CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761068Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 761068	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Crysvita Established/Proper Name: burosumab-twza Dosage Form: solution for injection		Applicant: Ultragenyx Pharmaceutical, Inc. Agent for Applicant (if applicable):
RPM: Samantha Bell		Division: Division of Bone, Reproductive, and Urologic Products

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)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is April 17, 2018	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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
☐ Rolling Review
☒ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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)? • If so, specify the type	☒ No ☐ Yes
❖ 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
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 4/17/18
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
• Original applicant-proposed labeling	☒ Included
❖ 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)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ 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
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	10/30/17 10/27/17
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 10/7/17 DMEPA: ☐ None 1/26/18; 2/26/18; 3/7/18 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None 4/2/18 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None See Integrated Quality Assessment dated 1/22/18 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	10/7/17 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed (Do not include)
❖ 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 *(indicate date)*
  ○ If yes, OC clearance for approval *(indicate date of clearance communication)*
	☐ Yes ☒ No
	
	☐ Not an AP action

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: The drug product for this indication has an orphan drug designation, and therefore is exempt from the PREA requirement.	
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	6/22/16
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	6/21/16
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	N/A
❖ 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.) *(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)*	Included
❖ 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)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA or BPD Type 4 meeting *(indicate date of mtg)*	☐ No mtg 6/19/17 7/18/17 (CMC only)
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 12/10/15
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 11/30/17
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 2/15/18
• Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None See Multi-Disciplinary Review dated 4/11/18
Division Director Summary Review *(indicate date for each review)*	☐ None See Multi-Disciplinary Review dated 4/11/18
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None See Multi-Disciplinary Review dated 4/11/18
PMR/PMC Development Templates *(indicate total number)*	☐ None 5

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review See Multi-Disciplinary Review dated 4/11/18
• Clinical review(s) *(indicate date for each review)*	See Multi-Disciplinary Review dated 4/11/18
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ 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 *(indicate date of review/memo)*	See Section 13.2 of the Multi-Disciplinary Review dated 4/11/18
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None COA 1/17/18 DPMH 1/17/18 and 1/24/18
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	None None ☒ None REMS not necessary; 3/22/18
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 2/12/18
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review See Multi-Disciplinary Review dated 4/11/18
Statistical Review(s) *(indicate date for each review)*	☐ None See Multi-Disciplinary Review dated 4/11/18
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review See Multi-Disciplinary Review dated 4/11/18
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review See Multi-Disciplinary Review dated 4/11/18
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None See Multi-Disciplinary Review dated 4/11/18
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 11/3/17

[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).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review See Multi-Disciplinary Review dated 4/11/18
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review See Multi-Disciplinary Review dated 4/11/18
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None See Multi-Disciplinary Review dated 4/11/18
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 1/17/18; 1/22/18; 2/28/18
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None DMA 2/8/18;
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See p. 41 of Multi-Disciplinary Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ 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)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ 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 *Application Product Names* 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/

SAMANTHA S BELL
04/19/2018

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Final PI with FDA edits
Date:	Tuesday, April 17, 2018 9:08:00 AM
Attachments:	BLA 761068 PI FDA edits 041718.docx

Dear Dr. Sandberg,
Please refer to your Biologic License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

Attached are FDA edits to the Prescribing Information (PI).

If you are in agreement, accept the changes and submit clean versions of the PI to the application.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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/s/

SAMANTHA S BELL
04/17/2018

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 PI with FDA edits
Date:	Monday, April 16, 2018 3:55:00 PM
Attachments:	BLA 761068 PI FDA edits 041618.docx

Dear Dr. Sandberg,
Please refer to your Biologic License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

Attached are FDA edits to the Prescribing Information (PI).

If you are in agreement, accept the changes and submit clean versions of the PI to the application.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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/s/

SAMANTHA S BELL
04/16/2018

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Final PI with FDA edits
Date: Thursday, April 5, 2018 4:23:00 PM
Attachments: BLA 761068 040518 PI_FDA edits.docx

Dear Dr. Sandberg,
Please refer to your Biologic License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

Attached are the final FDA edits and comments for the BLA 761068 Prescribing Information (PI).

Let us know as soon as possible if you would like a schedule a teleconference next week to discuss.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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/s/

SAMANTHA S BELL
04/05/2018

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 PI and PMR/PMC Comments
Date:	Tuesday, March 27, 2018 6:03:00 PM
Attachments:	BLA 761068 032718 Crysvita PMR_PMCs.docx BLA 761068 PI FDA edits_032718.docx

Dear Dr. Sandberg,
Please refer to your Biologic License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

Attached are FDA edits and comments for the BLA 761068 Prescribing Information (PI) as well as our version of the Postmarketing Requirements (PMR) and Postmarketing Commitments (PMC).

Let us know as soon as possible if either of these require further discussion as we should consider scheduling a teleconference next week to discuss.

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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/s/

SAMANTHA S BELL
03/27/2018

Rare Pediatric Disease Priority Review Voucher eligibility checklist (draft)

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 761068 (Burosumab)	**Review Division - DBRUP**
Requirement	**Meets? (yes/no)**
For prevention or treatment of a *rare pediatric disease? (OOPD makes determination)*	Yes 7/11/2017
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 confirmed from OND Reviewer (Theresa Kehoe) email receive 3/12/2018
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
03/27/2018

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Tuesday, February 27, 2018 11:34:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and request for the carton labeling based on your February 12, 2018, response to our Information Request. We are requesting a response by March 6, 2018.

As currently presented, there are two barcodes (i.e., linear and 2D data matrix) on the side panel of the carton labeling. Since the barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers.[b] Therefore, we recommend you move the 2D data matrix barcode to other side panel and present it in a size that does not compete with, or distract from the presentation of other required or recommended information on the carton labeling.

b Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-2.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
02/27/2018

From: Monica Sandberg
To: Borbor, Mammah
Subject: RE: BLA 761068 - Proprietary name
Date: Wednesday, February 14, 2018 12:26:37 PM

Hi Mammah,

Thank you very much for clarifying, very much appreciated.

Regards,

Monica

From: Borbor, Mammah [mailto:Mammah.Borbor@fda.hhs.gov]
Sent: Wednesday, February 14, 2018 8:19 AM
To: Monica Sandberg <MSandberg@ultragenyx.com>
Subject: RE: BLA 761068 - Proprietary name

No further action is required. Should your application receive full approval, the name Crysvita will be considered fully approved as well and can be used in marketing.

Mammah Borbor-Lebbie

From: Monica Sandberg [mailto:MSandberg@ultragenyx.com]
Sent: Thursday, February 08, 2018 9:55 AM
To: Borbor, Mammah <Mammah.Borbor@fda.hhs.gov>
Subject: BLA 761068 - Proprietary name

Dear Mammah,

I wanted to follow up with you regarding the approval of the proprietary name Crysvita. As was communicated last year, we received conditional approval of the proprietary name during BLA review (see attached). Are there any other steps that needs to occur for Crysvita to us to have full approval of the proprietary name? Is it just a matter of the BLA receiving approval or are other actions required?

Many thanks in advance for your guidance.

Best regards,

Monica

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/s/

MAMMAH S BORBOR-LEBBIE
02/16/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

GENERAL ADVICE

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandburg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Ct.
Suite 200
Novato, CA 94949

Dear Dr. Sandburg:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for UX023/KRN23.

We also refer to our December 11, 2017, correspondence, notifying of the Agency's intention to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning for its product in an advice letter.

We have the following comment:

> We find the nonproprietary name, burosumab-twza, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, burosumab-twza will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of the proposed suffix will be re-evaluated when you respond to the deficiencies. If we find the proposal unacceptable upon our re-evaluation, we would inform you of our finding.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Mammah Borbor-Lebbie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-7731. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager in the Office of New Drugs, at 301-796-9687.

Sincerely,

{See appended electronic signature page}

Lubna Merchant, M.S., Pharm.D.
Acting Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
02/13/2018

LUBNA A MERCHANT
02/13/2018

From:	Borbor, Mammah
To:	MSandberg@ultragenyx.com
Subject:	BLA 761068
Date:	Wednesday, February 07, 2018 5:47:00 PM
Importance:	High

Hello Ms. Sandberg

We refer to BLA 761068 and the carton labeling submitted with your January 30, 2018 response to our information request. We note the addition of a placeholder for a 2D barcode beneath the linear barcode on the carton labeling. We also note you state the barcode is intended for packaging and production purposes only. We ask that you confirm the 2D barcode is a 2D data matrix barcode that contains the NDC, lot number, and expiration date.

We kindly request that you respond by February 12, 2018.

Thanks kindly,

Mammah

Mammah Sia Borbor-Lebbie, MS, MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

FDA
White Oak Complex, Bldg 22, Rm 4433
10903 New Hampshire Ave.
Silver Spring, MD 20993
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MAMMAH S BORBOR-LEBBIE
02/07/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

INFORMATION REQUEST

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by February 7, 2018 in order to continue our evaluation of your application.

FDA comments on the response submitted in amendment (sequence # 0042) dated February 05, 2018:

1. Revise Table 3.2.P.5.2.1 in section 3.2.P.5.2 to indicate the correct revalidated dye ingress CCI test method used for testing stability samples.
2. Description of revalidated dye ingress CCI test method is not provided in section 3.2.P.5.2.2.2 "Container Closure Integrity". Update section 3.2.P.5.2.2.2 with the description of revalidated dye ingress CCI test method used for CCI testing of stability samples. Description should include the critical parameters (concentration of dye, pressure challenge and time of exposure of sample and control units to the challenge and dye) used for the CCI testing.

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Melinda Bauerlien

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Date: 2/06/2018 01:47:32PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

INFORMATION REQUEST

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by February 5, 2018 in order to continue our evaluation of your application.

FDA comments on the response submitted in amendment (sequence # 0041) dated January 31, 2018:
Update section 3.2.P.5.2 with revalidated CCI test method and indicate that a defective vial with a breach size of 20 µm will be included as system suitability control during container closure integrity testing of stability samples

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Thursday, January 25, 2018 12:23:00 PM

Dear Dr. Sandberg:

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following requests for additional information. We are requesting a response by January 30, 2018.

For Protocol UX023-CL201, provide a certified copy, with audit trails, of the Rickets Severity Score (RSS) Score and the Radiographic Global Impression of Change (RGI-C) Global Score for all subjects at Baseline, Week 40 and Week 64.

For Protocol UX023-CL303, provide a certified copy, with audit trails, for all subjects of the serum phosphorus (mg/dL) levels.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
01/25/2018

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Carton and Container Comments
Date: Tuesday, January 23, 2018 11:06:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for the carton and container labeling submitted on January 5, 2018. We are requesting a response by January 30, 2018.

A. Vial Container Label

1. We acknowledge the space limitation. Per 21 CFR 610.60(a)(2), the U.S. license number must appear. This may be accomplished by removing the non-required words (b) (4) appearing at the bottom of the label to ensure that required information appears. Once the official BLA license transfer has occurred, then the Applicant as it appears on Form FDA 356h may appear on labels and labeling. Revise as follows:

"Ultragenyx Pharmaceutical Inc. US License No. xxx"

2. The strength expression (i.e., 10 mg/mL, 20 mg/mL, 30 mg/mL) is located on the side panel of the container labels and may be overlooked due to vial curvature. The strength statement is customarily located below the proper name on US labels and labeling such that the principal display panel (PDP) presents the proprietary name, proper name, finished dosage form, strength statement, etc. in such order. Relocate the strength statement to the PDP to minimize the risk of wrong-strength medication errors.

3. We note that the container label lacks a net quantity statement. We are concerned that practitioners may not be able to easily identify the volume supplied with each vial, which may result in confusion leading to delay in therapy or the wrong quantity being dispensed. We recommend you indicate the net quantity on the container labels (e.g., 1 mL). Ensure the net quantity statement appears away from the product strength and has less prominence. This may be accomplished by adding "1 mL" to the "single-dose vial" statement and relocating the statement to the side panel ("1 mL single-dose vial").

B. Carton Labeling

1. We note that (b) (4) on the carton labeling (b) (4) (b) (4), which appears on the side panel and the PDP is redundant and may be easily overlooked due to visual clutter. We recommend you consider revising the (b) (4) statement on the carton labeling (b) (4) to "1 vial" and relocating the (b) (4) statement to the bottom right corner of the PDP to minimize visual clutter and improve readability. Lastly, to decrease clutter, consider removing (b) (4) (b) (4) from the side panel.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
01/23/2018

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Information Request
Date:	Monday, January 22, 2018 2:42:00 PM

Dear Dr. Sandberg:

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information. We are requesting a response by February 5, 2018.

We note that the original BLA reported two patients (b) (6) (b) (6)) underwent surgery for cervical spinal stenosis during studies. According to the 120-Day Safety Update, 4 additional patients have undergone spinal surgery: patients (b) (6). In each of these cases, it appears that there was pre-existing spinal stenosis, and it is unclear to what extent symptoms worsened during the study and when the decision for surgery was made. Provide any available information on the incidence of spinal stenosis and/or cord compression or spinal surgery in patients with XLH, the potential role of spinal ligament calcification (enthesopathy) in this process, and any evidence that burosumab may benefit or worsen these conditions.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
01/22/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

INFORMATION REQUEST

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by January 25, 2018 in order to continue our evaluation of your application.

Section 3.2.S.7 – Stability

1. Bioburden (microbial enumeration) samples are not required during stability for US licensure. Please remove those samples from your post-approval stability protocols.

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

LABELING PMR/PMC DISCUSSION COMMENTS

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your Biologic License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We also refer to our October 25, 2017, letter in which we notified you of our target date of January 17, 2018, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2018 Through 2022." **OR** "Biosimilar Biological Product Reauthorization Performance Goals and Procedures - Fiscal Years 2018 Through 2022."

We received your December 15, 2017, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by February 22, 2018. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader and Deputy Division Director.

We have the following proposed Postmarketing Requirements:

1. A postapproval surveillance program to evaluate whether there is an association between treatment with burosumab, the occurrence of nephrocalcinosis and renal failure. This program will be incorporated into your X-linked Hypophosphatemia Disease Monitoring Program with the current objective of collecting information on the disease for up to 10 years. You will need to incorporate an additional safety objective into this program of identifying the risk of nephrocalcinosis in this population. Collection for the safety data from program will begin within 90 days of protocol agreement and after the first marketed dose of burosumab. Progress reports will be submitted to the FDA at six month, one year and annual thereafter with an emphasis on evaluating the effectiveness of surveillance in meeting your objective of obtaining data from a minimum of 500 subjects of whom 200 will be pediatric patients.
2. Conduct a study to reanalyze banked immunogenicity serum samples from XLH clinical trials including Study UX023-CL205, Study UX023-CL201, and Study UX023-CL303 to determine the presence of anti-drug antibodies (ADA) using a validated ADA assay with improved drug tolerance. Characterize the neutralizing activity of ADA for samples tested positive for ADA. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy and safety in subjects with XLH based on the ADA data generated with the newly validated assay.

We have the following proposed Postmarketing Commitments:

1. Conduct studies to further characterize the burosumab master cell bank (MCB) and to confirm the monoclonality of the MCB.
2. Conduct studies to evaluate effector functions (i.e., antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) of burosumab. The final Postmarketing Commitment report should be submitted based on the outcome of the studies per 21 CFR 601.12.

If you have any questions, call me at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Samantha Bell, B.S., B.A., R.A.C.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

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

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/s/

SAMANTHA S BELL
01/17/2018

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Information Request
Date:	Wednesday, January 17, 2018 11:09:00 AM

Dear Dr. Sandberg:

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following requests for additional information. We are requesting a response by January 18, 2018.

For the following figures, provide an updated figure for mean (+/-SD) of the parameter instead of mean (+/-SE).

In study CL205 report

- Figure 10.2.1.1 Serum Phosphorus Concentration and Change in Serum Phosphorus (mg/dL) (Mean ± SE) over Time (PK/PD Analysis Set)

- Figure 11.2.3 Recumbent Length/Standing Height Z Score and Change in Z Score (Mean ± SE) over Time (Efficacy Analysis Set)

- Figure 10.2.2.1 Serum 1,25-Dihydroxyvitamin D Concentration and Change from Baseline (pg/mL) (Mean ± SE) over Time (PK/PD Analysis Set)

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC

Regulatory Health Project Manager

FDA/Center for Drug Evaluation and Research

Division of Bone, Reproductive, and Urologic Products

WO22 - Room 5374

10903 New Hampshire Avenue

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samantha.bell@fda.hhs.gov

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research

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/s/

SAMANTHA S BELL
01/17/2018

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Information Request
Date:	Tuesday, January 16, 2018 9:11:00 AM

Dear Dr. Sandberg:

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following requests for additional information. We are requesting a response by January 17, 2018.

For the following figures, provide an updated figure for mean (+/-SD) of the parameter instead of mean (+/-SE).

In study 201

- Figure 10.2.1.1 Serum Phosphorus Level and Change from Baseline (mg/dL) (Mean ± SE) by Regimen (PK/PD Analysis Set)

- Figure 10.2.2.1.1 TmP/GFR and Change from Baseline (mg/dL) (Mean ± SE) by Regimen (PK/PD Analysis Set)

- Figure 10.2.3.1 Serum 1,25-Dihydroxyvitamin D Level and Change from Baseline (pg/mL) (Mean ± SE) by Regimen (PK/PD Analysis Set)

- Figure 11.1.10.1 Serum ALP Level and Change from Baseline (U/L) (Mean ± SE) (only the first part) by Regimen (PK/PD Analysis Set)

- Figure 11.1.10.2 Serum BALP Level and Change from Baseline (U/L) (Mean ± SE) by Regimen (PK/PD Analysis Set)

In study 303

- Figure 14.2.3.2.1 Serum 1, 25-Dihydroxyvitamin D Level (pg/mL) (Mean ± SE) by Randomized Treatment Primary Analysis Set, Week 24 Analysis

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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SAMANTHA S BELL
01/16/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068 **INFORMATION REQUEST**

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by January 11, 2018 in order to continue our evaluation of your application.

1. You referred to several Drug Master Files (DMFs) in your application. However, we did not find letters of cross-reference for either your vial, DMF (b) (4), or your stopper, DMF (b) (4). All DMFs that are indicated in your BLA need letters of cross-reference to be submitted to Section 1.4.4 as required by 21 CFR 314.420. Provide letters of cross-reference for all DMFs referenced in BLA 761068.

2. We do not agree with your proposed approach to post-approval stability studies for the drug substance or the drug product. You are proposing (b) (4) (b) (4)

   Update your stability protocol to align with ICH Q1A(R2). Finally, the stability of each presentation should be assessed individually because the concentrations of the API are different. You may justify a bracketing approach.

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Melinda Bauerlien

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068 **INFORMATION REQUEST**

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by January 12, 2018 in order to continue our evaluation of your application.

Section 3.2.S.2.4 – Control of Critical Steps and Intermediates

1. Provide endotoxin limits or acceptance criteria for product (b) (4) in routine manufacture of KRN23.

Section 3.2.S.4.2 – Analytical Procedures

2. Provide a description (b) (4) for the microbial enumeration test. (b) (4) (b) (4)
3. Provide a description of how the endotoxin method is conducted under routine conditions; (b) (4) (b) (4)

Section 3.2.S.2.5 – Validation of Analytical Procedures

4. Justify use of data obtained (b) (4) to qualify the microbial enumeration method (b) (4) (b) (4)
5. Submit a protocol and qualification report for the microbial enumeration method.
6. Submit a protocol and qualification report for the endotoxin test method.
7. Regarding the Low Endotoxin Recovery Study:
    a. Specify the volume and concentration of reference standard endotoxin (b) (4) (b) (4).

b. Provide the raw data (in EU/mL) from the study, including any replicates that were averaged to produce table 3.2.S.4.3.1.2.2.1

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Melinda Bauerlien

Digitally signed by Melinda Bauerlien
Date: 1/05/2018 12:27:43PM
GUID: 508da6dc0002676de5faf5b4bf3d0f72

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Thursday, January 04, 2018 3:31:00 PM

Dear Dr. Sandberg:

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following requests for additional information.

Clarify if any adolescent subjects (13 to 17 years of age) have been enrolled or whether you plan to enroll adolescent subjects in Study UX023-CL301. If not, provide justification why Study UX023-CL301 only enrolls subjects 1 to 12 years of age. We also request that you provide information regarding whether you have planned to conduct any other clinical trial in adolescent XLH patients.

We are requesting a response by January 8, 2018.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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samantha.bell@fda.hhs.gov

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SAMANTHA S BELL
01/04/2018

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Information Request
Date:	Thursday, December 28, 2017 10:23:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information. We are requesting a response by January 9, 2018.

- Provide details on how analgesic use was captured in the burosumab clinical trials (UX023-CL303), as well as a summary of the results. If this information has already been submitted, please direct us to the appropriate submission.

- In your response to the November 30, 2017, Information Request, you state "Each site was trained by Ultragenyx via WebEx on the administration of PROs, including the modified instructions for the WOMAC, prior to the initiation of the study. It is important to note that the instruction changes were successfully tested in a cognitive debriefing exercise performed as part of the qualitative validation of the WOMAC for use in XLH." However, the case report form (CRF) does not provide the modified instructions or questions to this questionnaire. Provide the exact copy of the WOMAC questionnaire (with modified instructions) that was administered to the subjects. Also, please direct us to the appropriate section of the PRO Evidence Dossier that describes the cognitive testing of these modified instructions.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
12/28/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Thursday, December 21, 2017 9:16:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information. We are requesting a response by December 29, 2017.

Provide control background data for premature birth incidence and gestation duration in cynomolgus monkeys for the laboratory that conducted Study (b) (4) 303-043 (b) (4).

In Table 2.6.6.6.2.1.1. of the Toxicology Written Summary control background data for fetal losses are provided (2000-2009). For premature birth the value is 5.1 %, with range 0-14.3%. However, in the Expert report by (b) (4) another number is provided (3.3±4.3%). Provide the correct values. In your response, specify whether the values pertain to live offspring or live or dead offspring, and provide values for live offspring.

Provide control background data for gestation duration. In the report of Study (b) (4) 303-043, the control background value mentioned is 160.8 days (p. 102/1877), which represents all births including premature ones. The Expert report by (b) (4) (page 4, 2nd paragraph from bottom) also refers to a history control range of the (b) (4) laboratory that would be described in the study report. However, data for the range could not be found in the report. Confirm that the average value (160.8 days) is correct and pertains to both premature and non-premature births, and provide the range.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
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/s/

SAMANTHA S BELL
12/21/2017

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Information Request
Date:	Friday, December 15, 2017 3:03:00 PM
Attachments:	BLA 761068 Crysvita burosumab Container Carton Comments.docx

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the attached comments and requests for the carton and container labeling. We are requesting a response by January 5, 2018.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
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BLA 761068
Crysvita (burosumab-xxxx)
Container Labels and Carton Labeling Comments

We have the following comments regarding your proposed container labels and carton labeling submitted on August 17, 2017.

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.
2. Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).
3. Your NDC number format includes sequential numbers for the middle digits of the NDC product code numbers (i.e., 002, 003, and 004) which is not an effective differentiating feature and may lead to product selection medication error. Please revise the middle digits so they are not sequential. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX
4. The carton labeling and container label do not indicate the intended expiration date format and may pose risk of degraded drug medication administration errors. Please provide the intended expiration date format for evaluation. We recommend an expiration date format of MMMDDYYYY or MMM YYYY.

5. The storage statements as presented lack prominence. We recommend you use bold font for the storage statement and revise it to read, "Must be refrigerated, store at 36°F to 46°F (2°C to 8°C)." We recommend this revision to increase the prominence of this important information and minimize the risk of healthcare professionals overlooking the storage information which may lead to the administration of degraded drug product.

B. Vial Container Label

1. Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21CFR 610.60 (a)(2). Revise (b) (4) (b) (4) to read
   "Manufactured by: Ultragenyx Pharmaceutical Inc.
   US License No. xxx"
2. Add the statement "Discard unused portion." to appear after the package type term "single dose vial;" to ensure the label contains adequate directions of use and instructions for preparation of use per 21 CFR 201.5(g). This may be accomplished by relocating the "Rx Only" to appear in the upper right corner of the principal display panel.
3. Remove the (b) (4) appearing at the bottom of the label to ensure that non-required information is not competing in size and prominence with important required information per 21 CFR 201.15 (b)(1).

4. Ensure the linear bar code appears on the label per 21 CFR 201.25(b)(2) and (c). Ensure there is adequate white space around the linear bar code to facilitate scanning. Additionally, consider orienting the barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[1]
5. Revise the usual dose statement from "see insert" to read "See package insert" for clarity.

C. Carton Labeling

1. The applicant on Form FDA 356h is considered the licensed applicant, licensed manufacturer, or manufacturer. To comply with 21 CFR 610.61(b) the licensed manufacturer must appear as:
   "Manufactured by: Applicant on Form FDA 356h (Ultragenyx Pharmaceutical Inc.)
   Address
   US License No. xxxx"
2. Remove the statement (b) (4)
3. The applicant may include the distributor name and address on the carton labeling, however, confirm that the Distributor is Ultragenyx Pharmaceutical Inc.
4. Ensure "No preservative" appears on the carton labeling per 21 CFR 610.61 (e).
5. Revise the inactive ingredient list to appear in alphabetical order per USP <1091> Labeling of Inactive Ingredients with the qualitative list of inactive ingredients followed by their quantitative information (x mg) (b) (4) as follows: "Each 1 mL of solution contains: x mg burosumab, L-histidine (1.55 mg), L-methionine (1.49 mg), polysorbate 80 (0.5 mg), and D-sorbitol (45.91 mg).". Note that the side panel contains trailing zeros (i.e., 0.500 mg), which may be misinterpreted if the decimal point is not seen. Remove the trailing zeros to avoid misinterpretation (i.e., revise 0.500 mg to 0.5 mg).
6. Unbold "Each 1 mL of solution contains:"
7. Add the words "No U.S. standard of potency" per 21CFR 610.61 (r).
8. Remove the blocked orange words "Kyowa Kirin" appearing at the bottom of the label to ensure that non-required information is not competing in size and prominence with important required information per 21 CFR 201.15 (b)(1).

[1] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

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/s/

SAMANTHA S BELL
12/18/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Friday, December 15, 2017 11:56:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information. We are requesting a response by December 22, 2017.

Decreases in serum phosphorus and $1,25(OH)_2$VitD responses were noted over time in the 14-week repeat dose rabbit toxicity study. This was also observed in the 14-week monkey toxicity study and the 40-week adult and juvenile monkey toxicity studies, albeit it to a lesser extent. Provide an explanation for the attenuation of the pharmacologic response with repeat dosing in these animal studies. Also, provide an explanation for the attenuation of serum phosphorus and $1,25(OH)_2$VitD responses over time in the clinical studies, particularly KRN23-INT-002, UX023-CL203 and UX023-CL303.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
12/15/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068 **INFORMATION REQUEST**

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by December 19, 2017 in order to continue our evaluation of your application.

FDA comments on the response submitted in amendment (sequence # 0013) dated November 14, 2017

I. Drug product manufacturing process (3.2.P.3.3)

There is discrepancy (b) (4)

(b) (4)

II. Process Validation (Section 3.2.P.3.5)

(b) (4)

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If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

GENERAL ADVICE

Ultragenyx Pharmaceutical, Inc.
60 Leveroni Ct.
Suite 200
Novato, CA 94949

Attention: Monica Sandburg, Ph.D., RAC
Director, Regulatory Affairs

Dear Dr. Sandburg:

Please refer to your Biologic Licensing Application (BLA) 761068, submitted under section 351(a) of the Public Health Service Act on August 17, 2017.

On January 13, 2017, FDA issued final guidance entitled Nonproprietary Naming of Biological Products stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning. [1]

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 ("PRA"). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your 351(a) BLA is within the scope of this guidance. As such, we are sending this letter to inform you that FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

If you have any questions regarding the contents of this letter or any other aspects of the proper name review process, contact Lubna Merchant at 301-796-5162 or Jill Bordage at 301-796-5164. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager in the Office of New Drugs, at 301-796-9687.

Sincerely,

{See appended electronic signature page}

Lubna Merchant, MS, PharmD
Acting Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology Center for Drug Evaluation and Research

---

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/s/

LUBNA A MERCHANT
12/11/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Wednesday, December 06, 2017 4:00:00 PM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information. We are requesting a response by December 13, 2017.

1. Table 2.4.6.1.1. on p. 25 of the Nonclinical Overview summarizes NOAEL Safety Margins and the pharmacokinetic or toxicokinetic data that were used to calculate them. For adult monkeys, the AUC values at the NOAEL (ng.h/mL) at the 20th dose for males (0.03 mg/kg) and females (0.3 mg/kg) do not seem to agree with the values determined (ug.h/mL) in the studies as listed on page 22 of the Pharmacokinetic Summary. Additionally, since the animals at the NOAEL doses were dosed by the intravenous route, it is unclear how the Cmax values as listed under Table 2.4.6.1.1 were calculated. Provide clarification.

2. Define "simulated mean burosumab concentration (for adults)" and "mean Bayes exposure" (for pediatric patients), as described in (b) under Table 2.4.6.1.1, and justify the use of these parameters and not Cmax to calculate Cmax-based safety margins.

3. Provide [animal : human] AUC exposure multiples for all doses used in the repeat-dose toxicity studies in rabbits and cynomolgus monkeys. This includes the 14-week study in rabbits ((b) (4) 052-076/PKP0728), the 13-week and 40-week studies in adult monkeys (6691-185 and (b) (4) 303-044), and the 40-week study in juvenile monkeys ((b) (4) 303-020).

4. In the Toxicology Written Summary, Fig. 2.6.6.9.1 (p.47) shows the relationship between peak serum/plasma phosphorus and ectopic mineralization score for monkeys, rabbits, and Wt and Hyp mice. The data points for the monkeys in that figure appear to be different from those in Fig. 2.6.6.9.3 (p.48) representing data for both adult and juvenile monkeys. Did the data points in Fig. 2.6.6.9.1. represent adult monkeys only? And was the mineralization score calculated the same way for Fig. 2.6.6.9.1 and Fig. 2.6.6.9.3? Also, was the ectopic mineralization score calculated the same way for the three species, i.e., monkeys, rabbits and WT and Hyp mice, for which data are provided in Fig. 2.6.6.9.1.?

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
12/06/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Monday, December 04, 2017 10:19:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comment and request for additional information. We are requesting a response by December 11, 2017.

For Study (b) (4) 303-084, the 2-week study in Wild Type (WT) and Hyp mice, provide a graphic representation of the AUC of plasma phosphorus concentration over the [0 - 14 day] study period (pg.day/mL) vs. ectopic mineralization score. This is to address the difference in the relationship between peak plasma phosphorus concentration and mineralization score in WT vs. Hyp mice (Figure 2.6.6.9.2.in the Toxicology Written Summary).

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
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WO22 - Room 5374
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/s/

SAMANTHA S BELL
12/04/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Monday, December 04, 2017 10:10:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information. We are requesting a response by December 8, 2017.

1. In your response to FDA Information Request submitted on November 13, 2017, you stated that the between-subject variability (BSV) for EC50 could not be estimated for the pediatrics based on pediatric data only (Table 2). Clarify how the BSV for EC50 was included in your PK/PD simulations for the pediatric population (Figure 3 and Figure 4).

2. In your response to FDA Information Request submitted on November 13, 2017, for Figure 4, clarify if it is semi-log scales as you stated in the caption and if the grey shaded area represents 90% confidence interval as you stated in the note below the figure.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
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SAMANTHA S BELL
12/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

MID-CYCLE COMMUNICATION

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for burosumab.

We also refer to the teleconference between representatives of your firm and the FDA on November 30, 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 Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic 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: November 30, 2017, 11:00 A.M. to 12:00 P.M.

Application Number: BLA 761068
Product Name: burosumab
Proposed Indication: Treatment of X-linked hypophosphatemia (XLH)
Applicant Name: Ultragenyx Pharmaceutical, Inc.

Meeting Chair: Theresa Kehoe, M.D.
Meeting Recorder: Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products:
Audrey Gassman, M.D., Deputy Director
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Clinical Reviewer
Jacqueline Karp, M.D., Medical Officer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of New Drugs, Office of Drug Evaluation III:
Julie Beitz, M.D., Director

Office of Pharmaceutical Quality (OPQ)
Chikako Torigoe, Ph.D., Reviewer, Office of Biotechnology Products (OBP)
William Hallett, Ph.D., Team Leader, OBP
Bruce Huang, Ph.D., Reviewer, OBP
Scott Nichols, Office of Process and Facilities (OPF), Division of Microbiology Assessment (DMA) Microbiology Reviewer
Thuy Nguyen, OPF, Facility Reviewer

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Jie Wang, Ph.D., Clinical Pharmacology Team Leader (Acting)
Lin Zhou, Ph.D., Clinical Pharmacology Reviewer
Steven Li, Ph.D., Pharmacometrics Reviewer
Luning Zhuang, Ph.D., Pharmacometrics Reviewer
Jingyu Yu, Ph.D., Pharmacometrics Team Leader

OTS, Office of Biostatistics, Division of Biometrics III:
Mahboob Sobhan, Ph.D., Biometrics Team Leader
Jia Guo, Ph.D., Biometrics Reviewer

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Mammah Borbor-Lebbie, M.S., MBA, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
Mona Patel, Senior Risk Management Analyst, Division of Risk Management (DRISK)

OSE, Office of Pharmacovigilance and Epidemiology:
Samantha Cotter, Pharm.D., BCPS, FISMP, Division of Pharmacovigilance, Safety Evaluator
Wei Liu, Ph.D., Reviewer, Division of Epidemiology

Office of New Drugs, Immediate Office, Rare Diseases Program:
Kathryn O'Connell, M.D. Ph.D, Medical Officer

Office of Scientific Investigations (OSI)
Jenn Sellers, Ph.D., Reviewer

Office of New Drugs, Division of Pediatric and Maternal Health:
Yeruk Mulugeta, Ph.D., Clinical Analyst
Meshaun Payne, MHCA, BSMT, Regulatory Health Project Manager
Tamara Johnson, M.D., M.S., Lead Medical Officer, Maternal Health Team
Kristie Baisden, Medical Officer, Maternal Health Team
Alana Ferrari, Student

Office of New Drugs, Immediate Office, Clinical Outcome Assessments Staff:
Selena Daniels, Pharm.D., M.S., Team Lead

Office of the Commissioner, Office of Scientific Profession Development
Ramy Abdelrahman, Commissioner Fellow

APPLICANT ATTENDEES
Ultragenyx Pharmaceutical Inc.
So-ching Brazer, Ph.D., Director, Regulatory Affairs, CMC
Chao-Yin Chen, Ph.D., Executive Director, Biostatistics
Kelly Flagella Ph.D., DABT, Executive Director, Pharmacology and Toxicology
Meng Mao, Ph.D., Senior Manager, Biostatistics
Matt Mealiffe, M.D., Senior Medical Director, Clinical Science
Christine Murray, M.S., R.A.C., Vice President, Regulatory Affairs
Monica Sandberg, Ph.D., R.A.C., Director, Regulatory Affairs
Javier San Martin, M.D., Vice President, Clinical Sciences
Jack Shi, Ph.D., Executive Director, Pharmacokinetics
Alison Skrinar, Ph.D., Executive Director, Clinical Outcome and Evaluation
Julie Taylor, Ph.D., Executive Director, Bioanalytical Methods Development

Christina Theodore-Oklota, Ph.D., Associate Director, Clinical Outcome and Evaluation
Roo Vold, M.D., Executive Medical Director, Drug Safety and Pharmacovigilance
Tony Xu, Ph.D., Senior Associate, Regulatory Affairs

Kyowa Kirin International (PLC)
Ian Duguid, Ph.D., MRPharmS, Senior Vice President, Regulatory Affairs and Pharmacovigilance
Tomohiro Sudo, M.S., MBA, Executive Vice President, Global Product Leader, Strategic Product Portfolio Department

Kyowa Hakko Kirin Co. Ltd.
Rieko Waxman, M.S. Manager, CMC Technical Lead, Production Division

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

Office of Biotechnology Product (OBP):

Antibody-dependent cytotoxicity: Burosumab demonstrates antibody-dependent cellular cytotoxicity (ADCC) against cells that express FGF23 receptors. FGF23 receptors are widely expressed in human tissues and, therefore, ADCC is a potential safety concern. See discussion under Item 7.

Pharmacology/Toxicology: No significant issues identified thus far.

Clinical Pharmacology:

Adequacy of serum phosphorus assays: Refer to the information request sent on October 13, 2017. Responses we received on November 3, 2017. The adequacy of the responses regarding the validation and performance of serum phosphorous assays are under review. The FDA reiterated the importance of these assays as it directly relates to dose adjustment.

Clinical:

Antibody-dependent cytotoxicity: As outlined above, the occurrence of antibody-dependent cellular cytotoxicity against cells that express FGF23 receptors is a potential

clinical safety concern, particularly with respect to long-term effects on renal function. See discussion under Item 7.

Statistics: No significant issues identified thus far.

3.0 INFORMATION REQUESTS

The FDA acknowledged that a response to some of these information requests may have been received prior to this teleconference:

OBP:

Information request (IR) conveyed November 16, 2017, with the expected response due date of November 29, 2017. This request includes the assay and information for ADCC.

Division of Microbiology Assessment (DMA):

IR conveyed November 21, 2017, with the expected response due date of December 4, 2017. This is a request for additional information on microbial controls, bioburden, and endotoxin levels.

Clinical Pharmacology:

1) IR conveyed November 29, 2017, with the expected response due date of December 8, 2017:
    a) Based on Table 2 in your response to Question #3 in "Response to FDA Information Request for BLA 761068, Email Dated and Received on October 31, 2017", (b) (4) has used multiple instruments (Siemens ADVIA 1200, 1650/1800, 2400) to measure serum phosphorous levels in samples from burosumab XLH clinical trials (UX023-CL203, UX023-CL303, and UX023-CL304). You have only submitted validation reports for ADVIA 1800. Submit validation reports for the other instruments.
    b) For (b) (4), you have submitted serum phosphorous proficiency testing results for year 2016-17. For (b) (4), you have submitted serum phosphorous proficiency testing results for year 2017. Submit all proficiency testing results that cover the testing duration of serum samples from burosumab XLH clinical trials.
    c) With respect to the (b) (4) serum-phosphorous method validation summary report, submit detailed stability data that supported the sample stability information summarized in the Table presented in Section 2.3.4 Stability (b). In addition, there are no freeze and thaw stability results in this summary validation report. If freeze and thaw cycles were used during sample collection, storage and analysis, submit the relevant freeze and thaw stability data.
2) Submit bioanalytical reports for determination of serum phosphorous concentrations in Studies KRN23-INT-001, KRN23-INT-002, UX023-CL201, UX023-CL205, UX023-CL203, UX023-CL303, and UX023-CL304. If no bioanalytical reports are available, provide detailed information about how the samples were collected, stored, and analyzed.

Discussion at the Meeting:
Ultragenyx informed the FDA that bioanalytical reports are not available for the requested studies, but they do intend to provide the requested sample collection, storage, and analysis information for those studies.

Clinical:

IR conveyed September 19, 2017, for further information on the pregnancies that have occurred during the clinical trials. This information should be provided in the 120-day safety update.

Statistics:

1) IR conveyed November 21, 2017, regarding datasets for used for Study UX023-CL-205 Week 40 report and the shift tables for Study UX023-CL-201. The due date for this request is November 28, 2017.

2) Information request conveyed November 29, 2017, regarding Figures 2.7.3.3.2.1.1 and 2.7.3.3.2.2.1 in the summary of clinical efficacy (Module 2), to resubmit them with all plots in each figure on the same scale for X and Y axes. The due date for this response is November 5, 2017.

New Information Requests:

Clinical:

Provide the protocol for the planned postmarketing Disease Monitoring Program (DMP), or indicate where it is located in your BLA.

Discussion at the Meeting:
Prior to the teleconference, Ultragenyx confirmed the location in the BLA for the protocol. During the teleconference, Ultragenyx informed the FDA that an updated version of the DMP protocol is available. FDA agreed Ultragenyx should submit this updated version to the BLA.

Clinical Outcomes Assessment (COA)

IR sent November 30, 2017 with expected due date of December 8, 2017.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, based on the information currently available, we do not believe that a risk evaluation and mitigation strategy (REMS) will be necessary to ensure the benefits of the drug outweigh the risks. However, the potential safety concern regarding ADCC remains unresolved.

5.0 ADVISORY COMMITTEE MEETING

This application will not be presented before the Bone, Reproductive and Urologic Drug Advisory Committee for Reproductive Health Drugs.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting is scheduled for February 15, 2018.

7.0 ULTRAGENYX PRESENTATION

Ultragenyx presented slides on ADCC and the radiologist retraining and re-reading of the Study 303 x-rays for fracture/pseudofracture for discussion (see attachment).

Ultragenyx explained why they have determined the risk of ADCC with burosumab is low. The FDA explained that the concern is with chronic therapy and what could happen over time as FGF23 levels escalate. The FDA commented that the burosumab and FGF23 concentrations used in the ADCC assay were more than 10-fold lower than their levels observed in subjects who were on burosumab treatment for 64 weeks in Study UX023-CL201. The FDA stated they do not consider the comparison of ADCC activities of different antibodies against different target cells appropriate. The FDA also has the same concern with the complement dependent cytotoxicity (CDC) assay. The FDA inquired about the availability of C1q binding assay data and Ultragenyx confirmed data are available. However, Ultragenyx was unsure whether the C1q binding assay was qualified. The FDA may send an IR to review the available data on this binding assay. The FDA's recommendation may change based on clinical assessment of potential safety concern for burosumab effector functions. The FDA proposed that Ultragenyx could include summarized renal specific data for submission at the 120-day safety update and Ultragenyx agreed.

Ultragenyx explained why a re-reading was necessary for the Study 303 Week 24 primary analysis x-rays for fracture/pseudofracture healing. Ultragenyx presented the original and re-read results and concluded there was no overall change. Ultragenyx proposed to include the re-read data at the 120-day safety update. The FDA asked Ultragenyx to provide the information sooner as this is the type of submission that could trigger a clock extension. Ultragenyx agreed to submit the re-read data in 1 week with the datasets to follow shortly thereafter.

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/s/

THERESA E KEHOE
12/27/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Thursday, November 30, 2017 9:31:00 AM
Attachments: BLA 761068 113017 COA Information Request.docx

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the attached comments and request for additional information. We are requesting a response by December 8, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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Fax 301.796.9897
samantha.bell@fda.hhs.gov

1. In your clinical outcome assessment (COA) evidence dossier ("The Brief Pain Inventory-Short Form (BPI-SF) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) for Patients with X-linked hypophosphatemia"), you indicate the following in Section 4.3.3 (Training Methods):
   As the WOMAC® is a self-administered PRO instrument, no formal training for patients is necessary in terms of instrument completion aside from the detailed instructions provided on the first page of the instrument (see Figure 3 on the following page). Of note, while minimal instruction is needed, a user guide is available for those scoring the instrument (Bellamy, 2002).

   Clarify whether patients were trained to think about their overall disease condition when completing the WOMAC rather than "study joint" as specified in the WOMAC instructions.

2. Provide the following additional data for the WOMAC using UX023-CL303 trial data with both raw and transformed scores
   a. Item and Domain-level analyses
      i. Descriptive statistics (N, mean, standard deviation [SD], minimum, maximum, and % missing) for the WOMAC items, domain scores and total score by study visit
      ii. Baseline WOMAC item scores, domain scores and total score along with item distributions by response categories, and floor and ceiling effects for each item.

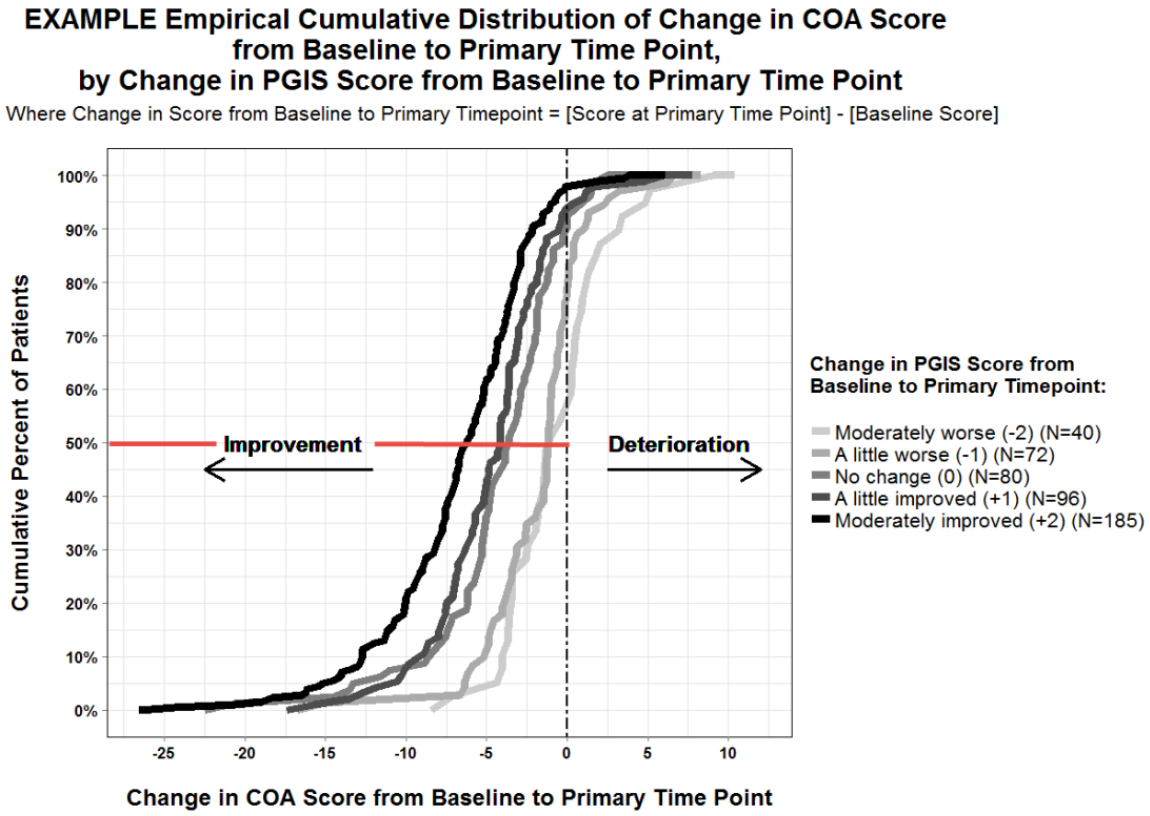
   b. Cumulative distribution function (CDF) and probability distribution function (PDF) plots
      - Provide the following CDF and PDF plots, including sample sizes for each CDF and PDF curve in each plot's legend, and median scores for each CDF and PDF curve. Adjacent anchor response categories can be collapsed if the sample size within a particular anchor response category is small (with justification provided); however, you should submit both the non-collapsed and collapsed plots. Examples of CDF and PDF are provided at the end of the document:

         i. CDF and PDF plots of the WOMAC Stiffness score change scores from baseline to Week 24 for all patients (both treatment and placebo arms pooled) by the different anchor response categories of the PGI-I at Week 24. Each anchor response category should be represented by a separate curve similarly to the example shown in Example 1. Similar CDF and PDF plots should be created for the WOMAC Physical Function score separately.

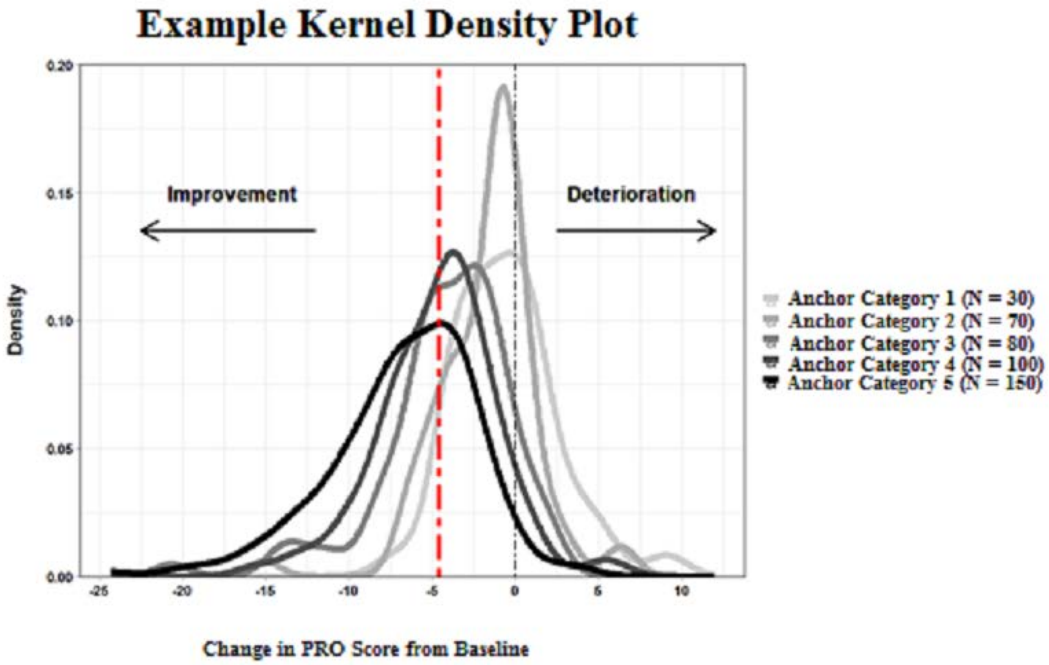
ii. CDF and PDF plots of the WOMAC Stiffness score change scores from baseline to Week 24 for all patients with separate curves for the different score point changes (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.) in the PGI-I from baseline to Week 24. Similar CDF and PDF plots should be created for the WOMAC Physical Function score separately.

3. Provide the following additional data for the BPI-Worst Pain item using UX023-CL303 trial data
   a. Cumulative distribution function (CDF) and probability distribution function (PDF) plots
   - Provide the following CDF and PDF plots, including sample sizes for each CDF and PDF curve in each plot's legend, and median scores for each CDF and PDF curve. Adjacent anchor response categories can be collapsed if the sample size within a particular anchor response category is small (with justification provided); however, you should submit both the non-collapsed and collapsed plots. Examples of CDF and PDF are provided at the end of the document:
     i. CDF and PDF plots of the BPI-Worst Pain item score change scores from baseline to Week 24 for all patients (both treatment and placebo arms pooled) by the different anchor response categories of the PGI-I at Week 24. Each anchor response category should be represented by a separate curve similarly to the example shown in Example 1.
     ii. CDF and PDF plots of the BPI-Worst Pain item score change scores from baseline to Week 24 for all patients with separate curves for the different score point changes (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.) in the PGI-I from baseline to Week 24.

Example 1. CDF Plot



Example 2. PDF Plot



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/s/

SAMANTHA S BELL
11/30/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Wednesday, November 29, 2017 11:03:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following request for additional information.

For Figures 2.7.3.3.2.1.1 and 2.7.3.3.2.2.1 in the summary of clinical efficacy (Module 2), resubmit them with all plots in each figure on the same scale for X and Y axes.

We are requesting a response by December 5, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
11/29/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Wednesday, November 29, 2017 10:18:00 AM

Dear Dr. Sandberg,

We are reviewing your November 3, 2017, response to our Information Request regarding serum phosphorous assay for BLA 761068. We have the following comments and requests for additional information.

- Based on Table 2 in your response to Question #3 in "Response to FDA Information Request for BLA 761068, Email Dated and Received on 31 October 2017", (b) (4) (b) (4) have used multiple instruments (Siemens ADVIA 1200, 1650/1800, 2400) to measure serum phosphorous levels in samples from burosumab XLH clinical trials (UX023-CL203, UX023-CL303, and UX023-CL304). You have only submitted validation reports for ADVIA 1800. Submit validation reports for the other instruments.

- For (b) (4), you have submitted serum phosphorous proficiency testing results for year 2016-17. For (b) (4), you have submitted serum phosphorous proficiency testing results for year 2017. Submit the proficiency testing results that cover the testing duration of serum samples from burosumab XLH clinical trials.

- With respect to the (b) (4) serum-phosphorous method validation summary report, submit detailed stability data that supported the sample stability information summarized in the Table presented in Section 2.3.4 Stability (b). In addition, there are no freeze and thaw stability results in the validation report. If freeze and thaw cycles were used during sample collection, storage and analysis, submit the relevant freeze and thaw stability data.

In addition, we have the following information request:

- Submit bioanalytical reports for determination of serum phosphorous concentrations in Studies KRN23-INT-001, KRN23-INT-002, UX023-CL201, UX023-CL205, UX023-CL203, UX023-CL303, and UX023-CL304. If no bioanalytical reports are available, provide detailed information about how the samples were collected, stored and analyzed.

We are requesting a response by December 8, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
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/s/

SAMANTHA S BELL
11/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068 **INFORMATION REQUEST**

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by December 4, 2017 in order to continue our evaluation of your application.

Section 3.2.S.2.2

1. Provide the following information regarding microbial control of the Burosumab DS manufacturing process and update the BLA accordingly.
    a. All bioburden and endotoxin sampling points. Specify where samples are taken (b) (4)
    b. All bioburden (b) (4) (b) (4)
    c. All proposed hold times (include temperatures).

A diagram conveying all the requested information and added to the Section 3.2.S.2.2 of the BLA could be submitted in lieu of written responses.

2. When multiple chromatography cycles are used (for one batch), specify (b) (4) (b) (4). Indicate whether bioburden and endotoxin are monitored (b) (4).
3. Clarify (b) (4) bioburden excursions and update Module 3.2.S.2.2. of the BLA accordingly.

Section 3.2.S.2.4

4. Confirm that (b) (4) mL are used for all bioburden (b) (4) controls.
5. (b) (4) include a bioburden monitoring sample (b) (4) and provide bioburden limits. Update Module 3.2.S.2.4 of the BLA accordingly.

Section 3.2.S.2.5

6. Provide bioburden and endotoxin acceptance criteria used [redacted].
7. Justify the high acceptance criteria (< [redacted] EU/mL) for endotoxin [redacted]).
8. Provide data supporting microbial control [redacted]. Include bioburden data taken [redacted].
9. Clarify if the bioburden samples in the concurrent validation protocol (refer to protocol VAL-PV-AB-15-028) [redacted].

Section 3.2.S.4.3

10. Provide maximum valid dilution (MVD) for endotoxin qualification of [redacted] release samples.

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Melinda
Bauerlien

Digitally signed by Melinda Bauerlien
Date: 11/21/2017 09:38:26AM
GUID: 508da6dc0002676de5faf5b4bf3d0f72

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Information Request
Date:	Monday, November 20, 2017 9:24:00 AM

Dear Dr. Sandberg,

We are reviewing your response to our November 15, 2017, information request regarding SAS macros/files. Explain why the following part of the SAS code was repeated multiple times in each SAS program with '-cl201-002-Pros-' in the name. We are requesting a response by November 21, 2017.

*********replace CL002 matched subjects********;*

proc sort data = treatment ; by idT; run;

proc sort data = final; by trt id; run;

…

data _null_;

set final;

file "&study\Data\Analysis\simulation\&output1" Mod;

put trt id age agesoc gender kneetot wrstotal total hazbase hpctbase base chg aval weight;

run;

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
11/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068 **INFORMATION REQUEST**

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by November 29, 2017 in order to continue our evaluation of your application.

S.2.2
Your development data in 3.2.S.2.6 identified key/critical process parameters that are not listed in 3.2.S.2.2. Generally, all key/critical process parameters should be listed in this section with acceptable ranges. Update this section with the following information or provide sufficient justification.

(b) (4)

S.2.3

1. You did not provide sufficient information to evaluate the clonality of burosumab MCB. Clarify the (b) (4) (b) (4) preparation of the MCB.

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If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Melinda
Bauerlien

Digitally signed by Melinda Bauerlien
Date: 11/16/2017 09:54:48AM
GUID: 508da6dc0002676de5faf5b4bf3d0f72

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Wednesday, November 15, 2017 11:36:00 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We are requesting submission of all SAS macros/files (e.g. init.sas, %desc_stats_se, %toc_map, etc.) for the propensity score analysis programs submitted on October 3, 2017, by November 16, 2017. Without these SAS files, your submitted programs are not executable.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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SAMANTHA S BELL
11/15/2017

From:	Bell, Samantha
To:	Monica Sandberg (MSandberg@ultragenyx.com)
Subject:	BLA 761068 Information Request
Date:	Tuesday, November 14, 2017 2:13:00 PM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. Regarding your model-independent pharmacokinetic (PK) comparability analysis of burosumab steady-state trough concentrations between the 10 mg/ml and 30 mg/ml product strengths, we have the following information requests:

1. We noted that 22 subjects received burosumab treatment in Study KRN-INT-002. Provide the concentration-time PK profiles (with and without dose normalization) of each subject who received the 10 mg/ml drug product in Study KRN-INT-001 and switched to the 30mg/ml drug product in Study-INT-002. The duration of the concentration-time profile should cover the first dose in Study KRN-INT-001 and the last dose in Study KRN-INT-002. Clearly demonstrate on the PK profile the time-point when the switch of drug products occurred and the time-points that were included in the PK comparability assessment. Submit the PK data for these subjects with necessary dosing and demographic information in a tabulated form.

2. Submit the analysis dataset for the "bioequivalence" testing which generated results presented in Table 2.7.1.3.1.1.1 and Figure 2.7.1.3.1.1.1 (Summary of Biopharmaceutics and Associated Analytical Methods) of your BLA.

We are requesting a response by November 20, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
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SAMANTHA S BELL
11/14/2017

M E M O R A N D U M

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

DATE: 11/3/2017

TO: Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to Inspect Memo**

RE: BLA 761068

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct the inspection of the analytical site. The rationale for this decision is noted below.

Rationale

OSIS has no inspection history for (b) (4), however, OSIS recommends that an inspection of the site will not be needed because, the requested review goal date of December 29, 2017 provides insufficient time for inspection completetion. In addition, the lack of study reports provides insufficient information to verify that (b) (4) conducted the phosphorus assays.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

M E M O R A N D U M

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

DATE: 10/31/2017

TO: Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: BLA 761068

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
11/03/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068 **INFORMATION REQUEST**

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by November 14, 2017 in order to continue our evaluation of your application.

I. Manufacturer(s) (3.2.P.3.1)

Update the BLA with the specific tests that are performed at Kyowa Hakko Kirin (KHK) site and clarify if the stability testing is also performed at KHK.

II. Drug product manufacturing process (3.2.P.3.3)

Provide the following information in section 3.2.P.3.3:

(b) (4)

[redacted]

III. Process Validation (Section 3.2.P.3.5)

(b) (4)

[redacted]

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Melinda
Bauerlien

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Date: 11/03/2017 07:45:00AM
GUID: 508da6dc0002676de5faf5b4bf3d0f72

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Tuesday, October 31, 2017 11:20:29 AM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information:

- You have used multiple different assays to measure serum KRN23 levels in XLH clinical trials. Submit cross-validation results of KRN23 assays to support that these pharmacokinetic (PK) assays are comparable and generate consistent PK data.

- Submit bioanalytical reports for determining serum KRN23 concentrations of clinical samples from Studies KRN23-001, UX023-CL203, UX023-CL303, UX023-CL201, and UX023-CL205.

- You have not provided any information for our assessment of the drug interaction potential for burosumab. While we understand that the potential for direct drug interaction between burosumab and CYP450 substrates are low, it is unclear whether the pharmacodynamic effect of burosumab may have an indirect impact on pharmacokinetics of small molecule drugs. For example, based on your proposed mechanism of action, by inhibiting FGF23, KRN23 can decrease excretion of phosphate from kidney and enhance intestinal absorption of phosphate and calcium. Provide justification for whether KRN23 could have an effect on the absorption and/or excretion of small molecule drugs in subjects with XLH.

We are requesting a response by November 13, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
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/s/

SAMANTHA S BELL
10/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Ultragenyx Pharmaceutical, Inc.
60 Leveroni Ct.
Suite 200
Novato, CA 94949

ATTENTION: Monica Sandburg, Ph.D., RAC
Director, Regulatory Affairs

Dear Dr. Sandburg:

Please refer to your Biologics License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for Burosumab, 10 mg/mL, 20 mg/mL, 30 mg/mL.

We also refer to your correspondence dated and received August 17, 2017, requesting review of your proposed proprietary name, Crysvita.

We have completed our review of the proposed proprietary name, Crysvita and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your August 17, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Mammah Borbor-Lebbie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-7731. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager in the Office of New Drugs, at 301-796-9687.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
10/30/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
10/30/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Friday, October 27, 2017 2:55:15 PM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following comments and requests for additional information:

Reference is made to your population pharmacokinetic (PK) and population PK/pharmacodynamic (PD) report "*ULTR-CSC-105: Population PK and PK/PD modeling of KRN23 in pediatrics and adults with X-linked hypophosphatemia*". Your population PK/PD modeling is based on pooled data from pediatric (1-12 years old) and adult subjects with XLH (e.g., Figure 12 on Page 53 and Table 14 on Page 59). While your approach to use population PK model to predict individual serum concentrations of KRN23 appears to be reasonable, your population PK/PD analysis assumes that the PK/PD relationship between serum concentrations of KRN23 and serum phosphorus change from baseline are similar between adult and pediatric subjects. We recommend that you conduct independent population PK/PD analysis for adult and pediatric subjects separately and compare whether the PK/PD parameters are similar between the two populations. We also recommend that you conduct additional PK/PD simulations to provide PD profiles at the proposed dose regimen in adolescent subjects using the population PK/PD model established only with the pediatric (1-12 years old) data.

Submit the PK/PD analysis results along with all the datasets and scripts used for the analysis by November 10, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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samantha.bell@fda.hhs.gov

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SAMANTHA S BELL
10/27/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Friday, October 13, 2017 1:03:44 PM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab.

We have the following requests for additional information:

1. Submit assay validation and analytical reports for the analytical methods used for the measurement of serum phosphorous concentrations in Studies KRN23-US-02, KRN23-001, KRN23-INT-001, and KRN23-INT-002.

2. You submitted "Method Validation Summary Report" from (b) (4) on September 20, 2017. This report does not contain detailed assay validation parameters and associated data for our review of the assay performance. Submit the full assay validation report that includes detailed data for evaluation of the following assay validation parameters: accuracy, precision, selectivity, sensitivity, reproducibility, and stability.

3. You have used multiple different assays to measure serum phosphorous levels in burosumab XLH clinical trials. Cross-validation of these phosphorus assays is needed to support pooling of the phosphorous data from different clinical studies in your population pharmacokinetic (PK) and PK/pharmacodynamics (PD) analysis. Our review of your population PK and PK/PD reports and the proposed dosing regimens based on the population PK/PD model could not proceed without information supporting that the phosphorous assays used in your clinical trials are comparable and generate consistent phosphorous data.

4. Submit the validation report(s) for assay(s) used to determine bone turnover markers (BTMs) serum concentrations. For each relevant clinical study, submit the bioanalytical study report for determination of serum BTMs concentrations.

5. Submit PK and PD datasets for clinical Studies KRN23-US-02 and KRN23-001.

6. Clarify why PK data from Study KRN23-001 were not included in the population PK analysis.

7. Provide Core Status text output and Model Text output files for the final population PK models in Population PK and PK/PD Reports LTR-CSC-105 and ULTR-PCS-103.

8. You stated that the final population PK models of burosumab were evaluated with several methods including bootstrap re-sampling as well as internal predictive check. Provide the summary of key bootstrap outputs for Population PK Report LTR-CSC-105.

9. Provide the datasets and the source code used for visual predictive check of the final population PK models.

We are requesting a response by October 25, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
10/13/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

PRIORITY REVIEW DESIGNATION

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your Biologics License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 601.2(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is April 17, 2018.

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, mid-cycle, 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 requirement/commitment requests by January 17, 2018.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before October 30, 2017.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

AUDREY L GASSMAN
10/03/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Friday, September 29, 2017 12:51:46 PM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab. We have the following request for additional information:

For Studies UX023-CL303, UX023-CL304, UX023–CL203, UX023-CL201, UX023-CL205, and UX023-CL301, provide the address, telephone, and email information, or location in the BLA, for the Principal Investigators (b) (4) (b) (4)

We are requesting this information by October 4, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
09/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068 **INFORMATION REQUEST**

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

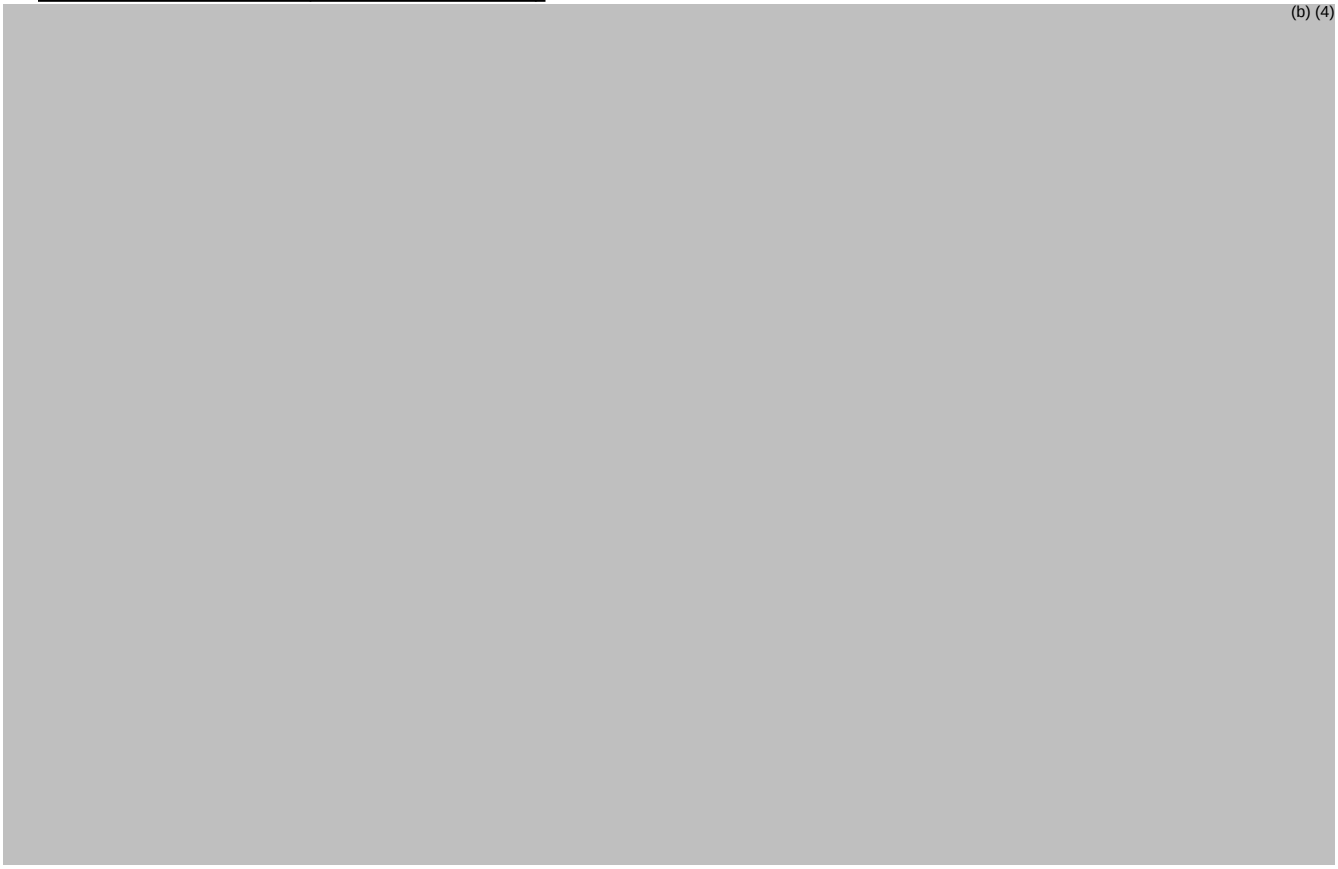
Please refer to your original Biologics License Application resubmission received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for burosumab.

We are reviewing your submission and have the following request for information. We request a prompt written response in order to continue our evaluation of your application.

Please respond to the following by October 6, 2017.

Process Validation (Section 3.2.P.3.5)

(b) (4)



Please respond to the following by October 20, 2017.
The information provided on your in-house host cell protein (HCP) assay is not sufficient to determine the appropriateness of the assay. Provide the qualification/validation report for the HCP assay which includes, but not limited to, detailed methods to prepare HCP for immunization, the HCP standard, and detailed methods to determine the coverage of the assay (e.g., number of detected spots).

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Melinda Bauerlien

Digitally signed by Melinda Bauerlien
Date: 9/28/2017 02:10:07PM
GUID: 508da6dc0002676de5faf5b4bf3d0f72

From: Bell, Samantha
Sent: Tuesday, September 19, 2017 12:33 PM
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request

Dear Dr. Sandberg:

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab.

In our preliminary review of your submission, it appears that there are three reported cases of pregnancy during clinical trials with burosumab. Confirm if there are any other reports of pregnancy that occurred during clinical trials of burosumab. Provide the following information in the 120 day Safety Update:

- Gestational age during which drug was administered, including the dose and duration.
- Pregnancy outcome (live birth, spontaneous abortion, termination of pregnancy, stillbirth, ectopic pregnancy, preterm delivery, etc.)
- Infant outcomes (gestational age at birth, congenital malformations, Apgar scores, Neonatal Intensive Care Admission, etc.).

In addition, confirm if there are any reports of infants who were exposed to burosumab through breastfeeding. If so, provide the following information:

- Were breast milk samples collected and evaluated?
- Were there any drug effects on the breastfed infant?
- Were there any drug effects on milk production?

Sincerely,
Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
09/19/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Friday, September 15, 2017 1:16:00 PM

Dear Dr. Sandberg:

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab.

We are not able to locate the assay validation report(s) for the analytical method(s) used to determine serum phosphorous concentrations in your clinical trials. Lack of information to evaluate the validity of the analytical assays when the dosing criteria and primary efficacy endpoint focuses on a laboratory value is a potential filing issue as well as a major review issue. We have the following information request:

- Submit the analytical assay validation report(s) for measurement of serum phosphorous levels.

- Clarify whether central laboratory or local laboratory was used in your clinical trials for measurement of serum phosphorous levels. For each laboratory, clarify what analytical methods were used and provide associated assay validation information.

Refer to the following guidance for more information.

Guidance for Industry: Bioanalytical Methods Validation
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf

We request a prompt written response by September 20, 2017. If additional time is needed, clarify if the assay validation reports exist and how much additional time is needed to provide the information.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
09/15/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

PROPRIETARY NAME ACKNOWLEDGEMENT

Ultragenyx Pharmaceutical, Inc.
60 Leveroni Ct.
Suite 200
Novato, CA 94949

ATTENTION: Monica Sandburg, Ph.D., RAC
Director, Regulatory Affairs

Dear Dr. Sandburg:

Please refer to your Biologics License Application (BLA) dated and received August 17, 2017, submitted under section 351(a) of the Public Health Service Act for Burosumab, 10 mg/mL, 20 mg/mL, 30 mg/mL.

We acknowledge receipt of your correspondence dated and received August 17, 2017, requesting a review of your proposed proprietary name, Crysvita.

If the application is filed, the user fee goal date will be November 15, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Mammah Borbor-Lebbie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7731. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager, in the Office of New Drugs at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Mammah Borbor-Lebbie, M.S., MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR-LEBBIE
09/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

BLA ACKNOWLEDGMENT

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: burosumab

Date of Application: August 17, 2017

Date of Receipt: August 17, 2017

Our Reference Number: BLA 761068

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 October 16, 2017, in accordance with 21 CFR 601.2(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions to the following address:

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

If you have any questions, call me at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Samantha Bell, B.S., B.A., R.A.C.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

SAMANTHA S BELL
08/30/2017

From: Bell, Samantha
To: Monica Sandberg (MSandberg@ultragenyx.com)
Subject: BLA 761068 Information Request
Date: Wednesday, August 23, 2017 1:42:00 PM

Dear Dr. Sandberg,

We are reviewing your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for burosumab.

We have the following comment and request for additional information regarding the submitted Statistical Analysis Plan (SAP), entitled, "To Evaluate the Long-term Efficacy of Burosumab (UX023-CL021) Compared to Conventional Therapy (UX023-CL002) using Propensity Score Methodology":

In general, we agree with the SAP. However, we need some clarification on which method you will consider as the primary approach in the propensity score analyses.

We are requesting a response by September 6, 2017.

Sincerely,

Samantha Bell

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993

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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
08/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 76488

MEETING PRELIMINARY COMMENTS

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Ct, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KRN23 (anti-FGF23 human IgG1 mAb), USAN: burosumab.

We also refer to your June 23, 2017 correspondence requesting a CMC Meeting to update the FDA on Ultragenyx's strategy on addressing the FDA's CMC requirements and to review the proposed updated burosumab CMC development program against agency expectations for product licensure.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Business Process Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comment

PRELIMINARY MEETING COMMENTS

Meeting Type:	C
Meeting Category:	CMC
Date:	July 24, 2017
Time:	9:00 AM
Phone Arrangements:	Please provide a CALL-IN NUMBER and PASSCODE to the FDA
Application Number:	IND 76488
Product Name:	KRN23 (anti-FGF23 human IgG1 mAb), USAN: burosumab
Indication:	For the treatment of X-linked Hypophosphatemia
Sponsor/Applicant Name:	Ultragenyx Pharmaceutical, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 24, 2017 at 9:00 AM between Ultragenyx Pharmaceutical, Inc. and the Office of Pharmaceutical Quality. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory business process manager (RBPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

To update the FDA on Ultragenyx's strategy on addressing the FDA's CMC requirements and to review the proposed updated burosumab CMC development program against agency expectations for product licensure.

2. DISCUSSION

Question 1:
Does the Agency agree with Ultragenyx's plan to address the FDA's CMC comments from the Type B Breakthrough Therapy meeting (Official Meeting Minutes, 10 November 2016)?

Agency Response:
The proposed strategy appears to be adequate; however, the acceptability of this approach will be addressed during the review.

Question 2:
Does the Agency agree that the proposed CMC content, structure, and format of the CTD sections provide sufficient quality information to support the filing of a BLA?

Agency Response:
The proposed CMC content, structure, and format of the CTD as summarized in Appendix 5 appears to be adequate. However, for the (b) (4) replace the rejection limit with an action limit in accordance with ICH guidance document Q6B.

Question 3:
BLA submission is targeted for end of July / early August 2017. The GMP production of the DS is currently planned for the months of November (WCB vial open) to December (filling) in 2017 only. Will the FDA be able to accommodate a pre-approval inspection during this production campaign?

Agency Response:
The proposed schedule is acceptable. However to facilitate the pre-license inspection, please provide in Module 1 of the BLA a manufacturing schedule detailing the upstream and downstream manufacture and bulk filling for the drug substance and the formulation and filling/stoppering/capping for the drug product at Kyowa Hakko Kirin Co., Ltd., Takasaki Plant, in Gumma, Japan.

Question 4:
Does the Agency have any comments on the proposed drug substance and drug product specifications?

DMA Response:
The provided release and stability tests appear reasonable. To facilitate our review of the appropriateness of the acceptance criterion for each test, identify the process by which each lot was manufactured, usage of each lot, and statistical methods used to derive each acceptance criterion. The proposed acceptance criteria for each test, including bioburden, endotoxin and sterility will be a review issue.

Question 5:
Does the Agency have any comments on the proposed stability data package to support the proposed 36 month shelf life?

Agency Response:
The proposed stability data package is sufficient for the BLA submission. The shelf life will be determined based our review of available stability data of the commercial lots and our evaluation of comparability of the Process 3 and Process 4 lots.

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/s/

MELINDA J BAUERLIEN
07/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076488

MEETING MINUTES

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Associate Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for burosumab (KRN23).We also refer to the meeting between representatives of your firm and the FDA on June 19, 2017. The purpose of the meeting was to discuss submission of a Biologics License Application (BLA) for burosumab for the treatment of adult patients and pediatric patients over the age of 1 with X-linked hypophosphatemia (XLH).

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 Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic 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:	June 19, 2017, 1:00 P.M. to 2:30 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 076488
Product Name:	Burosumab (KRN23)
Indication:	The treatment of adults and children 1 years of age and older with X-linked hypophosphatemia (XLH)
Sponsor/Applicant Name:	Ultragenyx Pharmaceutical, Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products:
Audrey Gassman, M.D., Deputy Director
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Clinical Reviewer
Jacqueline Karp, M.D., Medical Officer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of New Drugs, Office of Drug Evaluation III:
Julie Beitz, M.D., Director
Kendall A. Marcus, M.D., Acting Deputy Office Director

Office of Pharmaceutical Quality (OPQ)
Chikako Torigoe, Ph.D., Reviewer, Office of Biotechnology Products (OBP)
William Hallett, Ph.D., Team Leader, OBP
Maria Jose Lopez-Barragan, Ph.D., Reviewer, Division of Microbiology Assessment (DMA)

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader
Christine Hon, Pharm.D., Clinical Pharmacology Reviewer

OTS, Office of Biostatistics, Division of Biometrics III:
Mahboob Sobhan, Ph.D., Biometrics Team Leader
Jia Guo, Ph.D., Biometrics Reviewer

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Shawnetta Jackson, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
Lolita White, Pharm.D., Team Lead, Division of Medication Error Prevention and Analysis (DMEPA)
CAPT Walter Fava, R.Ph., M.S.Ed., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Ameet Joshi, Risk Management Specialist, Division of Risk Management

Office of New Drugs, Immediate Office, Rare Diseases Program:
Larry Bauer, Regulatory Scientist
Kathryn O'Connell, M.D. Ph.D, Medical Officer

Office of Scientific Investigations (OSI)
Roy Blay, Ph.D., Reviewer

Office of New Drugs, Division of Pediatric and Maternal Health:
Jacquline Yancy, Regulatory Health Project Manager
John Alexander, Deputy Director
Hari Cheryl Sachs, M.D., Pediatrics Team Leader

Office of New Drugs, Immediate Office, Clinical Outcome Assessments Staff:
Yasmin Choudhry, M.D., Reviewer

SPONSOR ATTENDEES

Ultragenyx Pharmaceutical Inc.
Chao-Yin Chen, Ph.D., Senior Director, Biostatistics
Emil Kakkis, M.D., Ph.D., Chief Executive Officer and President
P. K. Tandon, Ph.D., Senior Vice President, Biometrics & Development Strategy
Christine Murray, M.S., R.A.C., Vice President, Regulatory Affairs
Monica Sandberg, Ph.D., R.A.C., Director, Regulatory Affairs
Javier San Martin, M.D., Vice President, Clinical Sciences
Jack Shi, Ph.D., Senior Director, Pharmacokinetics
Alison Skrinar, Ph.D., Executive Director, Clinical Outcome and Evaluation
Christina Theodore-Oklota, Ph.D., Associate Director, Clinical Outcome and Evaluation
Roo Vold, M.D., Executive Medical Director, Drug Safety and Pharmacovigilance

Julie Taylor, Ph.D., Executive Director, Bioanalytical Methods Development

Kyowa Kirin International (PLC)
Ian Duguid, Ph.D., M.R.Pharm.S., Senior Vice President, Regulatory Affairs and Pharmacovigilance
Tomohiro Sudo, M.S., M.B.A., Executive Vice President, Global Product Leader, Strategic Product Portfolio Department

(b) (4)

1.0 BACKGROUND

KRN23 (burosumab) is a recombinant human IgG1 monoclonal antibody targeting fibroblast growth factor 23 (FGF23) that is being developed for the treatment of X-linked hypophosphatemia (XLH). The Sponsor currently has Orphan Drug Designation for KRN23 and was granted Fast Track Designation on June 30, 2015. An End of Phase 2 meeting was held on December 10, 2015. The Sponsor was granted Breakthrough Therapy Designation for the treatment of XLH in pediatric patients one year of age and older on June 22, 2016. Ultragenyx met with the FDA on October 14, 2016, to gain FDA feedback on the quality, nonclinical, and clinical development program.

The purpose of this meeting is to discuss and reach agreement on the totality of the data to be submitted in the proposed BLA.

FDA sent Preliminary Comments to Ultragenyx on June 13, 2017.

2.0 DISCUSSION

General FDA Comment: We note that there are no questions or discussion focused on the Chemistry, Manufacturing and Controls or the Pharmacology/Toxicology portions of your proposed Biologics Licensing Application (BLA). The preBLA meeting is the time to reach agreement on the adequacy of the entire data package you intend to submit in support of your application.

You do have an option for a specific CMC preBLA meeting. We strongly recommend that you seek a separate meeting with the Office of Biotechnology Products for discussion about the content of the CMC section of your BLA and the adequacy of the data you propose for that section.

Discussion at the Meeting:
The FDA reminded Ultragenyx that the purpose of the pre-BLA meeting is to reach agreement on the entire data package for the proposed BLA and explained that we would not be able to agree on the entire package because we have yet to discuss some aspects of the package, specifically the CMC, Nonclinical, and Clinical Pharmacology sections. The FDA reiterated the

recommendation to have a CMC pre-BLA meeting. Ultragenyx stated they did not think a pre-BLA CMC meeting was necessary based on previous detailed CMC comments received at the Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting in October 2016 and because Ultragenyx does not have any new data since that meeting. Ultragenyx stated they fully understand the expectations for the CMC section of the BLA.

Question 1a: ***Does the Agency agree that the data presented from pediatric studies provide sufficient clinical information to adequately assess and demonstrate the benefits and risks of burosumab in the pediatric XLH population?***

FDA Response to Question 1a:
It is unclear whether the data from your retrospective historical control study UX023-CL002 will be of sufficient quality to compare the efficacy of burosumab with conventional therapy. It appears that the pediatric phase 2 studies (CL201 and CL205) may be adequate to assess the benefits and risks of treatment in the pediatric XLH population. Clarify whether any data from the phase 3 study (CL301) will be included in the BLA (see p. 29 of your background package).

Discussion at the Meeting:
Ultragenyx summarized the results from Studies CL201 and CL205 (see Slides 7 and 8). Ultragenyx intends to submit the Statistical Analysis Plan (SAP) and propensity score analyses to compare the effect on rickets of burosumab (CL201) versus conventional therapy (CL002). The FDA explained the SAP should be submitted prior to the BLA submission for our review. Ultragenyx will submit the SAP within the next week.

Ultragenyx confirmed that there is no interim analysis planned for the Phase 3 study (CL301) (b) (4)

The FDA recommended that Ultragenyx include data from Study CL304 in their BLA submission to support the pediatric package.

Question 1b: **Does the Agency agree that the data presented from adult studies provide sufficient clinical information to adequately assess and demonstrate the benefits and risks of burosumab in the adult XLH population?**

FDA Response to Question 1b:
In general, the placebo-controlled study CL303 provides clinical information regarding phosphate metabolism with burosumab therapy. The Patient Reported Outcome (PRO) endpoints will require in-depth review. Clarify what data (i.e. bone biopsy data) from study CL 304 will be included in the BLA. The Division views data from this study to be an important component in assessing burosumab safety and efficacy.

Discussion at the Meeting:
Ultragenyx presented primary and secondary endpoint, bone biomarker, and fracture data from Study CL303 (slides 15-17). The FDA asked how active fracture and pseudofracture were defined. Ultragenyx explained that pseudofracture did not cross the entire cortex. The FDA recommended that Ultragenyx provide details on these events, including the presenting symptoms, criteria used for diagnosis, and how the patients were treated clinically. FDA also recommended evaluation of PRO data in the subset of patients with fractures or pseudo-fractures, as well as in the overall study CL303 population. As XLH is a rare disease, FDA will evaluate the BLA based on the totality of the evidence, and data on individual patients may be important.

Regarding the available biopsy data (Study CL304), Ultragenyx currently has baseline data on all subjects demonstrating osteomalacia, and also post-treatment data for 1 subject showing substantial improvement from baseline. Paired biopsy data for 5 additional subjects are expected to be available in July-August and available at the 120-day safety update. The FDA stated that it would be beneficial for Ultragenyx to submit any biopsy data as soon as it is available, and clarified that a dataset would be needed for review, and the report could be submitted later when available. The FDA stressed the clinical importance of this data.

Question 2a: ***Based on the data from burosumab clinical studies, the Sponsor proposes the following indication:***
Burosumab is a monoclonal antibody inhibitor of fibroblast growth factor 23 (FGF23) indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients one year of age and older.
The indication statement will be supported by the detailed description of the key efficacy and safety data in the pediatric and adult patient population in the Clinical Trials section and Safety sections of the label, respectively. Does the Agency agree that the data package supports the proposed indication?

FDA Response to Question 2a:
See responses to 1a and 1b. Adequacy of the efficacy and safety data to support an indication in the proposed age groups and the exact indication language will be review issues.

Discussion at the Meeting:
See Discussion under Questions 1a and 1b.

Question 2b: ***The Sponsor is proposing the following subcutaneous (SC) dose and dosage regimens for pediatric and adult patients with XLH:***
Pediatric patients with X-linked hypophosphatemia (1 to <18 years of age): The recommended starting dose regimen in children over the age of 1 year is approximately 0.8 mg/kg of body weight (rounded to the nearest 10 mg; a minimum dose of 10 mg up to a maximum dose of 90 mg) administered subcutaneously every two weeks.
Adult Patients with X-linked Hyposphophatemia (18 years of age and older): The recommended starting dose regimen in adults is 1 mg/kg body weight (rounded to the

nearest 10 mg up to a maximum dose of 90 mg) administered subcutaneously every four weeks.
Does the Agency have any feedback on the Sponsor's proposed dose and dosage regimens?

FDA Response to Question 2b:
The proposed pediatric dosing scheme differs from that used in clinical trial CL201 and dose adjustments appear to differ from those in clinical trials CL205 and CL301; this will require in-depth review. The adult dosing scheme appears consistent with the clinical trials; whether your clinical trial data will support your proposed dosing will be a review issue. Provide a rationale for the maximum dose of 90 mg per dose.

The acceptability of the proposed dose in adolescents will be a review issue and will depend on the available pharmacokinetic (PK), pharmacodynamic (PD), and clinical data as well as the acceptability of the proposed scientific bridge.

Discussion at the Meeting:
See Discussion under Question 4.

Question 2c: ***The Sponsor's proposal for efficacy (including patient-reported outcomes) and safety information to be included in the USPI is presented in Section 4.1.5 of the briefing document. Does the Agency have any comments on the Sponsor's proposal?***

FDA Response to Question 2c:
It is premature to discuss labeling. Final determination of endpoints for labeling will be a review issue.

We have to following comments regarding your patient reported outcomes (PROs):

- From a measurement perspective, a high level review of content validity of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was largely supportive of content validity of the instrument items. However, the instrument instructions do not appear to be relevant in the context of this trial because they asked patients to consider their "study joint", while this particular clinical trial did not focus on any particular joint.
- Furthermore, the instrument instructions were not cognitively debriefed with patients; however, even if they had been, it's unlikely they would be relevant or well-understood among patients participating in the trial. Therefore, interpretability of the instrument is questionable because we don't know what body part(s) patients were considering when they responded to the instrument items or whether they were considering their body as a whole.

We recommend that you provide the WOMAC raw scores in addition to the transformed scores with the BLA submission. We also recommend item-level descriptive analyses by treatment group. After review, if the data from this instrument are sufficiently robust, the data might possibly overcome this limitation noted in the instrument's instructions and merit description in product labeling. This will be determined at the time of BLA review.

The Brief Pain Index (BPI) is a widely used instrument in pain research. Item 3 of the BPI has been previously accepted by the Agency in a variety of disease settings and appears fit-for-purpose for patients with X-linked hypophosphatemia. If the data are sufficiently robust, BPI item 3 might be used to support labeling claims. Ultimately, this will be determined at the time of BLA review.

At the time of the BLA submission, we will review the meaningfulness of intrapatient changes using anchor-based methods and agree with your proposal to provide cumulative distribution (CDF) curves. With the cumulative distribution function (CDF) curves, include sample sizes and median scores for each CDF curve. In addition:

- Provide CDFs of the PRO instrument change scores from baseline to week 24 for all patients (both treatment and placebo arms pooled) by the different anchor scale response options (if a global rating of change) or changes scores (if a current-state global) at Week 24.
- Provide CDFs of the PRO instrument change scores from baseline to week 24 by treatment arms (i.e., treatment vs. placebo).

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 3a: Does the Agency have any comments related to the proposed design of the Human Factors Validation Study?

FDA Response to Question 3a:
Our understanding is that for the initial BLA submission, your product is intended to be administered by healthcare providers (HCPs). We do not require human factors (HF) validation testing for healthcare providers administering burosumab.

Discussion at the Meeting:
Ultragenyx deferred discussion on this topic and clarified that the initial BLA submission is for healthcare provider administration.

Question 3b: (b) (4)

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(b) (4)

Question 4: ***Does the Agency agree with the proposed BLA content, structure, data format and D120 safety update?***

FDA Response to Question 4:
Clinical study reports and datasets for studies KRN23-INT-001, KRN23-INT-002, and UX023-CL203 should also be included in the BLA.

We note that that you are currently developing a single population pharmacokinetic (PK) model using adult and pediatric data from your clinical trials. You will further attempt to develop a population pharmacokinetics/pharmacodynamics (PK/PD) model based on the changes in serum phosphorus level in all ages and you are planning to use the model-based predictions (for all subjects, including adolescents) to support the proposed doses and dosing regimens, including dose adjustments. We remind you that whether the population PK/PD modeling can support the proposed doses and dosing regimens will a review issue. Provide adequate justification along with supporting data and data analyses for the proposed doses and dosing regimens, including the proposed dose adjustments.

In addition to the PK/PD modeling for serum phosphorus level, we recommend that you also evaluate the relationship between PK exposure and safety. Take into consideration the exposure-response relationship for safety in your justification for your proposed doses and dosing regimens. As part of your response, provide information on the typical baseline serum phosphorous by age (birth to adult). Values should be provided in as much granularity (by year) as feasible. In addition, results for your PK/PD analyses should be provided by age group, with a particular focus on any differences in safety between ages as well as if higher doses were needed to older pediatrics included in your studies.

As you plan to conduct simulations to justify the proposed doses and dosing regimens, provide the methodology you used for the simulations. Provide the datasets and codes for the key simulations.

Regarding the population PK and PK/PD datasets:

- Provide the unique subject identification number (e.g., USUBJID) for each subject
- 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 burosumab concentrations, serum phosphorus concentrations, and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

For all other PK/PD analyses using non-compartmental PK parameters, submit all datasets, including the original PK and PD data, PK/PD analysis datasets, and PK/PD parameter datasets for our review.

You plan to register your product in three formulation strengths, namely 10 mg/ml, 20 mg/mL, and 30 mg/mL for commercial use. The 10 and 30 mg/mL product strengths have been administered in clinical studies, and the 20 mg/mL product strength will be added at the time of the initial BLA filing. We remind you of our previous recommendations that your BLA submission needs to: (1) evaluate PK comparability between the 10 mg/mL drug product and 30 mg/mL drug product as well as (2) provide a comprehensive summary listing of the drug product used, including strength(s), manufacturing process, and formulation, for each of the clinical studies. Refer to Meeting Minutes dated November 10, 2016, for more information. Include the PK comparability data in a separate PK dataset.

In the BLA, provide assessments of the impact of immunogenicity on PK, PD, efficacy, and safety. We recommend that you evaluate the impact of the immunogenicity on PK by comparing observed trough concentrations and/or PK parameters from the non-compartmental analysis between anti-drug antibody (ADA) positive and ADA negative subjects, and the observed concentrations before and after ADA development within each ADA positive subjects. Perform similar between-subject and within-subject PK comparisons with respect to the status of neutralizing antibody (NAb). Explore the correlation of observed trough concentrations and/or PK parameters with ADA titers. Submit the analysis dataset(s) used for these immunogenicity assessments.

You have collected samples for *PHEX* mutation analysis in Studies UX023-CL203, UX023-CL303, UX023-CL201, and UX023-CL-205. We recommend that you explore the impact of *PHEX* genotype on PK, PD, efficacy, and safety. Provide the genotype analysis dataset to the BLA.

We remind you that the inclusion of all of the aforementioned datasets will be necessary for the BLA submission to be considered complete.

Discussion at the Meeting:
Ultragenyx summarized the immunogenicity assessments that they intend to include in the BLA (slides 21 and 22). Ultragenyx clarified that they have validation reports for the assays used in clinical studies including the NAb validation report and these will be included in the BLA. Ultragenyx has developed a new ADA assay with the intention to improve drug tolerance and is currently validating the new assay.

FDA reiterated the need to evaluate PK comparability between two product strengths (i.e., 10 mg/mL and 30 mg/mL) which can be used to support the proposed new strength of 20 mg/mL using a bracketing approach. Ultragenyx presented comparison of model-predicated PK parameters to support PK comparability. The Agency indicated that PK comparison based on observed data will be necessary. There was a discussion about potential options to perform the PK comparison, given the limited data available. FDA clarified that the recommendation to include a comprehensive summary of the product used in the clinical trials was to help devise a strategy for PK comparability evaluation using a non-model based approach.

Post-Meeting Comment:
Submission of the updated validation report for the anti-drug antibody screening assay no later than September 29, 2017, is acceptable.

Question 5: Does the Agency agree that, given the unmet medical need for patients with XLH and the data presented in burosumab clinical trials, that these data demonstrate a significant improvement in the treatment of patients with XLH, thus qualifying the proposed BLA for priority review?

FDA Response to Question 5:
We agree that the proposed BLA appears to meet the qualifying criteria for priority review. The final determination would be made after filing and communicated to you within 60 days of receipt of the BLA.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 6: Does the Agency foresee that the proposed BLA will be reviewed by an Advisory Committee?

FDA Response to Question 6:
At this time, we cannot rule out the need for discussion of burosumab for treatment of XLH at an Advisory Committee meeting.

Discussion at the Meeting:
There was no further discussion at the meeting.

Additional Comments
Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD, including 2.7.4 Summary of Clinical Safety, and 5.3.5 Reports of Efficacy and Safety Studies. For your BLA, provide an Integrated Summary of Immunogenicity to be included in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:

a) An immunogenicity risk assessment specific to your product
b) Details on the tiered immunogenicity strategy that you followed in your clinical program and validation summaries for the various immunogenicity assay methods you developed in your program
c) Links to method development and validation reports for all the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from your pivotal clinical study(ies)
d) Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed
e) Summary results of immunogenicity analysis for all clinical studies having an immunogenicity component, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data (Also see response to Question 4.)
f) Traceability of drug product lots used in all your clinical studies

In general, we agree with using the propensity score approach as you outlined in the meeting package to compare the treatment effects of conventional therapy and burosumab with historical study data. We request you submit the detailed statistical analysis plan for this comparison for review.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. See Discussion under FDA General Comment.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held.
  At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it

is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

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.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. 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. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   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.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   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

3. 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.

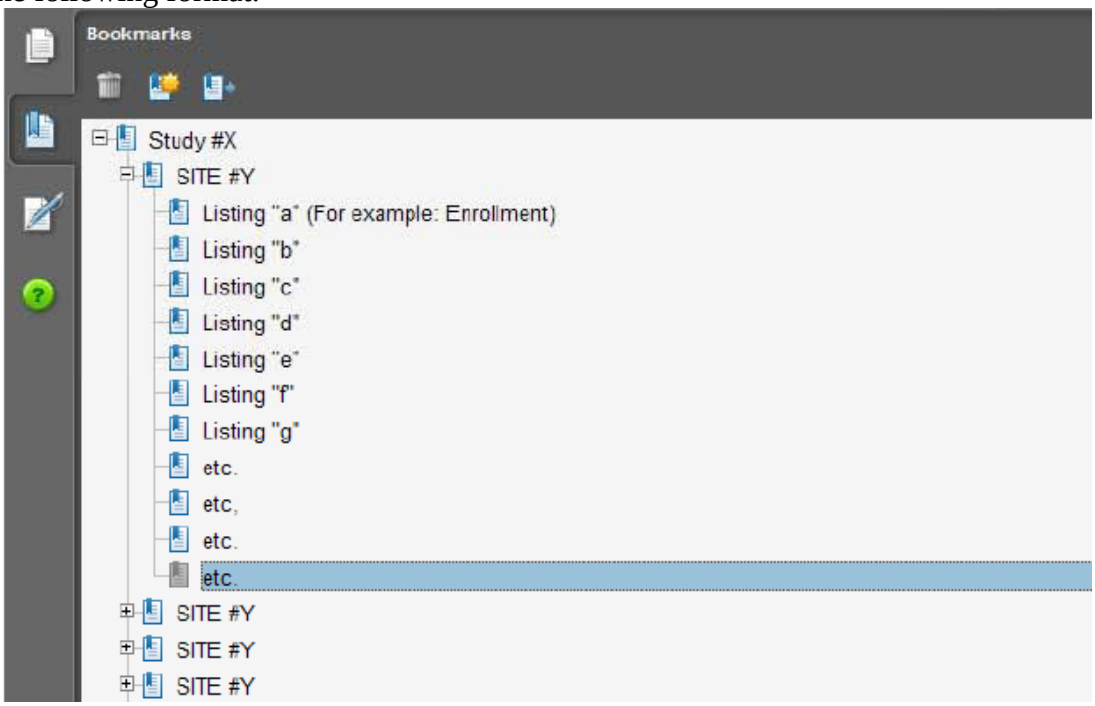
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

1. 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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Discussion at the Meeting:
FDA agreed with Ultragenyx's stated intention of providing Parts I and II but not Part III (the voluntary site level datasets) of the OSI Information Request in the BLA submission.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

- The FDA stated that agreement could not be reached on the adequacy of the application as the Sponsor had not presented their proposals for the CMC, nonclinical and clinical pharmacology sections.
- The FDA reiterated that the Sponsor should request a separate CMC pre-BLA meeting.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	July 19, 2017

5.0 ATTACHMENTS AND HANDOUTS

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/s/

THERESA E KEHOE
07/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076488

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Associate Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KRN23.

We also refer to your April 28, 2016, request for Breakthrough Therapy designation. We have reviewed your request and have determined that KRN23 for the treatment of X-linked hypophosphatemia (XLH) in pediatric patients one year of age and older meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of KRN23 for the treatment of XLH in pediatric patients one year of age and older to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics,* Attachment 1, for potential topics for discussion at this initial Breakthrough Therapy meeting.[2] Please refer to the *Guidance for Industry: Formal Meetings*

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

between FDA or Sponsors and Applicants[3] for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the Breakthrough Therapy designation for KRN23 for the treatment of XLH in pediatric patients one year of age and older is rescinded, submission of portions of the Biologics License Application (BLA) will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

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/s/

HYLTON V JOFFE
06/22/2016

CDER Breakthrough Therapy Designation Determination Review

IND/NDA/BLA #	IND 076488
Request Receipt Date	4/28/2016 (version with minor corrections received 5/2/2016)
Product	KRN23 (anti-FGF23 human IgG1 mAb) for SC injection
Indication	Treatment of X-linked hypophosphatemia (XLH) in pediatric patients
Drug Class/Mechanism of Action	Inhibitor of FGF23
Sponsor	Ultragenyx Pharmaceutical
ODE/Division	ODE III/ DBRUP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	6/28/2016

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

KRN23 is indicated for the treatment of X-linked hypophosphatemia (XLH) in the pediatric population.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

  i. Only animal/nonclinical data submitted as evidence ☐
  ii. Insufficient clinical data provided to evaluate the BTDR

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

X-linked hypophosphatemia (XLH) is an x-dominant genetic disease with an estimated prevalence of 3,000 pediatric and 12,000 adult patients in the U.S. XLH is linked to inactivating mutations in the phosphate-regulating gene *PHEX*, causing osteocytes to secrete excess fibroblast growth factor-23 (FGF23). FGF23 has two effects on proximal renal tubule cells: (1) reduced expression of sodium-phosphate cotransporters (NaPi-IIa and NaPi-IIc), which reduces the renal phosphate threshold (TmP-GFR) and causes urinary phosphate wasting; and (2) reduced secretion of 1,25 dihydroxyvitamin D, which reduces calcium and phosphate absorption in the gut. These two mechanisms lead to impaired skeletal mineralization, i.e. rickets and osteomalacia, which are the primary clinical manifestations of XLH. Biochemical manifestations of the disease include hypophosphatemia, decreased fractional tubular reabsorption of phosphate (TRP), decreased ratio of tubular maximum reabsorption of phosphare to glomerular filtration rate (TmP/GFR), and low-normal 1, 25 dihydroxyvitamin D levels. While there is a spectrum of disease severity with regard to skeletal manifestations, the underlying disorder of phosphate metabolism does not spontaneously resolve.

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[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Most patients with XLH are diagnosed in early childhood, either because of a family history or because of leg bowing after beginning to walk, and impaired growth. Most children have progressive bowing of femur and tibia with genu varum (outward bowing of the lower legs), resulting from abnormal growth plates (rickets) and bending of the bone shaft (osteomalacia). Other deformities may include genu valgum and rotational torsion of the tibia. This bone disease leads to gait abnormalities, short stature and lower extremity pain. Surgical correction of deformities is sometimes required; persistence of deformity in adulthood may lead to ongoing disability and early development of osteoarthritis. Other symptoms may include insufficiency fractures, dental abscesses and craniosynostosis. Current therapy for XLH (oral phosphate and active vitamin D) has some benefit in children, but does not completely correct the metabolic defect or skeletal complications, and there are significant safety and tolerability issues as well (see Section 8). Thus, there is a significant unmet need.

KRN23 is an IgG_1 monoclonal antibody designed to bind and inhibit the activity of the excess circulating FGF23 in XLH, thus providing a more specific therapy. KRN23 is administered by subcutaneous (SC) injection. Uncontrolled phase 2 studies of KRN23 in adults and children with XLH have demonstrated improvement in biochemical endpoints, with increased renal phosphate retention and increased serum levels of phosphorus and 1,25 dihydroxyvitamin D. Orphan Drug and Fast Track designations were granted in 2009 and 2015 respectively. On 7/30/15, based on initial radiographic evidence of improvement in rickets in pediatric study CL201, the Sponsor requested preliminary advice for a BTDR. DBRUP responded that such a request would be appropriate, but reminded the Sponsor of our concerns about the lack of controlled data with KRN23 and the need for comparison to standard of care. Because XLH treatment is ideally begun in early childhood, and the risks/benefits of treatment of adults with XLH are unclear, the Sponsor was also advised that a breakthrough therapy designation (BTD) would be most applicable to the pediatric XLH population. Accordingly this BTD request is limited to treatment of children with XLH, although the sponsor is continuing with adult and pediatric studies, with the eventual goal of an indication in both age groups.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The sponsor's request for BTD is based primarily on data from study UX023-CL201 that include two radiographic scales: the Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C). These scales are based on x-rays of the knees and wrists to assess rickets in growth plates of rapidly growing bones. The RGI-C and RSS are, respectively, primary and secondary endpoints of the phase 2 study supporting this BTDR, and will have the same roles in a planned phase 3 pediatric study, as the Sponsor believes that the radiographic features of rickets are the basis for, and correlate with the major morbidities of XLH.

The RSS, which was developed for nutritional rickets (deficiency of vitamin D and/or calcium), assigns scores for typical rachitic features: for distal radius and ulna, widening of the cartilaginous growth plate, irregular lucency of the metaphyseal margin and concave cupping of metaphysis; and for distal femur and proximal tibia, lucency and widening of the zone of provisional calcification (score is multiplied by 0.5 if only one condyle or plateau is involved). RSS scores can range from 0 (no rickets) to 10 (sum of worst possible scores of 2, 2, 3, 3 for radius, ulna, femur and tibia respectively). Films are read individually, so that the reader can be blinded to treatment and to radiograph sequence. In nutritional rickets, inter- and intra-observer correlation of RSS scores is high; both wrist and knee subscores correlate with alkaline phosphatase levels, another measure of rickets activity; and the RSS was found to be useful in assessing the response to therapy of nutritional rickets. However, the RSS developers recommended validation of the RSS in other (non-nutritional rickets) populations (Thacher 2000).

Prior to this IND there were no available data on use of the RSS in XLH, a condition with radiographic features that are similar to nutritional rickets but not identical. Literature reports indicate that XLH related rickets may be more likely than other types to involve lower (vs. upper) extremities, and to feature prominent leg bowing, likely related to greater

chronicity of the disease, and genu varum in which the distal femoral/ proximal tibial growth plates are often more affected medially than laterally, perhaps due to compressive stress (Shore 2013). To support the use of RSS in XLH, the Sponsor of this IND has submitted preliminary data indicating trends of more severe clinical features in children with XLH and higher RSS (see below).

The RGI-C evaluates the same growth plate/ metaphyseal abnormalities of wrists/knees as the RSS. Unlike the RSS, the RGI-C compares films from two different timepoints to assess improvement or worsening of rickets. Thus, readers can be blinded to treatment but not to film sequence. The RGI-C reader is asked to integrate the findings qualitatively into a score for the changes from baseline:

- -3 = severe worsening
- -2 = moderate worsening
- -1 = minimal worsening
- 0 = no change
- +1 = minimal healing
- +2 = substantial healing
- +3 = complete or near complete healing

Each of 3 independent readers assigns RGI-C scores for the wrist, the knee and a global score for both wrist and knee. The scores from the 3 readers are averaged to generate an RGI-C wrist score, an RGI-C knee score and a global RGI-C score.

There are no published data on the RGI-C used in this study, which the Sponsor devised for this development program and considers disease-specific to XLH. (An RGI-C previously used to support approval of asfotase alfa to treat hypophosphatasia [see below] was developed specifically for that disease and encompasses its unique features.) The Sponsor believes that the side-by-side comparison of pre- and post-treatment images in the RGI-C is a preferred method as it resembles the approach used in clinical practice.

The Sponsor presents other preliminary data from study CL201 (see below) in support of the BTD request: improvement in pharmacodynamic (PD) endpoints (serum phosphorus, TmP/GFR, PTH levels); changes in growth velocity and height Z-score; improvements in pain and physical function as assessed with the Pediatric Outcomes Data Collection Instrument (PODCI) developed by the Pediatric Orthopedic Society of North America (POSNA); and changes in the 6-Minute Walk Test (6MWT).

This study will also evaluate the following endpoints for which there are no data yet available: lower extremity deformity (e.g. bowing) via standing long leg x-rays; HR-pQCT of forearm and tibia (exploratory); gross motor function (BOT-2); muscle strength (HHD); and health-related quality of life (SF-10).

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

DBRUP considers that the RSS and RGI-C have the potential to be useful outcome measures for pediatric XLH. Because neither has been formally validated in this condition, there is not yet convincing evidence that these endpoints can predict clinically relevant benefits. The 10 point RSS was shown to be clinically relevant in nutritional rickets, however baseline scores in those studies were generally higher than in study CL201 (where children with XLH had RSS mean baseline of 1.4, ranging from 0-3.5); this may limit the ability of the RSS to adequately discriminate clinically meaningful changes.

In general, biochemical PD endpoints and/or radiographic changes alone are not sufficient for approval; clinical or functional endpoints are also needed. Improvement in leg deformities (e.g. bowing), growth, walking ability or pain are appropriate clinical outcome measures for pediatric XLH but may be difficult to interpret in an open label study, especially the PRO/ObsRO endpoints (i.e., POSNA-PODCI and SF-10). The Sponsor has no plans to conduct bone biopsies in children with XLH, however pre- and post-treatment biopsies are being done in an ongoing study of adults

with XLH; improvement in osteomalacia in adults would be convincing evidence of benefit, probably applicable to children as well.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

In theory, KRN23 may have a significant advantage in safety and tolerability over existing therapy (see Section 8 below); potentially, such evidence in an appropriately controlled study could help support approval.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no approved therapies for XLH. Most children with the disease receive (until cessation of growth) standard of care treatment which consists of phosphate and calcitriol (or other forms of activated vitamin D). Recommended doses vary widely, and patients require multiple daily dosing, individualized dose adjustments and frequent lab monitoring for safety (serum calcium, phosphate, PTH, creatinine; urine calcium and urine creatinine). It is believed that serum phosphorus should be maintained below the normal range to minimize the risk of hyperparathyroidism or nephrocalcinosis, though this may limit efficacy.

Current therapy for XLH

	Formulations	Dosing frequency	Adverse effects
Phosphate	Sodium and/or potassium phosphate Powder for oral solution, tablets	3-5 divided doses per day	Abdominal pain, diarrhea Hyperparathyroidism Nephrocalcinosis
Active vitamin D	Calcitriol (1,25-dihydroxyvitamin D) Alternatives: alfacalcidol, paricalcitol Oral solution, capsules	2-3 divided doses per day	Hypercalcemia Hypercalciuria Nephrocalcinosis Nephrolithiasis

In clinical practice, pediatric patients are assessed for treatment response by assessments of growth and improvement in symptoms (gait difficulty, bone pain, deformities etc.), and by periodic radiographs (usually the knees) to monitor healing of rickets. Some clinicians also monitor serum alkaline phosphatase, which is usually elevated at baseline and declines with treatment, as a surrogate marker for bone healing.

According to literature reports, phosphate/calcitriol treatment, if begun at an early age, tends to improve but often does not eliminate growth deficits and leg deformities. Despite the universal use of x-rays, there are almost no published data on radiographic changes (e.g. RSS) during treatment. In pediatric study CL201 (see below), most children who had been treated with phosphate/active vitamin D for an average of 6.6 years, beginning early in life, had persistent rickets with baseline RSS scores of up to 3.5 (mean 1.4) and substantial deformities and disability. Retrospective studies of children with XLH have shown little change in height Z-scores over years of standard treatment. Approx. 25-40% of patients have an adult height Z-score <-2 despite optimal treatment; mean final height was 5'3" for boys and 5'0" for girls (Linglart 2014). Osteotomy to correct residual bowing became less common with the advent of medical therapy, but was still required in 11% of patients at one center (Linglart 2014).

Nephrocalcinosis, detected through recommended periodic ultrasound monitoring, develops in about one-half of patients after several years of treatment. This is generally considered an indication to reduce dose, as higher phosphate doses appear to correlate with risk. The clinical significance is unclear; renal function has been unaffected in most patients.

Tertiary hyperparathyroidism requiring parathyroidectomy has developed in some patients; cinacalcet for control of excess PTH is not currently considered safe in children.

Growth hormone is sometimes used as adjunctive therapy in children with XLH and severe short stature, but adequately controlled trials to show improved adult height have not been conducted, and adverse effects including worsening leg deformities have been reported.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

We are not aware of other drugs under development for XLH, or other hypophosphatemic disorders, that have requested breakthrough therapy designation.

Breakthrough therapy designation was granted on 5/21/13 for asfotase alfa (Strensiq, IND 100619, BLA 125513), an enzyme replacement therapy for hypophosphatasia (HPP). Childhood rickets is among the prominent clinical features of HPP, though the mechanism differs from XLH (patients do not have phosphate wasting or hypophosphatemia). Patients with infantile-onset HPP may also have serious morbidity/mortality from respiratory failure and chest wall deformities, and BTD designation in this age group was based mainly on evidence of improved ventilator-free survival. There were preliminary RGI-C (HPP-specific for features unique to this disease) and RSS efficacy data for patients with infantile-onset HPP (without controls) and juvenile-onset HPP (with untreated historical controls), showing significant improvements. In addition, paired bone biopsies showed improvement in osteomalacia in 10/10 children age 5-12 years old with treatment. The BTDR review stated that for these older children, the radiographic changes "would not be acceptable to demonstrate efficacy of a drug in the absence of evidence correlating the X-ray findings with acceptable measures of HPP disease improvement or decline, such as bone mineralization changes as seen on bone biopsy"; the biopsy findings were considered a clinically meaningful endpoint. (Subsequently, the sponsor demonstrated correlation of RSS and RGI-C with height, weight and functional scores, and RSS with bone biopsy parameters.) For older children, the review also cited consistent trends toward improvement in several functional assessments.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

The BTDR is based on interim data from ongoing pediatric study UX023-CL201. The Sponsor has not included data from the adult XLH phase 1 and 2 studies in this BTDR.

Protocol UX023-CL201: Study design

Study ID	Phase	Study design	Study endpoints	Treatment groups
UX023-CL201	2	Randomized, open-label, multicenter, dose finding; 64 week duration Total enrollment = 52 1-2 wk washout for existing standard therapy	PD: phos, TmP/GFR, 1,25(OH)vit D Radiographic: rickets (RSS, RGI-C), bowing Clinical: growth; 6MWT; functional disability and pain (POSNA-PODCI) gross motor function (BOT-2); muscle strength (HHD); health-related QOL (SF-10) Safety: serum Ca,P,PTH; urine Ca, creat; ectopic mineralization (renal US, Echo, ECG)	Q2 week vs. Q4 week injections Within each group, 3 different starting doses w/ titration based on serum phosphate at 2 wk post-dose (target 3.5-4.5 mg/dL = low-normal range) No placebo or active-control group

Study CL-201 is enrolling 52 children age 5-12 years old with Tanner stage ≤2; XLH w/ *PHEX* mutation or FGF23 level ≥30 pg/mL; serum phosphate ≤2.8 mg/dL (normal range for this age group is approximately 3.2-6.1 mg/dL); below average height; and radiographic evidence of rickets (wrists and/or knees) and/or femoral/tibial bowing. For the first 36 patients there was no enrollment criterion for baseline rickets severity; based on early data showing more robust response with higher baseline RSS (see below), RSS ≥ 1.5 was required for later enrollees, and the phase 3 study will enroll patients with RSS ≥ 2.0.

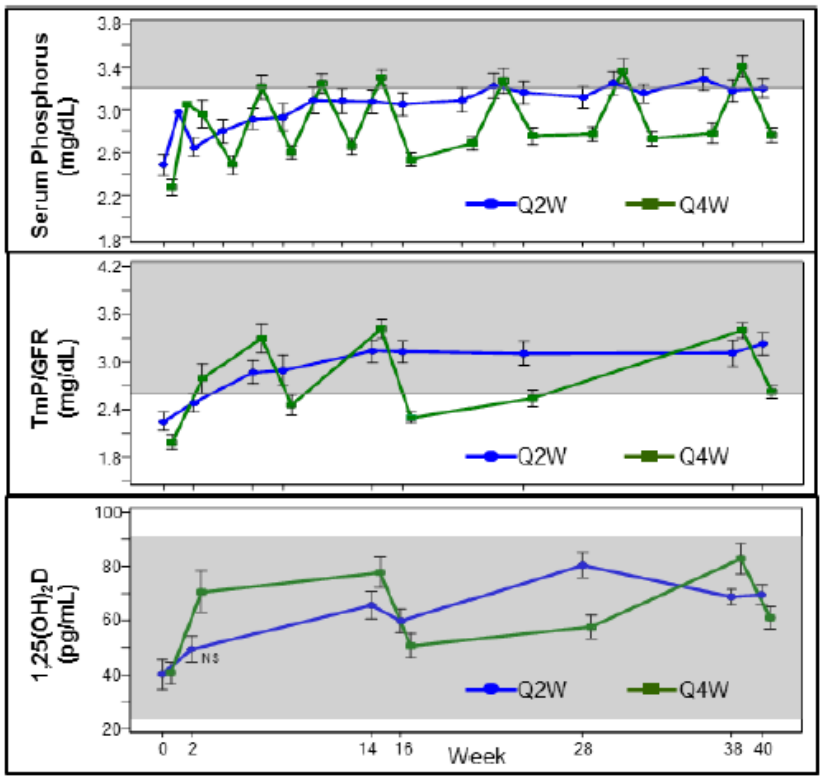
Interim data for the first 36 patients in the study (n=18 each for Q2wk and Q4wk regimens) through week 40 are summarized in the BTD request. All except one patient had received conventional therapy (phosphate, active vitamin D), mostly beginning before 2 years of age, for an average of 6.6 years (range 0-11.7 yr). Data are presented for two prespecified subgroups:baseline RSS ≥1.5 ("higher RSS") and RSS <1.5 ("lower RSS"). The former group shows trends toward greater disability on some baseline assessments:

Study CL201: Baseline characteristics and functional assessments, higher vs lower RSS patients

	Higher-RSS (≥ 1.5) (n=18)	**Lower-RSS (< 1.5)** (n=18)
Mean age, yrs (SD)	8.3 (1.6)	8.1 (2.1)
Female, n	10	8
Height percentile, mean	3.9	14.0
Growth velocity pre-treatment, mean cm/year	5.3	5.9
Mean 6MWT, meters	87	97
PODNA-PODCI normative score*		
Mean sports/physical functioning	28.6	40.9
Mean pain/comfort score	33.6	45.3
6MWT=6 minute walk test *Normative value=50, 1 SD=10		

All 36 patients had increases from baseline in serum phosphate and TmP/GFR, to levels close to or within the normal range, and also increases in serum 1,25-dihydroxyvitamin D. In the Q4wk dose group, PD parameters returned to near baseline at the end of the 4 week intervals, therefore the sponsor concluded that the more stable PD effects of the Q2wk regimen are preferred and this will be the pediatric dosing frequency in an extension of this study and in phase 3. In the Q2wk group, mean serum phosphorus increased from 2.5 mg/dL at baseline to 3.2 mg/dL (which is approx. the lower limit of normal in this age group).

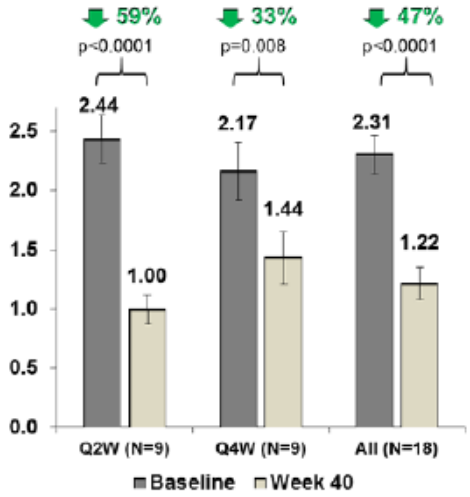
Figure 6: Serum Phosphorus, TmP/GFR, and 1,25(OH)$_2$D Time Course During Study UX023-CL201



Shaded areas in the above graphs represent the normal range

Interim radiographic rickets data at week-40 also were generally more favorable with the Q2 wk regimen. Mean RSS score decreased from 1.53 at baseline to 0.86 at week 40 among the 18 children treated with the Q2 wk regimen, and from 1.33 to 1.14 among the 18 children treated with the Q4 wk regimen. Declines were greatest in the high-baseline RSS (≥1.5) group:

Study CL201: RSS scores at baseline and week 40 for patients with higher baseline RSS (≥1.5)



In this higher-RSS group (n=18), the mean RGI-C global score at week 40 (i.e. change from baseline) was +1.85; for the subset treated Q2 weeks (n=9), the mean RGI-C global score was +2.00 (the level defined as "substantial healing"). The mean RGI-C global score for all 36 patients was +1.38 ($p<0.0001$ for each of these scores). Each of the specific rickets findings (metaphyseal lucency, separation, fraying and concavity) showed improvements.

Femur/tibia bowing, which is expected to take longer to improve compared to rickets findings, will be assessed via standing long leg x-rays at week 64; none of these results are yet reported.

There were moderate improvements in growth over 40 weeks of treatment, especially in children with more severe rickets. In the higher-RSS subgroup, mean height Z-score increased from -2.37 to -2.19; among children in this subgroup treated every 2 weeks, mean height Z-score increased from -2.36 to -2.09.

Pain and physical function were assessed with the Pediatric Outcomes Data Collection Instrument (PODCI) developed by the Pediatric Orthopedic Society of North America (POSNA). In the Sports/Physical Function and Pain/Comfort scales, there were substantial improvements among the 18 higher-RSS children: from mean of 28.6 to 42.1 and from 33.6 to 44.7 respectively, where average-normal is 50 and 10 points equals 1 SD.

In the 6-Minute Walk Test (6MWT), there was a modest increase in mean distance walked by 26 meters ($p=0.0007$). Increases were greatest in patients with 80% of predicted normative values at baseline.

b. Include any additional relevant information. Consider the following in your response:

For all the KRN23 efficacy data presented, there are no data (concurrent or historical) with current phosphate/calcitriol therapy to permit direct comparisons, nor any placebo controlled data. Since all (except one) of the study CL201 patients was on long-term standard therapy prior to the study, improvements from baseline may be considered possible evidence of substantial improvement over current therapy, which must be confirmed with appropriately controlled data.

Unlike current standard therapy, KRN23 at the doses used in pediatric study CL-201, and in several adult studies has not induced clinically significant increases in serum or urine calcium, or in serum PTH, or in nephrocalcinosis by ultrasound, and there have been no instances of significant hyperphosphatemia. Therefore, KRN23 is expected to have a relatively lower risk of ectopic mineralization and of hyperparathyroidism, thus a possible advantage over current therapy. However, this hypothesis also requires confirmation in a controlled trial. Injection site reactions have been the most common treatment related adverse event. There is no evidence to date of immunogenicity.

There are completed phase 2 studies in adults with XLH. The Sponsor has not included these data in the BTDR but no endpoints related to bone were included in those studies. Some possibly relevant additional evidence is provided from an open label study of KRN23 in treatment of tumor-induced osteomalacia: one patient had apparent marked improvement in multiple fractures or pseudofractures by Tc99 bone scan, and another exhibited increased bone mineral density by DXA of 21% (lumbar spine) and 6% (total hip) at week 24 – consistent with marked improvement in osteomalacia (pre- and post-treatment bone biopsies will be conducted).

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

XLH is a lifelong disease that may cause severe deformity and disability, for which current (unapproved) therapy is only partially efficacious and may cause serious toxicity. Because KRN23 is more specific to the underlying metabolic defect as shown by very consistent and robust PD data, it offers the possibility of improved efficacy and/or safety. The Sponsor has submitted evidence of significant improvement in radiographic rickets in children with XLH after 40 weeks of treatment, following many years of standard therapy. Though the radiographic scales used have not been rigorously validated and there is no control group, it is unlikely that these changes would have occurred with continued standard therapy. Other data involving parameters of growth, physical function and pain are also presented but are not as convincing in the absence of a control group. This deficiency will be addressed in the phase 3 trial CL-301 comparing KRN23 and standard therapy as active-control.

☐ DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor has submitted two phase 3 protocols for KRN23 treatment of XLH: one in adult patients which is a placebo controlled trial; and one in pediatric patients age 1 – 12 years currently treated with standard of care, which is active, standard of care controlled. The sponsor is also conducting a study in patients age 1 – 4 years which allows treatment naïve patients to be enrolled (i.e., patients who have not yet been exposed to standard of care). In addition, the sponsor is conducting a phase 3 protocol evaluating iliac crest histomorphometry with KRN23 treatment in adults to evaluate the direct effects on bone mineralization.

The Sponsor has expressed interest in submitting an application for accelerated approval based on the data from study UX023-CL201. The Division believes that such an application would be premature and further clinical data from phase 3 trials are needed. The Division intends to work with the Sponsor to develop a clear path forward to expedite development.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

Thacher T et al, Radiographic Scoring Method for the Assessment of the Severity of Nutritional Rickets, *J Trop Pediatr* (2000), 46: pp. 132-139

Shore RM and Chesney RW, Rickets: Part II, *Pediatr Radiol* (2013), 43: pp. 152-172

Linglart A et al, Therapeutic management of hypophosphatemic rickets from infancy to adulthood, *Endocr Connect* (2014), 3: R13-R30

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES XX NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio

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

/s/

STEPHEN R VOSS
06/21/2016

THERESA E KEHOE
06/21/2016

HYLTON V JOFFE
06/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076488

MEETING MINUTES

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

Dear Dr. Sandberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KRN23.

We also refer to the meeting between representatives of your firm and the FDA on December 10, 2015. The purpose of the meeting was to discuss the proposed Phase 3 pediatric protocol (UX023-CL301) (b) (4) (b) (4)

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 Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic 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:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 10, 2015, 12:00 P.M. to 1:00 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 076488
Product Name:	KRN23
Proposed Indication:	Treatment of X-linked hypophosphatemia (XLH)
Sponsor/Applicant Name:	Ultragenyx Pharmaceutical Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products:
Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Medical Officer
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Mukesh Summan, Ph.D., DABT, Acting Pharmacology and Toxicology Supervisor
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader
Lin Zhou, Ph.D., Clinical Pharmacology Reviewer

OTS, Office of Biostatistics, Division of Biometrics III:
Mahboob Sobhan, Ph.D., Biometrics Team Leader
Jia Guo, Ph.D., Biometrics Reviewer

Office of New Drugs, Division of Pediatric and Maternal Health:
Ethan Hausman, M.D., Medical Officer
Denise Pica-Branco, Ph.D., Senior Regulatory Health Manager

Office of New Drugs, Immediate Office, Clinical Outcome Assessments Staff:
Yasmin Choudhry, M.D., Reviewer
Wen-Hung Chen, Ph.D., Reviewer

Office of New Drugs, Immediate Office, Rare Diseases Program:
Larry Bauer, Regulatory Scientist
Kathryn O'Connell, M.D. Ph.D, Medical Officer

SPONSOR ATTENDEES
Sunil Agarwal, M.D., Chief Medical Officer and Sr. Vice President
Chao-Yin Chen, Ph.D., Director, Biostatistics
Michelle Hack, Associate Director, Regulatory Affairs
Kathleen McKeever Ph.D., Vice President, Pharmacology and Toxicology
Cori Leonard, RAC, Vice President, Regulatory Affairs
Javier San Martin, M.D., Vice President, Clinical Sciences
Monica Sandberg, Ph.D., Sr. Manager, Regulatory Affairs
Alison Skrinar, Ph.D., Exec. Director, Clinical Sciences
Stephen Letrent, PharmD., Ph.D., MBA, Sr. Vice President, Drug Development, KHK (KRN23 Development Partner)
Ian Duguid, Sr. Vice President, Regulatory Affairs, KHK

1.0 BACKGROUND

KRN23 is a recombinant human IgG1 monoclonal antibody targeting fibroblast growth factor 23 (FGF23) that is being developed for the treatment of X-linked hypophosphatemia (XLH). The Sponsor currently has Orphan Drug Designation for KRN23 and was granted Fast Track Designation on June 30, 2015.

The Sponsor has conducted three clinical trials in adult subjects with XLH (KRN23-US-02, KRN23-INT-001, and KRN23-INT-002) and two Phase 2 studies (UX023-CL201 and UX023-CL205) are ongoing in the XLH pediatric population.

The Agency met with the Sponsor on May 28, 2014, to discuss the Phase 2 pediatric protocol (UX023-CL201) and potential endpoints, including patient reported outcomes (PROs) for the Phase 3 study. The Agency met with the Sponsor most recently on February 26, 2015, to discuss a Phase 3 adult protocol (UX023-CL303) and PRO measures to be included.

The purpose of this meeting is to discuss a proposed Phase 3 pediatric protocol (UX023-CL301) (b) (4)

(b) (4) .

FDA sent Preliminary Comments to the Sponsor on December 9, 2015.

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2.3. Nonclinical

Question 3: *Does the Agency agree that the existing nonclinical package for KRN23 is adequate to support the planned Biologic License Application (BLA) for KRN23 in the treatment of adults and children with XLH?*

FDA Response to Question 3:
The completed nonclinical studies appear adequate to support BLA submission. However, justify the lack of a nonclinical assessment of carcinogenic potential. This can be based on a review of all available and relevant information. For guidance, refer to "S6 Preclinical Safety and Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1) and "S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals": http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm304390.htm.

Discussion at the Meeting:
There was no discussion at the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For

more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. 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. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   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.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   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

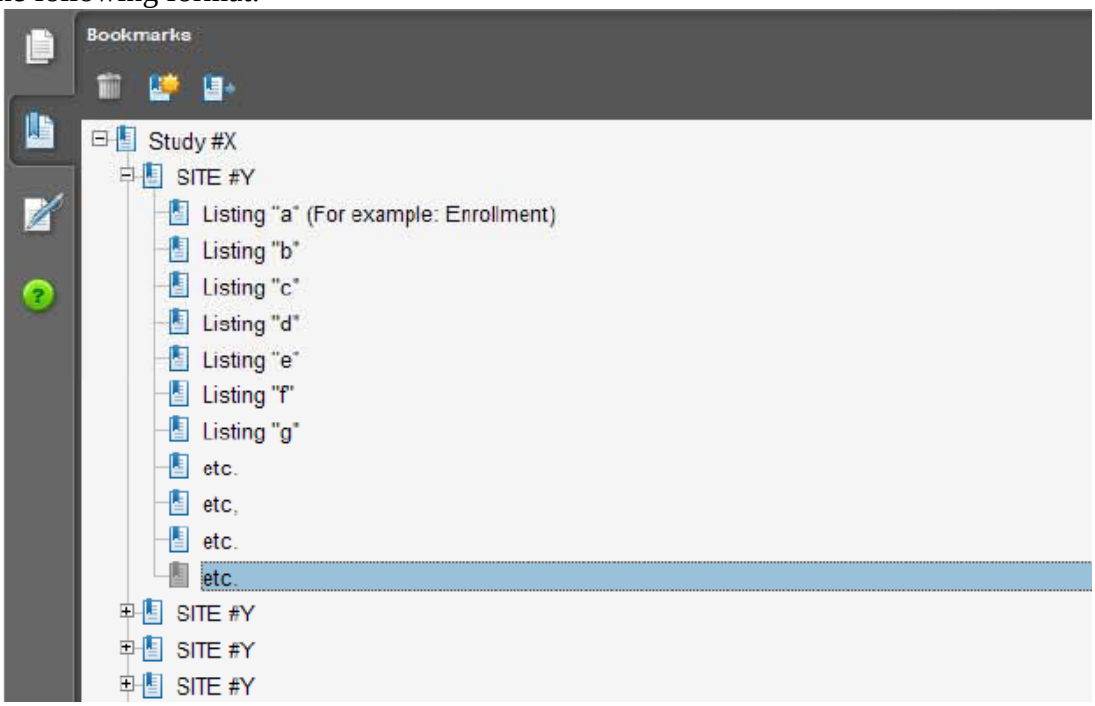
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, 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.

4. 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).
5. 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).

II. Request for Subject Level Data Listings by Site

1. 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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Several topics need further discussion (b) (4) (b) (4) (b) (4). The Sponsor will provide more detailed information (b) (4) (b) (4) for Study UX023-CL301. (b) (4) (b) (4) (b) (4)

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	January 9, 2016

6.0 ATTACHMENTS AND HANDOUTS

20151210_KRN23_EOP2 meeting

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/s/

THERESA E KEHOE
01/04/2016

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

LATE-CYCLE MEETING MINUTES

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for burosumab.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 15, 2018.

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 Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time:	February 15, 2018, 2:00 P.M. to 3:30 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	BLA 761068
Product Name:	burosumab
Indication:	The treatment of X-linked hypophosphatemia (XLH)
Applicant Name:	Ultragenyx Pharmaceutical Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products:
Audrey Gassman, M.D., Deputy Director
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Clinical Reviewer
Mukesh Summan, Ph.D., DABT, Pharmacology and Toxicology Supervisor
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of New Drugs, Office of Drug Evaluation III:
Julie Beitz, M.D., Director

Office of Pharmaceutical Quality (OPQ)
Chikako Torigoe, Ph.D., Reviewer, Office of Biotechnology Products (OBP)
William Hallett, Ph.D., Team Leader, OBP
Bruce Huang, Ph.D., Immunogenicity Reviewer
Juhong Liu, Ph.D., Team Leader
Scott Nichols, Office of Process and Facilities (OPF), Division of Microbiology Assessment (DMA) Microbiology Reviewer

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Jie Wang, Ph.D., Clinical Pharmacology Team Leader
Lin Zhou, Ph.D., Clinical Pharmacology Reviewer
Steven Li, Ph.D., Pharmacometrics Reviewer

OTS, Office of Biostatistics, Division of Biometrics III:
Mahboob Sobhan, Ph.D., Biometrics Team Leader

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Mammah Borbor-Lebbie, M.S., MBA, Project Manager
Sarah Harris, Pharm.D., R.Ph., Team Leader

OSE, Office of Medication Error Prevention and Risk Management:
Mona Patel, Risk Management Specialist, Division of Risk Management (DRISK)

OSE, Office of Pharmacovigilance and Epidemiology:
Samantha Cotter, Pharm.D., BCPS, FISMP, Safety Evaluator
Wei Liu, Ph.D., Reviewer, Division of Epidemiology

Office of New Drugs, Immediate Office, Rare Diseases Program:
Kathryn O'Connell, M.D. Ph.D, Medical Officer

Office of New Drugs, Division of Pediatric and Maternal Health:
Yeruk Mulugeta, Ph.D., Clinical Analyst
Meshaun Payne, MHCA, BSMT, Regulatory Health Project Manager
Tamara Johnson, M.D., M.S., Lead Medical Officer, Maternal Health Team
Kristie Baisden, Medical Officer, Maternal Health Team

Office of New Drugs, Immediate Office, Clinical Outcome Assessments Staff:
Yasmin Choudhry, M.D., Reviewer
Selena Daniels, Pharm.D., M.S., Team Lead

APPLICANT ATTENDEES

Ultragenyx Pharmaceutical Inc.
So-ching Brazer, PhD, Director, Regulatory Affairs, CMC
Chao-Yin Chen, PhD, Executive Director, Biostatistics
Matt Mealiffe, MD, Senior Medical Director, Clinical Science
Christine Murray, MS, RAC, Vice President, Regulatory Affairs
Monica Sandberg, PhD, RAC, Director, Regulatory Affairs
Javier San Martin, MD, Vice President, Clinical Sciences
Julie Taylor, PhD, Executive Director, Bioanalytical Methods Development
Christina Theodore-Oklota, PhD, Associate Director, Clinical Outcome and Evaluation
Elaine Eborall, VP, Clinical QA & Compliance, Quality

Kyowa Kirin International (PLC)
Tomohiro Sudo, MS, MBA. Executive Vice President, Global Product Leader, Strategic Product Portfolio Department
Jonathan Barber, Director, Regulatory Affairs CMC (Kyowa Kirin Development Inc, Princeton)

Kyowa Hakko Kirin Co. Ltd.
Yasunobu Murakami, PhD, Head of Quality Assurance, Head of QQ, Takasaki Plant

Via Teleconference:
John Paul Gabriel, BSc., Executive Director, Manufacturing Management, Technical Operations
Roo Vold, MD, Executive Medical Director, Drug Safety and Pharmacovigilance

1.0 BACKGROUND

BLA 761068 was submitted on August 17, 2017, for burosumab.

Proposed indication: The treatment of X-linked Hypophosphatemia (XLH).

PDUFA goal date: April 17, 2018

FDA issued a Background Package in preparation for this meeting on January 31, 2018.

2.0 DISCUSSION

1. Introductory Comments

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

The following substantive review issues have been identified to date:

Inspectional Issues:

1. FDA issued a nine item Form 483 to the burosumab drug substance and drug product manufacturing site following the December 2017 pre-license inspection. Quality oversight of the Quality Control operation was not in compliance with current Good Manufacturing Practices (cGMP) and a remediation plan was communicated to the applicant. The due date for a response to the remediation issues is March 1, 2018.

2. Verification of the endpoint data for one of the clinical sites for Studies UX023-CL201 and UX023-CL303 is ongoing and the status is under review.

Discussion at the Meeting:
Ultragenyx updated the Agency on the status of the QA review of QC testing records (see Slides 2 and 3). Kirin thanked the Agency for their review and intends to take this opportunity to improve their proceeses to prevent future deviations. The Agency suggested Kirin manage any discrepancies through their Quality system as any future inspection(s) would likely include review of these records.

MINOR REVIEW ISSUES

a. Imbalance in spinal surgery procedures – We note a total of 6 adult subjects required spinal surgery during the burosumab trials. We are concerned that burosumab therapy may worsen underlying spinal pathologies in treated patients with XLH.

Discussion at the Meeting:

The Agency explained that they had reviewed literature cases of spinal stenosis and spinal cord compression, some of which were associated with active Vitamin D therapy, and their concern with the number of cases reported with burosumab therapy is whether to include this safety issue in the product labeling. Ultragenyx explained they carefully reviewed the data in the 6 subjects and concluded there is no evidence that burosumab contributed to the progression of spinal stenosis (Slides 5-7). The Agency stated the issue should be followed as a safety outcome in the Disease Monitoring Program.

2. Additional Applicant Data

Discussion at the Meeting:

(b) (4)

Regarding the Study CL304 bone biopsy data, Ultragenyx now has data from 11 patients (versus 6) available. Ultragenyx confirmed that datasets have not been submitted for any of the patients. The Agency explained the datasets are important for the adult indication, safety, and labeling and would need to be submitted and reviewed. There was a discussion about what file types would the Agency require for the datasets. Ultragenyx indicated they would provide the datasets in 1-2 weeks.

Post-Meeting Comment:

Following the meeting, Ultragenyx proposed to provide both demographic information and the bone biopsy data. Ultragenyx will submit the data package containing two Study Data Tabulation Module (SDTM) and one analysis dataset with the supporting documentation including annotated case report form (CRF) and data specification files (PDF format) that serve the purpose of a define file. The detailed components of this data package are:

SDTM Data:

1. Demographic and Bone Biopsy SDTM Datasets.
2. Annotated CRF.pdf for Demographics and Bone Biopsy.
3. Data specification for Demographics and Bone Biopsy (PDF file)

Analysis Data:

1. Bone Biopsy Analysis Dataset
2. Data specification for Bone Biopsy Analysis Dataset (PDF file)

The Agency agreed with the proposal.

3. Pending Information Requests

    a. Serum phosphorus (mg/dL) levels, Rickets Severity Score (RSS) Score and the Radiographic Global Impression of Change (RGI-C) Global Score audit trail request sent 1/25/18, due 1/30/18
    b. Additional information requested regarding patients who had surgery for cervical spinal stenosis sent 1/22/18, due 2/5/18
    c. Revalidation data for the container closure integrity test method is pending and will be submitted on January 31, 2018

Discussion at the Meeting:
The Agency acknowledged responses have been received for these information requests.

4. Post-marketing Requirements/Post-marketing Commitments

    Post-marketing Requirements:

    a. A post-approval surveillance program to evaluate whether there is an association between treatment with burosumab, the occurrence of nephrocalcinosis, and renal failure. This program will be incorporated into your X-linked Hypophosphatemia Disease Monitoring Program with the current objective of collecting information on the disease for up to 10 years. You will need to incorporate an additional safety objective into this program of identifying the risk of nephrocalcinosis in this population. Collection for the safety data from program will begin within 90 days of protocol agreement and after the first marketed dose of burosumab. Progress reports will be submitted to the FDA at six months, one year, and annually thereafter with an emphasis on evaluating the effectiveness of surveillance in meeting your objective of obtaining data from a minimum of 500 subjects of whom 200 will be pediatric patients.

        We have the following comments regarding the Disease Monitoring Program protocol submitted on December 1, 2017:

        i. In general the study design appears appropriate to collect safety data. The protocol should provide more detail about the method to be used for assessment of nephrocalcinosis, (b) (4) In addition, the safety objectives should include the evaluation of renal function, and assessments should include not only serum creatinine, but urine protein quantitation because of the potential for renal tubule toxicity.

        ii. In order to ensure capture of the key data elements related to burosumab exposure during pregnancy, we refer you to the FDA Guidance for Industry: "Establishing Pregnancy Exposure Registries" (Attachment B).

    b. Perform a lactation trial in lactating women who have received therapeutic doses of burosumab using a validated assay to assess concentrations of burosumab in breast

milk, the effects on milk composition (to include calcium and phosphorus levels), and the effects on the breastfed infant.

c. Conduct a study to reanalyze banked immunogenicity serum samples from XLH clinical trials including Study UX023-CL205, Study UX023-CL201, and Study UX023-CL303 to determine the presence of anti-drug antibodies (ADA) using a validated ADA assay with improved drug tolerance. Characterize the neutralizing activity of ADA for samples tested positive for ADA. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy and safety in subjects with XLH based on the ADA data generated with the newly validated assay.

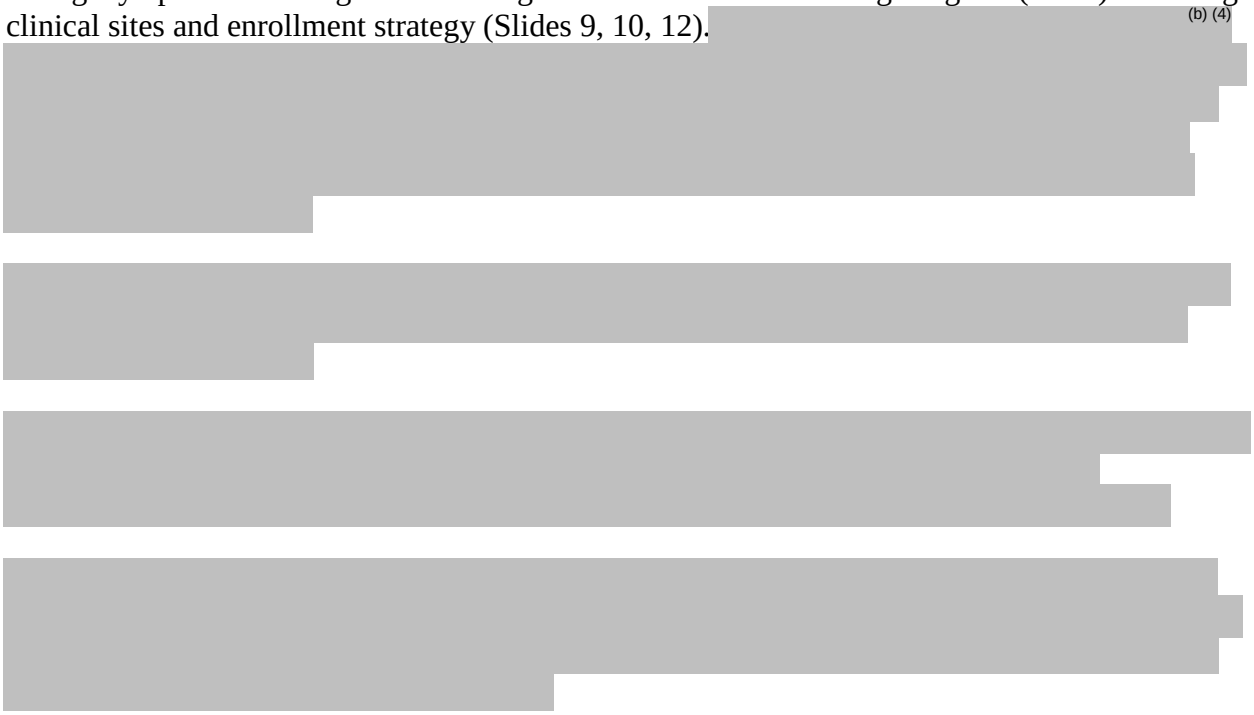
Postmarketing Commitments:

a. Conduct studies to further characterize the burosumab master cell bank (MCB) and to confirm the monoclonality of the MCB.

b. Conduct studies to evaluate effector functions (i.e., antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) of burosumab. The final Postmarketing Commitment report should be submitted based on the outcome of the studies per 21 CFR 601.12.

Discussion at the Meeting:

Ultragenyx presented the goals and design of the Disease Monitoring Program (DMP) including clinical sites and enrollment strategy (Slides 9, 10, 12). (b) (4)



Ultragenyx agreed to conduct the study to reanalyze banked serum immunogenicity samples and to evaluate the immunogenicity impact. The reanalysis of ADA and NAb data will be available Q4 2018 and the assessment of immunogenicity impact will be available Q2 2019.

Ultragenyx proposed a MCB clonality study design (b) (4) [redacted]

Ultragenyx presented proposed PMC timelines (Slide 17). The Agency asked Ultragenyx to formally submit the timelines to the BLA in the next 1 to 2 weeks.

5. Major labeling issues – 10 minutes
    a. Phosphorus level for dose adjustment – aligning with the clinical trial

Discussion at the Meeting:
Ultragenyx explained their recently submitted revisions to the PI regarding phosphorus level for dose adjustment in Section 2.1 (Slide 19).

Ultragenyx proposed (b) (4) [redacted] (b) (4) The Agency said they would discuss the topic further internally.

6. Review Plans – 5 minutes

    The team will continue to finalize reviews.

    With completion of reviews, labeling changes will also be completed.

Discussion at the Meeting:
The Agency will continue to discuss labeling and plans to respond to the recently submitted PI.

7. Wrap-up and Action Items

Discussion at the Meeting:
Ultragenyx provided an update on the US commercial batches (Slide 29). The Agency acknowledges the new commitments made for future DS and DP batches and has no additional comments.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

33 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

THERESA E KEHOE
03/14/2018