(b)(2) applications) of the FD&C Act or section 351(a) of the Public Health Service Act?	Yes
Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population?	Yes
Does not seek approval for a different adult indication in the original rare pediatric disease product application?	Yes

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/s/

ALTHEA CUFF
09/25/2017
PRV Eligibility Checklist



BLA 761047

MID-CYCLE COMMUNICATION

Ultragenyx Pharmaceutical Inc.
Attention: Min Chen Young, Ph.D., RAC
Associate Director, Regulatory Affairs
60 Leveroni Court
Novato, CA 94949

Dear Dr. Young:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Mepsevii (vestronidase alfa) injection 10 mg/5mL.

We also refer to the teleconference between representatives of your firm and the FDA on June 14, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Jenny Doan, BSN, MSN, PMP
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MID-CYCLE COMMUNICATION

Meeting Date and Time: June 14, 2017; 12:30 PM-1PM EST

Application Number: 761047
Product Name: Mepsevii
Indication: Treatment of MPS VII
Applicant Name: Ultragenyx

Meeting Chair: Kathleen Donohue, MD
Meeting Recorder: Jenny Doan, RPM

FDA ATTENDEES (tentative)

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Dragos Roman, MD, Deputy Director
Kathleen Donohue, MD, Clinical Team Leader
Dina Zand, MD, Clinical Reviewer
Jenny Doan, MSN, BSN, Regulatory Project Manager

Office of Clinical Pharmacology

Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader
Christine Hon, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics/ Division of Biometrics III

Yeh-Fong Chen, PhD, Biostatistics Team Leader
Feiran Jian, Biostatistics Reviewer

Clinical Outcome Assessment Staff

Michelle Campbell, PhD, Reviewer

Office of Surveillance and Epidemiology (OSE)

Kelli Taylor, Associate Director, Office of Medication Error Prevention and Risk Management

APPLICANT ATTENDEES

Christine Murray, MS, RAC, Vice President, Regulatory Affairs
Min Chen Young, Ph.D., RAC, Associate Director, Regulatory Affairs
Christine Haller, M.D., Vice President, Clinical Sciences and Drug Safety, Medical Monitor
Qais Abu Ali, M.D., Medical Director, Clinical Sciences, Clinical Sciences
Wenjie Song, Ph.D., Associate Director, Biostatistician
Tricia Cimms, MPH, Director, Clinical Outcomes Research & Evaluation, Clinical Sciences

Julie Taylor, Ph.D., Executive Director, Bioanalytical Methods Development, Quality
Kathleen McKeever, Ph.D., DABT, Vice President, Pharmacology & Toxicology
Yulan Qi, Ph.D., Associate Director, Pharmacokinetics, Pharmacology/Toxicology

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical - Efficacy:

The Agency is appreciative of Ultragenyx's prompt and thorough responses to our Information Requests (IRs). Our assessment of efficacy is ongoing. We expect that your responses to ongoing information requests (IRs) will require additional analyses. For example, we consulted our ophthalmologic experts during our efficacy review. Based upon their input we have reservations about how informative the visual acuity endpoint data will be in our evaluation of the totality of evidence to support vestronidase alfa.

Clinical – Benefit/Risk Assessment:

Preliminary review of the safety profile of vestronidase alpha suggests that anaphylaxis is an important safety signal, and we anticipate that labeling changes would be needed to ensure safe use. Our assessment of safety is ongoing and will depend in part upon responses to information requests (IRs) and the 120 day safety update anticipated for July 2017.

3.0 INFORMATION REQUESTS

The following information requests are outstanding:

- 1) CMC microbiology IR sent on June 9, 2017; response requested by June 28, 2017
- 2) CMC IR sent on June 2, 2017; responses expected on June 21 and July 31, 2017

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, a need for a Risk Evaluation and Mitigation Strategy (REMS) is still under review.

5.0 ADVISORY COMMITTEE MEETING

There are no plans to convene an advisory committee meeting at this time.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting (LCM) is September 20, 2017. In addition, please note the following projected milestone dates:

- Labeling comments for the CMC and non-clinical sections to Applicant: August 16, 2017
- Other labeling comments and PMR/PMC comments: Timeline is to be determined pending the progress of application review
- LCM Background Package to the Applicant: September 15, 2017
- PDUFA Goal Date: November 16, 2017

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/s/

JENNY N DOAN
06/14/2017



IND 123788

MEETING MINUTES

Ultragenyx Pharmaceutical
Attention: Min Chen Young, Ph.D., RAC
Senior Manager, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, California 94949

Dear Dr. Chen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for UX003.

We also refer to the meeting between representatives of your firm and the FDA on October 5, 2016. The purpose of the meeting was to discuss the proposed BLA submission plan in support of filing and licensure of UX003 for the treatment of MPS VII.

A copy of the official minutes of the meeting is enclosed 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) 796-1023.

Sincerely,

{See appended electronic signature page}

Jenny Doan
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: October 5, 2016; 1:00p.m. - 2p.m. EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: 123788
Product Name: UX003
Indication: For the treatment of MPS VII
Sponsor/Applicant Name: Ultragenyx Pharmaceutical Inc.

Meeting Chair: Rachel Witten, MD, Team Leader
Meeting Recorder: Jenny Doan, RPM

FDA ATTENDEES

Office of New Drug/Office of Drug Evaluation III (ODEIII)

Julie Beitz, MD, Director

Amy Egan, MD, Deputy

Maria Walsh, RN, MSN, Associate Director of Regulatory Affairs

Division of Gastroenterology and Inborn Errors

Donna Griebel, MD, Director

Dragos Roman, MD, Associate Director

Laurie Muldowney, MD, Medical Team Leader

Rachel Witten, MD, Medical Team Leader

Dina Zand, MD, Medical Reviewer

Sushanta Chakder, PhD, Pharmacology Team Leader

Tracy Behrsing, PhD, Pharmacology Reviewer

Kevin Bugin, MS, RAC, Chief Project Management Staff

Jenny Doan, MSN, BSN, PMP, Regulatory Health Project Manager

Division of Pediatric and Maternal Health

Rosemary Addy, Project Management Team Leader

Office of Biotechnology Products/Division of Biotechnology Review and Research IV

Cris Ausin, PhD, Product Quality Team Leader

Rukman DeSilva, PhD, Product Quality Reviewer

Office of Biostatistics/Division of Biometrics
Yeh-Fong Chen, PhD, Biostatistics Team Leader

Office of Surveillance and Epidemiology

Sue Kang, Pharm D., Senior Safety Regulatory Project Manager, Team Leader
Aleksander Winiarski, Pharm.D., Senior Safety Regulatory Project Manager
Sherly Abraham, R.Ph, Division of Medication Error Prevention and Analysis Primary Reviewer
Mishale Mistry, Pharm.D., M.S., Division of Medication Error Prevention and Analysis Team Leader
Kimberly Swank, Pharm.D., Division of Pharmacovigilance Safety Evaluator
Eileen Wu, Pharm.D., Division of Pharmacovigilance Team Leader
Sukhminder Sandhu, PhD, MPH, M.S., Division of Epidemiology Team Leader
Kira Leishear White, PhD, M.S., Division of Epidemiology Epidemiologist
Jamie Wilkins Parker, Pharm.D., Division of Risk Management Team Leader
Laura Zendel, Pharm.D., BCPS, Division of Risk Management, Risk Management Analyst

Clinical Outcome Assessment Staff

Michelle Campbell, PhD, Reviewer
Elektra Papadopoulos, MD, MPD, Associate Director (acting)

SPONSOR ATTENDEES

Emil Kakkis, MD, PhD, CEO and President of Ultragenyx Pharmaceutical Inc.
Christophe Beraud, Ph.D., Sr. Director, Regulatory Affairs
Min Chen Young, Ph.D., RAC, Sr. Manager, Regulatory Affairs
Christine Haller, M.D., Vice President, Drug Safety and Clinical Science, Medical Monitor
Karen Jacobs, RN, BSN, Director, Drug Safety and Pharmacovigilance
Wenjie Song, Ph.D., Associate Director, Biostatistician
Kathleen McKeever, Ph.D., DABT, Vice President, Pharmacology & Toxicology
Tricia Cimms, MPH, Director, Clinical Outcomes Research & Evaluation, Medical Affairs

1.0 BACKGROUND

On July 21, 2016, the sponsor (Ultragenyx) submitted a Type B meeting request to discuss the proposed BLA submission plan in support of filing and licensure of UX003 for the treatment of MPS VII. The meeting was granted and scheduled to take place on October 5, 2016. The meeting briefing package was received on September 2, 2016. FDA sent Preliminary Comments to Ultragenyx on September 30, 2016.

2. DISCUSSION

Clinical

Question 1: In the context of the ultra-rare nature, heterogeneity and progressive course of MPS VII disease, does the Agency have any comment on the proposed clinical data

package at the time of initial BLA submission, including the data from the pivotal Phase 3 placebo-controlled, blind-starts, single cross-over Study UX003-CL301?

FDA Response:

We are concerned that the data that you are proposing at this time to include in a BLA may not be sufficient to adequately assess the safety and efficacy of UX003 at the currently proposed dose (4.0mg/kg/QOW). While we recognize the rarity of MPS 7 and the challenges associated with a clinical program for this rare and heterogeneous condition, after reviewing the briefing package, we have reservations as to whether you have provided enough evidence of effectiveness to allow for a meaningful review. The absence of rigorously collected natural history data to ensure a reliable comparator for efficacy analyses, combined with very heterogeneous clinical manifestations expected and observed in this small cohort, raise serious challenges in assessing and demonstrating a treatment effect to support definitive efficacy conclusions for your product. We also reiterate reservations regarding [REDACTED] (b) (4)

[REDACTED] - refer to previous discussions held during the type B, pre-IND meeting held on 29 July 2014, [REDACTED] (b) (4)

In addition, we have the following observations and comments:

1. Following review of the data presented to date we are also questioning whether a 24-week treatment duration is sufficient to allow a definitive conclusion of efficacy. We note a lack of improvement on the pulmonary function and shoulder flexion tests in all 12 patients and a lack of the improvement in six out of 12 patients in the multi-domain clinical responder index (MDRI) in your pivotal trial. Interpretation of these observations as evidence of “stabilization” is challenging in absence of reliable natural history data.
2. You have not provided sufficient information such as comprehensive patient medical histories for all the patients, including a complete description of when symptoms appeared in the disease course, and how symptoms progressed in these patients. Because of the existing heterogeneity of age and presentation, background information should include exact age/birthdate, age at the onset of symptoms age at the time of diagnosis, % enzymatic activity, method of diagnosis, genotype and complete phenotypic baseline including growth parameters. All of this will be critical information in the consideration of the totality of evidence for each patient in our review.
3. We are concerned about missing data, which will significantly affect efficacy analyses.
4. To date you have provided only limited information on the quality of the immunogenicity assays and the exact extent of immunogenicity testing. Please

clarify the extent of the immunogenicity monitoring in your program. Immunogenicity information will be critical in assessing the safety (and potentially efficacy) of your product.

Ultragenyx's Response:

Immunogenicity

1. Comprehensive information on immunogenicity assays (including assay development data, assay SOP and validation) will be included in the BLA Module 2.7.1 and Module 5.3.1.4 at time of the BLA submission. The available immunogenicity data will be included in the BLA Module 2 and Module 5 individual clinical study reports.
2. Anti-Drug Antibodies (ADA) assay to rhGUS: Immunogenicity of UX003 was evaluated by quantifying total anti-drug antibodies (ADA), independent of isotype, in human serum, using a bridging electrochemiluminescent assay. The bridging format utilizes the bivalency of the antibody molecule and allows all isotypes to be detected. The validation results show that the ADA screening, confirmatory and titration assay is sensitive, specific, reproducible, tolerant to drug, precise and is suitable for use in the UX003 clinical program. All the validation parameters passed the pre-specified acceptance criteria outlined in the validation protocol. Validation was performed in compliance with the EMA guideline on immunogenicity assessment of biotechnology derived therapeutic proteins, September 2015. The sensitivity of the ADA assay is also well within the most recent FDA recommendation in the draft Guidance for Industry, Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products, April 2016.
3. Neutralizing antibodies (NAb) assay to rhGUS was only performed on subject samples that showed positive signals in both the ADA screening assay and the confirmatory assay (ADA assay). The NAb assay procedure is a modified version of the cellular uptake assay (UGA-QC-008/UGA-QC-018, Module 3.2.S.4.2) to evaluate the potential for anti-rhGUS antibodies present in patient serum to impact the uptake of rhGUS into GUS-deficient fibroblasts. The assay is qualitative and not quantitative; the results are either positive or negative.
4. Immunogenicity is being monitored as a safety objective in UX003 clinical development program (in all 4 clinical studies) per protocol defined schedule of events.
 - a. UX003-CL201: Week 0, 4, 8, 12, 22, 30, 36, 48, 60, 72, then every 12 weeks [Week 74-End of Trial]
 - b. UX003-CL301: Every 2 weeks (0-40), then Week 46
 - c. UX003-CL203: Every 8 weeks (0-48), then every 12 weeks [Week 48-240]
 - d. UX003-CL202: Every 12 weeks [Week 0-144]
5. Per the Agency's requests, ADA assay to rhGUS (development data, SOP and validation report) and NAb assay to rhGUS (development data, SOP and validation report) were submitted to IND 123788, Module 2.7.1 and Module 5.3.1.4, Serial No.

0016, dated 02 July 2015 and Serial No. 0020, dated 21 September 2015, respectively for the Agency's review prior to sample analysis.

Discussion:

See attached Sponsor's presentation.

The Sponsor acknowledged the Agency's concerns regarding the amount of missing data in the pre-BLA meeting package. In this context FDA re-iterated its reservations regarding the ability to draw clear conclusions of effectiveness in final analysis given the small rate of apparent clinical response for several of the endpoints analyzed (see for example shoulder flexion and BOT-2 fine motor). FDA also pointed out that lack of clinical deterioration cannot be interpreted as "disease stabilization" since the natural history of the disease is not well characterized. Figure 4.1.4.4.2.1 of the briefing package was projected and discussed at the meeting and FDA opined that the 6-minute walk and the fatigue assessments seem the most informative assessments based on this graphic display of the efficacy data. The sponsor has been advised to provide clear descriptions of the instrument used to measure fatigue, its performance characteristics (reliability, validity, etc.) so that the data can be adequately analyzed and interpreted. FDA also emphasized that the individual patient data have to be presented in a comprehensive manner, and the endpoint assessments need to be fully integrated with patient's history and baseline characteristics to support a patient specific review and decision of effectiveness. FDA asked that all datapoints of interest should be presented including information about patients in the expanded access program who may have exposures longer than the 24 months proposed for the BLA submission. The FDA asked that if published data are used and relied upon for the BLA submission, the original source data should be available for review. The FDA recommends the inclusion of individual patient profiles in a single lattice plot for each measurement in the BLA package, to facilitate comparison of results across patients and for patients' performance over time.

The FDA reiterated the reservations already communicated to the sponsor about (b) (4)

The Sponsor offered to facilitate discussion between study investigators and the Agency. The FDA agreed that this might be helpful during the BLA review.

Post Meeting Comments:

The Agency requests that the Sponsor provides comprehensive medical history including information of the disease progression (with milestones), age at the time diagnosis of MPS 7, how the diagnosis of MPS 7 was made and what interventions were performed (medical and cognitive) prior to treatment with UX003 to allow adequate assessment of the safety and efficacy of the product.

As a reminder, the submission of the BLA should include complete information about each evaluation used in the study (e.g., BOT-2 Fine, BOT-2 Gross, Fatigue MID) for the Agency to review. In addition, the 2009 Guidance for Industry Patient-Reported Outcome Measures:

Use in Medical Product Development to Support Labeling Claims discourages the use of proxy reporting. <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf> Interpretation of proxy reporting for fatigue will require clear information regarding the proxy reporter (e.g. one proxy reporter vs different proxy reporters) and the adequacy of the measurements will ultimately be a review issue.

Question 2: Does the Agency agree with Ultragenyx's proposal to not include an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in the application?

FDA Response:

We do not agree. The sections Integrated Summary of Effectiveness [CFR 314.50(d)(v)], Integrated Summary of Safety [21 CFR 314.50(d)(5)(vi)] and Integrated Summary of the Benefits and Risks of the drug product [21 CFR 314.50(d)(5)(viii)] are sections of an application required by regulation. Omission of any of these sections renders the application incomplete, which could result in a refuse-to-file action. We acknowledge that MPS VII is a rare disease and a limited number of patients enrolled in your studies. If the size of the text portion of your ISS and ISE are within the size limitations of sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety, in Module 2, repeating the text portions of the ISE and the ISS in Module 2 may be acceptable. For further information see guidance for industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.

Ultragenyx's Response:

Ultragenyx acknowledges the regulatory requirements to include Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) in the application. Due to the small size of the studies, the different designs, including doses administered, efficacy endpoints, duration of follow-up, and patient population, pooling efficacy and safety data does not appear scientifically justified and would provide little added value to the assessment of efficacy and safety. As part of the Summary of Clinical Efficacy (Module 2.7.3) and the Summary of Clinical Safety (Module 2.7.4), Ultragenyx will include in the relevant sections on Comparison and Analyses of Results Across Studies, qualitative comparisons of the results between the three clinical studies included in the application. Accordingly, we propose to repeat Modules 2.7.3 and 2.7.4 in Module 5.3.5.3. Since no pooled statistical analyses will be conducted, tables, figures, listings and electronic datasets will be included under each Clinical Study Report in Module 5.

Does the Agency agree that this approach would satisfy the statutory requirements for provision of an ISE and ISS in the application?

Discussion:

Yes, this is acceptable.

Question 3: Does the Agency agree with the proposed plan for the BLA 120-day safety update?

FDA Response:

Yes, this is acceptable.

Question 4: Does the Agency agree that a REMS will not be required for UX003 based on the clinical safety profile to date?

FDA Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. Based on the limited information currently available, we believe that REMS is unlikely. However, we will make a final determination for the need for REMS during the review of your application.

Question 5: Does the Agency agree that the data from the two completed developmental and reproductive toxicity (DART) studies (UX003-PC008, Segment I/II combined in SD rats, and UX003-PC009, Segment II in rabbits) are acceptable to support the UX003 BLA filing?

FDA Response:

Yes, the two definitive developmental and reproductive toxicity studies with UX003 (i.e., a combined fertility and embryofetal development toxicity study in rats and embryofetal development toxicity in rabbits) appear adequate to support the filing of a BLA for your proposed indication.

Question 6: Does the Agency agree with the proposal not to conduct a Segment III (pre- and postnatal development, including maternal function) study in rats post-licensure?

FDA Response:

No, we do not agree. As previously commented, you need to conduct a pre- and postnatal development study with UX003 as a post-marketing study.

Ultragenyx's Response:

Ultragenyx acknowledges the Agency's reiteration that a pre- and postnatal development study should be conducted as a post-marketing study. Given the rationale provided in the briefing package that highlights the lack of exposure in the fetus, would the Agency provide a brief written rationale for the request? If there are particular issues based on the Agency's insights, this would be helpful information for the design of the Segment III rat study.

Discussion:

The Sponsor agreed to conduct the pre- and postnatal development study with UX003 as a post-marketing study, and inquired about the Agency's rationale for the request. The Agency indicated that pre- and postnatal development studies are conducted to assess potential adverse effects following exposure of the female from implantation through weaning. While the Sponsor's briefing package asserted that there is little evidence of transplacental transfer based in part on two completed developmental and reproductive toxicity (DART) studies with UX003 (i.e., a combined fertility and embryofetal development toxicity study in rats and an embryofetal development toxicity study in rabbits), potential lactational exposures have not been addressed. Furthermore, there are cases where adverse effects were observed in the pre- and postnatal development studies and excretion into the milk of animals occurred following administration of ERTs. Thus, the Division continued to recommend that the Sponsor conduct a pre- and post-natal development study with UX003 as a post-marketing requirement.

Question 7: Does the Agency have any comments on the dossier table of contents and proposed location of reports?

FDA Response:

From a technical standpoint (not content related), the proposed Table of Contents for the planned BLA is acceptable.

Question 8: Does the Agency agree that an advisory committee meeting will not be required to support UX003 licensure?

FDA Response:

No, we cannot agree at this time. Determination for an advisory committee meeting can only be made during review of your BLA.

Question 9: Does the Agency agree that UX003 for treatment of MPS VII could qualify for a Rare Pediatric Disease Priority Review Voucher should the program be renewed?

FDA Response:

There is a possibility that your product may qualify for a Rare Pediatric Disease priority review voucher. If you are interested in pursuing this possibility, please consult the guidance, "Rare Pediatric Disease Priority Review Vouchers, Draft Guidance for Industry" (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf>). Please see section "C" page 13 which describes the process for requesting a voucher. Please note that the requirement to include prevalence estimates is a critical element of the request. Determination of whether an application qualifies for a Rare Pediatric Disease Priority Review Voucher is a review issue and only determined during the review of an

NDA or BLA. Please note that the FDA will not issue a Rare Pediatric Disease Priority Review Voucher for marketing applications approved beyond September 30, 2016, the date set by the Bipartisan Budget Act of 2015 (PL 1114-74), unless the program is extended. Therefore, even if all the applicable statutory requirements are satisfied, if the Rare Pediatric Disease Priority Review Voucher program is not extended, a voucher cannot be awarded for marketing applications approved after September 30, 2016

Question 10: Does the Agency expect Ultragenyx to provide the randomization codes for the pivotal Phase 3 Study UX003-CL301? If so, would the Agency provide direction for provision of this information?

FDA Response:

Yes, randomization codes for Study UX003-CL301 should be provided for appropriate data review.

Ultragenyx Response:

Given the meeting time constraint, can the Agency provide directions on how to provide the randomization list generated by the (b) (4) vendor? Specifically, does the Agency require the randomization list to be provided in a tamper-resistant envelope generated by the vendor for us to submit to DGIEP directly?

Discussion: FDA clarified that the data should to be submitted in the BLA.

Additional Comments:

Clinical:

We note that the assessments in the longitudinal observational study UX003-CL401 do not include evaluation of shoulder flexion or BOT-2 fine and gross motor skills (unlike the assessments of the phase 3 Study UX003-301). We also note that the in-clinic assessments (b) (4) in protocol UX003-CL401, (b) (4)

. Therefore this data from the longitudinal observational study UX003-CL401 may not be fully informative and may not be comparable to Study UX003-CL30 outcomes.

Ultragenyx's Response:

Ultragenyx acknowledges the Agency's feedback and will wait for additional comments from the Agency on the review of UX003-CL401 protocol. In particular, we determined in the Phase 3 study that shoulder restriction is minimal or none in the MPS VII population, unlike MPS I and MPS VI. Therefore, following this parameter did not seem worthwhile. We are open to ways to improve the protocol to capture long-term efficacy information in the post-marketing setting. Our design of the DMP protocol and strategy is part of our goals to conduct a more comprehensive, higher quality study than a traditional registry study and for the in-clinic portion

to be done in a GCP compliant manner with monitoring to obtain higher quality data for longer term review.

Division of Medication Error Prevention and Analysis (DMEPA)

You are proposing that the product will be available as an injection in a 10 mg/5 mL (2 mg/mL) vial. However, since the proposed dose is 4 mg/kg every other week, the pharmacist would need 28 vials to prepare a dose of 280 mg using the 10 mg/5 mL vials for a 70 kg patient. FDA is concerned with the large number of vials that will be needed to prepare a dose. This may lead to pharmacy confusion and increase the likelihood of pharmacy dispensing errors resulting in the wrong dose. Therefore, please clarify whether you intend to pursue an appropriate vial size and fill volume to accommodate this dosing regimen.

Ultragenyx's Response:

- 1. Ultragenyx acknowledges the FDA's concern and want to clarify that the 10mg/5 mL (2 mg/mL) vial is the intended commercial presentation based on available clinical development and CMC data to support the BLA submission. An advantage with the smaller vial size is more precise dosing for a variety of patients of different sizes with limited product waste. A similar situation of multiple vial doses exists for other MPS ERTs. Most infusion sites are familiar with MPS ERT therapies and are comfortable with handling multiple vials.*
- 2. For the approved ERTs (Aldurazyme®, Elaprase®, Vimizim® and Naglazyme®) for treatment of MPS I, II, IVA, VI diseases, respectively, a presentation of 5 mL extractable volume (or less in the case of Elaprase®) has been developed and approved by Regulatory Authorities worldwide. This 5 ml (or less) presentation has been used successfully in the commercial setting for over a decade, with no issues noted in the public literature regarding the size of vial presentation. As such, Ultragenyx does not expect any issues with the current vial presentation given the public knowledge learned from the ERTs for the other 4 MPS disorders.*
- 3. To date, out of 453 UX003 infusions in total, including 345 infusions at 4mg/kg dose, there has been no pharmacy dispensing errors due to confusion resulting from handling of large vial numbers.*
- 4. Upon BLA approval, UX003 will be available through prescription only via Specialty Pharmacy, who will be responsible for ensuring correct number of vials based on current patient weight is delivered to the infusion site on a per-infusion order basis. There would not be a need to store the vials at the infusion site.*
- 5. MPS VII is an ultra-rare disease, with only 19 living patients identified in the US currently. Based on current data and commercial distribution consideration upon approval, Ultragenyx considers the 10 mg/5 mL vial is a suitable presentation for commercial patient use to cover all patients with accurate dosing and minimal waste,*

including infants and young children. We agree this makes dose preparation a challenging process for the full size adult, but overall this is the optimal vial size.

Office of Scientific Investigations:

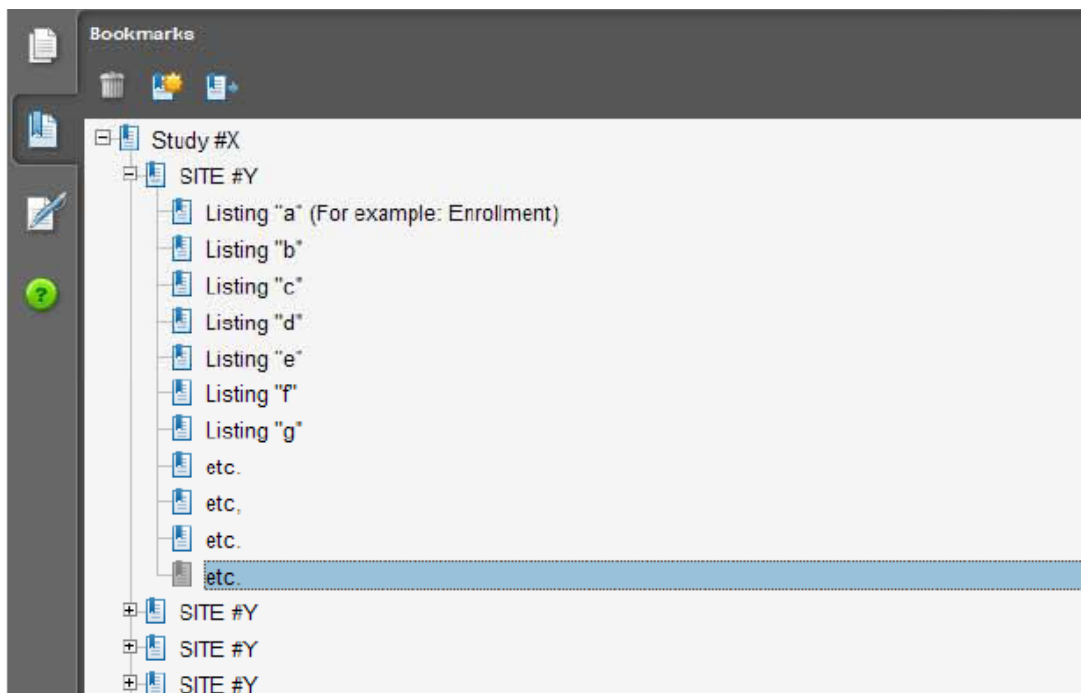
Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

- 1. In order to facilitate FDA inspection of your clinical sites, please include the following in a tabular format in the original BLA for the completed pivotal clinical trial**
 - a. A. Site number**
 - b. B. Principal investigator**
 - c. C. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)**
 - d. D. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.**
- 3. Please include the following information in a tabular format, *by site*, in the original BLA for the completed pivotal clinical trial:**
 - a. Number of subjects screened at each site**
 - b. Number of subjects randomized at each site**
 - c. Number of subjects treated who prematurely discontinued for each site by site**
- 4. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:**
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.**
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.**
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.**

5. **For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).**
6. **For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).**

Request for Subject Level Data Listings by Site

7. **For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:**
 - a. **Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated**
 - b. **Subject listing for treatment assignment (randomization)**
 - c. **Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued**
 - d. **Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol**
 - e. **By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)**
 - f. **By subject listing, of AEs, SAEs, deaths and dates**
 - g. **By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation**
 - h. **By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.**
 - i. **By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)**
 - j. **By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring**
8. **We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:**



Ultragenyx Response:

Ultragenyx acknowledges the requests and will include the requested info, including the subject level data listings by site in the BLA.

3.0 Other Important Information

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 1, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

4.0 ATTACHMENTS AND HANDOUTS



UX003 F2F Clin-NC
pre-BLA mtg slides_ 0

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/s/

JENNY N DOAN
10/14/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123788

MEETING MINUTES

Ultragenyx Pharmaceutical Inc.
Attention: Min Chen Young, Ph.D.
RAC Senior Manager, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Young:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for UX003.

Please refer to the meeting between representatives of your firm and the FDA on August 24, 2016.

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

If you have any questions please contact the Regulatory Business Project Manager, Andrew Shiber at 301-796-4798.

Sincerely,

{See appended electronic signature page}

Patricia Hughes, Ph.D.
Branch Chief (Acting)
Division of Microbiology Assessment
Office of Process and Facility
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEETING MINUTES

Meeting Type: C
Meeting Category: CMC Only
Meeting Date and Time: August 24, 2016 11:00 A.M. Eastern Daylight Savings Time
Format: Teleconference

Office of Biotechnology Products

Michele Dougherty, Ph.D.	Review Chief
Joslyn Brunelle, Ph.D.	Team Leader
Ying Xin Fan, Ph.D.	Product Quality

Division of Microbiology Assessment

Lakshmi Narasimhan, Ph.D.	Microbiologist
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Office of Program and Regulatory Operations

Andrew Shiber, Pharm.D.	Regulatory Business Project Manager
-------------------------	-------------------------------------

Ultragenyx, Inc.

Cordelia K. Leonard, B.S., RAC	Vice President, Regulatory Affairs
Llorente Bonaga, Ph.D.	Director, Regulatory Affairs
Min Chen Young, Ph.D., RAC	Sr. Manager, Regulatory Affairs
Sean Cullen, B.A.	Director, Technical Operations
Joseph Chen, Ph.D.	Executive Director, CMC Quality Control
Daniel Candelario, B.S.	Director, Quality Validation, CMC Quality Assurance

1.0 BACKGROUND

Purpose of meeting: The purpose of this meeting is to reach agreement with the Agency on the proposed CMC BLA submission plan, including the data package at the time of initial BLA submission and planned CMC data updates during BLA review, in support of filing and licensure of UX003 for the treatment of MPS 7.

2.0 DISCUSSION

Question 1B: In accordance with the pre-IND/EOP2 meeting (FDA letter reference ID #3609572, dated 13 August 2014), would the Agency comment on the regulatory mechanism to submit the results from the remainder of (b) (4) batches post-approval and associated approval timeline?

FDA response to Question 1B (FDA Preliminary Comments to UX003 CMC pre-BLA briefing book, Reference ID: 3974460, dated 19 August 2016):

Please note that the BLA should be complete at the time of submission under the PDUFA V program. (b) (4) should be completed to validate the drug substance/drug

product manufacturing process from a microbial control perspective using either a suitable
(b) (4).

Ultragenyx Response and Question to the FDA response to Question 1B aforementioned above:

Ultragenyx agrees that the (b) (4) should be complete at time of submission of BLA.

For Drug Product (DP), the (b) (4) have been completed as follows:

(b) (4)

For Drug Substance (DS), the hold time validation studies at scale are described in the briefing book (BB) (Section 4.4.4.5.2.2 Drug substance process validation, (b) (4), page 71 of 112). **Ultragenyx intends to conduct** (b) (4)

Ultragenyx will include the data from both lots in the initial BLA filing. Is this approach acceptable to the Agency?

The use of (b) (4) is supported by the following considerations:

(b) (4)

2) The Sponsor considers that the (b) (4) is a suitable material to use in the studies because (b) (4)

[REDACTED] (b) (4)
[REDACTED].

Minutes: The Agency inquired if there is any hold step in which the [REDACTED] (b) (4)
[REDACTED]. The sponsor stated that all [REDACTED] (b) (4)
[REDACTED]. The Agency asked whether the [REDACTED] (b) (4). The
Sponsor stated that there is a [REDACTED] (b) (4)
[REDACTED]. The Agency told the sponsor that if all hold steps are performed in [REDACTED] (b) (4)
[REDACTED], the proposal of submitting the hold time data [REDACTED] (b) (4) in the
initial BLA filing is acceptable.

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/s/

PATRICIA F HUGHES TROOST
09/08/2016



IND 123788

GRANT FAST TRACK

Ultragenyx Pharmaceutical
Attention: Min Chen, Ph.D., RAC
Senior Manager, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, California 94949

Dear Dr. Chen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for UX003.

We also refer to your June 19, 2015, request for Fast Track designation. We have reviewed your request and concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of UX003 (recombinant human beta-glucuronidase), an enzyme replacement therapy for the treatment of mucopolysaccharidosis 7 (MPS 7), Sly Syndrome. Please note that if the clinical development program you pursue does not continue to meet the criteria for Fast Track designation, the application will not be reviewed under the Fast Track program.

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics"¹. This document may be requested from the Office of Communications, Division of Drug Information at 301-796-3400 or 1-888-463-6332.

If you have any questions, contact Lisa Pitt, Regulatory Project Manager, at (240) 402-9651.

Sincerely,

{See appended electronic signature page}

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

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/s/

DRAGOS G ROMAN

07/15/2015

Signing on behalf of Dr. Donna Griebel

LATE-CYCLE COMMUNICATION
DOCUMENTS



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

BLA 761047

LATE CYCLE MEETING MINUTES

Ultragenyx Pharmaceutical Inc.
Attention: Min Chen Young, Ph.D., RAC
Associate Director, Regulatory Affairs
60 Leveroni Court
Novato, CA 94949

Dear Dr. Young:

Please refer to your Biologics License Application (BLA) submitted under the Public Health Service Act for Mepsevii (vestronidase alfa) injection 10 mg/5 mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 20, 2017.

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

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

Sincerely,

{See appended electronic signature page}

Kathleen Donohue, M.D.
Medical Officer Team Leader
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Minutes

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 20, 2017; 11:00 AM – 12 PM EST
Meeting Location: White Oak Building 22, Conference Room 1309
10903 New Hampshire Ave,
Silver Spring, MD 20903
Application Number: 761047
Product Name: Mepsevii (vestronidase alfa)
Indication: Treatment of MPS VII
Applicant Name: Ultragenyx

Meeting Chair: Kathleen Donohue, MD
Meeting Recorder: Jenny Doan, RPM

FDA ATTENDEES

Office of Drug Evaluation III

Hylton V. Joffe, MD, MMSc, Acting Deputy Director
Victor Crentsil, MD, Deputy Director

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Joyce Korvick, MD, Safety Deputy Director
Lisa Soule, MD, Acting Associate Director
Kathleen Donohue, MD, Clinical Team Leader
Dina Zand, MD, Clinical Reviewer
Sushanta Chakder, PhD, Pharmacology Team Leader
Yolanda Branch, PhD, Pharmacology Reviewer
Joette Meyer, PharmD, Associate Director for Labeling
Jenny Doan, MSN, BSN, Regulatory Project Manager (RPM)
Jacqueline LeeHoffman, PharmD, RPM

Office of Clinical Pharmacology

Christine Hon, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics/ Division of Biometrics III

Yeh-Fong Chen, PhD, Biostatistics Team Leader

Clinical Outcome Assessment Staff

Michelle Campbell, PhD, Reviewer

Office of Biotechnology Products

Cristina Ausin, PhD, Team Leader

Division of Microbiology Assessment
Dupeh Palmer, PhD, Acting Team Leader
Virginia Carroll, PhD, Reviewer

Office of Scientific Investigation
Susan Libenhaut, MD

Office of Safety and Epidemiology
Robert Pratt, PharmD, Risk Management Analyst, Division of Risk Management
Sarah Vee, PharmD, Team Leader, Division of Medication Error Prevention and Analysis
Nicholas Miles, RPM

Rare Disease Program
Kempf Lucas, MD

APPLICANT ATTENDEES

F2F attendees:

- Christine Murray, MS, RAC, Vice President, Regulatory Affairs
- Min Chen Young, Ph.D., RAC, Associate Director, Regulatory Affairs
- Christine Haller, M.D., Vice President, Clinical Sciences and Drug Safety, Medical Monitor
- Wenjie Song, Ph.D., Associate Director, Biostatistician
- Annette Hillebrand, Ph.D., Associate Director, CMC Regulatory Affairs
- Sean Cullen, BA, Director, Contract Manufacturing, Technical Operations
- Paula Kong, BS, Associate Director, CMC Quality Control

Remote attendees from Novato, CA:

- Virginie Bryan, MPH, Senior Director, Commercial Regulatory Affairs
- Julie Taylor, Ph.D., Executive Director, Bioanalytical Methods Development, Quality
- Kathleen McKeever, Ph.D., DABT, Vice President, Pharmacology & Toxicology
- Yulan Qi, Ph.D., Associate Director, Pharmacokinetics, Pharmacology & Toxicology
- Qais Abu Ali, M.D., Medical Director, Clinical Sciences, Clinical Sciences
- Tricia Cimms, MPH, Director, Clinical Outcomes Research & Evaluation, Biometrics & Development Strategy
- Joseph Chen, Ph.D., Executive Director, CMC Quality Control
- Daniel Candelario, B.S., Director, Quality Validation, CMC Quality Assurance

1.0 BACKGROUND

BLA 761047 was submitted on March 16, 2017 for Mepsevii (vestronidase alfa).

Proposed indication(s): Treatment of MPS VII

PDUFA goal date: November 16, 2017

FDA issued a Background Package in preparation for this meeting on September 15, 2017.

2.0 DISCUSSION

1. Introductory Comments – 2 minutes (Jenny Doan, RPM/Kathleen Donohue, M.D.)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 2 minutes
3. Discussion of Minor Review Issues – 2 minutes
4. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

Discussion:

Please refer to Ultragenyx's slide presentation.

PMR-1. Ultragenyx proposed changes to the FDA PMR, including a smaller sample size and (b) (4). The FDA, while understanding the sponsor's desire to decrease the sample size, reiterated the position for the current numbers. An analysis of enrollment and retention may justify different numbers of patients if the target cannot be reached. Before finalizing the PMR, the FDA also noted that we would need to resolve challenges with evaluating (b) (4). Ultragenyx will provide a proposal for the evaluation of (b) (4) for FDA consideration. After review of additional information provided by Ultragenyx, the FDA will provide feedback on Ultragenyx's proposed changes to PMR-1, including the revised timelines. Ultragenyx agreed to provide the available phenotype/genotype data from patients currently enrolled in trials.

Regarding PMR-1 and PMC-3, Ultragenyx will provide additional justification for why vestronidase alfa (b) (4) to subjects who are participating in Study UX003-CL401 and why this will not impact both recruitment and retention in that study. The Agency will provide feedback on the proposed protocol and timeline for Study UX003-CL401. Ultragenyx clarified that they would like to initiate Study CL401 as soon as possible.

Regarding PMR-2, the Agency agrees with Ultragenyx's proposed timeline.

5. Major labeling issues – 10 minutes
Section 12.2- PD section: Description of uGAG data
Section 14: Description of Clinical Studies
6. Information Requests
 - CMC information request sent on 8/1/2017 - Ultragenyx anticipates to submit a response on 9/29/2017
 - Clinical pharmacology information request sent on 9/12/17 and 9/14/17.
 - Clinical information request sent 9/13/17 regarding methodology for liver and spleen imaging
7. Review Plans – 5 minutes
We plan to take action on this application by the user fee goal date, November 16, 2017, as noted in our filing communication dated May 12, 2017.
8. Wrap-up and Action Items

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/s/

KATHLEEN M DONOHUE
09/20/2017

BLA 761047

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Ultragenyx Pharmaceutical Inc.
Attention: Min Chen Young, Ph.D., RAC
Associate Director, Regulatory Affairs
60 Leveroni Court
Novato, CA 94949

Dear Dr. Young:

Please refer to your Biologics License Application (BLA) submitted under the Public Health Service Act for Mepsevii (vestronidase alfa) injection 10 mg/5mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 20, 2017. Attached is our background package, including our agenda, for this meeting.

Please email a list of your attendees to Jenny.Doan@fda.hhs.gov, at least one week prior to the meeting.

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

Sincerely,

{See appended electronic signature page}

Dragos Roman, M.D.
Deputy Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 20, 2017; 11:00 AM – 12 PM EST
Meeting Location: White Oak Building 22, Conference Room 1309
10903 New Hampshire Ave,
Silver Spring, MD 20903
Application Number: 761047
Product Name: Mepsevii (vestronidase alfa)
Indication: Treatment of MPS VII
Applicant Name: Ultragenyx

FDA ATTENDEES (tentative)

Office of Drug Evaluation III

Hylton V. Joffe, MD, MMSc, Acting Deputy Director

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Kathleen Donohue, MD, Clinical Team Leader
Dina Zand, MD, Clinical Reviewer
Sushanta Chakder, PhD, Pharmacology Team Leader
Yolanda Branch, PhD, Pharmacology Reviewer
Joette Meyer, PharmD, Associate Director for Labeling
Jenny Doan, MSN, BSN, Regulatory Project Manager

Office of Clinical Pharmacology

Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader
Christine Hon, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics/ Division of Biometrics III

Yeh-Fong Chen, PhD, Biostatistics Team Leader
Min Min, Biostatistics Reviewer

Office of Biotechnology Products

Cristina Ausin, PhD, Team Leader
Rukman De Silva, PhD, Product Quality Reviewer

Division of Microbiology Assessment

Max Van Tassell, PhD, Reviewer
Bo Chi, PhD, Reviewer
Virginia Carroll, PhD, Reviewer

APPLICANT ATTENDEES

Christine Murray, MS, RAC, Vice President, Regulatory Affairs

Min Chen Young, Ph.D., RAC, Associate Director, Regulatory Affairs
Christine Haller, M.D., Vice President, Clinical Sciences and Drug Safety, Medical Monitor
Qais Abu Ali, M.D., Medical Director, Clinical Sciences, Clinical Sciences
Wenjie Song, Ph.D., Associate Director, Biostatistician
Tricia Cimms, MPH, Director, Clinical Outcomes Research & Evaluation, Clinical Sciences

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Quality Microbiology – Drug Product

The following issues should be resolved prior to approval. We acknowledge that the relevant study results were planned to be submitted on September 15, 2017.

- Establish a container closure integrity method with adequate sensitivity and provide the validation data
- Provide results from a crimping validation study performed with the new container closure integrity method to support the crimping parameters
- Conduct two additional media fills using the (b) (4) and provide the results

Clinical

The review of clinical efficacy is ongoing.

3. Minor Review Issues

Quality Microbiology – Drug Product

We acknowledge that a microbial hold time study to support the label's post-dilution storage conditions is in progress and will be submitted by October 10, 2017, as indicated in the amendment dated August 31, 2017 (sequence 0043). The post-dilution hold time in the label should be changed to 36 hours at 2-8°C or 6 hours at (b) (4) without storage at 2-8°C if the results from the study do not support the proposed hold time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

POST-MARKETING REQUIREMENTS/COMMITMENTS (PMRs/PMCs)

We have identified the following potential PMRs/PMCs at this time (please note that additional PMRs/PMCs may be considered upon finalization of reviews). A teleconference with the (b) (4) is scheduled for October 5, 2017 to facilitate regulatory cooperation. Note that we propose one clinical PMR (PMR-1), and one clinical PMC (PMC-3), and anticipate that the same patients could be enrolled in both studies.

PMR-1: Analyze long-term immunogenicity and hypersensitivity reactions (including anaphylaxis) in Study Protocol UX003-CL401 patients followed up to three years on vestronidase alfa. The following analyses will be conducted: (1) incidence rates for hypersensitivity reactions, (2) incidence rates for the appearance of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against vestronidase alfa, (3) temporal associations between ADA or Nab formation and hypersensitivity reactions, (4) associations between beta-glucuronidase (GUSB) genotype and hypersensitivity reaction risk, (5) association between intrinsic GUSB enzymatic activity and hypersensitivity reaction risk, and (6) assess clinical impact of immunogenicity. To complete these analyses, protocol UX003-CL401 will require collection of molecular genotype and intrinsic GUSB enzymatic activity (apart from any concurrent enzyme replacement). Submit annual study reports that contain results from analyses of interim data. We expect the final study report to be based on a study population that contains at least 20 patients (including at least six patients less than one year old) who initiated vestronidase alfa treatment under Study Protocol UX003-CL401.

Draft Protocol Submission: 02/2018

Final Protocol Submission: 07/2018
Study/Trial Completion: 10/2021
Final Report Submission: 06/2022

PMR-2: Perform a pre- and post-natal developmental study in rats to assess the effects of vestronidase on pre- and post-natal development.

Draft Protocol Submission: 03/2018
Final Protocol Submission: 06/2018
Study/Trial Completion: 03/2019
Final Report Submission: 07/2019

PMC-3: Create a 10-year registry of patients with mucopolysaccharidosis type VII (MPS VII) from patients enrolled in Study Protocol UX003-CL401. The following critical data elements will be collected in this registry, (1) beta-glucuronidase (GUSB) genotype, (2) intrinsic GUSB enzymatic activity apart from any concurrent enzyme replacement treatment, (3) complete record of pre-registry and registry treatments with vestronidase alfa, (b) (4), and (6) results from registry baseline and periodic tests for MPS VII clinical outcomes to include liver and spleen size, pulmonary function, motor function, and neurocognitive function.

Draft Protocol Submission: 02/2018
Final Protocol Submission: 07/2018
Study/Trial Completion: 10/2028
Final Report Submission: 10/2029

PMC-4: Conduct studies to address the bioanalytical method validation of the two assays used to measure the pharmacodynamic marker glycosaminoglycans, (b) (4) the Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) method by (b) (4). Specifically, perform incurred sample reanalysis (ISR) for (b) (4). Complete the ongoing assessment of long-term sample storage stability of the LC-MS/MS method to cover the storage duration of all study samples from clinical trials. Use freshly prepared calibrator standards and quality controls in conducting the ISR and long-term sample storage stability analysis for the LC-MS/MS method.

Draft Protocol Submission: 02/2018
Final Protocol Submission: 04/2018
Study/Trial Completion: 07/2018
Final Report Submission: 09/2018

PMC-5: To conduct the bioburden and endotoxin method qualification to include a total of three lots (b) (4)

Proposed timeline: The final study report will be submitted by December 2019.

PMC-6: To re-evaluate all Mepsevii drug substance and drug product release and stability acceptance criteria when a statistically significant number of lots (25) of drug substance have been manufactured using the commercial manufacturing process and tested using commercial specification. The corresponding data, the analytical and statistical plan used to evaluate the specification, and any proposed changes to the specifications will be provided in the final study report.

Proposed timeline: The final study report will be submitted by December 2035.

PMC-7: To perform a leachable study to evaluate leachables in the UX003 drug product container closure system. The analysis will be performed using one drug product lot that has passed the end of shelf-life under the long term (5 ± 3 °C) and accelerated (25 °C/60% RH) storage conditions. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi volatile species and metals. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

Proposed timeline: The final study report will be submitted by January 2019.

LABELING

The labeling review is ongoing. We provided preliminary comments on the carton/vial labeling and product labeling on August 11, 2017. We received the revised carton/vial and product labeling on August 22, 2017.

LCM AGENDA

1. Introductory Comments – 2 minutes (Jenny Doan, RPM/Kathleen Donohue, M.D.)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 2 minutes

3. Discussion of Minor Review Issues – 2 minutes

4. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

5. Major labeling issues – 10 minutes

Section 12.2- PD section: Description of uGAG data

Section 14: Description of Clinical Studies

6. Information Requests

- CMC information request sent on 8/1/2017 - Ultragenyx anticipates to submit a response on 9/29/2017
- Clinical pharmacology information request sent on 9/12/17 and 9/14/17.
- Clinical information request sent 9/13/17 regarding methodology for liver and spleen imaging

7. Review Plans – 5 minutes

We plan to take action on this application by the user fee goal date, November 16, 2017, as noted in our filing communication dated May 12, 2017.

8. Wrap-up and Action Items

FDA Foreign Visitor Request

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITIZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER: COUNTRY THAT ISSUED PASSPORT: ISSUANCE DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE	
POINT OF ENTRY (This is the building that the foreign visitor will enter)	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

DRAGOS G ROMAN
09/15/2017