CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761068Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**BLA 761068/000**
PMR/PMC Set (####-#)	3370-1
Product Name:	Crysvita (burosumab)
Applicant Name:	Ultragenyx
ODE/Division:	**ODE3/DBRUP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

A post-approval surveillance program with safety objectives of evaluating the potential association between burosumab treatment and the risks of nephrocalcinosis, renal failure, and spinal stenosis. Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. This program will be incorporated into the X-linked Hypophosphatemia Disease Monitoring Program (study UX023-CL401) that collects information on the disease for up to 10 years. Safety data collection will begin within 90 days of protocol agreement. After marketing starts, submit progress reports to the FDA at six months, one year, and annually thereafter, with an evaluation of the effectiveness of meeting the surveillance program's safety objectives. Collect surveillance data from a minimum of 500 subjects, 200 of whom will be pediatric patients, and approximately two-thirds treated with burosumab.

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission: 04/2018

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

Final Protocol Submission:	08/2018
Study/Trial Completion:	12/2018
Final Report Submission:	08/2029

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

XLH is a life long disease. Increased risks associated with XLH include nephrocalcinosis and enthesopathy which may lead to surgical intervention for spinal stenosis. These risks may be exacerbated by treatment with conventional therapy (phosphate supplements and active vitamin D). Long-term data are needed to evaluate these risks with burosumab therapy. In-vitro data suggest that antibody dependent cellular toxicity may occur with enal tubule cell as the predominant taget. Although a signal was not seen in the short term clinical trials, long-term data are needed to adequately evaluate the risk.

The Sponsor is committed to conducting a 10-year disease monitoring study in XLH patients and these safety outcomes will be included. Additionally, pregnancy exposure data will be collected

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- X FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- X Longer-term data needed to further characterize the safety/efficacy of the drug
- X Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- X Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval

☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination

☐ Other reason (describe in text box below)

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

☐ Assess a known serious risk related to the use of the drug

☐ Assess a signal of serious risk related to the use of the drug

X Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.

☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.

☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.

☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☒ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☒ Serious risk (adverse event) of concern cannot be identified in the database.
- ☒ The population(s) of interest cannot be identified in the database.
- ☒ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☒ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either "Yes" or "No" and provide the appropriate responses.]

☒ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. <u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☒ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☒ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Insert electronic signature (usually the Deputy Director for Safety)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

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Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**BLA 761068/000**
PMR/PMC Set (####-#)	3370-2
Product Name:	Crysvita (burosumab)
Applicant Name:	Ultragenyx
ODE/Division:	**ODE3/DBRUP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

In XLH patients enrolled in the prospective, longitudinal, surveillance study, perform a lactation sub-study 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.

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	04/2018
Final Protocol Submission:	08/2018
Study/Trial Completion:	12/2028
Final Report Submission:	08/2029

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

There are no data on the presence of burosumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. However, the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to burosumab are unknown. The lack of clinical data during lactation precludes a clear determination of the risk of burosumab to an infant during lactation. Therefore, this lactation study is needed to provide data on the presence of burosumab presence in human milk and the effects on the breastfed infant.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- X FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- X Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- X Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- X Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☒ Other

The potential safety outcomes from burosumab exposure in the breastfed infant have yet to be characterized at this time; and FAERS cannot provide information on amount of burosumab in breastmilk.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☒ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☒ Other

The potential safety outcomes from burosumab exposure in the breastfed infant have yet to be characterized at this time; and FAERS cannot provide information on amount of burosumab in breastmilk.

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either "Yes" or "No" and provide the appropriate responses.]

☒ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

☒ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☒ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☒ Other

A properly designed and conducted prospective trial to evaluate drug concentrations in breast milk and effects on the breastfed infant necessary provide the information needed.

f. ☒ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. <u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☒ Other (describe) **Lactation study**

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

☐ *For non-PREA pediatric studies/trials only*: Pediatric population

☐ Geriatric population

X Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☒ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Insert electronic signature (usually the Deputy Director for Safety)

Appendix A
PMR/PMC Development Template (FRM-ADMIN-60)
Instructions for Use

[click here to return to the template]

Purpose:

The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:

The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:

The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.[10] The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:

The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.[11] This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

[11] A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click here to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click here to return to Section B of the template]

1. **PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

   PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.[12]

   Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

   Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed ***[see Appendix B for examples]***.

2. **PMR/PMC Milestones**: List the PMR/PMC milestones in the specified format.

   Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

   The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

[12] The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.[13]

"Other" milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.[14]

SECTION C: PMR/PMC Rationale [Click here to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

[13] "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See FDA guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

[14] Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B "reportable" PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS[15] and Sentinel's ARIA[16] system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

***Question 4.a*: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

***Questions 4.b-d*: Explanation of whether FAERS and Sentinel's postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency*

[15] FDA Adverse Event Reporting System (FAERS)
[16] Active Risk Identification and Analysis (ARIA)

Memorandum, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

***Question Q4.e*: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, in include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f*: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either "type of study" or "type of clinical trial." Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click here to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select "yes" if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select "not applicable."

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 "core" milestones).

Note: Additional milestones also must be tracked by the division (see MAPP 6010.2, *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click here to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. **The PMR/PMC is clear, feasible, and appropriate because (select all that apply):**

   Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. **The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

   This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

   It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. **This PMR/PMC has been reviewed for clarity and consistency… reliability of drug quality**.

   This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy.

- Drug-Drug Interactions (gastric acid reducing agents)

  Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

  Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Anti-Drug Antibody Responses

  Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient's test sample at each sampling point.

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**761068/000**
PMR/PMC Set (####-#)	3370-3
Product Name:	Crysvita (burosumab)
Applicant Name:	Ultragenyx
ODE/Division:	**ODE3/DBRUP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

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 adult and pediatric subjects with XLH based on the ADA data generated with the newly validated assay.

2. PMR/PMC Schedule Milestones[2, 3]

Study/Trial Completion:	12/2018
Final Report Submission:	06/2019

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

No subjects were found positive for treatment-emergent anti-drug antibodies (ADA) in burosumab XLH clinical studies due to the limitation of the immunogenicity assays in the BLA. There were limitations in the immunogenicity assays used – the drug tolerance level of the assay was lower than the mean steady state drug concentrations observed in the burosumab clinical trials, limiting the evaluation of antidrug antibody incidence and the clinical impact, including safety. The Sponsor developed a new assay to reevaluate the samples.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- X FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- X Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

☐ Assess a known serious risk related to the use of the drug

☐ Assess a signal of serious risk related to the use of the drug

X Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.

☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.

☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.

X An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. <u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
X Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

X No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

☐ *For non-PREA pediatric studies/trials only*: Pediatric population
☐ Geriatric population
☐ Lactating/nursing mothers
☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
☒ Orphan or rare disease population
☐ Pregnant women
☐ Racial/ethnic population
Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

The Sponsor has developed a new assay to re-analyzed stored samples to detect ADAs. No protocol is needed; therefore, no milestone date for final protocol is needed.

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.
☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
☒ The applicant has adequately justified the choice of milestone dates.
☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Insert electronic signature (usually the Deputy Director for Safety)

Appendix A
PMR/PMC Development Template (FRM-ADMIN-60)
Instructions for Use

[click here to return to the template]

Purpose:

The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:

The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:

The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.[10] The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:

The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.[11] This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

[11] A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click here to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click here to return to Section B of the template]

1. **PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

   PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.[12]

   Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

   Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed ***[see Appendix B for examples]***.

2. **PMR/PMC Milestones**: List the PMR/PMC milestones in the specified format.

   Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

   The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

[12] The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.[13]

"Other" milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.[14]

SECTION C: PMR/PMC Rationale [Click here to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

[13] "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See FDA guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

[14] Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B "reportable" PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS[15] and Sentinel's ARIA[16] system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

***Question 4.a*: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

***Questions 4.b-d*: Explanation of whether FAERS and Sentinel's postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency*

[15] FDA Adverse Event Reporting System (FAERS)
[16] Active Risk Identification and Analysis (ARIA)

Memorandum, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

***Question Q4.e*: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, in include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f*: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either "type of study" or "type of clinical trial." Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click here to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select "yes" if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select "not applicable."

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 "core" milestones).

Note: Additional milestones also must be tracked by the division (see MAPP 6010.2, *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click here to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. **The PMR/PMC is clear, feasible, and appropriate because (select all that apply):**

   Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. **The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

   This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

   It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. **This PMR/PMC has been reviewed for clarity and consistency… reliability of drug quality**.

   This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy**.**

- Drug-Drug Interactions (gastric acid reducing agents)

  Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

  Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Anti-Drug Antibody Responses

  Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient's test sample at each sampling point.

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/s/

CHRISTINE P NGUYEN
04/17/2018

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 761068
Product Name: Crysvita (burosumab)

PMC #1 Description: Conduct studies to further characterize the burosumab master cell bank (MCB) and to support the monoclonality of the MCB.

PMC Schedule Milestones:

Final Protocol Submission:	12/2018
Study/Trial Completion:	
Final Report Submission:	06/2020
Other:	

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

☐ Need for drug (unmet need/life-threatening condition)
☐ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
☐ Improvements to methods
X Theoretical concern
☐ Manufacturing process analysis
☐ Other

The specifications for burosumab drug substance and drug product are acceptable to ensure adequate quality and safety for the initial marketed product. Assurance of the monoclonality of the burosumab MCB will reduce the risk of the generation of product variants and ensure the consistency of product quality throughout the product life cycle.

2. Describe the particular review issue and the goal of the study.

The establishment of burosumab MCB includes multiple selection procedures for the cells that produce burosumab with adequate growth profiles. However, a formal cloning procedure was conducted only once (b) (4). Therefore, there is residual uncertainty for the monoclonality of burosumab MCB. The goal of the study is to demonstrate consistent genetic profiles for the subclones of burosumab MCB to ensure the monoclonality of burosumab MCB.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☐ Dissolution testing
   ☐ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   X Other

   Describe the agreed-upon study:

   The analysis of genetic characteristics of a sufficient number of subclones of burosumab MCB.

5. To be completed by ONDQA/OBP Manager:

   ☒ Does the study meet criteria for PMCs?
   ☒ Are the objectives clear from the description of the PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 761068
Product Name: Crysvita (burosumab)

PMC #2 Description: Conduct studies to evaluate effector functions (i.e., antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) of burosumab. The final Post Marketing Commitment report should be submitted based on the outcome of the studies per 21 CFR 601.12.

PMC Schedule Milestones:

Final Protocol Submission:	12/2018
Study/Trial Completion:	
Final Report Submission:	12/2019
Other:	

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

☐ Need for drug (unmet need/life-threatening condition)
☐ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
☐ Improvements to methods
X Theoretical concern
☐ Manufacturing process analysis
☐ Other

The specifications for burosumab drug substance and drug product are acceptable to ensure adequate quality and safety for the initial marketed product. However, insufficient information was provided in the BLA on the levels of observed effector functions of burosumab.

2. Describe the particular review issue and the goal of the study.

Burosumab demonstrates antibody-dependent cellular cytotoxicity (ADCC) against HEK#18 cells that overexpress FGF receptor 1 and Klotho. However, it is inconclusive whether observed ADCC levels are potentially significant in patients. The goal of the study is to demonstrate that the levels of ADCC and complement-dependent cytotoxicity (CDC) of burosumab are not significant compared to those of an IgG that has established ADCC and CDC.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☐ Dissolution testing
   ☐ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   X Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   ☐ Other

   Describe the agreed-upon study:

   The evaluation of the levels of ADCC and CDC of burosumab relative to the levels of ADCC and CDC of a control IgG for which ADCC and CDC have been established. The final report must be submitted per 21 CFR 601.12.

5. To be completed by ONDQA/OBP Manager:

   ☒ Does the study meet criteria for PMCs?
   ☒ Are the objectives clear from the description of the PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

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/s/

CHRISTINE P NGUYEN
04/17/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: April 2, 2018

To: Samantha Bell
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA 761068**
OPDP labeling comments for CRYSVITA® (burosumab-xxxx) injection, for subcutaneous use

---

In response to DBRUP consult request dated September 7, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for CRYSVITA® (burosumab-xxxx) injection, for subcutaneous use.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DBRUP (Samantha Bell) on March 27, 2018,and are provided below.

OPDP has reviewed the attached proposed carton and container labeling and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

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/s/

JINA KWAK
04/02/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 7, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	BLA 761068
Product Name and Strength:	Crysvita (burosumab-twza) Injection 10 mg/mL, 20 mg/mL, and 30 mg/mL
Applicant/Sponsor Name:	Ultragenyx Pharmaceuticals Inc.
FDA Received Date:	March 6, 2018
OSE RCM #:	2017-1717-3
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised carton labeling for Crysvita (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling for Crysvita is acceptable from a medication error perspective. We have no further recommendations at this time.

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

[a] Rider B. Label and Labeling Review for Crysvita (BLA 761068). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 26. RCM No.: 2017-1717-2.

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/s/

BRIANA B RIDER
03/07/2018

LOLITA G WHITE
03/07/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 26, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	BLA 761068
Product Name and Strength:	Crysvita (burosumab-twza) Injection 10 mg/mL, 20 mg/mL, and 30 mg/mL
Applicant/Sponsor Name:	Ultragenyx Pharmaceuticals Inc.
Submission Date:	January 30, 2018 and February 12, 2018
OSE RCM #:	2017-1717-2
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised container labels and carton labeling for Crysvita (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Crysvita are unacceptable from a medication error perspective.

3 RECOMMENDATIONS FOR ULTRAGENYX PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this BLA:

[a] Rider B. Label and Labeling Review for Crysvita (BLA 761068). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 18. RCM No.: 2017-1717-1.

A. Carton Labeling

1. 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.

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

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

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/s/

BRIANA B RIDER
02/26/2018

LOLITA G WHITE
02/26/2018

Clinical Inspection Summary

Date	02/12/2018
From	Jenn Sellers, Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Samantha Bell, RPM Stephen Voss, Medical Officer Theresa Kehoe, Clinical Team Leader Audrey Gassman, Deputy Director Division of Bone, Reproductive, and Urologic Products (DBRUP)
BLA #	761068
Applicant	Ultragenyx Pharmaceutical, Inc.
Drug	Burosumab
NME	Yes
Therapeutic Classification	Human Immunoglobulin G subclass 1 (IgG1)
Proposed Indication	Treatment of X-linked Hypophosphatemia (XLH) in Adult and Pediatric Patients 1 Year of Age and Older
Consultation Request Date	September 22, 2017
Summary Goal Date	February 16, 2018
Action Goal Date	April 17, 2018
PDUFA Date	April 17, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEBLATIONS

The clinical sites of Drs. Portale, Imel, Linglart and Kamenicky were inspected in support of this BLA. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The preliminary classification of the inspection of Dr. Portale was Voluntary Action Indicated (VAI), and the preliminary classifications of the inspections of Drs. Imel, Linglart and Kamenicky were No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this BLA to support the use of burosumab for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

Inspections were requested for the following protocols in support of this application:

Protocol UX023-CL201, "A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)"

This was a randomized, open-label, dose finding study of KRN23 in pediatric subjects aged 5 to 12 years with XLH. The main study objectives were to:

- Identify a dose and dosing regimen of KRN23, based on safety and PD effects in pediatric XLH patients
- Establish the safety profile of KRN23 for the treatment of children with XLH, including ectopic mineralization risk, cardiovascular effects, and the immunogenicity profile.

The primary efficacy endpoint was change from Baseline (Week 0) to Week 40 and Week 64 in severity of rickets as measured by the Rickets Severity Scale (RSS) total score assessment of wrist and knee radiographs.

Important secondary efficacy and pharmacodynamic endpoints included:

- Change from Baseline in the radiographic appearance of rickets and bowing as measured by the Radiographic Global Impression of Change (RGI-C) global, knee, wrist, and long leg scores
- Serum phosphorous levels

Protocol UX023-CL303, "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with Open-Label Extension to Assess the Efficacy and Safety of KRN23 in Adults with X-linked Hypophosphatemia (XLH)"

This was a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of KRN23 in adult subjects aged 18 to 65 years with XLH.

The primary study objective was to establish the effect of KRN23 treatment compared with placebo on increasing serum phosphorus levels in adults with XLH.

The primary efficacy endpoint was the proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (2.5 mg/dL) at the midpoint of the dose interval (that is, Weeks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between Baseline (Week 0) and Week 24.

Key secondary efficacy endpoints included change from Baseline to Week 24 in the:

- Brief Pain Inventory (BPI) Worst Pain score
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Stiffness score
- WOMAC Physical Function score

Rationale for Site Selection

The US sites (#139 and #156) were selected due to large enrollment. The foreign sites (#141 and #186) were selected to ensure consistency of treatment and study conduct between US and foreign sites.

III. RESULTS (by site):

Site #/ Name of CI Address	**Protocol #/ # of Enrolled Subjects**	**Inspection Dates**	**Classification**
Site #139 **Anthony A. Portale, M.D.** UCSF Medical Center at Mission Bay 550 16th street, 5th Floor San Francisco, CA 94158	UX023-CL201 Subjects: 8 UX023-CL303 Subjects: 9	15-17 Nov 2017 20-22 Nov 2017 28 and 30 Nov 2017 01, 05, and 08 Dec 2017	VAI*
Site #156 **Erik Imel, M.D, M.S** Indiana University Department of Medicine University Hospital 550 North University Blvd. Indianapolis, IN 46202	UX023-CL201 Subjects: 6 UX023-CL303 Subjects: 12	11-14 Dec 2017	NAI*
Site #141 **Agnes Linglart, M.D., Ph.D.** Hospital Bicetre Service d'endocrinologie et diabetologie de l'enfant 78 Rue di General Leclerc Le Kremlin-Bicetre, 94275 France	UX023-CL201 Subjects: 2	18-22 Dec 2017	NAI*
Site #186 **Peter Kamenicky, M.D.** CHU de Bicêtre Service d'Endocrinologie et des Maladies de la Reproduction 70 rue du Général Leclerc Le Kremlin-Bicêtre, 94275 France	UX023-CL303 Subjects: 12	11-15 Dec 2017	NAI*

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Anthony A. Portale, M.D.

For Protocol UX023-CL201, 9 subjects were screened and 8 were enrolled in the study, all of whom were being followed in the extension phase at the time of inspection. For Protocol UX023-CL303, 12 subjects were screened and 9 were enrolled study, all of whom were being followed in the open label extension phase. For both protocols, records reviewed included all informed consent forms for enrolled subjects; all enrolled subject records and source documents for primary and secondary efficacy endpoint data available at the study site; all enrolled subject records and source documents for eligibility, adverse events (including serious adverse events), and protocol deviations; test article accountability; training records; and regulatory documents.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection with an observation of protocol violations. Specifically, the protocol violations were:

- For Protocol UX023-CL201, five of the 8 enrolled pediatric subjects received an X-ray of the standing long leg at Week 40, which was not required by the protocol.

Reviewer's comment: This protocol violation was reported to the IRB within the appropriate timeframe as well as to the FDA.

- For Protocol UX023-CL303, the AE of mild general bone pain for Subject (b) (6) (in the placebo group) was not reported. The bone pain resolved after the treatment of three doses of ibuprofen 200 mg.

There was no evidence of under-reporting of other adverse events. Dr. Portale adequately responded to the inspection findings in a letter dated December 28, 2017.

Of note, the source data necessary to verify the primary efficacy endpoint were not available at the site during the inspection. However, OSI later obtained source electronic data from the vendor (through the sponsor) and was able to verify the RSS and RGI-C scores for Study UX023-CL201 and the serum phosphorous levels for Study UX023-CL303.

2. Erik Imel, M.D.

For Protocol UX023-CL201, 11 subjects were screened and 6 were enrolled, all of whom were being followed in the extension phase at the time of inspection. For protocol UX023-CL303, 16 subjects were screened and 12 were enrolled, all of whom were being followed in the open label extension phase. The inspection covered (but was not limited to) the following issues: protocol adherence; inclusion/exclusion criteria; informed consent forms; data verification between source documentation and endpoint line listings; sponsor and IRB communications; investigators agreements; financial disclosure; monitoring; drug accountability; and training.

No significant regulatory violations were noted. The primary endpoint data were verifiable. There was no evidence of under-reporting of AEs.

3. Agnes Linglart, M.D., Ph.D.

At this site for Protocol UX023-CL201, 5 subjects were screened and 2 were enrolled, all of whom were being followed in the extension phase at the time of inspection. The study records for these two enrolled subjects were reviewed.

No significant regulatory violations were noted. The primary endpoint data were verifiable. There was no evidence of under-reporting of AEs.

4. Peter Kamenicky, M.D.

At this site for Protocol UX023-CL303, 12 subjects were screened and enrolled. Eleven subjects were randomized and received the study drug. Three subjects were discontinued, and 8 subjects were in the extension phase at the time of inspection. A review of all subjects' records was completed, focusing on informed consent, eligibility, adverse events, and efficacy endpoint data.

No significant regulatory violations were noted. The primary endpoint data were verifiable. Two adverse events for Subject (b) (6) were not reported by the site. One was mild right heel pain and the other was mild "flu symptoms". The FDA field inspector discussed these two unreported AEs with the CI and emphasized that all AEs should be reported. The CI stated that they planned to create a spreadsheet tool to tract AEs to ensure all AEs are captured and assessed in the future. There was no evidence of under-reporting of other AEs.

{See appended electronic signature page}

Jenn W. Sellers, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation

cc:
Central Doc. Rm. BLA #761068
DBRUP/Medical Officer/Stephen Voss
DBRUP/Clinical Team Leader/Theresa Kehoe
DBRUP/Deputy Division Director/Audrey Gassman
DBRUP /Project Manager/Samantha Bell
OSI /Office Director/David Burrow
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

JENN W SELLERS
02/12/2018

PHILLIP D KRONSTEIN
02/12/2018

KASSA AYALEW
02/12/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs—ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Lily (Yeruk) Mulugeta, PharmD, Clinical Reviewer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Team Leader

John J. Alexander, MD, MPH, Deputy Division Director DPMH

To: Division of Bone, Reproductive and Urologic Products (DBRUP)

Drug: Burosumab (Crysvita™)

BLA: 761068

Proposed Indication:
Treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older

Dosage form and route of administration: Solution for subcutaneous injection (10 mg/ml, 20 mg/ml, or 30 mg/ml single-dose vials)

Sponsor: Ultragenyx Pharmaceutical

Consult Request: DBRUP requested input from DPMH regarding the burosumab label

Background

Burosumab is a monoclonal antibody inhibitor of fibroblast growth factor 23 (FGF23) evaluated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older. FGF23 is a hormone produced by osteocytes that inhibits renal tubular phosphate reabsorption, leading to renal phosphate wasting and hypophosphatemia. FGF23 suppresses production of 1, $25(OH)_2$vitamin D, which impairs intestinal calcium and phosphate absorption. XLH is a genetic disorder

characterized by high levels of circulating FGF23 by osteocytes and subsequent hypophosphatemia resulting in defective bone mineralization and impacts to other tissues such as muscle. Pathologic consequences include rickets, reduced growth, and skeletal deformities in children and osteomalacia, skeletal deformities and fractures in adults. Currently, there is no approved therapy for XLH. Management of patients with XLH includes treatment with oral phosphate salts and active vitamin D.

Burosumab is a fully human monoclonal antibody designed to bind and thereby inhibit the excessive biologic activity of FGF23. The product was granted Breakthrough Designation (BTD) in June 2016. The efficacy and safety of burosumab were evaluated in 8 completed and ongoing clinical studies that include adult and pediatric patients 1 to 12 years of age with XLH. The clinical development program examined the effects of burosumab on clinical, biochemical, and radiographic aspects of XLH in children and adults. In addition, the program provided pharmacokinetics (PK) and pharmacodynamics (PD) data (serum phosphorus) to support the selected doses and dose regimens. The program also included a historical control study in pediatric patients 5 to 14 years. The relevant phase 2 and 3 trials are described below:

- Study CL303 was a placebo controlled phase 3 study evaluating 1 mg/kg of burosumab every 4 weeks (n=68) compared to placebo (n=66) in adult patients with XLH. The primary endpoint was change in serum phosphate level from baseline to week 24. A total of 94.7% of patients in the burosumab group achieved serum phosphorus levels above the lower limit of normal as compared with 7.6% of subjects in the placebo arm. Nine out of the 68 subjects receiving burosumab had elevated serum phosphorous levels >4.5 mg/dL; five out of the nine required dose reduction per protocol. Rates of injection site reactions were similar between the treatment and placebo arm. There were no discontinuations due to adverse events.
- Study CL201was a Phase 2 study in 52 patients 5 to 12 years of age with XLH. The primary efficacy endpoint was change in Rickets Severity Score (RSS) a radiographic scoring method. The study consists of two Screening Visits, a 16-week Titration Period, a 48-week Treatment Period, and a 96-week Treatment Extension Period. Overall, there was a 50% reduction in RSS from baseline at weeks 40 and 64. Mean burosumab dose after titration was 1 mg/kg every 2 weeks or 1.5 mg/kg every 4 weeks. Injection site reactions occurred in 65% of patients; all were mild (grade 1). Other adverse events reported include headache (65%), cough (54%), nasopharyngitis (48%) and vomiting (42%). There were no reports of hyperphosphatemia or discontinuations. This study is ongoing.
- Study CL205 was a phase 2 open-label, dose ranging study in 13 patients 1 to 4 years (mean 2.9 years) of age with XLH. The burosumab dose ranged from 0.8 to 1.2 mg/kg every 2 weeks. In this study, there was a 59% reduction in RSS total score from baseline. Injection site reactions were reported in 23% of patients; all were grade 1 reactions. Other adverse events include cough (77%), pyrexia (62%), upper respiratory tract infection (54%), and vomiting (46%). There were no reports of hyperphosphatemia or discontinuations. This study is ongoing. This

submission includes primary analyses of data to Week 40 additional safety data available through the data cutoff date (20 April 2017).

The development program also included an ongoing single arm, open label study in 14 adult subjects with XLH (Study UX023-CL304). Patients received burosumab at 1 mg/kg every 4 weeks. The primary efficacy endpoint was percent change from baseline in osteoid volume/bone volume (OV/BV) at Week 48 based on analysis of iliac crest bone biopsies. Subjects had osteomalacia at baseline as demonstrated by an excess of osteoid tissue (as assessed by osteoid volume, surface, and thickness) and delay in mineralization lag time (time from osteoid deposition to mineralization). Based on the interim report included in this submission, biopsies were available at Week 48 for two subjects. Both showed decreases in OV/BV (-65% and -74%) and in OS/BS (-23% and -41%). Mineralization lag time decreased -48% in one subject but was not evaluable in a second subject.

Efficacy in adolescents

Although, adolescents (13 to less than 17 years) were not enrolled in the trials, the disease progression, response to therapy, and general goal of therapy are expected to be similar between adolescents and young children with open epiphyseal plates who have XLH (Carpenter et al. 2011). Therefore, it is reasonable to assume that the effects of burosumab (biochemical and radiographic) are not expected to be different between adolescents and younger children with open epiphyseal plates. Because burosumab is titrated based on biochemical markers (serum phosphate levels), dosing in adolescents can be derived from modeling and simulation using a population PK/PD model developed with data from pediatric XLH patients 1 to 12 years of age. The proposed starting dose in adolescents is the same as the dose used in the pediatric study (0.8mg/kg Q2Weeks).

Reviewer's comments: *DPMH agrees that efficacy can be extrapolated. The approach to dose selection appears appropriate, provided that it is acceptable from a clinical pharmacology standpoint. Additional data on the pharmacodynamic effects of burosumab (serum phosphorus and TmP/GFR levels) will be collected in the ongoing pediatric study (Study CL201).*

Of note, hyperphosphatemia and ectopic mineralizations including renal, cardiac and aortic calcification were observed in studies conducted in non-XLH animals. These findings occurred at supraphysiologic serum phosphate concentrations at or above 9 mg/dL (at peak) and 5.5 mg/dL (at trough) in adult monkeys, and 9.5 mg/dL (peak) and 8.5 mg/dL (trough) in juvenile monkeys. There were no reports of nephrocalcinosis in pediatric patients.

Reviewer's comments: *The product labeling appropriately provides language around dose reduction and interruptions based on patients' serum phosphorus levels.*

Sponsor proposed labeling of specific sections with DPMH recommended edits (strikethroughs represent deletions and underlining represents additions)

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

CRYSVITA is a [redacted] (b) (4) fibroblast growth factor 23 (FGF23) indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older. (1)

Reviewer's comments: This section appropriately describes the entire pediatric age range for which the efficacy and safety have been established.

DOSAGE AND ADMINISTRATION

For subcutaneous use only (2)

- Pediatric XLH: Starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. (2.1)

Dose may be increased up to approximately 2 mg/kg, administered every two weeks to achieve normal serum phosphorus. (2.1)

Reviewer's comments: The recommended dosing regimen appears appropriate from a clinical standpoint and is in general consistent with the dosing used in the studies. As mentioned above, the dosing in adolescents was derived from modeling and simulation using a population PK/PD model developed with data from pediatric XLH patients 1 to 12 years of age. Extrapolation of the pediatric dose to adolescents appears appropriate provided that the PK/PD model and simulations are acceptable.

FULL PRESCRIBING INFORMATION

Note**: The focus will be on Dosing and Administration and 8.4 section of the label. These are recommendations by the Pediatric Team. A separate review is available from the Maternal Health Team.**

1 INDICATIONS AND USAGE

CRYSVITA is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Pediatric patients with X-linked hypophosphatemia (1 to less than 18 years of age)

The recommended starting dose regimen is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg.

After initiation of treatment with CRYSVITA, measure fasting serum phosphorus every 4 weeks for the first 3 months of treatment, and thereafter as appropriate. If serum phosphorus is [redacted]. Follow dose adjustment schedule below to maintain serum phosphorus within the reference range for age.

Dose increase

If serum phosphorus is below the reference range for age, the dose may be increased stepwise up to approximately 2 mg/kg, administered every two weeks (maximum dose of 90 mg) according to the dosing schedule shown in Table 1. [redacted]

Table 1: Dose Schedule for Stepwise Dose Increase

Body Weight (kg)	Dose (mg)	First Dose Increase to (mg)	Second Dose Increase to (mg)
10 - 14	10	15	20
15 - 18	10	20	30
19 - 31	20	30	40
32 - 43	30	40	60
44 - 56	40	60	80
57 - 68	50	70	90
69 - 80	60	90	90
81 - 93	70	90	90
94 - 105	80	90	90
≥ 106	90	90	90

Dose decrease

If serum phosphorus is above [redacted], withhold the next dose and reassess the serum phosphorus level in 4 weeks. The patient must have serum phosphorus below the reference range for age to reinitiate CRYSVITA. Once serum phosphorus is below the reference range for age, treatment may be restarted according to the dose schedule shown in Table 2. Reassess serum phosphorus level 4 weeks after dose adjustment. If the level [redacted] below the reference range for age after the re-initiation dose, the dose can be adjusted [redacted]

Table 2: Dose Schedule for Re-initiation of Therapy

Previous Dose (mg)	Re-initiation Dose (mg)
10	5
15	10
20	10
30	10
40	20
50	20
60	30
70	30
80	40
90	40

Reviewer's comments: The proposed dosing in general appears to match the doses used in the pediatric studies. As noted above, although adolescents 13 years and older were not included in the pediatric trials, the proposed dosing appears reasonable if supported by the population PK/PD model.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients with CRYSVITA. Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment *[see Adverse Reactions (6.1)]*.

5.2 Hyperphosphatemia and Risk of Nephrocalcinosis

Increases in serum phosphorus may be associated with an increased risk of nephrocalcinosis. For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels *[see Dosage and Administration (2)]*.

5.3 Injection Site Reactions

Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA, if severe injection site reactions occur and administer appropriate medical treatment *[see Adverse Reactions (6.1)]*.

Reviewer's comments: The warnings and precautions appropriately outline the potential risk for hyperphosphatemia and nephrocalcinosis observed in the animal studies described above. The dosing and administration section provides language around dose reduction and interruptions based on patients' serum phosphorus levels.

8.4 Pediatric Use

Safety and (b) (4) of CRYSVITA have been (b) (4) established (b) (4) in pediatric patients 1 year and older. Efficacy in pediatric patients 1 year and older with XLH is based on open label studies (b) (4) of 52 pediatric patients 5 to 12 years of age ~~with XLH~~ (Study 1), and ~~in~~ 13 pediatric patients 1 to 4 years of age ~~with XLH~~ (Study 2) evaluating serum phosphorus levels and radiographic findings. Efficacy in adolescents is supported by studies in pediatric patients less than (b) (4) years of age. Dosing in (b) (4) was derived using modeling and simulation of adult and pediatric PK and PD data.

Safety and (b) (4) for CRYSVITA in pediatric patients with XLH below the age of 1 have not been established.

[see Adverse Reactions (6.1) and Clinical Studies (14)].

Reviewer's comments:

This section should clearly state that the safety and efficacy of the product have been established in patients 1 year and older as well as summarize the basis for that determination (e.g., include a brief description of the type of trials conducted, the duration and endpoints, including PD marker(s). In addition, the section should describe how dosing was derived in adolescents.

Conclusions:

DBRUP requested input from DPMH regarding the burosumab label. DPMH participated in labeling meetings on 01/03/2018 and 01/11/2018. DPMH found the labeling acceptable in general and provided input primarily on section 8.4:

> Safety and (b) (4) of CRYSVITA have been (b) (4) established (b) (4) in pediatric patients 1 year and older. Efficacy in pediatric patients 1 year and older with XLH is based on open label studies (b) (4) of 52 pediatric patients 5 to 12 years of age ~~with XLH~~ (Study 1), and ~~in~~ 13 pediatric patients 1 to 4 years of age ~~with XLH~~ (Study 2) evaluating serum phosphorus levels and radiographic findings. Efficacy in adolescents is supported by studies in pediatric patients less than (b) (4) years of age. Dosing in (b) (4) was derived using modeling and simulation of adult and pediatric PK and PD data.
>
> Safety and (b) (4) for CRYSVITA in pediatric patients with XLH below the age of 1 year of age have not been established.

The reader is directed to final negotiated labeling which may reflect changes not discussed in this review.

Suggested information to be copied into Unireview
DPMH agrees that the clinical, biochemical, radiographic findings in children 1 to 12 years of age support the efficacy of burosumab in adolescents. The proposed dosing in adolescents was derived from modeling and simulation using a population PK/PD model developed with data from pediatric XLH patients 1 to 12 years of age. The dosing appears appropriate provided that the PK/PD model and simulations are acceptable. In addition, the ongoing pediatric study (Study 201) will include collection of PD data (serum phosphorus) in adolescents.

DPMH recommends the following changes to section 8.4 of the label (strikethroughs represent deletions and underlining represents additions):

> Safety and (b) (4) of CRYSVITA have been (b) (4) established (b) (4) in pediatric patients 1 year and older. Efficacy in pediatric patients 1 year and older with XLH is based on open label studies (b) (4) of 52 pediatric patients 5 to 12 years of age ~~with XLH~~ (Study 1), and ~~in~~ 13 pediatric patients 1 to 4 years of age ~~with XLH~~ (Study 2) evaluating serum phosphorus levels and radiographic findings. Efficacy in adolescents is supported by studies in pediatric patients less

than (b) (4) years of age. Dosing in (b) (4) was derived using modeling and simulation of adult and pediatric PK and PD data.

Safety and (b) (4) for CRYSVITA in pediatric patients with XLH below the age of 1 year of age have not been established.

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/s/

YERUK A MULUGETA
01/24/2018

HARI C SACHS
01/24/2018
I agree with these recommendations.

JOHN J ALEXANDER
01/24/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: January 17, 2018 **Date Consulted:** August 24, 2017

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Samantha Bell, Regulatory Project Manager (RPM)
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Drug: CRYSVITA (burosumab)

BLA: 761068

Indication: CRYSVITA is a monoclonal antibody inhibitor of fibroblast growth factor 23 (FGF23) indicated for the treatment of X-linked hypophosphatemia (XLH).

Applicant: Ultragenyx Pharmaceutical Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- BLA 761068 submitted on August 17, 2017

Consult Question: **"**DBRUP requests assistance with the labeling review including PLLR implementation in this new product"

INTRODUCTION

This consult provides pregnancy and lactation labeling recommendations to DBRUP for use in the labeling of CRYSVITA (burosumab). DPMH's labeling recommendations are based on a review of the nonclinical studies, published literature, and pharmacovigilance database for burosumab. Formerly, DBRUP consulted DPMH on August 24, 2017 to provide input on the labeling for burosumab to be in compliance with the Pregnancy and Lactation Labeling Rule.

REGULATORY HISTORY

On August 17th, 2017, Ultragenyx submitted an original BLA for CRYSVITA (burosumab). Burosumab is a monoclonal antibody that inhibits fibroblast growth factor 23 (FGF 23). Burosumab is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older. Because XLH is a rare disease, burosumab was granted Orphan Drug, Fast Track, and Breakthrough Therapy Designation.

BACKGROUND

Burosumab Drug Characteristics[1]

- *Drug Class:* A human monoclonal antibody IgG1 produced by recombinant DNA technology using Chinese hamster ovary cell culture.
- *Mechanism of action*: Binds to and inhibits the activity of FGF 23, thus restoring renal tubular reabsorption of phosphate and increasing serum vitamin D.
- *Administration:* Subcutaneously every 4 weeks (adults), every 2 weeks (pediatrics).
- *Molecular weight:* 147,000 Daltons
- *Half-life:* 19 days
- *Bioavailability:* Approximately 100% (90-128%) following subcutaneous injection
- *Adverse reactions:* Back pain, headache, tooth infection, restless leg syndrome, decreased vitamin D, dizziness, constipation, increased blood phosphorus

X-linked hypophosphatemia (XLH) and Pregnancy

- *Prevalence:* 1:20,000 patients.[2] The most common cause of heritable rickets.
- *Disease description:* An X-linked dominant disorder caused by PHEX gene deficiency (phosphate-regulating gene with homologies to endopeptidases on the X chromosome).[3] Consequently, FGF23 levels are increased which leads to urine phosphate loss, hypophosphatemia, and bone hypomineralization.[4]
- *Clinical manifestations:* Children have short stature and leg bowing which progress as adults into joint pain, stiffness, dental abscesses, osteomalacia, and pseudofractures.
- *Current treatment*: Multiple daily doses of oral phosphate and vitamin D which require monitoring to avoid risks of nephrocalcinosis, hypercalciuria, and hyperparathyroidism.[4]
- *Treatment in pregnancy:* No data are available on whether pregnant women with XLH should use phosphate and vitamin D. Patients receiving treatment at conception generally continue in pregnancy with careful monitoring of serum calcium, phosphorus, and

[1]CRYSVITA (BLA 761068) proposed package insert
[2] Imel et al. Fibroblast Growth Factor 23: Roles in Health and Disease. J Am Soc Nephrol 16:2565-75, 2005.
[3] Sabbagh et al. Part 21: Membrane Transport Disorders. Chapter 197: Mendelian Hypophosphatemias. The Online Metabolic & Molecular Bases of Inherited Disease. McGraw-Hill. 2008.
[4] Carpenter et al. A Clinician's Guide to X-linked Hypophosphatemia. Journal of Bone and Mineral Research, Vol. 26, No. 7, July 2011, pp 1381-1388.

urinary calcium-to-creatinine ratios.[5] In contrast, patients not receiving treatment at conception generally do not initiate treatment in pregnancy.

- *Pregnancy outcomes:* A limited number of normal pregnancies have been reported in women with XLH that have received and have not received treatment with oral phosphorus and vitamin D.[6]
- *Fetal outcomes:* Evidence from animal studies and limited human studies indicate the placenta extracts adequate calcium and phosphophorus for the fetus even when maternal phosphorus concentrations are low.[7] The fetal kidneys do not become responsive to FGF23 until the neonatal period, which explains why rickets develops postnatally.

REVIEW

PREGNANCY

Nonclinical Experience

Burosumab was evaluated in a pre- and post-natal (PPND) study in pregnant monkeys without XLH at intravenous doses of 0, 0.3, 3, and 30mg/kg every 2 weeks from GD 20 to delivery. Relevant findings included ectopic mineralization in maternal tissues and the placenta (NOAEL 0.9x human AUC), increased incidence in abortions and embryofetal deaths (NOAEL 7.3x human AUC), increased incidence in non-adverse premature births (NOAEL 0.9x human AUC), and a decrease in gestation in all treated groups. However, there were no teratogenic effects and no effects on pre- or postnatal growth including survivability of the offspring.

The FDA Pharmacology/Toxicology reviewer concluded[8]: "if the evidence supporting treatment relatedness for these animal findings is equivalent, then they should all be included in the label." Although the reviewer cautioned that the animal data was obtained in monkeys without XLH and thus may have limited clinical relevance for humans with XLH. In addition, the animal findings occurred at a drug exposure that was considerably higher (64-fold by AUC) than the human exposure at the adult dose of 1mg/kg every 4 weeks.

Reviewer's Comment:
This reviewer agrees the above findings in pregnant monkeys without XLH are of uncertain clinical relevance to humans with XLH. Specifically, humans with XLH are hypophosphatemic at baseline, whereas the pregnant monkeys without XLH were normophosphatemic at baseline. Therefore, the reproductive risks observed in pregnant monkeys may have been related to an exaggerated hyperphosphatemia and placental mineralization that occurred due to burosumab use in test animals without XLH at doses much greater than the anticipated human exposure. Regardless, hyperphosphatemia is listed as an adverse reaction in the burosumab draft labeling based on results from human clinical trials in a small percentage of patients, so a potential reproductive risk in humans cannot be fully excluded.

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[5] Latta et al. Therapeutics of X-linked hypophosphatemic rickets. Pediatr Nephrol (1993) 7: 744-748.
[6] Ruppe MD. X-Linked Hypophosphatemia. 2012 Feb 9 [Updated 2017 Apr 13]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi nlm nih.gov/books/NBK83985
[7] Kovacs, Christopher. Calcium, Phosphorus, and Bone Metabolism in the Fetus and Newborn. Early Human Development 91 (2015) 623-628.
[8] Gemma Kuijpers, PhD. Pharmacology/Toxicology Review and Evaluation IND(76488)/BLA(761068). Aug 2017.

The significance of placental calcifications in human pregnancy is not clear and may be influenced by the gestational timing at which calcifications form. For example, late placental calcifications at term have been associated with normal physiology.[9] In contrast, early preterm placental calcifications have been associated with adverse outcomes such as postpartum hemorrhage, placental abruption, preterm birth, low birth weight, and stillbirth.[10,11] The gestational timing of placental calcifications was not evaluated by the applicant. However, based on the drug's mechanism of action, burosumab has the potential to cause hyperphosphatemia which could result in early preterm placental calcifications. Nevertheless, findings from studies in non-XLH pregnant monkeys suggest the observed adverse reproductive effects occurred at burosumab exposures much greater (64-fold by AUC) than the anticipated human exposure.

Overall, the human reproductive risk of burosumab treatment in patients with XLH is likely to be much lower than that observed in pregnant monkeys without XLH. Nevertheless, in an effort to mitigate risk, prescribers should be instructed to closely monitor serum phosphorus levels throughout pregnancy and adjust the burosumab dose as needed to achieve and maintain normal serum phosphorus levels. Due to the physiologic changes in pregnancy, even patients on stable doses of burosumab should have regular serum phosphorus monitoring. However, the recommended frequency of serum phosphorus monitoring with use of burosumab during pregnancy has not been studied.

Applicant's Review of Literature
The applicant did not provide a review of the literature.

DPMH's Review of Literature
No reports of burosumab use during pregnancy were found in the published literature.

A search was performed in PubMed, Embase, Micromedex[12], TERIS,[13]Reprotox[14], and Briggs[15], using the terms "burosumab and pregnancy," "burosumab and pregnant women," "burosumab and pregnancy and birth defects," "burosumab and pregnancy and congenital malformations," "burosumab and pregnancy and stillbirth," "burosumab and spontaneous abortion," and "burosumab and pregnancy and miscarriage."

[9] Mastrolia et al. Review Article: Placental calcifications: a clue for the identification of high-risk fetuses in the low-risk pregnant population? J of Maternal-Fetal and Neonatal Medicine, 2016; 29 (6):921-927.
[10] Chen KH et al. Exploring the relationship between preterm placental calcification and adverse maternal and fetal outcome. Ultrasound Obstet Gynecol 2011; 37:328-34.
[11] Chen KH et al. The role of preterm placental calcification on assessing risks of stillbirth. Placenta. 2015:36(9):1039-44.
[12]Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 9/8/17.
[13]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 9/8/17.
[14]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 9/8/17.
[15]Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

Review of Pharmacovigilance Database

Pregnant or lactating females were excluded from clinical trials. Subjects were required to maintain contraception. Table 1 summarizes the three pregnancies that occurred in clinical trials.

Table 1: Pregnancies Reported in XLH Patients during Clinical Trials with Burosumab*

Maternal Age (years)	Timing of Exposure	Subcutaneous Dose	Maternal Outcome	Fetal Outcome
32	Positive pregnancy test 10 weeks after last dose	0.3mg/kg	Normal delivery	Live infant C-section at term Weight 8lb Apgars 9/9
26	1st trimester	1mg/kg (60mg)	Pregnancy ongoing (Estimated Due Date: 12/2017)	Pending
35	1st trimester	1 mg/kg (40mg)	Pregnancy ongoing (Estimated Due Date: 12/2017)	Pending

*Source: Reviewer's Table (based on the 120-Day Safety Update submitted on December 15, 2017)

Reviewer's Comment

The above limited clinical data are insufficient to draw meaningful safety conclusions about the effects of burosumab treatment in pregnancy on maternal and fetal outcomes. Of the three pregnancies that occurred in clinical trials, only one outcome is currently available for review. In addition, the reportedly normal outcome provides limited evidence considering burosumab was discontinued prior to the onset of pregnancy in this patient due to an injection site reaction.

XLH-Disease Monitoring Program (XLH-DMP)

The applicant is proposing an XLH-DMP (b) (4) (b) (4) in the postmarketing setting. The purpose of the program is to further evaluate the long-term safety and efficacy of burosumab. (b) (4) (b) (4)

Summary

There is insufficient evidence to determine the risks of burosumab use in pregnancy. Considering that we are reviewing an original BLA submission for burosumab and this product has not been previously marketed outside the United States, maternal and fetal outcomes have not been reported in the published literature. In addition, pregnant women were excluded from the applicant's clinical trials. Consequently, burosumab was discontinued in the three pregnancies that occurred during clinical trials.

Thus, the main evidence available to determine the developmental and reproductive risks of burosumab is from the applicant's nonclinical studies in pregnant monkeys without XLH. Relevant findings included increased abortions and embryofetal death, increased non-adverse premature births, and a decrease in gestational period. However, these pregnant monkeys without XLH had normal baseline phosphorus levels, whereas patients with XLH are generally hypophosphatemic at baseline. Thus, the adverse reproductive findings observed in pregnant monkeys without XLH treated with burosumab at exposures much higher than the anticipated human exposure may have limited clinical relevance for XLH patients. Nonetheless, a potential risk to the fetus related to burosumab treatment in pregnancy cannot be fully excluded considering the findings from animal studies and the drug's mechanism of action.

Therefore, DPMH discussed with DBRUP the recommendation for a pregnancy surveillance substudy to be incorporated into the applicant's proposed XLH-DMP as a postmarketing requirement. This pregnancy surveillance substudy could enroll women with XLH who become pregnant to further monitor the maternal and fetal outcomes in patients exposed to burosumab. Because XLH is a rare disease, the pregnant population is likely to be small. Thus, a dedicated pregnancy registry is would not likely be feasible. Section 8.1 of the labeling should include the contact information for the program. See Appendix A for DMPH's recommended data elements for collecting pregnancy exposure data.[16]

LACTATION

Nonclinical Experience

There is no information regarding the presence of burosumab in animal milk.

Applicant's Review of Literature

The applicant did not provide a review of the literature.

DPMH's Review of Literature

In addition, no reports of burosumab use in lactation were found in the published literature.

A search was performed in *Medications and Mother's Milk*[17], LactMed[18], Micromedex[12], PubMed, and Embase using the terms "burosumab and lactation" and "burosumab and breastfeeding."

Review of Pharmacovigilance Database

The applicant reported that no infants were exposed to burosumab through breastfeeding during clinical trials.

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[16]FDA Guidance for Industry: Establishing Pregnancy Exposure Registries. August 2002

[17]Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

[18]http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 9/8/17.

Reviewer's Comment
Calcium and phosphorus are important minerals for infant growth and skeletal development. The mineral content in breast milk is variable between individuals and also differs with infant prematurity and postnatal age. In a recent meta-analysis, the mean phosphorus (11-17mg/dL) and calcium (26-29mg/dL) concentrations in breast milk were reported. [19]

Phosphorus and calcium concentrations in the breastmilk of XLH patients have not been adequately studied. However, a case report describes the breast milk mineral content in a lactating woman with untreated XLH due to poor compliance with medical advice.[20] Calcium and phosphorus concentrations were reduced in the patient's early milk. Overtime, the patient's milk phosphorus concentration remained low, while the milk calcium concentration returned to normal levels reported in mature milk. The author recommended the mineral content of breastmilk in lactating mothers with XLH be carefully monitored, as the breastfed infant may require mineral supplementation.

The theoretical risk of systemic absorption of burosumab by the breastfed infant during lactation based on the drug's mechanism of action is hyperphosphatemia. Rising serum phosphate levels may lead to hypocalcemia which can present with neuromuscular problems such as irritability, poor feeding, emesis, paresthesia, tetany, seizures, and cardiac arrhythmia. However, burosumab is administered subcutaneously because monoclonal antibodies are reported to have poor oral bioavailability.[21] Therefore, the likelihood of systemic exposure to burosumab from oral intake by the breastfed infant is low. Nevertheless, the effects of gastrointestinal exposure to burosumab by the breastfed infant are unknown.

In conclusion, considering the lack of data regarding the effects of burosumab exposure on lactation, DPMH recommends the applicant perform a postmarketing lactation study. This lactation study should use a validated assay in women who have received therapeutic doses of burosumab. Data should be collected on the burosumab concentration in breast milk, the effect on milk composition (to include phosphorus and calcium levels), and the effects on the breastfed infant. Justification for this lactation study includes the anticipated use of burosumab in females of reproductive potential, the lack of data on safe use, and the theoretical risk to the breastfed infant. Information obtained from this lactation study can be used to help inform patient counseling and the lactation subsection of burosumab labeling.

Summary
The lack of clinical data precludes a clear determination of the risk of burosumab use during lactation. Specifically, there is no data on the presence of burosumab in milk, the effects on milk production, or the effects on the breastfed infant. Maternal IgG is known to be present in human milk, however monoclonal antibodies have poor oral bioavailability. Consequently, the systemic exposure to burosumab in the breastfed infant is expected to be limited but has not been studied.

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[19] Gidrewicz, D et al. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr. 2014; 14:216.
[20] Jonas, A. et al. Low Breast Milk Phosphorus Concentration in Familial Hypophosphatemia. Journal of Pediatric Gastroenterology and Nutrition. 8:541-543. 1989.
[21] Wang, W et al. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008 Nov; 84 (5): 548-58.

Therefore, DPMH recommends the applicant perform a postmarketing lactation study to further assess the safety of burosumab use in lactation. This lactation study should be performed using a validated assay in women who have received therapeutic doses of burosumab to provide data on the extent of drug transfer into breast milk, effect on milk composition (e.g., phosphorus and calcium levels), and the effects on the breastfeed infant. DPMH discussed this PMR recommendation with DBRUP and is available to review the lactation study protocol. For further information, the reader is referred to the FDA guidance on Clinical Lactation Studies.[22]

In addition, DPMH agrees with the applicant that the following risk/benefit statement should be included in Section 8.2 "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for burosumab and any potential adverse effects on the breastfed infant from burosumab or from the underlying maternal condition."

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No specific animal fertility studies were conducted with burosumab. However, in repeat-dose toxicology studies up to 40 weeks duration, mineralization of the rete testis/seminiferous tubules was observed in monkeys at the 30mg/kg dose (exposures >37-fold higher than anticipated at human adult dose of 1mg/kg every 4weeks); although no changes were observed in the semen analysis. Overall, no adverse effects on female reproductive organs were observed.

For more information, refer to the Pharmacology/Toxicology review by Gemma Kuijpers, PhD.[7]

Applicant's Review of Literature

The applicant did not provide a review of the literature.

DPMH's Review of Literature

No reports were found in the published literature related to burosumab and fertility or interactions with hormonal contraceptives.

A search was performed in PubMed, Embase, and Reprotox[14] using the terms, "burosumab and fertility," "burosumab and contraception," "burosumab and oral contraceptives," and "burosumab and infertility."

Summary

DPMH recommends omitting Section 8.3 Females and Males of Reproductive Potential from burosumab labeling. As mentioned, there are no human data regarding the effects of burosumab on fertility or contraception. In addition, specific animal fertility studies have not been conducted. Per DPMH's discussion with the DBRUP Pharm/Tox Reviewer, the mineralization of the rete testis/seminiferous tubules observed in repeat-dose toxicology studies is likely of low clinical significance. This finding was likely related to increased serum phosphorus (8-11mg/dL) in monkeys without XLH at levels that were not attained during clinical trials in XLH patients.

[22] FDA Guidance for Industry. Clinical Lactation Studies-Study Design, Data Analysis, and Recommendations for Labeling. February 2005.

CONCLUSIONS

DPMH concludes there is insufficient evidence to clearly determine the risk of burosumab use in pregnancy, lactation, and reproduction. Specifically, pregnant and lactating women were excluded from the applicant's clinical trials for this original BLA. Furthermore, the applicant's nonclinical studies in pregnant monkeys indicated a potential reproductive risk of embryo-fetal loss and premature birth but at exposures much greater than the anticipated human dose exposure and in test animals without XLH. Thus, the clinical relevance of the animal findings is uncertain.

Therefore, DPMH recommends a pregnancy surveillance substudy be incorporated into the applicant's proposed XLH-DMP as a postmarketing requirement to further evaluate the risks and benefits of burosumab exposure in pregnancy. In addition, DMPH recommends the applicant conduct a lactation trial as a post marketing requirement to further assess the risks of burosumab use in lactating women and breastfed infants.

In addition, the CRYSVITA labeling subsections for Pregnancy, Lactation, and Females and Males of Reproductive Potential were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Subsection 8.1**
  - The "Pregnancy" subsection of labeling was formatted in the PLLR format to include: "Risk Summary" and "Data" sections.
- **Lactation, Subsection 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include: "Risk Summary" section.
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of labeling was updated to correspond with changes made to subsection 8.1 of labeling.

RECOMMENDATIONS

DPMH recommends the following:

1. A pregnancy surveillance substudy PMR should be incorporated into the applicant's proposed XLH-DMP to further study the outcomes of women and infants exposed to burosumab during pregnancy. (see Appendix A– Data Elements for Collecting Pregnancy Exposure Data).[15] DMPH suggested language for this substudy in Section 8.1.

2. The applicant should conduct a lactation trial in burosumab treated patients, using a validated assay, in order to inform the lactation subsection of labeling. The following PMR language is suggested:

   > "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."

3. DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DBRUP on January 3, 2018 and on January 11, 2018. The recommendations below reflect input from the Pharmacology/Toxicology Review Team. DPMH refers to the final NDA action for final labeling.

DPMH Proposed CRYSVITA (burosumab) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on CRYSVITA use in pregnant women to inform a drug associated risk of adverse developmental outcomes. In utero burosumab exposure in non-XLH cynomolgus monkeys did not result in teratogenic effects. Adverse effects such as preterm birth and late fetal loss were observed in burosumab-treated pregnant non-XLH monkeys, however, these effects are unlikely to indicate clinical risk because they occurred at a drug exposure that was 64-fold higher, by AUC, than the human exposure of 1mg/kg every 4 weeks and were accompanied by maternal hyperphosphatemia and placental mineralization *(see Data)*. Serum phosphorus levels should be monitored throughout pregnancy *[see Dosage and Administration (2.2)]*. Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-800-756-8657.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. (b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a reproductive toxicity study in pregnant cynomolgus monkeys without XLH, burosumab was administered intravenously once every two weeks from Day 20 of pregnancy to parturition or cesarean section on Day 133, which includes the period of organogenesis, at doses of 1-, 7- and 64-fold human exposure at the adult human dose of 1mg/kg every 4 weeks. The treatment did not result in teratogenic effects in fetuses or offspring. An increase in late fetal loss, a shortened gestation period, and an increased incidence of preterm births were observed at 64-fold the human exposure at the adult human dose of 1mg/kg every 4 weeks, concomitant with maternal hyperphosphatemia and placental mineralization. Burosumab was detected in the serum from fetuses indicating transport across the placenta. Hyperphosphatemia but no ectopic mineralization was present in fetuses and offspring of dams exposed to 64-fold human exposure at the 1mg/kg dose every 4 weeks. Burosumab did not affect pre-and postnatal growth including survivability of the offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of burosumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. However, the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to burosumab are unknown. The lack of clinical data during lactation precludes a clear determination of the risk of CRYSVITA to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CRYSVITA and any potential adverse effects on the breastfed infant from CRYSVITA or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-800-756-8657 *[see Use in Specific Populations (8.1)]*.

APPENDIX A[15]

DPMH Recommended Data Elements for Collecting Pregnancy Exposure Data

A. General

- Patient identifier
- Name of reporter at initial contact
- Date of initial contact
- Dates of any follow-up contacts
- Telephone number of reporter
- Additional contact names and phone numbers (if reporter is the patient)

B. Maternal Information

- Source of information (e.g., obstetrician, pregnant woman, other)
- Birth date
- Race
- Occupation
- Maternal medical history (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, allergic disorders, heart disease, connective disease, autoimmune disease, hepatitis, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures, other)
- Obstetrical History:
    - Number of pregnancies and outcome of each (live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy)
    - Previous maternal pregnancy complications
    - Previous fetal/neonatal abnormalities and type
- Current Pregnancy:
    - Date of last menstrual period
    - Complications during pregnancy (including any adverse drug reactions) and dates
    - Number of fetuses
    - Labor/delivery complications
    - Disease course(s) during pregnancy and any complications
    - Medical product exposures (prescription drugs, OTC products & dietary supplements):
        - Name
        - Dosage & route
        - Date of first use & duration
        - Indication
    - Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount
- Family History (specify type, maternal/paternal, etc.):
    - Spontaneous Abortions
    - Anomalies/Malformations
    - Multiple fetuses/births

C. Neonatal Information

Initial:

- Source of information (e.g., obstetrician, pediatrician, mother)
- Date of receipt of information
- Date of birth or termination
- Gestational age at birth or termination
- Gestational outcome (live born, fetal death/stillborn, spontaneous abortion, elective termination)
- Sex
- Pregnancy weight gain of mother
- Obstetric complications (e.g. pre-eclampsia, premature labor, premature delivery)
- Pregnancy order (singleton, twin, triplet)
- Results of neonatal physical examination including:
    - Anomalies diagnosed at birth or termination
    - Anomalies diagnosed after birth
    - Weight at birth indicating whether small, appropriate, or large for gestational age
    - Length at birth
    - Condition at birth (including when available Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
- Neonatal illnesses, hospitalizations, drug therapies

Follow-up:

- Source of information (e.g., pediatrician, mother)
- Date of receipt of information
- Anomalies diagnosed since initial report
- Developmental assessment
- Infant illnesses, hospitalizations, drug therapies

Note: Infants should be followed for 12 months with assessment times at birth, at 12 months, and some point in between.

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/s/

KRISTIE W BAISDEN
01/17/2018

TAMARA N JOHNSON
01/17/2018

LYNNE P YAO
01/17/2018

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761068

Application Type: New BLA

Drug Name(s)/Dosage Form(s): burosumab/solution for injection

Applicant: Ultragenyx Pharmaceutical Inc.

Receipt Date: August 17, 2017

Goal Date: April 17, 2017

1. Regulatory History and Applicant's Main Proposals

Ultragenyx Pharmaceuticals has submitted an original BLA for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

SAMANTHA S BELL
10/05/2017

MARGARET M KOBER
10/07/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 761068	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Crysvita (proposed) Established/Proper Name: burosumab Dosage Form: solution for injection Strengths: 10 mg/mL; 20 mg/mL; 30 mg/mL Route(s) of Administration: subcutaneous		
Applicant: Ultragenyx Pharmaceutical Inc. Agent for Applicant (if applicable):		
Date of Application: August 17, 2017 Date of Receipt: August 17, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: April 17, 2018	Action Goal Date (if different):	
Filing Date: October 16, 2017	Date of Filing Meeting: September 15, 2017	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): The treatment of X-linked hypophosphatemia (XLH)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☒ 351(a) ☐ 351(k)	

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☒ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 076488	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

- Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**

- Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?**

If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

- If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

Note: Pharmaceutical equivalents *are drug products in identical dosage forms and route(s) of administration that:* ***(1)*** *contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period;* ***(2)*** *do not necessarily contain the same inactive ingredients;* ***and*** ***(3)*** *meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☐	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	☒		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***DPMH on August 24, 2017*** ***COA on August 24, 2017***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** December 10, 2015	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** June 19, 2017 July 24, 2017 (CMC only)	☒	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 15, 2017

BACKGROUND: Burosumab (KRN23) is a recombinant human IgG1 monoclonal antibody targeting fibroblast growth factor 23 (FGF23). Ultragenyx Pharmaceuticals has submitted an original BLA for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

The Applicant currently has Orphan Drug Designation for KRN23. The applicant was granted Fast Track Designation on June 30, 2015, and breakthrough therapy designation for the treatment of XLH in pediatric patients one year of age and older on June 22, 2016. On July 11, 2017, the applicant also received "rare pediatric disease" designation from the Office of Orphan Products Development. The BLA submission also includes a request for Rare Pediatric Disease Priority Review Voucher.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Samantha Bell	Y
	CPMS/TL:	Margaret Kober	Y
Cross-Discipline Team Leader (CDTL)	Theresa Kehoe		
Division Director/Deputy	Audrey Gassman		Y
Office Director/Deputy	Hylton Joffe		Y
Clinical	Reviewer:	Stephen Voss	Y
	TL:	Theresa Kehoe	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Lin Zhou	Y

	TL:	Jie Wang	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Jia Guo	Y
	TL:	Mahboob Sobhan	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Gemma Kuijpers	Y
	TL:	Mukesh Summan	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	William Hallett	N
	RBPM:	Melinda Bauerlin	N
• Drug Substance	Reviewer:	Chikako Torigoe	Y
• Drug Product	Reviewer:	Bruce Huang	Y
• Process	Reviewer:	Reyes Candau-Chacon	N
• Microbiology	Reviewer:	Lakshimi Narasimhan	Y
• Facility	Reviewer:	Thuy Nguyen	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:	Bruce Huang	Y
• Labeling (BLAs only)	Reviewer:	Vicky Borders-Hemphill	N
• Other (e.g., Branch Chiefs, EA Reviewer)	Jihong Liu Peter Zhihao Qiu (DIA)		Y Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sarah Harris	Y
	TL:	Lolita White	N
OSE/DRISK (REMS)	Reviewer:	Theresa Ng	Y
	TL:	Leah Hart	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:	Philip Kronstein	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• DPMH	Reviewer:	Ethan Hausman	Y
	Reviewer	Yeruk Mulugeta	Y
• COA	Reviewer:	Yasmin Chowdry	Y
Other attendees	Kathleen O'Connell		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The application did not raise significant safety or efficacy issues
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): November 21, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

SAMANTHA S BELL
10/05/2017

MARGARET M KOBER
10/07/2017