

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761052Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 761052	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Brineura Established/Proper Name: cerliponase alfa Dosage Form: 300mg via intraventricular infusion every 2 weeks		Applicant: BioMarin Agent for Applicant (if applicable):
RPM: Jenny Doan		Division: Division of Gastroenterology and Inborn Errors Products
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☒ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
• Proposed action • User Fee Goal Date is <u>April 27, 2017</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics³		

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

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

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

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 - Restricted distribution (21 CFR 314.520)
- Subpart I
- Approval based on animal studies

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 - Restricted distribution (21 CFR 601.42)
- Subpart H
- Approval based on animal studies

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

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

Comments:

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

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	BLA Approval- April 27, 2017

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	

• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included April 26, 2017

• Original applicant-proposed labeling	☒ Included May 27, 2016

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None

• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	None

• Original applicant-proposed labeling	None

❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	

• Most-recent draft labeling	☒ Included Administration Kit Carton 02/13/17 Intraventricular Electrolytes Injection Vial 02/13/17 Brineura Carton 12/22/16 Brineura Vial 12/22/16 UDI Sticker for Administration Kit 05/27/16

❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	Brineura Granted letter 8/15/16 Review Memo 8/10/16

❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 04/18/17 DMEPA: Amendment 4/14/17 DMEPA Review: 1/27/17 DMPP/PLT (DRISK): ☒ None OPDP: 4/24/17 SEALD: ☒ None CSS: ☒ None Product Quality 3/31/17 Other: DPMH (Peds) 4/11/17 DPMH (MH) 02/06/17

Administrative / Regulatory Documents

❖ RPM Filing Review⁴/Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	4/18/17 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Drug Designation</u>	Pediatric Page 4/18/17
❖ Breakthrough Therapy Designation	
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	8/27/15
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	08/27/15
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	04/29/15
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Labeling/PMRs/PMCs- 4/20/17 Labeling/PMRs/PMCs- 4/13/17 Review Extension-09/02/16 Filing Review Issues-08/09/16 UDI IR- 07/25/16 Priority Review Designation- 07/13/16 BLA Acknowledgement-06/01/16
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Brineura Intracerebroventricular ROA Terminology Meeting- 12/28/16
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	Amended Meeting Minutes- 05/09/16 Meeting Minutes- 04/20/16 Meeting Date- 03/29/16
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg

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

• Mid-cycle Communication (<i>indicate date of mtg</i>)	Mid-Cycle Communication Letter- 12/19/16 Meeting Date- 12/16/16
• Late-cycle Meeting (<i>indicate date of mtg</i>)	Meeting Minutes- 03/15/17 Meeting Date-02/21/17 Background Package- 02/17/17
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	4/27/17
Division Director Summary Review (<i>indicate date for each review</i>)	4/26/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	Joint Primary/Secondary Safety Review- 4/26/17
PMR/PMC Development Templates (<i>indicate total number</i>)	6 templates – 4/26/17
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	Joint Primary/Secondary Review- 04/26/17 Filing Review- 06/29/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Division Direction Review Appendix 2 - 4/26/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	Epidemiology (ARIA) Primary Review- 04/26/17 Intercenter (CDRH) Primary Review- 04/20/17 Clinical Outcome Assessment Primary Review- 04/14/17 Division of Neurology-02/27/17 CDRH Filing Review- 07/14/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	Primary Review-4/27/17

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

❖ Risk Management	
- REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	N/A N/A 4/25/17
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	Compliance Review- 04/06/17 Clinical Inspection Summary- 12/16/16 Inspection Letter-02/09/17 Inspection Letter- 1/31/17 Inspection Letter- 1/31/17 Inspection Letter- 11/18/16
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	Primary Review- 4/26/17 Filing Review- 07/28/16
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	Primary Review- 4/20/17 Filing Review- 07/26/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
- ADP/T Review(s) (<i>indicate date for each review</i>) - Supervisory Review(s) (<i>indicate date for each review</i>) - Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	AD Memo- 4/14/17 Team Leader Secondary Memo- 4/18/17 Primary Review- 04/14/17 Filing Review- 07/07/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality		☐ None
❖ Product Quality Discipline Reviews ⁶		
• Tertiary review (<i>indicate date for each review</i>)		☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)		☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)		Executive Summary- 4/07/17; Integrated Quality Assessment- 4/13/17 Filing Review- 07/18/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)		☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)		
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)		See the environmental assessment is on page 6 of the DS review- 4/13/17
☐ Review & FONSI (<i>indicate date of review</i>)		
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)		
❖ Facilities Review/Inspection		
☒ Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)		☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>) N/A
• Finalize 505(b)(2) assessment	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

BLA #: 761052 Supplement Number: NDA Supplement Type (e.g., SE5):
Division Name: DGIEP PDUFA Goal Date: Stamp Date: n/a
April 27, 2017

Proprietary Name: Brineura
Established/Generic Name: cerliponase alfa
Dosage Form: Injection for Infusion
Applicant/Sponsor: BioMarin

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1)
(2)
(3)
(4)

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: Supplement #: PMR #:

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed):
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):							
		minimum		maximum		Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	wk. mo.		wk. mo.		☐	☐	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed):

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

NDA/BLA# **Error! Reference source not found.****Error! Reference source not found.****Error! Reference source not found.** Page 4
drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy):							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):							
Population		minimum		maximum		PeRC Pediatric Assessment form attached?.	
☐	Neonate	wk.	mo.	wk.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum		maximum	
☐	Neonate	wk.	mo.	wk.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.	

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	wk. mo.	wk. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

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

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

JENNY N DOAN
04/18/2017

From: [Lisa Malandro](#)
To: [Doan, Jenny](#)
Cc: [Elizabeth Moyle](#)
Subject: RE: BLA 761052 BMN 190: Submission of revised USPI and PMR/PMC commitment
Date: Thursday, April 20, 2017 10:23:29 AM

Thank you Jenny!

From: Doan, Jenny [mailto:Jenny.Doan@fda.hhs.gov]
Sent: Thursday, April 20, 2017 7:11 AM
To: Lisa Malandro <lisa.malandro@bmrn.com>
Cc: Elizabeth Moyle <EMoyle@bmrn.com>
Subject: RE: BLA 761052 BMN 190: Submission of revised USPI and PMR/PMC commitment
Importance: High

Lisa,

Here you go. Please see attached draft labeling for the additional comments. We'll discuss during the t-con regarding the resubmission date. In addition, please see the updated PMRs and PMCs list. See minor changes in PMR 3207-3 (in red). Let me know if BioMarin has any further comments/concerns on the PMRs and PMCs.

Brineura (cerliponase alfa) PMRs/PMCs

3207-1 Conduct a non-interventional post approval safety study (Study 190-501) to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease), and further assess the occurrence of serious hypersensitivity reactions including anaphylaxis, vital sign abnormalities, and device related complications. In addition, this study will evaluate the CLN2 motor and language clinical scales.

Final Protocol Submission: 12/2017
Study Completion: 06/2036
Final Report Submission: 06/2037

3207-2 Develop and validate a cellular uptake assay with sensitivity adequate to evaluate the neutralizing capacity of anti-drug antibodies of Brineura (cerliponase alfa) detected in patient serum and CSF samples. Submit assay validation report and assay SOP to the FDA.

Final Report Submission: 12/2018

3207-3 Develop and validate an assay to measure the capacity of anti- drug antibodies detected in the patient serum and CSF samples to neutralize Brineura (cerliponase alfa) enzymatic activity using conditions mimicking **lysosomal environment**. Submit assay validation report and assay SOP to the

FDA.

Final Report Submission: 12/2018

3207-4 Conduct an immunogenicity study to evaluate the relationship between Brineura (cerliponase alfa) treatment and neutralizing antibody status. ADA-positive serum and CSF samples detected in Studies 190-201 and 190-202 will be re-tested with validated neutralizing antibody assays for enzyme neutralization and cellular uptake, and patient serum and CSF samples will be collected and analyzed for immunogenicity assessment in Study 190-203.

Final Report Submission: 12/2023

3207-5 Conduct a clinical trial (Study 190-203) to further evaluate the safety and immunogenicity of Brineura (cerliponase alfa) in CLN2 patients, including tolerability and device related adverse events and/or complications with routine use. Perform a root-cause analysis on any device related complications and/or failures including, but not limited to, an analysis of the material integrity of the intraventricular access device reservoir. In addition, this trial will evaluate the CLN2 motor and language clinical scales. Include at least 5 patients below the age of 2 years.

Final Protocol Submission 07/2017

Trial Completion: 12/2022

Final Report Submission: 12/2023

3207-6 For patients in Studies 190-203 and 190-501, obtain a blood sample prior to cerliponase alfa treatment to determine TPP1 enzyme activity at baseline and collect the *TPP1* genotype information. Evaluate the association of enzyme activity with efficacy and safety data from PMR 3207-1 and PMR 3207-5. Derive the predicted protein function from the *TPP1* genotype for each patient, and compare efficacy and safety in patients with different *TPP1* genotypes based on their predicted protein function. In addition, perform similar analyses using a combined dataset from 4 clinical studies, including Studies 190-203, 190-501, 190-201 and 190-202.

Final Report Submission: 12/2037

3207-7 To add cellular uptake as a release assay for drug product, Brineura (cerliponase alfa), and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

Final Report Submission: 06/2019

3207-8 To develop and validate an additional identity test method for the Intraventricular Electrolytes Injection

(b) (4)

(b) (4)

Final Report Submission: 09/2017

3207-9 To revalidate RP-HPLC and SEC-HPLC release and stability assays using impurities generated by subjecting Brineura (cerliponase alfa) to stressed stability conditions.

Final Report Submission: 12/2017

Regards,

Jenny

WO Bldg. 22, Room 5345

(301) 796-1023

From: Lisa Malandro [<mailto:lisa.malandro@bmrn.com>]

Sent: Wednesday, April 19, 2017 12:48 AM

To: Doan, Jenny

Cc: Lisa Malandro; Elizabeth Moyle

Subject: BLA 761052 BMN 190: Submission of revised USPI and PMR/PMC commitment

Dear Jenny,

Attached for FDA review is the revised USPI (clean and tracked changes versions) which addresses FDA comments received on April 18, 2017.

A few notations:

1. The source for Figure 7 is attached (b) (4)
2. With respect to comments A25 & A26 in Table 4, the list of the Study 901 IDs with responder information and the source document for addition of the odds ratio(95% CIs) as determined by McNemar's exact test are attached (Listing 1 Study 901 Responders and Source document for Table 3).

In addition, BioMarin made a few modifications (noted in track changes, attached) to the PMRs/PMCs received from FDA this morning. BioMarin commits to these PMRs/PMCs with the minor modifications.

BioMarin will submit these documents along with the programs for the outputs formally Wednesday, April 18th.

Please do not hesitate to contact me should I be of further assistance.

Warm regards,

Lisa

Lisa M Malandro, MBA

Executive Director, Regulatory Affairs

Phone: 415-455-7986

Cell: 415-408-1619

Email: lisa.malandro@bmrn.com

This message is intended only for the confidential use of the intended recipient(s). If you have received this communication in error, please notify the sender by reply e-mail, and delete the original message and any attachments. Any unauthorized disclosure, copying, or distribution of this message (including the attachments), or the taking of any action based on it, is strictly prohibited.

This message is intended only for the confidential use of the intended recipient(s). If you have received this communication in error, please notify the sender by reply e-mail, and delete the original message and any attachments. Any unauthorized disclosure, copying, or distribution of this message (including the attachments), or the taking of any action based on it, is strictly prohibited.

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

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

/s/

JENNY N DOAN
04/20/2017

From: [Doan, Jenny](#)
To: "[Lisa Malandro](#)"
Subject: Updated PMRs/PMCs RE: Labeling Comments vApril 13 for BLA 761052
Date: Thursday, April 13, 2017 11:11:07 AM

Hi Lisa,

Please see updated draft for the PMRs/PMCs. We also added a PMC for immunogenicity. Let me know if you have any questions. Thanks.

PMR (clinical #1)- Conduct a clinical trial (Study 190-203) to further evaluate the safety and immunogenicity of Brineura (cerliponase alfa) in CLN2 patients, including tolerability and device related adverse events and/or complications with routine use. Perform a root-cause analysis on any device related complications and/or failures including, but not limited to, an analysis of the material integrity of the intraventricular access device reservoir. In addition, this trial will evaluate the CLN2 motor and language clinical scales. Include at least 5 patients below the age of 2 years.

PMR (clinical #2) Conduct a non-interventional post approval safety study (Study 190-501) to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2) disease, including the occurrence of serious hypersensitivity reactions including anaphylaxis, vital sign abnormalities, and device related complications. In addition, this study will evaluate the CLN2 motor and language clinical scales.

PMR (OBP/Immunogenicity #1)- Develop and validate a cellular uptake assay with sensitivity adequate to evaluate the neutralizing capacity of anti-drug antibodies detected in the patient serum and CSF samples. Submit assay validation report and assay SOP to the FDA.

PMR (OBP/Immunogenicity #2)- Develop and validate an assay to measure the capacity of anti- drug antibodies detected in the patient serum and CSF samples to neutralize cerliponase alfa enzymatic activity. Submit assay validation report and assay SOP to the FDA.

PMR (OBP/Immunogenicity #2)- Re-test patient serum and CSF samples from Studies 190-201 and 190-202 with validated neutralizing antibody assays for enzyme neutralization and cellular uptake. In addition, collect patient serum and CSF samples for immunogenicity assessment in Study 190-203 and analyze these samples for neutralizing capabilities of the antibodies. Using the immunogenicity data obtained from these studies, perform assessments of the impact of immunogenicity on cerliponase alfa pharmacokinetics, efficacy, and safety.

PMC (OBP/Immunogenicity)- For patients in Studies 190-203 and 190-501, obtain a blood sample prior to cerliponase alfa treatment to determine TPP1 enzyme activity at baseline and collect the *TPP1* genotype information. Evaluate the association of enzyme activity with efficacy and safety data from PMR xxxx-1 and PMR xxxx-2. Derive the predicted protein function from the *TPP1* genotype for each patient, and compare efficacy and safety in patients with different *TPP1* genotypes based on their predicted protein function. In addition, perform similar analyses using a combined dataset from 4 clinical studies, including Studies 190-203, 190-501, 190-201 and 190-202.

CMC

PMC- To add cellular uptake as a release assay for drug product and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

PMC- To develop and validate an additional identity test method for the Intraventricular Electrolytes Injection [REDACTED] (b) (4)

PMC- To revalidate RP-HPLC and SEC-HPLC release and stability assays using impurities generated by subjecting cerliponase alfa to stressed stability conditions.

Regards,

Jenny
WO Bldg. 22, Room 5345
(301) 796-1023

From: Doan, Jenny
Sent: Thursday, April 13, 2017 7:47 AM
To: 'Lisa Malandro'
Subject: Labeling Comments vApril 13 for BLA 761052

Good morning Lisa,

Per our discussion, please use this version (April 13, 2017) for the updates. Please use the CLEAN copy for further edits and resubmission to the application COB April 14. Let me know if you have any questions. Thanks.

Regards,

Jenny
WO Bldg. 22, Room 5345
(301) 796-1023

From: Doan, Jenny
Sent: Wednesday, April 12, 2017 1:19 PM
To: 'Lisa Malandro'
Subject: Labeling Comments vApril 12 for BLA 761052

Hi Lisa,

Please see attached draft labeling comments. I'll send you the PMRs/PMCs tomorrow. Let me know if your team still wants to have the tcon this afternoon.

Jenny Doan, BSN, MSN, PMP
CAPTAIN, United States Public Health Service (USPHS)
Regulatory Project Manager

Division of Gastroenterology and Inborn Errors
Products (DGIEP)|Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Building 22 Room: 5345
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** if shipping via United States Postal Service (USPS)
(301) 796-1023 (office)
(301) 796-9904 (fax)
Jenny.Doan@fda.hhs.gov

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1023. Thank you.

To Sponsor/Applicant

Secure Email

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). [It is the only way FDA can communicate confidential information to you via email.](#) If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

/s/

JENNY N DOAN
04/13/2017



BLA 761052

LATE CYCLE MEETING MINUTES

BioMarin Pharmaceutical Inc.
Attention: Lisa Malandro, MBA
Executive Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Malandro:

Please refer to your Biologic License Application (BLA) 761052 dated and received May 27, 2016, submitted under the Public Health Service Act for Brineura (cerliponase alfa) 30mg/mL Solution for Infusion.

We also refer you to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 21, 2017.

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

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Minutes

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 21, 2017, from 10:30AM to 12NN, ET
Meeting Location: White Oak Building 22, Conference Room 1415
10903 New Hampshire Ave,
Silver Spring, MD 20903

Application Number: 761052
Product Name: Brineura (cerliponase alfa)
Indication: Treatment of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)
Applicant Name: BioMarin

Meeting Chair: Dragos Roman, MD
Meeting Recorder: Jenny Doan

FDA ATTENDEES

Center for Drug Evaluation and Research

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODEIII)
Victor Crentsil, Associate Director for Regulatory Science, ODEIII
Maria Walsh, RN, MS, Associate Director for Regulatory Affairs, ODEIII
Richard Ishihara, Regulatory Officer, ODEIII
Dragos Roman, MD, Associate Director, Division of Gastroenterology and Inborn Errors Products (DGIEP), ODEIII
Laurie Muldowney, MD, Medical Team Leader, DGIEP, ODEIII
Elizabeth Hart, MD, Medical Reviewer, DGIEP, ODEIII
David Joseph, PhD, Pharmacology Team Leader, DGIEP, ODEIII
Fang Cai, PhD, Pharmacology Reviewer, DGIEP, ODEIII
Joette Meyer, PharmD, Associate Director for Labeling, DGIEP, ODEIII
Jenny Doan, BSN, Regulatory Project Manager, ODEIII, DGIEP
Brian Strongin, MS, RAC, Chief, Project Management Staff
Kevin Bugin, MS, RAC, Change Management Lead, Office of New Drugs, Immediate Office
Stephen Wilson, Director, OB, Division of Biometrics III (DBIII)
Laura Lee Johnson, PhD, Deputy Director, OB, DBIII
Yeh-Fong Chen, PhD, Biostatistics Team Leader, OB, DBIII
Min Min, PhD, Biostatistics Reviewer, OB, DBIII
Lili Garrard, PhD, Biostatistics Reviewer, OB, DBIII
Christine Hon, PharmD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Cristina Ausin, PhD, Team Leader, Office of Biotechnology Products (OBP)
Rukman De Silva, PhD, Product Quality Reviewer, OBP
Patricia Hughes, PhD, Team Leader, Division of Microbiology Assessment (DMA), Office of Process and Facilities (OPF)
Frederick Mills, PhD, Immunogenicity Reviewer, OBP
Susan Thompson, MD, Team Leader, Office of Scientific Investigation (OSI)
Susan Leibenhaut, MD, OSI

Elektra Papadopoulos, MD, Associate Director, Clinical Outcome Assessment Staff (COA)
Selena Daniels, PharmD, M.S., Reviewer, COA
Nicholas Miles, PharmD, Safety Regulatory Project Manager, Office of Safety and Epidemiology (OSE)
Mishale Mistry, PharmD, Team Leader, DMEPA, OSE
Kimberly Swank, PharmD, Division of Pharmacovigilance Safety Evaluator, OSE
Robert Pratt, PharmD, Risk Management Analyst, Division of Risk Management (DRISK), OSE
Donella Fitzgerald, Risk Management Analyst, DRISK, OSE
Amy Taylor, MD, Reviewer, DPMH
Benneth Blumenkopf, MD, Reviewer, Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH)
Kempf Lucas, MD, Rare Disease Program
Diem-Kieu Ngo, Team Leader, Division of Advisory Committee and Consultant Management (DACCM)
Moon Choi, DACCM

APPLICANT ATTENDEES
Patient Meeting (10:30-11:30am)

BioMarin Attendees (in-person):

Henry J. Fuchs, M.D., President, Worldwide Research & Development, Global Clinical Sciences
Geoffrey Nichol, M.B., Ch.B., Vice President, Clinical Sciences
David Jacoby, M.D., Ph.D., Executive Group Medical Director, Clinical Sciences
Camilla V. Simpson, Group Vice President, Regulatory Affairs, Regulatory Affairs
Mary O'Donovan, Executive Director, Regulatory Affairs

Additional Attendees (in-person):

[Redacted] (b) (4)

Angela Schulz, M.D., Principal Clinical Investigator, University Medical Center Hamburg-Eppendorf, Germany
Emily de los Reyes, M.D., Principal Clinical Investigator, Nationwide Children's Hospital, USA

[Redacted] (b) (4)

[Redacted] (b) (6)

Late-cycle Meeting (11:30am – 12pm):

BioMarin Attendees (in-person):

Henry J. Fuchs, M.D., President, Worldwide Research & Development, Global Clinical Sciences
Geoffrey Nichol, M.B., Ch.B., Vice President, Clinical Sciences
David Jacoby, M.D., Ph.D., Executive Group Medical Director, Clinical Sciences
Temitayo Ajayi, M.D., Senior Director, Clinical Sciences
Camilla V. Simpson, Group Vice President, Regulatory Affairs, Regulatory Affairs

Bradley J. Glasscock, Pharm.D., Vice President, Regulatory Affairs, Clinical/Nonclinical
Lisa Malandro, Executive Director, Regulatory Affairs, Clinical/Nonclinical
Steven Fagliarone, Senior Manager, Regulatory Affairs, Clinical/Nonclinical
Linda Wilbur, Associate Director, Regulatory Affairs, CMC
Chito Hernandez, Ph.D., Vice President, Biometrics
Peter Slasor, Sc.D., Director, Biostatistics, Global Clinical Sciences

(b) (4)

BioMarin Attendees (via Web-ex):

Heather Cahan, M.D., Medical Director, Pharmacovigilance
Michelle Fong, Senior Director, Regulatory Affairs, Clinical/Nonclinical
Joshua Henshaw, Ph.D., Senior Scientist II, Pharmacological Sciences
Tessa Verbanic, Associate II, Regulatory Affairs, Clinical/Nonclinical
Richard Morse, MSc, MA, Sr. Director, Clinical Operations, Development Sciences Operations
Anu Cherukuri, Ph.D., Senior Scientist I, Pharmacological Sciences
Jim Nickas, Pharm.D., Vice President, Pharmacovigilance
Art Blum, Vice President, Regulatory Affairs, CMC
Namita Nayak, Senior Director, Regulatory Affairs, CMC

1.0 BACKGROUND

BLA 761052 was submitted on May 27, 2016 for Brineura (cerliponase alfa) 30mg/mL Solution for Infusion.

Proposed indication(s): Treatment of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)

PDUFA goal date: April 27, 2017

FDA issued a Background Package in preparation for this meeting on February 17, 2017.

2.0 DISCUSSION

1. Introductory Comments – 2 minutes

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Patient Meeting – 60 minutes

Meeting Discussion: The Patient Advocacy Group and Principal Investigators provided testimonies and patient videos illustrating the clinical status of children receiving treatment with Brineura. The purpose of these presentations was to provide evidence of drug's effectiveness to complement the efficacy assessments in trials 201/202. FDA requested BioMarin to submit the parent testimonials and videos to the application (they were received on March 2, 2017).

3. Discussion of Substantive Review Issues – 30 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Clinical
 - Study Conduct/Data Quality: There are multiple data discrepancy issues which we plan to continue discussing with you during the subsequent data reconciliation meeting. Additionally, we were unable to verify the 190-901 source data (only a sub-set of the scoring sheets were available for review by OSI). There are no videotapes from study 190-901 available for our review limiting comparability assessments for the CLN2 scale used in studies 190-901 and 190-201/202. We are concerned that the CLN2 exams may not have been performed in a uniform manner. Neither study 190-901 nor studies 190-201/202 collected data on non-drug concurrent therapies, and study 190-901 did not collect information on concurrent medications, limiting our ability to control for potentially important confounding variables. The data on past medical history from 190-901 is limited and it is unclear if the dates accurately represent the emergence of symptoms rather than when those symptoms were first recorded in available medical records, thus limiting our ability to ensure comparable disease courses prior to treatment of 190-201 subjects.
 - External Control Group: There are concerns regarding the comparability between the 190-201/202 population and the 190-901 historical controls. There are concerns related to different endpoints measured in the two studies, training and the method of rating, anchor point definitions used for the CLN2 scales administered, and the differences in the intervals between CLN2 assessments in the two studies.
 - CLN2 Scale (especially the Language domain): Disagreement between ratings were noted on the scales used in study 190-901 and studies 190-201/202 based on the data from the Video Comparability Study indicating that the scales are not completely equivalent and have some reliability issues, particularly with the Language domain. Please refer to the graphical presentation of the Motor domain and the Language domain based on the Video Comparability Study from the mid-cycle meeting.
 - Safety
 - Device Replacement: We are awaiting the results of the bench-top testing to assess septum degradation to assist in our assessment of device related safety.
 - Blood Pressure: During the BLA review of data from 190-201/202, hypotension has emerged as a safety signal. Therefore, we strongly recommend that you revise protocol 190-202, 190-203 and 190-502 to monitor BP more appropriately and uniformly. Specifically, using an appropriate size BP cuff and measuring the BP in the upper arm. If the BP is abnormal, a manual BP should be obtained by a trained healthcare professional. In study 190-502, the frequency of BP monitoring should be increased and continued for 24 hours after the infusion (as is being performed in 190-202).

- Cytopenias: During our BLA review of the data from 190-201/202, cytopenias have emerged as a potential safety signal. To more appropriately monitor this signal, please revise protocol 190-502 to collect CBCs every 12 weeks.
- Statistical
 - Questions related to IRs and FDA Responses
 -
4. Discussion of Minor Review Issues – 5 minutes
 - Safety
 - Device Benchtop Testing
 5. Additional Applicant Data – 15 minutes (Applicant)

Meeting Discussion: See Applicant's slides presentation. The Applicant presented analyses for the 96 week time point. FDA and the Applicant agreed to further discuss the data during the data reconciliation meeting.
 6. Information Requests –
 - CMC information request sent on 2/7/2017- BioMarin anticipates to submit a response on 3/31/17
 - Clinical Pharmacology information request (genotype nomenclature & missing data) sent on 2/14- BioMarin anticipates to submit a response on 2/17/17
 - Clinical information request (CSF labs with corrected units) sent on 2/13/17- BioMarin anticipates to submit a response on 2/17/17.
 7. Postmarketing Requirements/Postmarketing Commitments (PMRs/PMCs)
 8. Major labeling issues

The labeling review is ongoing. We provided preliminary comments on the carton labeling on December 20, 2016, and product labeling on January 30, 2017. We received the revised labeling on February 13, 2017.
 9. Review Plans – 5 minutes
 - Data Reconciliation Meeting
 - Benchtop Protocol Review
 - Labeling
 - PMRs/PMCs
 10. Wrap-up and Action Items – 2 minutes

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

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

/s/

JENNY N DOAN
03/15/2017



BLA 761052

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

Please refer to your Biologic License Application (BLA) 761052 submitted under the Public Health Service Act for Brineura (cerliponase alfa). We also refer you to the Late-Cycle Meeting (LCM) scheduled for February 21, 2017. Attached is our background package, including the agenda for this meeting.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: February 21, 2017, from 11:00AM to 12NN, ET
Meeting Location: White Oak Building 22, Conference Room 1415
10903 New Hampshire Ave,
Silver Spring, MD 20903

Application Number: 761052
Product Name: Brineura (cerliponase alfa)
Indication: Treatment of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)
Applicant Name: BioMarin

FDA ATTENDEES (tentative)

Center for Drug Evaluation and Research

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODEIII)
Dragos Roman, MD, Associate Director, Division of Gastroenterology and Inborn Errors Products (DGIEP), ODEIII
Victor Baum, MD, Medical Team Leader, DGIEP, ODEIII
Laurie Muldowney, MD, Medical Team Leader, DGIEP, ODEIII
Elizabeth Hart, MD, Medical Reviewer, DGIEP, ODEIII
David Joseph, PhD, Pharmacology Team Leader, DGIEP, ODEIII
Fang Cai, PhD, Pharmacology Reviewer, DGIEP, ODEIII
Joette Meyer, PharmD, Associate Director for Labeling, DGIEP, ODEIII
Jenny Doan, BSN, Regulatory Project Manager, ODEIII, DGIEP
Lisa LaVange, PhD, Director, Office of Biostatistics (OB)
Laura Lee Johnson, PhD, Deputy Director, OB, Division of Biometrics III (DBIII)
Yeh-Fong Chen, PhD, Biostatistics Team Leader, OB, DBIII
Min Min, PhD, Biostatistics Reviewer, OB, DBIII
Lili Garrard, PhD, Biostatistics Reviewer, OB, DBIII
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Christine Hon, PharmD, Clinical Pharmacology Reviewer, OCP
Nitin Mehrotra, PhD, Team Leader, Division of Pharmacometrics (DPM), OCP
Justin Earp, PhD, Reviewer, DPM, OCP
Cristina Ausin, PhD, Team Leader, Office of Biotechnology Products (OBP)
Ralph Bernstein, PhD, Product Quality Reviewer, OBP
Rukman De Silva, PhD, Product Quality Reviewer, OBP
Patricia Hughes, PhD, Team Leader, Division of Microbiology Assessment (DMA), Office of Process and Facilities (OPF)
Candace Gomez-Broughton, PhD, Reviewer, DMA, OPF
Natalia Pripuzova, PhD, Reviewer, DMA, OPF
Laura Fontan, PhD, Consumer Safety Officer, Division of Inspectional Assessment, OPF
Gerald Feldman, PhD, Team Leader, OBP
Frederick Mills, PhD, Immunogenicity Reviewer, OBP
Amy Rosenberg, MD, Immunogenicity Reviewer, OBP

Jibril Abdus-Samad, Labeling Reviewer, OBP
Susan Thompson, MD, Team Leader, Office of Scientific Investigation (OSI)
Susan Leibenhaut, MD, Reviewer, OSI
Elektra Papadopoulos, MD, Associate Director, Clinical Outcome Assessment Staff (COA)
Selena Daniels, PharmD, M.S., Reviewer, COA
Teresa Burrachio, MD, Reviewer, Division of Neurology Product (DNP)
Nick Kozauer, MD, Team Leader, DNP
Nicholas Miles, PharmD, Safety Regulatory Project Manager, Office of Safety and Epidemiology (OSE)
Matthew Barlow, BSN, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA), OSE
Mishale Mistry, PharmD, Team Leader, DMEPA, OSE
Robert Pratt, PharmD, Risk Management Analyst, Division of Risk Management, OSE
Donella Fitzgerald, PharmD, Team Leader, Division of Risk Management, OSE
Jane Liedtka, MD, Reviewer, Division of Pediatric and Maternal Health (DPMH)
Amy Taylor, MD, Reviewer, DPMH
Benneth Blumenkopf, MD, Reviewer, Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH)
John McMichael, Reviewer, ODE, CDRH
Diem-Kieu Ngo, Team Leader, Division of Advisory Committee and Consultant Management (DACCM)
Moon Choi, DACCM

APPLICANT ATTENDEES

Patient Meeting (10:30-11:00am)

BioMarin Attendees (in-person):

Henry J. Fuchs, M.D., President, Worldwide Research & Development, Global Clinical Sciences
Geoffrey Nichol, M.B., Ch.B., Vice President, Clinical Sciences
David Jacoby, M.D., Ph.D., Executive Group Medical Director, Clinical Sciences
Camilla V. Simpson, Group Vice President, Regulatory Affairs, Regulatory Affairs
Mary O'Donovan, Executive Director, Regulatory Affairs

Additional Attendees (in-person):

[Redacted] (b) (4)

Angela Schulz, M.D., Principal Clinical Investigator, University Medical Center Hamburg-Eppendorf, Germany

Emily de los Reyes, M.D., Principal Clinical Investigator, Nationwide Children's Hospital, USA

[Redacted] (b) (4)

[Redacted] (b) (6)

Late-cycle Meeting (11:00am – 12pm):

BioMarin Attendees (in-person):

Henry J. Fuchs, M.D., President, Worldwide Research & Development, Global Clinical Sciences
Geoffrey Nichol, M.B., Ch.B., Vice President, Clinical Sciences
David Jacoby, M.D., Ph.D., Executive Group Medical Director, Clinical Sciences
Temitayo Ajayi, M.D., Senior Director, Clinical Sciences
Camilla V. Simpson, Group Vice President, Regulatory Affairs, Regulatory Affairs
Bradley J. Glasscock, Pharm.D., Vice President, Regulatory Affairs, Clinical/Nonclinical
Lisa Malandro, Executive Director, Regulatory Affairs, Clinical/Nonclinical
Steven Fagliarone, Senior Manager, Regulatory Affairs, Clinical/Nonclinical
Linda Wilbur, Associate Director, Regulatory Affairs, CMC
Chito Hernandez, Ph.D., Vice President, Biometrics
Peter Slasor, Sc.D., Director, Biostatistics, Global Clinical Sciences

(b) (4)

BioMarin Attendees (via Web-ex):

Heather Cahan, M.D., Medical Director, Pharmacovigilance
Michelle Fong, Senior Director, Regulatory Affairs, Clinical/Nonclinical
Joshua Henshaw, Ph.D., Senior Scientist II, Pharmacological Sciences
Tessa Verbanic, Associate II, Regulatory Affairs, Clinical/Nonclinical
Richard Morse, MSc, MA, Sr. Director, Clinical Operations, Development Sciences Operations
Anu Cherukuri, Ph.D., Senior Scientist I, Pharmacological Sciences
Jim Nickas, Pharm.D., Vice President, Pharmacovigilance
Art Blum, Vice President, Regulatory Affairs, CMC
Namita Nayak, Senior Director, Regulatory Affairs, CMC

INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical/Statistics - Efficacy:

Multiple efficacy analyses conducted by BioMarin and FDA were discussed at a briefing of the CDER Center Director on December 15, 2016, and January 27, 2017. At this juncture, our view is that substantial evidence of effectiveness has not been demonstrated for cerliponase alfa. However, we plan to analyze additional longitudinal data from study 190-202 that you submitted with the November 2016 data-cut, the additional external control data from the Cornell study and, when submitted, available efficacy data from study 190-203 (the sibling study) and study 190-502 (your expanded access trial). The major issues identified during the review have already been communicated to you and include:

- Data quality issues have precluded us from conducting all the necessary analyses, and in particular sensitivity analyses of efficacy.
- There are differences in patient population characteristics between the natural history study (190-901) and the intervention study (190-201/202). These differences and the lack of standardization of scale administration and training (i.e., different data collection methodologies, frequency of assessments, and scale anchor definitions) impede direct comparison between studies 190-901 and 190-201/202.
- We have concerns about the measurement properties of the Language domain of the CLN2 scale, specifically its reliability; as such we believe that determination of efficacy will need to rely on the Motor domain.
- There are multiple issues surrounding the methodologies employed in the data analyses presented to compare studies 190-901 to 190-201/202.

Clinical/Statistics – Benefit/Risk Assessment:

At this juncture, our view is that the benefit of treatment with cerliponase alfa does not outweigh the identified drug- and device-related safety findings and risks. Our assessment of benefit/risk will be revisited following the additional efficacy analysis.

ADVISORY COMMITTEE MEETING

A final decision has not been reached for an Advisory Committee. As previously communicated to BioMarin, an Advisory Committee Meeting could take place only if the data discrepancies identified during the application review can be successfully addressed and reconciled.

REMS OR OTHER RISK MANAGEMENT ACTIONS

- Additional review is needed to better understand the risks of hypotension, hypersensitivity reactions, device related complications, cytopenias, and serious infections that have been identified during our review.
- At this time, the need for a REMS is still under review.

POST-MARKETING REQUIREMENTS/COMMITMENTS (PMRs/PMCs)

We have identified the following potential PMRs/PMCs at this time (please note that additional PMRs/PMCs may be considered upon finalization of reviews):

PMR:

1. Conduct a clinical study to assess the incidence of immunogenicity in CSF and serum, as well as the impact of immunogenicity on safety and efficacy after long-term administration of cerliponase alfa in CLN2 patients.

PMCs:

1. To develop and validate an additional identity test for the Intraventricular Electrolytes Injection (b) (4)
2. To add cellular uptake as a release assay for drug product and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.
3. To revalidate RP-HPLC and SEC-HPLC release and stability assays using impurities generated by subjecting cerliponase alfa to stressed stability conditions.

LCM AGENDA

1. Introductory Comments – 2 minutes

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Patient Meeting – 30 minutes
3. Discussion of Substantive Review Issues – 30 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Clinical
 - Study Conduct/Data Quality: There are multiple data discrepancy issues which we plan to continue discussing with you during the subsequent data reconciliation meeting. Additionally, we were unable to verify the 190-901 source data (only a sub-set of the scoring sheets were available for review by OSI). There are no videotapes from study 190-901 available for our review limiting comparability assessments for the CLN2 scale used in studies 190-901 and 190-201/202. We are concerned that the CLN2 exams may not have been performed in a uniform manner. Neither study 190-901 nor studies 190-201/202 collected data on non-drug concurrent therapies, and study 190-901 did not collect information on

concurrent medications, limiting our ability to control for potentially important confounding variables. The data on past medical history from 190-901 is limited and it is unclear if the dates accurately represent the emergence of symptoms rather when those symptoms were first recorded in available medical records, thus limiting our ability to ensure comparable disease courses prior to treatment of 190-201 subjects.

- External Control Group: There are concerns regarding the comparability between the 190-201/202 population and the 190-901 historical controls. There are concerns related to different endpoints measured in the two studies, training and the method of rating, anchor point definitions used for the CLN2 scales administered, and the differences in the intervals between CLN2 assessments in the two studies.
- CLN2 Scale (especially the Language domain): Disagreement between ratings were noted on the scales used in study 190-901 and studies 190-201/202 based on the data from the Video Comparability Study indicating that the scales are not completely equivalent and have some reliability issues, particularly with the Language domain. Please refer to the graphical presentation of the Motor domain and the Language domain based on the Video Comparability Study from the mid-cycle meeting.
- Safety
 - Device Replacement: We are awaiting the results of the bench-top testing to assess septum degradation to assist in our assessment of device related safety.
 - Blood Pressure: During the BLA review of data from 190-201/202, hypotension has emerged as a safety signal. Therefore, we strongly recommend that you revise protocol 190-202, 190-203 and 190-502 to monitor BP more appropriately and uniformly. Specifically, using an appropriate size BP cuff and measuring the BP in the upper arm. If the BP is abnormal, a manual BP should be obtained by a trained healthcare professional. In study 190-502, the frequency of BP monitoring should be increased and continued for 24 hours after the infusion (as is being performed in 190-202).
 - Cytopenias: During our BLA review of the data from 190-201/202, cytopenias have emerged as a potential safety signal. To more appropriately monitor this signal, please revise protocol 190-502 to collect CBCs every 12 weeks.
- Statistical
 - Questions related to IRs and FDA Responses

4. Discussion of Minor Review Issues – 5 minutes

- Safety
 - Device Benchtop Testing

5. Additional Applicant Data – 15 minutes (Applicant)

6. Information Requests –

- CMC information request sent on 2/7/2017- BioMarin anticipates to submit a response on 3/31/17
- Clinical Pharmacology information request (genotype nomenclature & missing data) sent on 2/14- BioMarin anticipates to submit a response on 2/17/17
- Clinical information request (CSF labs with corrected units) sent on 2/13/17- BioMarin anticipates to submit a response on 2/17/17.

7. Postmarketing Requirements/Postmarketing Commitments (PMRs/PMCs)

8. Major labeling issues

The labeling review is ongoing. We provided preliminary comments on the carton labeling on December 20, 2016, and product labeling on January 30, 2017. We received the revised labeling on February 13, 2017.

9. Review Plans – 5 minutes

- Data Reconciliation Meeting
- Benchtop Protocol Review
- Labeling
- PMRs/PMCs

10. Wrap-up and Action Items – 2 minutes

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

/s/

DRAGOS G ROMAN
02/17/2017

October 18, 2016 Meeting Minutes: Appropriate ROA for BRINEURA Labeling and Other Product Labeling with Same ROA

Attendees:

Bennett Blumenkopf, Medical Officer, Division of Neurological and Physical Medicine Devices, Office of Device Evaluation, CDRH

Laurie Muldowney, Clinical Team Leader, Division of Gastroenterology and Inborn Errors Products (DGIEP)

Joette Meyer, Associate Director for Labeling (ADL), DGIEP

Billy Dunn, Director, Division of Neurology Products (DNP)

Eric Bastings, Deputy Director, DNP

Tracy Peters, ADL, DNP

Michael Monteleone, ADL, Division of Cardiovascular and Renal Products (DCRP)

Eric Brodsky, Associate Director, Labeling Development Team (LDT)

Ann Marie Trentacosti, Medical Lead, LDT

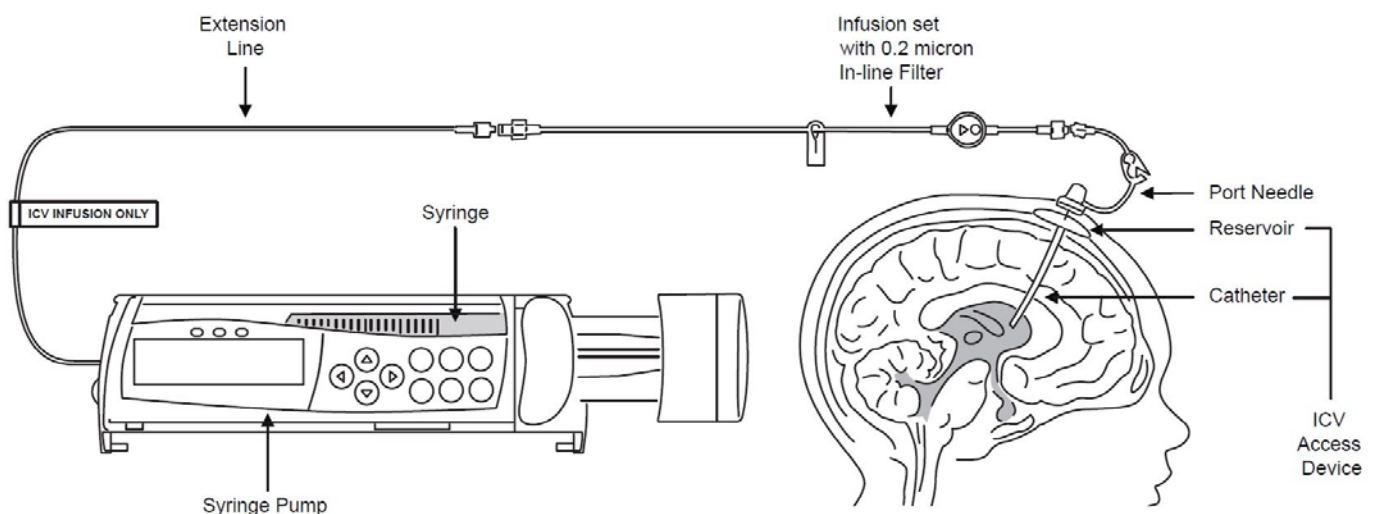
Farrokh Sohrabi, Labeling Reviewer, LDT

Debra Beitzell, Labeling Reviewer, LDT

Jeanine Best, Labeling Reviewer, LDT

Purpose: To obtain alignment on the appropriate route of administration (ROA) terminology to use in the BRINEURA labeling and other product labeling with similar ROA.

Background: BioMarin submitted a BLA (BLA 761052) for BRINEURA (cerliponase alfa), a new enzyme replacement therapy, with the following proposed indication: “*treatment of patients with ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase -1 (TPP1) deficiency.*” In the DOSAGE AND ADMINISTRATION section of labeling, BioMarin proposes that BRINEURA is to be administered in the cerebrospinal fluid by infusion via a surgically implanted reservoir and catheter (intracerebroventricular access device). See the figure below for their proposed procedure.



(b) (4)

Attendees thought that the intraventricular ROA was accurate for the BRINEURA labeling. Although the attendees were not aware of any approved products that are administered directly into the right or left ventricle of the heart, attendees wondered about the appropriate ROA that should be used for future products that are administered directly into the right or left ventricle of the heart.

Path Forward: The attendees agreed that the BRINEURA labeling and other future product labeling with the same ROA should:

- Include the “intraventricular” terminology in the product title:
 - **BRINEURA (cerliponase alfa) injection, for intraventricular use**
- Clarify in several parts of the labeling (e.g., DOSAGE AND ADMINISTRATION and CLINICAL STUDIES sections) that the ventricles refer to the ventricles of the brain rather than the heart.

(b) (4)

Furthermore, other sections of the labeling (e.g., DOSAGE AND ADMINISTRATION and CLINICAL STUDIES sections) could clarify that the product is to be administered into the right or left ventricle of the heart.

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

/s/

JOETTE M MEYER
12/28/2016



BLA 761052

MID-CYCLE COMMUNICATION

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Brineura (cerliponase alfa) 30 mg/mL.

We also refer to the teleconference held between representatives of your firm and the FDA on December 16, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: December 16, 2016; 11:00 AM – 12NN EST

Application Number: BLA 761052

Product Name: Brineura

Indication: Treatment of Neuronal Ceroid Lipofuscinosis
Type 2 (CLN2) Disease or TPP1 Deficiency

Applicant Name: BioMarin Pharmaceutical, Inc

Meeting Chair: Julie Bietz, MD

Meeting Recorder: Jenny Doan, RPM

FDA ATTENDEES

Julie Beitz, MD, CDER, Director, Office of Drug Evaluation III (ODE III)

Dragos Roman, MD, CDER, ODEIII, Associate Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)

Laurie Muldowney, MD, CDER, ODEIII, Clinical Team Leader, DGIEP

Elizabeth Hart, MD, CDER, ODEIII, DGIEP

Kevin Bugin, MS, RAC, CDER, ODEIII, DGIEP

Jenny Doan, MSN, CDER, ODEIII, DGIEP

Yeh-Fong Chen, PhD, CDER, Office of Biostatistics (OB), Team Leader

Min Min, PhD, CDER, OB

Laura Lee Johnson, PhD, CDER, OB, Division of Biometrics III, Deputy Director

Lili Garrard, PhD, CDER, OB

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

Christine Hon, PharmD, CDER, OCP

Cristina Ausin, PhD, CDER, Office of Biotechnology Products (OBP), Team Leader

Ralph Bernstein, PhD, CDER, OBP

Rukman De Silva, PhD, CDER, OBP

Candace Gomez-Broughton, PhD, CDER, Office of Process and Facilities (OPF)

Natalia Pripuzova, PhD, CDER, OPF

Laura Fontan, PhD, CDER, OPF

Frederick Mills, PhD, CDER, OBP

Gerald Feldman, PhD, CDER, OBP

Patricia Hughes, PhD, CDER, OPF

Colleen Thomas, PhD, CDER, OPF

Jibril Abdus-Samad, CDER, OBP

Susan Leibenhaut, MD, CDER, Office of Scientific Investigation

Selena Daniels, PharmD, CDER, Clinical Outcome Assessment Staff (COA)

Elektra Papadopoulos, MD, CDER, COA, Associate Director
Teresa Burrachio, MD, Division of Neurology Product (DNP)
Nick Kozauer, MD, DNP
Nicholas Miles, CDER, Office of Safety and Epidemiology (OSE)
Matthew Barlow, CDER, OSE, Division of Medication Error Prevention and Analysis (DMEPA)
Mishale Mistry, CDER, OSE, DMEPA
Robert Pratt, OSE, Division of Risk Management
Donella Fitzgerald, OSE, Division of Risk Management
Jane Liedtka, MD, CDER, Division of Pediatric and Maternal Health (DPMH)
Amy Taylor, MD, CDER, DPMH
Benneth Blumenkopf, MD, Center for Devices and Radiological Health (CDRH)
John McMichael, CDRH, Office of Device Evaluation
Diem-Kieu Ngo, Division of Advisory Committee and Consultant Management (DACCM)
Moon Choi, DACCM

APPLICANT ATTENDEES

Henry J. Fuchs, M.D., Executive Vice President, Chief Medical Officer, Global Clinical Sciences
Chito Hernandez, Ph.D., Vice President, Biometrics
Gordon Sun, Ph.D., Executive Director, Biostatistics, Clinical Sciences and CMO's Office
Peter Slasor, Sc.D., Director, Biometrics
Janet Hsu, Senior Director, Corporate Compliance and Ethics
Laurie Bray, Associate Director, Statistical Programming, Global Clinical Sciences
Leslie Barnes, Vice President, Development Sciences Operations
Rafael Escandon, Vice President, Clinical Operations
Richard Morse, MSc, MA, Sr. Director, Clinical Operations, Development Sciences Operations
Sarah Noonberg, M.D., Ph.D., Group Vice President, Global Clinical Development
Geoffrey Nichol, M.B., Ch.B., Vice President, Clinical Sciences
David Jacoby, M.D., Ph.D., Executive Group Medical Director, Clinical Sciences
Temitayo Ajayi, M.D., Sr. Director, Clinical Sciences
Charles O' Neill, Ph.D., DABT, Vice President, Pharmacological Sciences
Jason Pinkstaff, Ph.D., DABT, Director, Pharmacological Sciences
Joshua Henshaw, Ph.D., Senior Scientist II, Pharmacological Sciences
Anu Cherukuri, Ph.D., Senior Scientist I, Pharmacological Sciences
Jim Nickas, Pharm.D., Vice President, Pharmacovigilance
Heather Cahan, M.D., Medical Director, Pharmacovigilance
Camilla V. Simpson, Group Vice President, Regulatory Affairs
Brad Glasscock, PharmD, Vice President, Regulatory Affairs
Lisa Malandro, MBA, Executive Director Regulatory Affairs, Clinical/Nonclinical
Michelle Fong, Sr. Director, Regulatory Affairs, Clinical/Nonclinical
Steven Fagliarone, Sr. Manager, Regulatory Affairs, Clinical/Nonclinical
Tessa Verbanic, Associate II, Regulatory Affairs, Clinical/Nonclinical
Art Blum, Vice President, Regulatory Affairs, CMC
Victoria Sluzky, Ph.D., Group Vice President, Quality and Process Development
Namita Nayak, Senior Director, Regulatory Affairs, CMC

Linda Wilbur, Associate Director, Regulatory Affairs, CMC
Catherine Campbell, Manager, Regulatory Affairs, CMC
Mary O'Donovan, Executive Director, Regulatory/Pharmacovigilance
Elizabeth Moyle, Senior Director, Regulatory/Pharmacovigilance
Robert Baffi, Ph.D., Executive Vice President, Technical Operations

(b) (4)

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Clinical - Efficacy:

Multiple efficacy analyses conducted by BioMarin and FDA were discussed at a briefing of the Center Director on December 15, 2016. At this juncture, our view is that substantial evidence for effectiveness has not been demonstrated for cerliponase alfa. However, we plan to request, and also conduct, additional efficacy analyses prior to making a final assessment of the efficacy of this product. A second Center Director briefing is planned in late January 2017 to discuss these additional analyses. We will communicate the outcome of this briefing to you shortly thereafter.

Clinical – Benefit/Risk Assessment:

At this juncture, our view is that the demonstrated benefits of treatment with cerliponase alfa do not outweigh the identified drug- and device-related safety findings. Our assessment of benefit/risk will be revisited at the next planned Center Director briefing.

Product Quality:

- Sterilization validation data for (b) (4)
- Sterilizing (b) (4): implementation of this control parameter
- Validation of the revised drug substance manufacturing process

3.0 INFORMATION REQUESTS

The following information requests are outstanding:

Clinical/Clinical Pharmacology:

1. DEM-Child data (07/20/16)
2. Cornell Weil data (10/27/16)
3. 201/202 Safety Data (11/16/16)
4. Biomarker Information (12/15/16)
5. Clinical Pharmacology (12/14/16)

Product Quality:

1. IR #4 (9/14/2016)- Revised (b) (4) validation expected by mid-late December
2. IR #5 (9/19/2016)
 - Analytical assays transfer: expected 12/16/2016
 - Revised specifications: expected 12/30/2016
 - Drug Product content uniformity validation: expected 12/30/2016
 - Sterilization validation data for (b) (4) : expected 12/16/2016
 - Sterilization (b) (4) : expected 12/30/2016
 - Sterility and bioburden method verification: expected 12/30/2016
 - Increase of (b) (4) batch size: expected 1/31/2017
3. IR #10 (12/5/2016)- DS micro: expected 12/16/2016

Device:

1. IR #18 (10/27/2016) - Benchtop study protocol to simulate in-life use of the ICV access device: expected 12/16/2016

New Information Requests:

A request for additional statistical analyses of efficacy will be sent by December 23, 2016.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- Additional review is needed to better understand the risks of hypotension, hypersensitivity reactions, device related complications, and non-CNS infections that have been identified.
- We encourage you to conduct the benchtop study regarding the compatibility of the ICV access device and the needle as soon as possible. Comments on the study protocol, once submitted, will be provided.
- At this time, a need for a REMS is still under review.

5.0 ADVISORY COMMITTEE MEETING

We plan to postpone the March 2, 2017, advisory committee meeting to discuss this application, as review of additional data is currently anticipated..

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting (LCM) is February 21, 2017. In addition, please note the following projected milestone dates:

- Labeling comments for the CMC and non-clinical sections to Applicant: January 24, 2017
- Other labeling comments and PMR/PMC comments: Timeline is to be determined pending the progress of application review
- LCM Background Package to the Applicant: February 11, 2017
- PDUFA Goal Date: April 27, 2017

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

/s/

JENNY N DOAN
12/19/2016



BLA 761052

**REVIEW EXTENSION –
MAJOR AMENDMENT**

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

Please refer to your Biologics License Application (BLA) dated and received May 27, 2016, submitted under section 351(a) of the Public Health Service Act for BMN 190 (cerliponase alfa).

On August 29, 2016, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 27, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 27, 2017.

Furthermore, we will be communicating new dates for major review milestones (i.e., mid-cycle, late cycle, advisory committee meeting) in the near future.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

DRAGOS G ROMAN
09/02/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761052

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

ATTENTION: Michelle Fong
Senior Director, Regulatory Affairs

Dear Ms. Fong:

Please refer to your Biologics License Application (BLA) dated and received May 27, 2016, submitted under section 351(a) of the Public Health Service Act for Cerliponase Alfa, 30 mg/mL.

We also refer to your correspondence, dated and received May 27, 2016, requesting review of your proposed proprietary name, Brineura.

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

If any of the proposed product characteristics as stated in your May 27, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5295. For any other information regarding this application, contact Jenny Doan, Regulatory Project Manager in the Office of New Drugs at 301-796-1023.

Sincerely,

{See appended electronic signature page}

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

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

/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/15/2016



BLA 761052

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

Please refer to your Biologics License Application (BLA) dated and received May 27, 2016, submitted under section 351(a) of the Public Health Service Act for BMN 190 (cerliponase alfa).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is January 27, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 27, 2016. In addition, the planned date for our internal mid-cycle review meeting is August 31, 2016.

We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. Clinical:

The clinical review will include assessments of whether the historical controls and the treated subjects are comparable, and whether the CLN2 motor and language scales (including the modifications made to the scales) used to assess efficacy of BMN 190 are reliable. To assist with our review, we have sent multiple information requests. At the time of this filing review, the following information requests remain outstanding:

- Provide updated efficacy data by performing a data-cut in June 2016. Specifically, provide the following for the updated datasets:
 - a. Date and age in months at new assessment time points for all subjects in 190-202 and their scores on the motor subscale, language subscale, motor-language combined score, vision subscale, seizure subscale, number of language delays and cautions on Denver II developmental tests, and number of gross motor delays and cautions on Denver II developmental test
 - b. Updated individual graphic patient profiles with combined motor-language CLN2 scores, motor scores and language scores
 - c. Summary descriptive statistics for CLN2 score changes over 84 weeks (e.g. number and percent of patients who had 2 point improvement, 1 point improvement, no change, 1 point decline, 2 point decline, 3 point decline on motor, language and motor-language score; length of time mean, standard deviation, median, range for treated subjects to decline from 3 to 2, 2 to 1 and 1 to 0 on motor and language subscales)
 - d. A responder analysis (defined as absence of an unreversed 2 point decline and defined as an absence of an unreversed 1 point decline) based on change in motor-language score over 84 weeks in the ITT population and the subset who had a 300mg baseline motor-language score that was between 3-5. Also perform a responder analysis for motor and language scores separately (defined as absence of an unreversed 1 point decline) over the 84 weeks in the entire ITT population.
 - e. Slope of rate of change from 300mg baseline to final measurement for motor-language combined score, motor score only and language score only for ITT and Efficacy (CLN2 <6) populations. As an additional sensitivity analysis, determine slope from study baseline to final measurement for, and study baseline to final motor-language combined score, motor score only and language score only in the ITT and efficacy populations.
- Review the registry and/or original source data for the natural history subjects and provide the following data:
 - a. How each CLN2 assessment was made (e.g. whether the data was derived from parental report, post-hoc scoring based on a review of

- medical records, or prospectively evaluated in clinic by a trained rater) in as many subjects during as many time points as possible.
- b. Indicate if any subject had a significant inter-current illness during any of these assessments.
 - c. The absolute number and percentage of total assessments, motor assessments with a score of 1 or 2, and language assessments with a score of 1 or 2 that were performed prospectively (and clarify if prospective CLN2 motor and language scores were performed consistently across sites).
 - d. Graphic patient profiles for the natural history subjects with age in months on the x axis, onset of different symptoms, concomitant medications and therapies above this for as many DEM-CHILD subjects as data is available.
- Obtain the protocol and complete dataset with additional cross-sectional data and longitudinal data from Cornell and submit to the BLA.

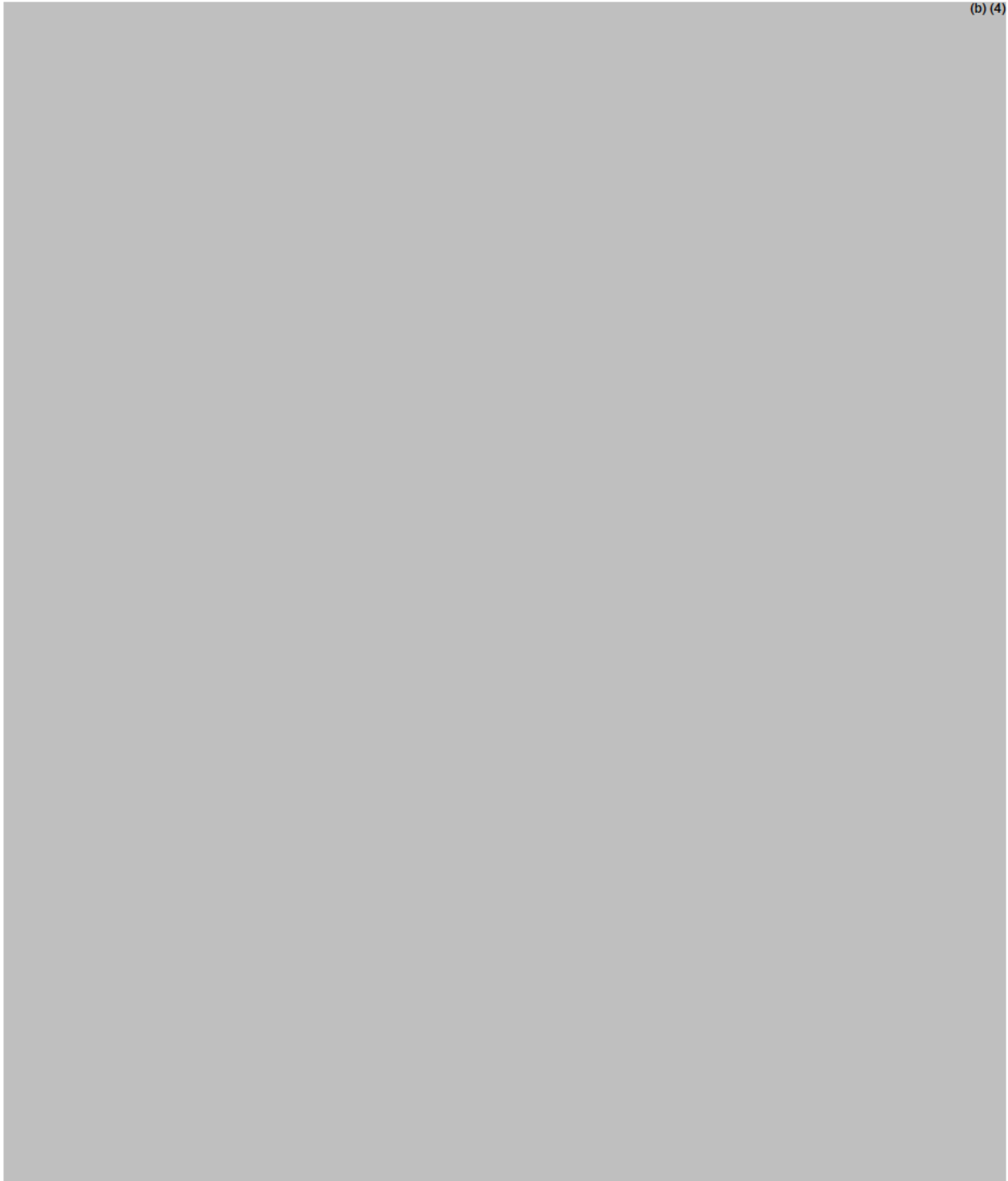
2. Product Quality:

- a. We note that you performed a compatibility assessment to demonstrate that the BMN 190 drug product (DP) and BMN 190 flushing solution (FS) are stable over the duration of the commercial use and that the components of the infusion kit are compatible with the DP and FS. In your compatibility study, the analysis of BMN 190 FS samples by the Size Exclusion Chromatography (SEC) assay reported in Section 3.2.P.2.6, Figure 3.2.P.2.6.2.2.3 shows a ~ (b) (4) minute peak in the chromatogram. However, you have not provided any details of this peak. To determine if the presence of the (b) (4) minute peak constitutes a safety concern, provide the SEC chromatograms collected during the compatibility analysis of BMN 190 FS for the 3 hours and 4 hours samples. In addition, please provide details of any studies performed to characterize the (b) (4) minute peak. Alternatively provide a justification why such studies are not necessary.
- b. You have submitted data reporting the (b) (4) content found on BMN190 in the development, clinical and commercial batches. You have submitted (b) (4) data in multiple sections, including “batch analyses” and “elucidation of structure.” See “batch analyses” Table 3.2.S.4.4.3, and “elucidation of structure” Table 3.2.S.3.1.3.5.2, below:

From “batch-analyses”

Table 3.2.S.4.4.3: Batch Analysis Results for Clinical and Developmental Batches (Potency)

(b) (4)



From “elucidation of structure”

[Trade Name] (cerliponase alfa)

Page 33

(b) (4)

It is not clear to the Agency what (b) (4) refers to in Table 3.2.S.4.4.3, versus Table 3.2.S.3.1.3.5.2, e.g., clinical lot 12002 is reported (b) (4) of 13% in Table 3.2.S.4.4.3 but as 19% in Table 3.2.S.3.1.3.5.2. This apparent discrepancy appears in several other batches as well, (see 12003, 12005 and others) while several from each table are more similar, e.g., 14106.

To allow the Agency to effectively evaluate the consistency of manufacture and analytical comparability between clinical and commercial lots of BMN190, explain the discrepancy in % (b) (4) between the different sections within the same BLA.

3. Combination Product Manufacturing and Quality:

- a. Provide a summary of information related to Management Responsibilities. The summary should address the management structure with executive responsibility who manage, perform, and assess work affecting quality of the combination product (i.e. drug product, device constituent part, combination product) and related controls to ensure that the firm’s quality policies are appropriately implemented and followed, and the product is appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements as per 21 CFR 820.20.
- b. Provide a summary of how you fulfill the requirements related to Purchasing Controls as per 21 CFR 820.50. The summary should include how you demonstrate control and documentation for components, products, or services (example sterilization) received at the final combination product manufacturing facility. The summary should include the evaluation process for your suppliers. Notification of changes by the suppliers should be considered in the firm’s Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final

combination product. If you have considered supplier evaluation as per 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures, this information may be leveraged to augment the requirement for the 21 CFR 820.50 and 21 CFR Part 4.

- c. Provide a summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100. The summary should explain establish how the CAPA requirements for the combination product are met. Identify the facility that processes returned products.

4. Device:

- a. We note that the proposed labeling does not specify any particular intracerebroventricular (ICV) access device to be used in the delivery of BMN 190. In order to ensure the safe administration of BMN 190 please provide updated labeling that specifies the ICV access device, including the ventricular catheter, that was utilized in the clinical trials and verified for performance on the bench. Note that the indications for use of the ICV access device that you plan to label for use with your drug product should not prohibit delivery of medication into the ICV space.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and request that you submit the following information:

Sections 2.2 (Method of Administration), 2.3 (Preparation for Administration), and 2.4 Instructions for Use of the PI contains dense and lengthy text. We recommend you revise the text in these sections to include discrete, step-by-step instructions with corresponding figures/diagrams to ensure the drug/device are properly prepared and administered to avoid medication errors. We refer you to other approved products, for example: Eyelea® (afibercept) injection¹ and Faslodex (fulvestrant) injection.²

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by August 31, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

¹ Eylea® (afibercept) injection, PI dated 5/24/2016:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s051lbl.pdf

² Faslodex® (fulvestrant) injection, PI dated 7/12/16:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021344s029lbl.pdf

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

DRAGOS G ROMAN

08/09/2016

Signing on behalf of Dr. Donna Griebel

From: [Linda Wilbur](#)
To: [Doan, Jenny](#)
Cc: [Michelle Fong](#); [Bugin, Kevin](#)
Subject: RE: STN 761052: BMN 190 (cerliponase alfa) BLA Submission Device Labeling Question
Date: Friday, July 22, 2016 11:39:04 AM

Hi Jenny,

Thank you so much for looking into this for us. We will contact the UDI helpdesk again and ask for additional assistance. We will let you know if we have any further questions or need additional advice.

Thanks again,

Linda

From: Doan, Jenny [mailto:Jenny.Doan@fda.hhs.gov]
Sent: Friday, July 22, 2016 8:32 AM
To: Linda Wilbur <lwilbur@bmrn.com>
Cc: Michelle Fong <mfong@bmrn.com>; Bugin, Kevin <Kevin.Bugin@fda.hhs.gov>
Subject: RE: STN 761052: BMN 190 (cerliponase alfa) BLA Submission Device Labeling Question

Good afternoon Linda,

We have reviewed the submission and labeling for the administrative kit, and we agree that it should have a Unique Device Identification (UDI) since it will be stored separately. You can get a UDI for a device approved under the BLA. But, you cannot use the basic device electronic link to do so. You should contact the UDI helpdesk to ask for assistance. You may reach them via email at: guidsupport@fda.hhs.gov.

Let me know if you have further questions. Thanks.

Regards,

Jenny
WO Bldg. 22, Room 5345
(301) 796-1023

From: Linda Wilbur [mailto:lwilbur@bmrn.com]
Sent: Tuesday, July 19, 2016 1:10 PM
To: Doan, Jenny
Cc: Michelle Fong
Subject: STN 761052: BMN 190 (cerliponase alfa) BLA Submission Device Labeling Question

Dear Ms. Doan,

I hope you are well. We have a few questions related to the requirements for device labeling for the BMN 190 Administration Kit (device-constituent part under BLA 761052). Can you assist us in identifying the appropriate contact within FDA to confirm the requirements and discuss next steps?

Background:

BioMarin believes that the Administration Kit will be subject to the Unique Device Identification System (UDI) Final Rule as a Class II device (§ 801.20) because the Administration Kit will be supplied separately from the BMN 190 drug product (DP) and flushing solution (FS) and therefore we think it cannot bear the biologic product National Drug Code (NDC) alone. We would like to confirm this.

We have been in contact with a few representatives from FDA (primarily the GUDID Help Desk), but have not been able to determine a path forward at this point. We have been told that our Administration Kit would need its own premarket number (PMA or 510(k)) in order to be issued a GUDID Account, but as the kit would be sold exclusively for use with BMN 190 and be approved under the BLA, we do not have such a number. We would like some guidance on who the appropriate contacts are at FDA to help us sort through the requirements.

Is this something you can help with or something a representative from the Office of Combination Products may be able to assist us with?

We are available this week for a phone call and can provide a bit more background information prior to the discussion. Feel free to call me to discuss any questions or for scheduling. Thank you so much in advance for your assistance.

Kind regards,
Linda

Linda Wilbur
Regulatory Affairs CMC
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949 USA
Tel +1 415-506-6154
Fax +1 415-506-6306

This message is intended only for the confidential use of the intended recipient(s). If you have received this communication in error, please notify the sender by reply e-mail, and delete the original message and any attachments. Any unauthorized disclosure, copying, or distribution of this message (including the attachments), or the taking of any action based on it, is strictly prohibited.

This message is intended only for the confidential use of the intended recipient(s). If you have received this communication in error, please notify the sender by reply e-mail, and delete the original message and any attachments. Any unauthorized disclosure, copying, or distribution of this message (including the attachments), or the taking of any action based on it, is strictly prohibited.

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

/s/

JENNY N DOAN
07/25/2016



BLA 761052

PRIORITY REVIEW DESIGNATION

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

Please refer to your Biologics License Application (BLA) dated May 27, 2016 received May 27, 2016, submitted under section 351(a) of the Public Health Service Act for BMN 190 (cerliponase alfa).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 601.2(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is January 27, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 27, 2016.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before August 9, 2016.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

DRAGOS G ROMAN

07/13/2016

Signing on behalf of Dr. Donna Griebel



BLA 761052

BLA ACKNOWLEDGMENT

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

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

Name of Biological Product: BMN 190 (cerliponase alfa) Solution for Infusion 30mg per mL

Date of Application: May 27, 2016

Date of Receipt: May 27, 2016

Our Reference Number: BLA 761052

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 26, 2016, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Inborn Errors
Products5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

JENNY N DOAN
06/01/2016



IND 122472

AMENDED MEETING MINUTES

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cerliponase alfa, BMN 190.

We also refer to the meeting between representatives of your firm and the FDA on March 29, 2016. The purpose of the meeting was to discuss the content of the Clinical and Quality sections of your proposed Biologics License Application (BLA).

Also, we refer the official meeting minutes issued on April 20, 2016 and to your email correspondence dated May 3, 2016, requesting revisions to the official minutes.

We have considered your requests and a copy of the official amended minutes of the meeting is enclosed for your information.

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

Sincerely,

{See appended electronic signature page}

Kevin B Bugin, MS, RAC
Chief, Project Management Staff (A)
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Amended Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

AMENDED MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: PreBLA

Meeting Date and Time: March 29, 2016, from 2:00 to 3:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 122472
Product Name: cerliponase alfa, BMN 190
Indication: treatment of CLN2
Sponsor/Applicant Name: BioMarin Pharmaceutical Inc

Meeting Chairperson: Laurie Muldowney
Meeting Recorder: Kevin Bugin

Attendees:

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, MD, Director
Dragos Roman, MD, Associate Director
Laurie Muldowney, MD, Medical Team Leader
Elizabeth Hart, MD, Clinical Reviewer
David Joseph, PhD, Nonclinical Team Leader
Ke Zhang, PhD, Nonclinical Reviewer
Kevin B Bugin, MS, RAC, Chief, Project Management Staff (A)

Office of Clinical Pharmacology

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

Office of Biostatistics

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

Office of Biotechnology Products

Michele Dougherty, PhD, Acting Review Chief
Serge Beaucage, PhD, Quality Team Leader
Jacek Cieslak, PhD, Quality Reviewer
Cristina Ausin, PhD, Acting Quality Team Leader

Office of Product Quality, Office of Process and Facilities, Division of Microbiology Assessment

Patricia Hughes, PhD, Acting Branch Chief
Colleen Thomas, PhD, Acting Quality Assessment Lead
Natalia Pripuzova, PhD, Quality Microbiology Reviewer

Office of the Commissioner/Office of Special Medical Programs/Office of Combination Products

Patricia Love, MD, Deputy Director

Center for Devices and Radiological Health/Office of Device Evaluation/General Hospital Devices Branch

John McMichael, Device Reviewer
CDR Alan Stevens, MS, Acting Branch Chief

Sponsor Attendees:

Temitayo Ajayi, M.D., Senior Director, Clinical Sciences
Robert Baffi, Ph.D., Executive Vice President, Technical Operations
Art Blum, Vice President, Regulatory Affairs, CMC
Heather Cahan, M.D., Medical Director, Pharmacovigilance
Jessica Cohen, M.D., Senior Medical Director, Medical Services
Steven Fagliarone, Senior Manager, Regulatory Affairs, Clinical/Nonclinical
Michelle Fong, Senior Director, Regulatory Affairs, Clinical/Nonclinical
Brad Glasscock, Pharm.D., Vice President, Regulatory Affairs, Clinical/Nonclinical
Joshua Henshaw, Ph.D., Senior Scientist II, Pharmacological Sciences
Chito Hernandez, Ph.D., Vice President, Biometrics
Lisa Malandro, Executive Director Regulatory Affairs, Clinical/Nonclinical
Elizabeth Moyle, Senior Director, Regulatory Affairs, Labeling
Sarah Noonberg, M.D., Ph.D., Group Vice President, Global Clinical Development
Charles O' Neill, Ph.D., DABT, Vice President, Pharmacological Sciences
Camilla V. Simpson, Group Vice President, Regulatory Affairs, Regulatory/Pharmacovigilance
Peter Slasor, Sc.D., Director, Biometrics
Victoria Sluzky, Ph.D., Group Vice President, Quality and Process Development
Linda Wilbur, Associate Director, Regulatory Affairs, CMC

(b) (4)

Tessa Verbanic, Associate II, Regulatory Affairs, Clinical/Nonclinical

1.0 BACKGROUND

On January 22, 2016, the Sponsor (BioMarin) submitted a meeting request to discuss the content of the Clinical, Chemistry, Manufacturing and Control sections and the 120-day safety update for a proposed Biologics License Application (BLA) planned for submission in Q2 (May) 2016. The meeting was granted and scheduled to take place on March 29, 2016.

2.0 DISCUSSION

CMC

1. Question 1

- a. Does the FDA agree that long term stability data generated on clinical drug product (both 1 mL and 5 mL extractable volumes) can be used to support the assignment of expiry for commercial DP with a labeled storage condition of ≤ -15 °C?

FDA Response:

Your proposal appears reasonable, however the use of the long term stability data generated from clinical drug product (DP) lots to support the assignment of expiry for commercial DP would be acceptable if the manufacturing process used to produce the clinical lots is demonstrated to be representative of the commercial manufacturing process. Thus, a final determination on the acceptability of your proposal cannot be made until a review of the data supporting comparability of the manufacturing processes used for the production of clinical and commercial drug product is completed. Additionally, we recommend that your proposed storage condition of ≤ -15 °C for the DP be revised to include upper and lower limits (e.g., -20 ± 5 °C) and provide additional information on the DP shipping temperature and time requirements.

- b. Does the FDA agree that additional stability data can be submitted within 30 days of the BLA submission, without extending the PDUFA action date?

FDA Response:

Yes, we agree.

2. Question 2

Does the FDA agree with BioMarin's proposal to modify the target fill volume for BMN 190 and that additional PPQ validation is not necessary?

FDA Response:

No, we don't agree. You did not provide data supporting the change of the target fill volume to (b) (4) mL. An additional PPQ validation demonstrating your ability to consistently achieve your target fill volume of (b) (4) nL is necessary.

Discussion:

See Sponsor's presentation, slide 6. The Sponsor's proposal to include one drug product PPQ lot and one lot of "flushing solution" with the submission of the BLA, and then one additional lot of "flushing solution" during the first 30 days of filing, is acceptable.

3. Question 3

BioMarin is in discussions with [REDACTED]^{(b) (4)} for the disposable components to be co-packaged with BMN 190. If BioMarin is unable to reach agreements, does the FDA agree with our proposal for periodic monitoring and additional testing of the finished devices as described above?

FDA Response:

We strongly recommend reaching agreements with the manufacturers of the administration kit components. If you are unable to reach agreements, your proposal for periodic monitoring and additional testing may be adequate, pending review of the essential performance requirements, release criteria, and testing that you establish for each component. We remind you to address our comments provided in the September 30, 2015 meeting minutes, particularly questions 1 and 6, and also comments provided in our October 28, 2015 advice letter. You will also need to provide a contingency plan for any components that may be discontinued by the respective manufacturers. Your plan for monitoring the 510(k) database for any changes should also include a search for any related recalls. The acceptability of the periodic 510(k) database monitoring will be evaluated under the BLA. You will be required to submit any subsequent testing if changes are made to the disposable components. We recommend developing a long-term solution for supply of the disposable administration kit components so that the administration kit does not rely on the market availability of components from manufacturers with which you have no supply agreement.

Regarding the inclusion of the B Braun Perfusor pump, we remind you of our comments provided in response to question 1 of the October 28, 2015 advice letter.

Discussion:

See Sponsor's presentation, slide 4. The Agency reiterated its preference to have letters of authorization from each device constituent manufacturer. FDA noted that in some instances if a device firm did not wish to provide a full letter of authorization for the 510(k), it may be possible for them to provide the necessary information in a separate master file.

In response to questions on whether data may be provided after submission of the BLA, FDA recommends that BioMarin provide its proposal for any sequential submission and timelines. This should be provided to FDA for comment before the BLA is submitted. Since this application is for a new BLA, it will be managed under the PDUFA V Program, and therefore must be submitted as a complete application. The

Agency and Applicant can agree on the late submission (within the first 30 days) of minor components but these late submissions must be discussed and agreed upon prior to the submission of the application.

Post meeting comment:

FDA notes that because the devices are used for intracerebroventricular administration, the sterility assurance data and endotoxin data are of particular importance. In the event that agreements cannot be reached with the device manufacturer(s), or necessary data is not contained within a particular 510(k) submission, then we encourage BioMarin to seek provision of the sterilization validation methods, summary report and data for review in a master file. Visual inspection of the sterile components upon receipt from the manufacturer(s), in addition to data validating the components' sterilization, may be acceptable to assure sterility of the components.

If BioMarin is unable to produce sterilization validation information (via master file or otherwise), then BioMarin would need to reprocess the device components in order to validate sterility. Verification and validation of the final finished combination product device requirements/specifications would be required after any reprocessing of any device constituent parts to ensure that specifications have been maintained. Similarly, the Agency recognizes that device constituent parts may require reprocessing in the event of failed endotoxin testing (b) (4). Without provisions for providing this information the application would not be considered complete upon receipt.

4. Question 4

Does the FDA agree with BioMarin's proposed nomenclature (b) (4)

FDA Response:

(b) (4)

Clinical

5. Question 5

Does the FDA agree that the Clinical package provides an adequate basis for BLA submission?

FDA Response:

Yes, we agree that results of the 190-901, 190-201 and interim data from 190-202 may support a complete submission of a BLA, but whether the data will support approval will be a review issue.

Regulatory

6. Question 6

- a. Does the FDA agree that BMN 190 qualifies for Priority Review?

FDA Response:

We agree that CLN2 is a serious condition and, if approved, BMN 190 may provide a significant improvement over existing therapies. You can submit a priority review designation request at the time of your BLA submission, and we will formally evaluate your request and respond by day 60 of the review.

- b. Will the FDA consider the categorization of this BMN 190 BLA application for Expedited Review per the PDUFA V Program for Enhanced Review Transparency and Communication for Original BLAs?

FDA Response:

See our response to question 6.a, above. If the application is designated as a priority review, FDA review staff and managers will consider whether the marketing application qualifies for an expedited review. CDER staff will consider an expedited review of a marketing application for a breakthrough therapy-designated drug whenever possible.

- c. Does the FDA agree with the proposal to provide a Safety Update in mid-August?

FDA Response:

If an expedited review is planned, providing a Safety Update in mid-August is acceptable, however, for a priority review timeline, you should submit the Safety Update report at 120 days. (See 6b for additional information).

- d. Does FDA agree with the data to be provided in the Safety Update (refer to Section 8.5)?

FDA Response:

Yes, the proposed data to be included in the Safety Update appears acceptable. However, you should also provide updated subject narratives and hyperlinked case report forms for events of special interest (e.g. status epilepticus, hydrocephalus, meningitis, unexpected rapid decline on CLN2 rating scale not attributable to other causes, device related AEs, and immunogenicity related AEs), not just deaths and discontinuations as proposed.

In the event that a patient receiving BMN 190 dies or discontinues the drug due to an AE following submission of your Safety Update, while your BLA is still under review, you should submit SAE reports to the BLA in addition to the IND.

7. Question 7

Does the FDA agree that, based upon the data shared to date, an Advisory Committee is not likely?

FDA Response:

It is premature to determine whether an Advisory Committee meeting is needed. A determination regarding whether an Advisory Committee meeting is needed will be made during the filing review.

8. Question 8

- a. Does the FDA agree with the proposed structure and format of the BLA (see Section 8.3)?

FDA Response:

Please refer to the following recent eCTD guidance document that includes information on the location of combination product information (pages 13-15 and 17) -

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>.

It is acceptable that you submit a Clinical Pharmacology review aid in Module 1.11.4 in lieu of Module 2.7.2. You need to provide information for all relevant sections in the review aid, including but not limited to information on bioanalytical methods and pharmacokinetic (PK) characteristics, and the assessments of exposure-response relationships, immunogenicity, and the impact of immunogenicity on PK, efficacy, and safety.

You should submit design control documentation in addition to the proposed verification matrix to confirm that the device constituent parts meet your essential characteristic requirements. For example, we would expect the submission to include the design requirements documents, risk analysis, and any verification or validation data for the device constituent parts.

Additionally, your briefing package states that you plan to leverage sterility information based on 510(k) clearances. However, complete sterility data may not be contained under 510(k) submissions. Please propose a method of verifying the administration kit component sterility.

- b. Does the FDA agree with the proposed plan to summarize safety from Studies 190-201/202?

FDA Response:

We agree it is acceptable to provide the safety data from all subjects treated in Studies 190-201/202 within the interim Study 202 CSR, in lieu of providing a separate Integrated Summary of Safety in Module 5. We also consider

device related AEs and immunogenicity related AEs to be adverse events of special interest which should be included in the subject narratives. In addition to the proposed narratives, you should provide graphic patient profiles (see also our response to 8c below).

Please clarify how the additional safety data from Study 190-203 will be incorporated into your BLA at the time of your safety update. It may be acceptable to include the narrative portion of adverse events in the Summary of Clinical Safety, given the small number of patients. However, tables, figures, and datasets should be located in Module 5. If the safety data will be split across modules in this way, it is critical that you provide a clear explanation of where the safety data is located.

FDA has a number of relevant Guidance documents which provide additional recommendations on how to construct these summaries, including: **Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document and Guidance for Industry M4E: The CDT – Efficacy.**

<http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

- c. Does the FDA agree with the proposed subject narratives to be included in Module 5?

FDA Response:

We agree with the proposed subject narratives, and the proposed location of subject narratives in Module 5 is acceptable. However, in addition to the subject narratives you should also provide individual graphic patient profiles, as this may help to see the relationships between events by visually showing the timing of each event on a single time axis.

- d. Does the FDA agree with the proposed data tabulations/analysis datasets (see Section 8.4, Table 8.4.1)?

FDA Response:

We agree with your plan to submit the data tabulation datasets and the analysis datasets in the CDISC SDTM format and ADaM format, respectively. However, please refer to the meeting minutes from the teleconference held on 11Mar2016 for specific guidance on all of the statistical analyses, including the requested MMRM analysis. We remind you that the data with the same format in your earlier BTM application will be submitted.

Furthermore, you should provide all of your analysis programs, including those for the primary, the secondary and exploratory analyses. Please also include the study protocols, SAPs, any related amendments, and regulatory correspondence between you and the agency for all of the studies.

- e. Would the FDA be amenable to meeting with BioMarin post-BLA submission to orient the review team to the programs and datasets provided?

FDA Response:

We would be amenable to a meeting with you for purposes of orienting the review team to the content and format of the application. Please contact the regulatory project manager upon receipt of the acknowledgement letter to make arrangements. The meeting should take place within 45 days of submission.

Discussion

See Sponsor's presentation, slide 10 and 11. The Sponsor's proposal is acceptable.

9. Question 9

Does the FDA agree that submission of the videos of the clinical assessments for Studies 190-201 and 190-202 in the BLA is not necessary?

FDA Response:

No, we do not agree. As previously requested, please submit the videos of the clinical assessments for Study 190-201 and 190-202 with your BLA application. Please refer to the Preliminary Comments (dated 11 March 2016).

Please also refer to the Specifications for File Format Types Using eCTD

Specifications for acceptable file types:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf>. You should link the file(s) into the backbone and also provide a PDF file of the video for archival purposes. Video files should not be sent separately to individual reviewers, nor left out of the eCTD backbone. Any files submitted for review should always be linked into the backbone. Sponsor should include the word "video" in the leaf title of the video file, so reviewers can quickly identify the file. If you have additional questions, please contact esub@fda.hhs.gov.

ADDITIONAL FDA COMMENTS

Product Quality Microbiology Questions:

1. Please clarify whether the drug product and the flushing solution are filled on multiple lines.
2. Full evaluation of drug product shipping will be performed during the BLA review cycle. However, as soon as possible please respond to the following comments regarding the container closure integrity study performed (b) (4) (Tables 6.2.5.2 and 6.2.5.3). These responses should be submitted to the IND prior to

submitting the BLA for review and comment in order to facilitate the BLA review process. Additional data may be requested.

- a. Positive controls with smaller breaches (≤ 20 microns) are typically used to demonstrate that the integrity test method is capable of detecting breaches that could allow microbial ingress. Please explain why a positive control with a larger breach size was used for this study.

Discussion:

Sponsor proposed to submit responses to the above comments in the BLA. The Agency agreed.

Product Quality Microbiology Comments:

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

- I. All facilities should be registered with FDA at the time of BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Manufacturing facility information should be included in the BLA (3.2.A) as background information for the pre-license inspections. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.
- II. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The provided information should include, but not be limited to the following:



(b) (4)

III. The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry “*Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*” <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.

- a. Provide the following information in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

(b) (4)

- b. Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

(b) (4)

- c. Provide the following information regarding drug product testing:



Discussion:

See Sponsor's presentation, slide 9. The Agency indicated that it is standard policy to require rabbit pyrogen testing data from three lots of drug product. However, if data from only one lot is submitted with the original BLA, then it may be possible to submit data from the two additional lots post-marketing.

Product Quality Comments:

1. The footnote to table 6.2.4.1 indicates that the (b) (4) has a negligible impact on protein concentration of the vialled drug product. In the BLA provide data from release and stability testing to support this observation.
2. It is not clear as to whether the SDS-PAGE assay is carried out under non-reducing and reducing conditions (b) (4) for purity at release and on stability. Perform the SDS-PAGE assay under both non-reduced and reduced conditions employing the proposed (b) (4) technique for the detection of product- and process-related impurities (b) (4) at release and on stability. Alternatively, provide data in your BLA submission demonstrating that an alternate analytical method can detect the same impurities as either non-reducing or reducing SDS separation method would.

Immunogenicity Comment:

The summary of your immunogenicity studies provided in the pre-BLA meeting package are acknowledged. You selected a cell-based assay that measures anti-drug antibodies (ADA) capable of inhibiting the drug from binding to the cation-independent mannose-6-phosphate receptor (CI-M6PR) as your neutralizing antibody (NAb) assay. While cellular uptake of the drug is critical to the mechanism of action (MoA) of BMN190, the auto-activation of inactive

BMN190 and subsequent enzymatic activity are also critical components of the MoA. The enzymatic activity of BMN190 can potentially be affected by NABs that could either prevent activation of the pro-enzyme to its active, mature form or bind to the catalytic site of the enzyme. In order to fully evaluate the potential neutralization of the product's activity, develop additional assays that can measure the formation of ADAs capable of neutralizing the enzymatic activity of the drug after its uptake into the lysosome. Additionally, because of the relatively high antibody titers observed in the serum, both serum and CSF samples should be tested for the presence of NABs once appropriate assays are available.

Discussion:

The Sponsor agreed to attempt to develop the requested assays. The Agency acknowledged that the information might only be available in the post-marketing phase.

3.0 PEDIATRIC RARE DISEASE PRIORITY REVIEW VOUCHER

There is a possibility that your product may qualify for a Rare Pediatric Disease priority review voucher. If you are interested in pursuing this possibility, please consult the guidance, "Rare Pediatric Disease Priority Review Vouchers, Draft Guidance for Industry" (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf>). Please see section "C" page 13 which describes the process for requesting a voucher. Please note that the requirement to include prevalence estimates is a critical element of the request. Determination of whether an application qualifies for a Rare Pediatric Disease Priority Review Voucher is a review issue and only determined during the review of an NDA or BLA. Please note that the FDA will not issue a Rare Pediatric Disease Priority Review Voucher for marketing applications approved beyond September 30, 2016, the date set by the Bipartisan Budget Act of 2015 (PL 1114-74), unless the program is extended. Therefore, even if all the applicable statutory requirements are satisfied, if the Rare Pediatric Disease Priority Review Voucher program is not extended, a voucher cannot be awarded for marketing applications approved after September 30, 2016.

4.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

Agreements were reached regarding the submission of late components of the application. The following will be submitted via a quality information amendment to the BLA within the 30 days of the original BLA submission:

- Updated stability data (see FDA response to CMC Question 1.b).

- Data for the [REDACTED] (b) (4)
[REDACTED] (see discussion under CMC Question 2).

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

A preliminary discussion on the need for REMS was not held.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

5.0 PREA REQUIREMENTS

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

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

6.0 PRESCRIBING INFORMATION

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

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription*

Drug and Biological Products – Content and Format

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

7.0 SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types:

NDA, ANDA, BLA and Master Files must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

8.0 ABUSE POTENTIAL ASSESSMENT

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

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

9.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

10.0 OFFICE OF SCIENTIFIC INVESTIGATIONS COMMENTS

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

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

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

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

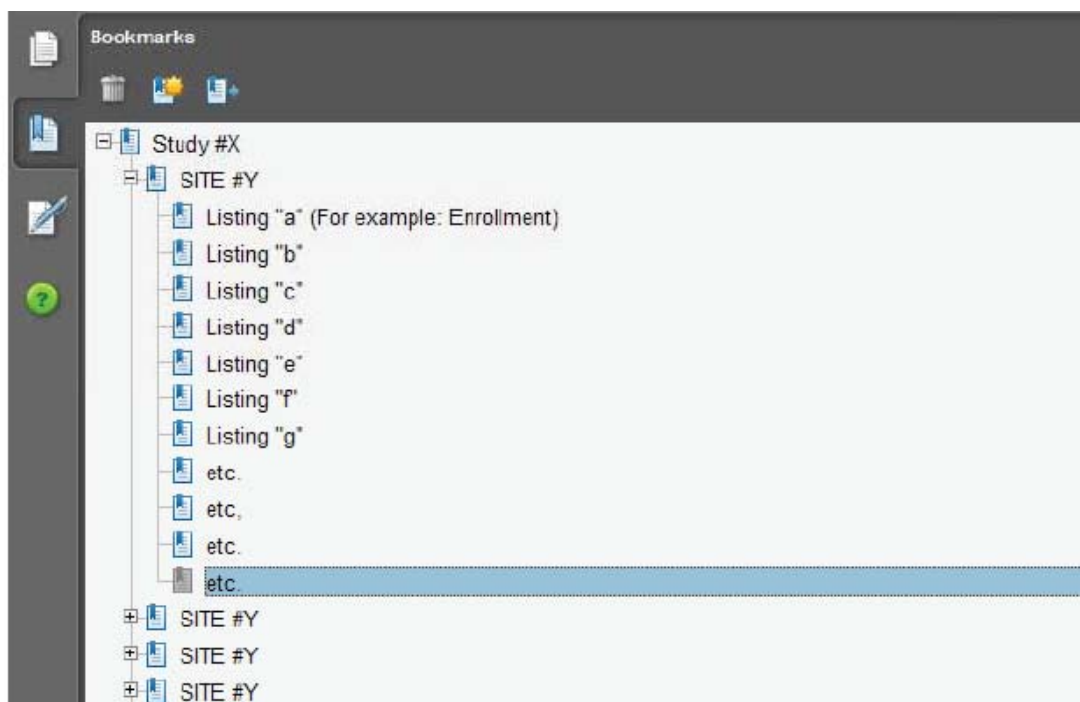
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

- d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

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

Discussion:

See Sponsor's presentation, slide 13. The Sponsor's proposal not to submit Item III for the OSI requests is acceptable.

11.0 Sponsor's Presentation

See attached.

APPEARS THIS WAY ON ORIGINAL

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

/s/

KEVIN B BUGIN
05/09/2016



IND 122472

MEETING MINUTES

BioMarin Pharmaceutical Inc.
Attention: Michelle Fong
Senior Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Fong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cerliponase alfa, BMN 190.

We also refer to the meeting between representatives of your firm and the FDA on March 23, 2016. The purpose of the meeting was to discuss the content of the Clinical and Quality sections of your proposed Biologics License Application (BLA).

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

If you have any questions, call me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin B Bugin, MS, RAC
Chief, Project Management Staff (A)
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING MINUTES

Meeting Type: Type B
Meeting Category: PreBLA

Meeting Date and Time: March 29, 2016, from 2:00 to 3:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 122472
Product Name: cerliponase alfa, BMN 190
Indication: treatment of CLN2
Sponsor/Applicant Name: BioMarin Pharmaceutical Inc

Meeting Chairperson: Laurie Muldowney
Meeting Recorder: Kevin Bugin



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Attendees:

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, MD, Director
Dragos Roman, MD, Associate Director
Laurie Muldowney, MD, Medical Team Leader
Elizabeth Hart, MD, Clinical Reviewer
David Joseph, PhD, Nonclinical Team Leader
Ke Zhang, PhD, Nonclinical Reviewer
Kevin B Bugin, MS, RAC, Chief, Project Management Staff (A)

Office of Clinical Pharmacology

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

Office of Biostatistics

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

Office of Biotechnology Products

Michele Dougherty, PhD, Acting Review Chief
Serge Beaucage, PhD, Quality Team Leader
Jacek Cieslak, PhD, Quality Reviewer
Cristina Ausin, PhD, Acting Quality Team Leader

Office of Product Quality, Office of Process and Facilities, Division of Microbiology
Assessment

Patricia Hughes, PhD, Acting Branch Chief
Colleen Thomas, PhD, Acting Quality Assessment Lead
Natalia Pripuzova, PhD, Quality Microbiology Reviewer

Office of the Commissioner/Office of Special Medical Programs/Office of Combination
Products

Patricia Love, MD, Deputy Director

Center for Devices and Radiological Health/Office of Device Evaluation/General Hospital
Devices Branch

John McMichael, Device Reviewer
CDR Alan Stevens, MS, Acting Branch Chief_____

Sponsor Attendees:

Temitayo Ajayi, M.D., Senior Director, Clinical Sciences
Robert Baffi, Ph.D., Executive Vice President, Technical Operations
Art Blum, Vice President, Regulatory Affairs, CMC
Heather Cahan, M.D., Medical Director, Pharmacovigilance
Jessica Cohen, M.D., Senior Medical Director, Medical Services
Steven Fagliarone, Senior Manager, Regulatory Affairs, Clinical/Nonclinical
Michelle Fong, Senior Director, Regulatory Affairs, Clinical/Nonclinical
Brad Glasscock, Pharm.D., Vice President, Regulatory Affairs, Clinical/Nonclinical
Joshua Henshaw, Ph.D., Senior Scientist II, Pharmacological Sciences
Chito Hernandez, Ph.D., Vice President, Biometrics
Lisa Malandro, Executive Director Regulatory Affairs, Clinical/Nonclinical
Elizabeth Moyle, Senior Director, Regulatory Affairs, Labeling
Sarah Noonberg, M.D., Ph.D., Group Vice President, Global Clinical Development
Charles O' Neill, Ph.D., DABT, Vice President, Pharmacological Sciences
Camilla V. Simpson, Group Vice President, Regulatory Affairs, Regulatory/Pharmacovigilance
Peter Slasor, Sc.D., Director, Biometrics
Victoria Sluzky, Ph.D., Group Vice President, Quality and Process Development
Linda Wilbur, Associate Director, Regulatory Affairs, CMC

(b) (4)

Tessa Verbanic, Associate II, Regulatory Affairs, Clinical/Nonclinical

1.0 BACKGROUND

On January 22, 2016, the Sponsor (BioMarin) submitted a meeting request to discuss the content of the Clinical, Chemistry, Manufacturing and Control sections and the 120-day safety update for a proposed Biologics License Application (BLA) planned for submission in Q2 (May) 2016. The meeting was granted and took place as scheduled on March 29, 2016.

2.0 DISCUSSION

CMC

1. Question 1

- a. Does the FDA agree that long term stability data generated on clinical drug product (both 1 mL and 5 mL extractable volumes) can be used to support the

assignment of expiry for commercial DP with a labeled storage condition of ≤ -15 °C?

FDA Response:

Your proposal appears reasonable, however the use of the long term stability data generated from clinical drug product (DP) lots to support the assignment of expiry for commercial DP would be acceptable if the manufacturing process used to produce the clinical lots is demonstrated to be representative of the commercial manufacturing process. Thus, a final determination on the acceptability of your proposal cannot be made until a review of the data supporting comparability of the manufacturing processes used for the production of clinical and commercial drug product is completed. Additionally, we recommend that your proposed storage condition of ≤ -15 °C for the DP be revised to include upper and lower limits (e.g., -20 ± 5 °C) and provide additional information on the DP shipping temperature and time requirements.

- b. Does the FDA agree that additional stability data can be submitted within 30 days of the BLA submission, without extending the PDUFA action date?

FDA Response:

Yes, we agree.

2. Question 2

Does the FDA agree with BioMarin's proposal to modify the target fill volume for BMN 190 and that additional PPQ validation is not necessary?

FDA Response:

No, we don't agree. You did not provide data supporting the change of the target fill volume to $(b) (4)$ mL. An additional PPQ validation demonstrating your ability to consistently achieve your target fill volume of $(b) (4)$ mL is necessary.

Discussion:

See Sponsor's presentation, slide 6. The Sponsor's proposal to include one drug product PPQ lot and one lot of "flushing solution" with the submission of the BLA, and then one additional lot of "flushing solution" during the first 30 days of filing, is acceptable.

3. Question 3

BioMarin is in discussions with $(b) (4)$ for the disposable components to be co-packaged with BMN 190. If BioMarin is unable to reach agreements, does the FDA agree with our proposal for periodic monitoring and additional testing of the finished devices as described above?

FDA Response:

We strongly recommend reaching agreements with the manufacturers of the administration kit components. If you are unable to reach agreements, your proposal for periodic monitoring and additional testing may be adequate, pending review of the essential performance requirements, release criteria, and testing that you establish for each component. We remind you to address our comments provided in the September 30, 2015 meeting minutes, particularly questions 1 and 6, and also comments provided in our October 28, 2015 advice letter. You will also need to provide a contingency plan for any components that may be discontinued by the respective manufacturers. Your plan for monitoring the 510(k) database for any changes should also include a search for any related recalls. The acceptability of the periodic 510(k) database monitoring will be evaluated under the BLA. You will be required to submit any subsequent testing if changes are made to the disposable components. We recommend developing a long-term solution for supply of the disposable administration kit components so that the administration kit does not rely on the market availability of components from manufacturers with which you have no supply agreement.

Regarding the inclusion of the B Braun Perfusor pump, we remind you of our comments provided in response to question 1 of the October 28, 2015 advice letter.

Discussion:

See Sponsor's presentation, slide 4. The Agency reiterated its preference to have letters of authorization from each device constituent manufacturer. FDA noted that in some instances if a device firm did not wish to provide a full letter of authorization for the 510(k), it may be possible for them to provide the necessary information in a separate master file.

In response to question on whether data may be provided after submission of the BLA, FDA recommends that BioMarin provide its proposal for any sequential submission and timelines. This should be provided to FDA for comment before the BLA is submitted. Since this application is for a new BLA, it will be managed under the PDUFA V Program, and therefore must be submitted as a complete application. The Agency and Applicant can agree on the late submission (within the first 30 days) of minor components but these late submissions must be discussed and agreed upon prior to the submission of the application.

Post meeting comment:

FDA notes that because the devices are used for intracerebroventricular administration, the sterility assurance data and endotoxin data are of particular importance. In the event that agreements cannot be reached with the device manufacturer(s), or necessary data is not contained within a particular 510(k) submission, then we encourage BioMarin to seek provision of the sterilization validation methods, summary report and data for review in a master file. Visual inspection of the sterile components upon receipt from the manufacturer(s), in addition

to data validating the components' sterilization, may be acceptable to assure sterility of the components.

If BioMarin is unable to produce sterilization validation information (via master file or otherwise), then BioMarin would need to reprocess the device components in order to validate sterility. Verification and validation of the final finished combination product device requirements/specifications would be required after any reprocessing of any device constituent parts to ensure that specifications have been maintained. Similarly, the Agency recognizes that device constituent parts may require reprocessing in the event of failed endotoxin testing [REDACTED] (b) (4). Without provisions for providing this information the application would not be considered complete upon receipt.

4. Question 4

Does the FDA agree with BioMarin's proposed nomenclature [REDACTED] (b) (4)

FDA Response:

[REDACTED] (b) (4)

Clinical

5. Question 5

Does the FDA agree that the Clinical package provides an adequate basis for BLA submission?

FDA Response:

Yes, we agree that results of the 190-901, 190-201 and interim data from 190-202 may support a complete submission of a BLA, but whether the data will support approval will be a review issue.

Regulatory

6. Question 6

a. Does the FDA agree that BMN 190 qualifies for Priority Review?

FDA Response:

We agree that CLN2 is a serious condition and, if approved, BMN 190 may provide a significant improvement over existing therapies. You can submit a priority review designation request at the time of your BLA submission, and we will formally evaluate your request and respond by day 60 of the review.

- b. Will the FDA consider the categorization of this BMN 190 BLA application for Expedited Review per the PDUFA V Program for Enhanced Review Transparency and Communication for Original BLAs?

FDA Response:

See our response to question 6.a, above. If the application is designated as a priority review, FDA review staff and managers will consider whether the marketing application qualifies for an expedited review. CDER staff will consider an expedited review of a marketing application for a breakthrough therapy-designated drug whenever possible.

- c. Does the FDA agree with the proposal to provide a Safety Update in mid-August?

FDA Response:

If an expedited review is planned, providing a Safety Update in mid-August is acceptable, however, for a priority review timeline, you should submit the Safety Update report at 120 days. (See 6b for additional information).

- d. Does FDA agree with the data to be provided in the Safety Update (refer to Section 8.5)?

FDA Response:

Yes, the proposed data to be included in the Safety Update appears acceptable. However, you should also provide updated subject narratives and hyperlinked case report forms for events of special interest (e.g. status epilepticus, hydrocephalus, meningitis, unexpected rapid decline on CLN2 rating scale not attributable to other causes, device related AEs, and immunogenicity related AEs), not just deaths and discontinuations as proposed.

In the event that a patient receiving BMN 190 dies or discontinues the drug due to an AE following submission of your Safety Update, while your BLA is still under review, you should submit SAE reports to the BLA in addition to the IND.

7. Question 7

Does the FDA agree that, based upon the data shared to date, an Advisory Committee is not likely?

FDA Response:

It is premature to determine whether an Advisory Committee meeting is needed. A determination regarding whether an Advisory Committee meeting is needed will be made during the filing review.

8. Question 8

- a. Does the FDA agree with the proposed structure and format of the BLA (see Section 8.3)?

FDA Response:

Please refer to the following recent eCTD guidance document that includes information on the location of combination product information (pages 13-15 and 17) -

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>.

It is acceptable that you submit a Clinical Pharmacology review aid in Module 1.11.4 in lieu of Module 2.7.2. You need to provide information for all relevant sections in the review aid, including but not limited to information on bioanalytical methods and pharmacokinetic (PK) characteristics, and the assessments of exposure-response relationships, immunogenicity, and the impact of immunogenicity on PK, efficacy, and safety.

You should submit design control documentation in addition to the proposed verification matrix to confirm that the device constituent parts meet your essential characteristic requirements. For example, we would expect the submission to include the design requirements documents, risk analysis, and any verification or validation data for the device constituent parts.

Additionally, your briefing package states that you plan to leverage sterility information based on 510(k) clearances. However, complete sterility data may not be contained under 510(k) submissions. Please propose a method of verifying the administration kit component sterility.

- b. Does the FDA agree with the proposed plan to summarize safety from Studies 190-201/202?

FDA Response:

We agree it is acceptable to provide the safety data from all subjects treated in Studies 190-201/202 within the interim Study 202 CSR, in lieu of providing a separate Integrated Summary of Safety in Module 5. We also consider device related AEs and immunogenicity related AEs to be adverse events of special interest which should be included in the subject narratives. In addition to the proposed narratives, you should provide graphic patient profiles (see also our response to 8c below).

Please clarify how the additional safety data from Study 190-203 will be incorporated into your BLA at the time of your safety update. It may be acceptable to include the narrative portion of adverse events in the Summary

of Clinical Safety, given the small number of patients. However, tables, figures, and datasets should be located in Module 5. If the safety data will be split across modules in this way, it is critical that you provide a clear explanation of where the safety data is located.

FDA has a number of relevant Guidance documents which provide additional recommendations on how to construct these summaries, including: Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document and Guidance for Industry M4E: The CDT – Efficacy. <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

- c. Does the FDA agree with the proposed subject narratives to be included in Module 5?

FDA Response:

We agree with the proposed subject narratives, and the proposed location of subject narratives in Module 5 is acceptable. However, in addition to the subject narratives you should also provide individual graphic patient profiles, as this may help to see the relationships between events by visually showing the timing of each event on a single time axis.

- d. Does the FDA agree with the proposed data tabulations/analysis datasets (see Section 8.4, Table 8.4.1)?

FDA Response:

We agree with your plan to submit the data tabulation datasets and the analysis datasets in the CDISC SDTM format and ADaM format, respectively. However, please refer to the meeting minutes from the teleconference held on 11Mar2016 for specific guidance on all of the statistical analyses, including the requested MMRM analysis. We remind you that the data with the same format in your earlier BTM application will be submitted.

Furthermore, you should provide all of your analysis programs, including those for the primary, the secondary and exploratory analyses. Please also include the study protocols, SAPs, any related amendments, and regulatory correspondence between you and the agency for all of the studies.

- e. Would the FDA be amenable to meeting with BioMarin post-BLA submission to orient the review team to the programs and datasets provided?

FDA Response:

We would be amenable to a meeting with you for purposes of orienting the review team to the content and format of the application. Please contact the regulatory project manager upon receipt of the acknowledgement letter to make arrangements. The meeting should take place within 45 days of submission.

Discussion

See Sponsor's presentation, slide 10 and 11. The Sponsor's proposal is acceptable.

9. Question 9

Does the FDA agree that submission of the videos of the clinical assessments for Studies 190-201 and 190-202 in the BLA is not necessary?

FDA Response:

No, we do not agree. As previously requested, please submit the videos of the clinical assessments for Study 190-201 and 190-202 with your BLA application. Please refer to the Preliminary Comments (dated 11 March 2016).

Please also refer to the Specifications for File Format Types Using eCTD Specifications for acceptable file

types: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf>. You should link the file(s) into the backbone and also provide a PDF file of the video for archival purposes. Video files should not be sent separately to individual reviewers, nor left out of the eCTD backbone. Any files submitted for review should always be linked into the backbone. Sponsor should include the word "video" in the leaf title of the video file, so reviewers can quickly identify the file. If you have additional questions, please contact esub@fda.hhs.gov.

ADDITIONAL FDA COMMENTS

Product Quality Microbiology Questions:

1. Please clarify whether the drug product and the flushing solution are filled on multiple lines.
2. Full evaluation of drug product shipping will be performed during the BLA review cycle. However, as soon as possible please respond to the following comments regarding the container closure integrity study performed for [REDACTED] (b) (4) (Tables 6.2.5.2 and 6.2.5.3). These responses should be submitted to the IND prior to

submitting the BLA for review and comment in order to facilitate the BLA review process. Additional data may be requested.

- a. Positive controls with smaller breaches (≤ 20 microns) are typically used to demonstrate that the integrity test method is capable of detecting breaches that could allow microbial ingress. Please explain why a positive control with a larger breach size was used for this study.

Product Quality Microbiology Comments:

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

- I. All facilities should be registered with FDA at the time of BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Manufacturing facility information should be included in the BLA (3.2.A) as background information for the pre-license inspections. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.
- II. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The provided information should include, but not be limited to the following:



- III. The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry “*Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*” <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.



- b. Provide information and validation data summaries in Section 3.2.P.3.5 for the following:



- c. Provide the following information regarding drug product testing:

Discussion:

See Sponsor's presentation, slide 9. The Agency indicated that it is standard policy to require rabbit pyrogen testing data from three lots of drug product. However, if data from only one lot is submitted with the original BLA, then it may be possible to submit data from the two additional lots post-marketing.

Product Quality Comments:

1. The footnote to table 6.2.4.1 indicates that the (b) (4) has a negligible impact on protein concentration of the vialled drug product. In the BLA provide data from release and stability testing to support this observation.
2. It is not clear as to whether the SDS-PAGE assay is carried out under non-reducing and reducing conditions (b) (4) for purity at release and on stability. Perform the SDS-PAGE assay under both non-reduced and reduced conditions employing the proposed (b) (4) technique for the detection of product- and process-related impurities (b) (4) at release and on stability. Alternatively, provide data in your BLA submission demonstrating that an alternate analytical method can detect the same impurities as either non-reducing or reducing SDS separation method would.

Immunogenicity Comment:

The summary of your immunogenicity studies provided in the pre-BLA meeting package are acknowledged. You selected a cell-based assay that measures anti-drug antibodies (ADA) capable of inhibiting the drug from binding to the cation-independent mannose-6-phosphate receptor (CI-M6PR) as your neutralizing antibody (NAb) assay. While cellular uptake of the drug is critical to the mechanism of action (MoA) of BMN190, the auto-activation of inactive BMN190 and subsequent enzymatic activity are also critical components of the MoA. The

enzymatic activity of BMN190 can potentially be affected by NABs that could either prevent activation of the pro-enzyme to its active, mature form or bind to the catalytic site of the enzyme. In order to fully evaluate the potential neutralization of the product's activity, develop additional assays that can measure the formation of ADAs capable of neutralizing the enzymatic activity of the drug after its uptake into the lysosome. Additionally, because of the relatively high antibody titers observed in the serum, both serum and CSF samples should be tested for the presence of NABs once appropriate assays are available.

Discussion:

The Sponsor agreed to attempt to develop the requested assays. The Agency acknowledged that the information might only be available in the post-marketing phase.

3.0 PEDIATRIC RARE DISEASE PRIORITY REVIEW VOUCHER

There is a possibility that your product may qualify for a Rare Pediatric Disease priority review voucher. If you are interested in pursuing this possibility, please consult the guidance, "Rare Pediatric Disease Priority Review Vouchers, Draft Guidance for Industry" (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf>). Please see section "C" page 13 which describes the process for requesting a voucher. Please note that the requirement to include prevalence estimates is a critical element of the request. Determination of whether an application qualifies for a Rare Pediatric Disease Priority Review Voucher is a review issue and only determined during the review of an NDA or BLA. Please note that the FDA will not issue a Rare Pediatric Disease Priority Review Voucher for marketing applications approved beyond September 30, 2016, the date set by the Bipartisan Budget Act of 2015 (PL 1114-74), unless the program is extended. Therefore, even if all the applicable statutory requirements are satisfied, if the Rare Pediatric Disease Priority Review Voucher program is not extended, a voucher cannot be awarded for marketing applications approved after September 30, 2016.

4.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

No agreements were reached regarding the submission of late components of the application. The application is expected to be submitted in its complete form.

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

A preliminary discussion on the need for REMS was not held.

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

to submit a complete application and therefore, there are no agreements for late submission of application components.

5.0 PREA REQUIREMENTS

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

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

6.0 PRESCRIBING INFORMATION

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

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

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

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

7.0 SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

8.0 ABUSE POTENTIAL ASSESSMENT

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

9.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

10.0 OFFICE OF SCIENTIFIC INVESTIGATIONS COMMENTS

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

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

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

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

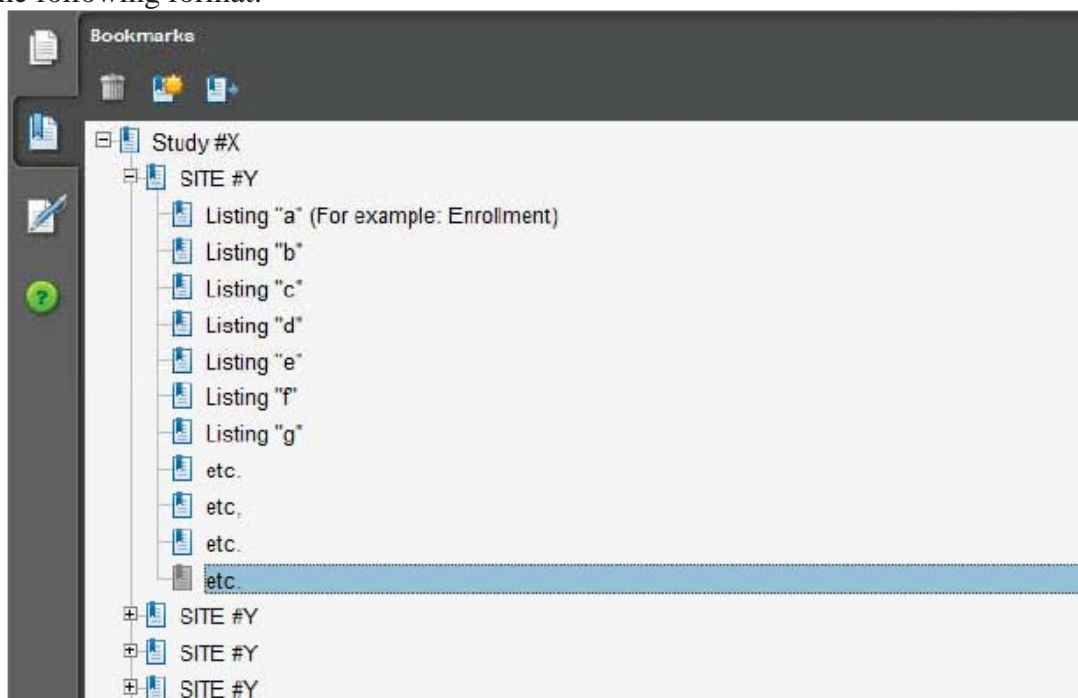
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing

Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

APPEARS THIS WAY ON ORIGINAL

Attachment 1

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

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

Discussion:

See Sponsor's presentation, slide 13. The Sponsor's proposal not to submit Item III for the OSI requests is acceptable.

11.0 Sponsor's Presentation

See attached.

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

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

/s/

KEVIN B BUGIN
04/20/2016



IND 122472

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

BioMarin Pharmaceutical
Attention: Michelle Fong
Senior Director, Regulatory Affairs
105 Digital Drive
Novato, CA 91949

Dear Ms. Fong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMN 190.

We also refer to your July 1, 2015, request for Breakthrough Therapy designation and your submissions dated July 24 and 31; August 13 and 21, 2015. We have reviewed your request and have determined that BMN 190 for the treatment of patients with CLN2 disease meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of BMN 190 for the treatment of patients with CLN2 disease to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting². Please refer to the *Guidance for Industry: Formal Meetings*

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

²

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

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

If the breakthrough therapy designation for BMN190 for the treatment of patients with CLN2 disease is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

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

Sincerely,

{See appended electronic signature page}

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

³ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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

/s/

DRAGOS G ROMAN

08/27/2015

Signing on behalf of Dr. Griebel

Benton, Sandra J

From: Benton, Sandra J
Sent: Wednesday, August 26, 2015 5:02 PM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa; Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Bugin, Kevin; Pitt, Lisa; Hart, Elizabeth; Muldowney, Laurie; Mulberg, Andrew; Griebel, Donna; Roman, Dragos
Subject: RE: August 28, 2015 Medical Policy Council – Breakthrough Therapy Designation - IND 122472

As the Council agrees with DGIEP's recommendation to grant BioMarin's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the August 28, 2015 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

From: Benton, Sandra J
Sent: Friday, August 21, 2015 3:22 PM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa; Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Bugin, Kevin; Pitt, Lisa; Hart, Elizabeth; Muldowney, Laurie; Mulberg, Andrew; Griebel, Donna; Roman, Dragos
Subject: August 28, 2015 Medical Policy Council – Breakthrough Therapy Designation - IND 122472

Hi! OMP has scheduled a Medical Policy Council discussion on August 28, 2015 regarding the breakthrough therapy designation request from BioMarin for its IND 122472, BMN 190 (cerliponase alpha) for the treatment of patients with Neuronal Ceroid Lipofuscinosis type 2 (CLN2) disease or TPP1 deficiency.

DGIEP recommends that this breakthrough therapy request be granted. Attached is DGIEP's background on the breakthrough therapy designation with its rationale for granting the request.

DGIEP has asked if this request can be reviewed by email.

Please note that this request was previously presented to the Council in April 2015 and the Council agreed with DGIEP to deny

(http://sharepoint.fda.gov/orgs/cdermedpolcouncil/FDASIA%20Breakthrough%20Therapy/April%2020%202015%20-%20Breakthrough%20Therapy%20Designation%20-%20IND%20122472%20cerliponase%20alfa/20150420_Medical%20Policy%20Council%20_BT%20Request_IND%20122472%20minutes.pdf; it is the second request).

Would you please review DGIEP's recommendation and let me know by COB Wednesday, August 26, 2015 if –

- You agree with DGIEP's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DGIEP's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DGIEP's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for this IND.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: BMN 190 August 2015 CDER-MPC FINAL version.doc >> << File: 122472 BTDR in Type C 01July2015.pdf >>

CDER Breakthrough Therapy Designation Determination Review Template

IND	122472
Request Receipt Date	July 2, 2015
Product	BMN 190 (cerliponase alpha)
Indication	Treatment of patients with Neuronal Ceroid Lipofuscinosis type 2 (CLN2) disease or TPP1 deficiency
Drug Class/Mechanism of Action	Enzyme replacement therapy
Sponsor	BioMarin
ODE/Division	ODE III/Division of Gastrointestinal and Inborn Errors Products
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	August 30, 2015 is the 60 day goal date which is a Sunday, so the goal date will be August 28, 2015

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

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

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

Treatment of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

YES NO

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

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

YES NO

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

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

YES the BTDR is adequate and sufficiently complete to permit a substantive review

Undetermined

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

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

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

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

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

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

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: { See appended electronic signature page }

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

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

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

BMN 190 is an enzyme replacement therapy (ERT) with the active ingredient of recombinant human tripeptidyl peptidase-1 (rhTPP1). BMN 190 is administered as an inactive proenzyme, and activated following lysosomal uptake by cells. Enzymatic activity is restricted to the lysosome where BMN 190 degrades accumulated storage materials. It is administered via an intra-cerebroventricular (ICV) catheter that has been surgically implanted.

CLN2 is a rare genetic disease with an estimated incidence in the U.S. of 0.5-1/100,000 births. It is caused by mutations in the CLN2 gene that encodes the lysosomal exopeptidase tripeptidyl peptidase 1 (TPP1), which is involved in protein catabolism and is responsible for cleaving 3-amino acid fragments from the N-terminus of small polypeptides. Deficiency of TPP1 leads to accumulation and storage of proteinaceous material in the

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

lysosomes. The phenotype of CLN2 is that of progressive neurological deterioration. The disease is inevitably fatal.

CLN2 most commonly presents as a late infantile form, but both a more accelerated infantile form and a more attenuated juvenile form of this disease have been described.(Kousi 2012) The classic late infantile form usually presents with seizures between 2 and 4 years of age, although some children present with speech delay during this same time period. Subsequently, motor skills, speech, vision and cognition decline leaving children blind, non-verbal, non-ambulatory, with dementia and severe bulbar dysfunction ultimately progressing to a vegetative state. Death usually occurs between 8 and 15 years of age.

The Sponsor is proposing BMN 190 as therapy for individuals with all stages of CLN2. There is no currently approved therapy for CLN2.

BMN 190 was granted orphan drug designation for the treatment of CLN2 on April 1, 2013. The Sponsor began conducting a Phase 1/2 open-label label study (Study 201) outside the United States in 2013. On March 7, 2013, the Sponsor submitted BMN190 under IND (b) (4) but subsequently withdrew this IND due to (b) (4). The Sponsor resubmitted under IND 122472 on July 9, 2014, and Study 201 began enrolling in the United State in December 2014.

The Sponsor initially submitted a request for breakthrough therapy designation on 2/27/2015 based on the preliminary results from Study 201, a Phase 1/2 open-label, single arm study. Breakthrough therapy was denied at that time based on inadequate data to indicate substantial improvement compared to the natural history of CLN2. Specific limitations of the data presented were identified as:

- Data for 9 subjects treated with BMN-190 reflect a short duration (9-12 months) of exposure. The analytical methods used to compare these preliminary data to historical controls do not provide preliminary clinical evidence that treatment with BMN-190 may demonstrate substantial improvement.
- Limitations in the rating scales used to obtain the clinical data presented in the Breakthrough Request including that in the scale used for the ongoing study, the domain elements were modified (two domains were left out and the remaining 2 domains used slightly different definitions). Furthermore, no rationale was provided for the modifications made.
- The natural history data included retrospective data in which outcomes were obtained from interviews of parents, relying on their recall. The absence of structured assessments raised questions about the validity of the reported outcomes.

On 5/20/2015, the Division met with the Sponsor and discussed the concerns that led to denial of Breakthrough Therapy Designation. The Sponsor agreed to provide additional data to address these concerns and submit a new meeting request/briefing document for a subsequent Type C meeting with a new Breakthrough Therapy Request. This briefing document represents a summary of the updated information provided by the Sponsor. See responses to questions 7A and 10A for details regarding the new information presented.

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

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

The primary efficacy endpoint considered by the sponsor as supporting the BTDR is a comparison of the rate of decline of motor and language function in a Phase 1/2 open-label study, scaled to a 48 week time period, compared to the rate of decline from a natural history dataset.

The CLN2 disease specific rating scale used in the Phase 1/2 study combines components of the motor/gait and language domains from the Hamburg clinical scale developed for CLN2 (original scale also includes domains for vision and seizures), however, the language is slightly modified and anchor point definitions were added for subscores within these domains. Within each domain a score of 0 to 3 is assigned, and overall scores are calculated by summing the two domains for a final rating of 0 (severely impaired) to 6 (normal).

Results obtained with this rating scale were compared to natural history data, which are derived from 29 German and Swiss children with CLN2 who were evaluated longitudinally. Disease severity in the natural history cohort was assessed using the Hamburg Scale, with the motor and language domains used for comparison to the treatment study.

The Division previously expressed concerns related to limitations in the rating scales used to obtain the clinical data presented in the Breakthrough Request. Specifically, in the scale used for the ongoing study, the domain elements were modified (two domains were left out and the remaining 2 domains used slightly different definitions). Furthermore, no rationale was provided for the modifications made.

At the Division’s request, in the current submission, the Sponsor clarified the differences between the 2 scales (See Table 1 provided by the Sponsor) and explained modifications that were made in order to provide anchor points for a multi-center trial (the original Hamburg Scale was developed for single-center use). While anchor points were not defined in the original Hamburg scale, prospective assessments were made by a consensus of at least 2 investigators who independently examined the patients, and the Sponsor contends there was never any discordance between the raters. Since the 190-201 study is a multi-center trial with multiple raters, anchor points were formulated by the senior physician who developed the original Hamburg rating scale. (b) (4)

Table 1. Differences between Hamburg and Adapted Hamburg Scale

Domain	Score	Hamburg Scale (190-901)	Adapted Hamburg Scale (190-201)	Rationale for Modifications
Motor	3	Walks normally	Grossly normal gait	Clarification
	2	Frequent falls, obvious clumsiness	Abnormal gait; independent ≥ 10 steps Frequent falls, obvious clumsiness	Added “step” criteria to clarify and harmonize the definition of gait changes across sites/investigators.
	1	No unaided walking or crawling only	No unaided walking or crawling only	No changes
	0	Immobile, mostly bedridden	Immobile, mostly bedridden	No changes
Language	3	Normal	Grossly normal	Clarification
	2	Recognizably abnormal	Has become recognizably abnormal (worse than the individual maximum)	Added the language baseline definition to loss of function
	1	Hardly understandable	Hardly understandable	No changes
	0	Unintelligible or no language	Unintelligible or no language	No changes

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

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

There is no regulatory precedent for endpoints established to support approval for this indication. The Division agrees with the Sponsor that the CLN2 rating scale represents clinically meaningful functional outcomes in this condition.

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

There are no known biomarkers for this indication.

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

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There is no approved therapy available for CLN2. The only available treatment is geared towards symptomatic relief and palliative care.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

BMN 190 is the only drug requesting breakthrough therapy designation.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

The Sponsor has submitted preliminary data from 9 subjects treated every other week for at least 36 weeks enrolled in study 190-201, the ongoing phase 1/2, single-arm, open label trial. Data from these subjects is compared to data from study 190-901, a single arm, natural history study of both prospective and retrospective data from 29 children with CLN2.

The Division previously expressed concerns because the natural history data included retrospective data in which outcomes were obtained from interviews of parents, relying on their recall. The absence of structured assessments raised questions about the validity of the reported outcomes.

At the Division's request, in the current submission, the Sponsor compared the rate of decline in the natural history data obtained prospectively with the natural history data as a whole (including that obtained retrospectively from patient and clinician interviews and medical records). The results showed no significant differences. In addition, the Sponsor conducted a more conservative analysis of the natural history data using a Mixed Effect Model for Repeated Measuring carrying observations forward when there was not a new measurement every 6 months, and this did not dramatically change the rate of decline in the control group.

The Division previously expressed concerns over the analytical methods used to compare these preliminary data to historical controls and asked the Sponsor to provide a new efficacy analysis based on conservative assumptions.

At the Division's request, in the current submission, the Sponsor performed a conservative analysis, comparing each of the 9 treated subjects to natural history subjects matched for baseline CLN2 score and age when available. In conducting this comparison, the Sponsor no longer time-adjusted the control data, but rather used the maximum amount of time that natural history subjects were at the matched score, assuming that the decline happened on the day that the decline was documented even though the observation period for controls was less frequent than for treated subjects. These data have been summarized by the clinical reviewer in Table 2.

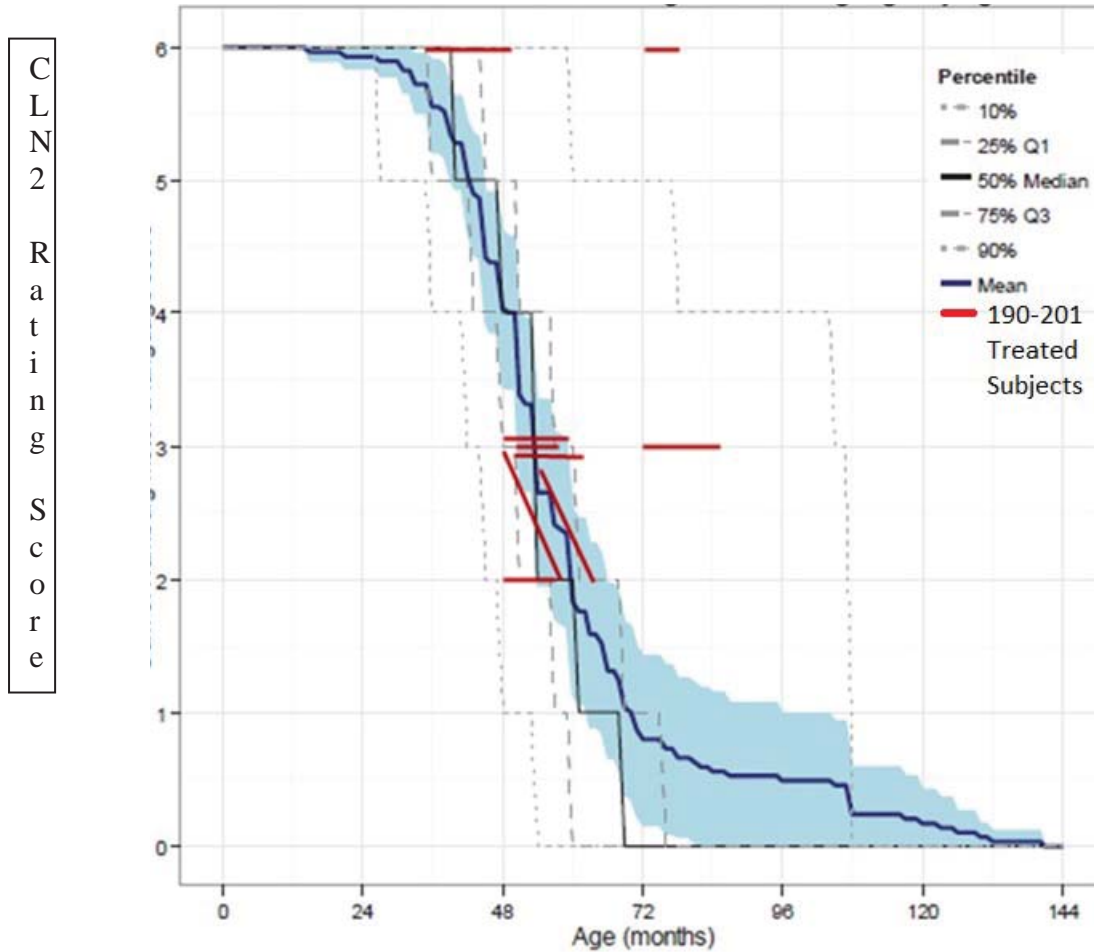
Table 2.**Summary of CLN2 Decline in Treated Subjects Compared to Natural History Subjects**

Subject (treated with BMN 190)	Treated Subject better than Hamburg control matched for age & baseline score	Treated Subject better than Hamburg control matched for baseline score
1244-1001 (4yo; CLN2 BL3)	Yes for 9/9 controls (100%)	Yes, for 18/18 controls (100%)
1244-1002 (6yo; CLN2 BL 3)	NA, no controls	Yes, for 18/18 controls (100%)
1244-1003 (3yo; CLN2 BL 6)	Yes for 10/12 controls (83%)	Yes for 10/12 controls (83%)
1244-1004 (6yo; CLN2 BL 3)	NA, no controls	Yes for 18/18 controls (100%)
1244-1006 (4yo; CLN2 BL 3)	Yes for 9/9 controls (100%)	Yes for 16/18 controls (89%)
1287-1005 (4yo; CLN2 BL 3)	Yes for 9/9 controls (100%)	Yes for 9/9 controls (100%)
1244-1008 (4yo; CLN2 BL 2)	Yes, 8/12 controls (67%)	Yes for 17/22 controls (77%)
1244-1009 (4yo; CLN2 BL 3)	Yes for 8/9 controls (89%)	Yes for 16/18 controls (89%)
1244-1010 (6yo; CLN2 BL 6)	NA, no controls	Yes for 9/12 controls (75%)

The Sponsor also separately analyzed the 7 treated subjects who have already started to decline (e.g. baseline scores less than 6). In our opinion, this represents a more conservative and appropriate population for comparison, as it avoids attributing lack of initial decline to the treatment, since natural history data indicates significant variability exists regarding the age at initial motor/verbal decline. Adjusting the rate of decline to 48 weeks, the median rate in the 29 control subjects is 1.87 units compared to 0 units in the 7 treated subjects with CLN2 scores less than 6. The median and 95th percent confidence intervals for combined language and motor/gait CLN2 score difference between the treated and untreated subjects was 1.85 units and 1.3-2.4 units, respectively; which appears to be a substantial difference between the treated and untreated subjects.

The difference between the treated subjects and the controls is depicted visually in Graph 1, which was made by the clinical review team. It depicts the change in combined gait/language CLN2 score for the treated subjects in red superimposed over the Sponsor's regression analysis of the relationship between combined motor and language CLN2 score and age from the natural history subjects. Based on technical graphing limitations, duration is approximated. Change in scores for treated subjects represents the linear decline from baseline to the final recorded assessment assuming an average linear decline. Based on the data provided by the Sponsor, we were unable to determine the exact age in months when the decline occurred. Nonetheless, based on this conservative analysis of the data presented, treatment with BMN-190 appears to slow decline and stabilize progression of verbal and motor decline in CLN2.

Graph 1. Progression of Treated Subjects Superimposed on Natural History Data



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

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation*

The Division believes that the data provided in the current submission represent preliminary evidence of clinical effectiveness. Compared to our review of the Sponsor’s initial submission for breakthrough therapy designation, we have increased confidence in the natural history data. The Sponsor has conducted sensitivity analyses that were reviewed by our statisticians and do not appear to show a substantive difference in the rate of decline between the prospectively collected data and the natural history data as a whole. In addition, the Sponsor conducted a more conservative analysis of the natural history data using a Mixed Effect Model for Repeated Measuring carrying observations forward when there was not a new measurement every 6 months, and this did not dramatically change the rate of decline

in the control group. With this more conservative analysis there was still a marked difference between the treated subjects and the controls, the confidence intervals for rate of decline did not overlap between the treated subjects and the natural history controls.

The greatest weakness of the study remains that 190-201 does not include a concurrent control group in whom blinded observations were performed using the exact same scale. The data from the historical control group continues to be limited as it includes a lot of retrospective data going back over three decades, however, the rate of decline in prospectively collected data appears similar to that observed for retrospectively collected data.

A final limitation of the data provided for breakthrough designation is that it only includes a small number of subjects who have been treated for a limited duration. However, based on the rate of decline from the more conservative natural history study, a greater than 1 point decline would be expected in each treated subject, and this was not observed. As CLN2 is an orphan disease, the division believes that data from these 9 subjects (and particularly the 7 subjects with CLN2 scores less than 6) represent adequate preliminary evidence of effectiveness to grant breakthrough therapy designation.

This recommendation is not negatively affected by safety data. Prior to allowing this IND to proceed and the enrollment of U.S. subjects, treatment related adverse events including hypersensitivity reactions and complications related to ICV device were reported. Hypersensitivity reactions are commonly seen with the approved ERTs, but have not required dose adjustments or discontinuation in this trial. To date, there has been a single report of a grade 3 intra-cerebral hemorrhage associated with the implantation of the ICV. Additional risks related to infection and death from the ICV are included in the consent form, but have not occurred in the context of the trial. The risks associated with the ICV will be included in the benefit-risk analysis for the BLA, but should not prevent granting of breakthrough therapy designation for BMN 190 to treat CLN2, a devastating and lethal pediatric disease with no available therapy.

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

GRANT :

Provide brief summary of rationale for granting:

CLN2 leads to rapid progressive deterioration in verbal and motor abilities, which represent clinically significant morbidities to patients and their families. There is preliminary evidence from 9 children treated with BMN 190 for at least 36 weeks that the drug slows decline in verbal and motor skills compared to natural history controls. The average rate of decline in the treated subjects was 0 units/48 weeks compared to 1.6 units/48 weeks in the natural history controls using conservative analysis assumptions. Each treated subjects did better than 67-100% of the age and baseline CLN2 matched natural history subjects even when using conservative assumptions. This preliminary clinical data combined with a biologically plausible rationale for the effectiveness of the drug constitutes adequate data to grant breakthrough therapy designation.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

DENY:

Provide brief summary of rationale for denial: N/A

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for

traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why.

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

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

The division has a face-to-face meeting scheduled with the Sponsor on 9/15/15 to discuss the data needed for a BLA submission and another meeting on 9/30/15 to discuss issues related to the device and marketing as a combination product. Although the Division believes that there are adequate data to grant breakthrough therapy at this time, we do not believe that these data are adequate for a BLA submission. Specifically, the Sponsor needs to further demonstrate comparability between the Sponsor's modification to the Hamburg rating scales. We will revisit with the Sponsor whether additional higher-quality control data are available (e.g. from another longitudinal natural history study that is currently underway). Additionally, the Sponsor needs to further analyze their natural history data to demonstrate the assumption of linear decline is appropriate and revisit analytical methods if this assumption is incorrect. This analysis of variability will further inform our advice to the Sponsor regarding duration of therapy and number of subjects anticipated to be needed for a BLA submission.

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

This is not applicable as the Division recommends granting breakthrough designation at this time.

13. List references, if any:

- Kousi et al. "Update of the mutation spectrum and clinical correlations of over 360 mutations in eight genes that underlie the neuronal ceroid lipofuscinosis." Hum Mutations 33[1], 42-63. 2012.
- Sondhi et al. "Feasibility of gene therapy for late neuronal ceroid lipofuscinosis." Arch Neurol 58, 1793-1798. 2001.
- Steinfield et al. "Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations." Am J Med Genetics 112[4], 347-354. 2002.
- Worgall et al. "Neurological deterioration in late infantile neuronal ceroid lipofuscinosis." Neurology 69[6], 521-535. 2007.

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

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

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

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

APPEARS THIS WAY ON ORIGINAL

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

/s/

SANDRA J BENTON
08/27/2015

DONNA J GRIEBEL
08/27/2015

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Gastroenterology and Inborn Errors Products
Date of MPC Meeting: April 20, 2015

1. **IND #:** 122472

2. **Sponsor:** Biomarin

3. **Drug:** BMN 190 (cerliponase alfa)

4. **Proposed Indication:** Treatment of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)

5. **Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition?** Yes. CLN2, a form of Batten Disease, is a progressive neurodegenerative disease that results in death in mid to late childhood.

6. **Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints?**

No. Although the preliminary data from an interim analysis of the ongoing trial suggest that 9 subjects (ranging in age from 3-6 years) on BMN 190 do not appear to have *deterioration* in their language and motor/gait scores over ~9 months, based on the Division's interpretation of the natural history data provided by the sponsor, the data do not represent adequate preliminary clinical evidence that there is a substantial improvement with BMN 190 treatment compared to the natural history of CLN2.

Accordingly, the Division has the following concerns that will be discussed with the sponsor at an upcoming industry meeting:

- The treatment duration of 9 months is too short to observe a substantial improvement with BMN 190 treatment.
- The clinical outcome rating scale the Sponsor used to measure deterioration in this disorder is inadequate. Content validity, inter-rater and intra-rater reliability have not been established, and on its face, the scale has elements that may not be readily interpretable.
- This is an open-label trial with subjective endpoints evaluated by un-blinded evaluators.
- The natural history data include assessments based on parental recall (spanning years) and do not account for potentially large confounders present in this disease, e.g., age.
- The analytical methods employed by the Sponsor for comparison to natural history data appear methodologically flawed, e.g., the scales used to assess treatment effect in prospectively treated BMN 190 subjects vs. natural history controls are not the same.

DGIEP intends to engage the sponsor in discussions to clarify and resolve these issues prior to submission of the BLA. A face-to-face meeting has been requested by the Sponsor and is scheduled for May 20, 2015.

Division: Gastroenterology and Inborn Errors Products (DGIEP)

Medical Officer: Elizabeth Hart, M.D.

Clinical Team Leader: Robert Fiorentino, M.D., M.P.H.

1. Brief description of the drug

BMN 190 is an enzyme replacement therapy (ERT) with the active ingredient of recombinant human tripeptidyl peptidase-1 (rhTTP1). BMN 190 is administered as an inactive proenzyme, and activated following lysosomal uptake by cells. Enzymatic activity is restricted to the lysosome where BMN 190 degrades accumulated storage materials. It is administered via an intra-cerebroventricular (ICV) catheter that has been surgically implanted.

2. Brief description of the disease and intended population

CLN2 is a rare genetic disease with an estimated incidence in the U.S. of 0.5-1/100,000 births. It is caused by mutations in the CLN2 gene that encodes the lysosomal exopeptidase tripeptidyl peptidase 1 (TTP1), which is involved in protein catabolism and is responsible for cleaving 3-amino acid fragments from the N-terminus of small polypeptides. Deficiency of TTP1 leads to accumulation and storage of proteinaceous material in the lysosomes. The phenotype of CLN2 is that of progressive neurological deterioration. The disease is inevitably fatal.

CLN2 most commonly presents as a late infantile form, but both a more accelerated infantile form and a more attenuated juvenile form of this disease have been described¹. The classic late infantile form usually presents with seizures between 2 and 4 years of age, although some children present with speech delay during this same time period. Subsequently, motor skills, speech, vision and cognition decline leaving children blind, non-verbal, non-ambulatory, with dementia and severe bulbar dysfunction ultimately progressing to a vegetative state. Death usually occurs between 8 and 15 years of age. The Sponsor is proposing BMN 190 as therapy for individuals with all stages of CLN2.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

There is no regulatory precedent for endpoints established to support approval for this indication.

Study 190-201 is an ongoing first-in-human, phase 1/2 open-label trial. The study has a primary efficacy endpoint defined as change from baseline in the Sponsor's Clinical Rating Scale after 12 months of treatment. Results obtained with this rating scale (which was developed by the Sponsor) were compared to natural history data (the "Hamburg data") which are derived from 29 German and Swiss children with CLN2 who were evaluated longitudinally using the motor and language components of the Hamburg scale (i.e., a scale different from the Sponsor's Clinical Rating Scale). Table 1 compares the rating scales used to analyze the historical control data and the Study 190-201 data.

The Clinical Rating Scale used by the Sponsor has two domains - language and motor/gait - which are derived from two separate, broader scales that were historically used for this disease: the "Hamburg" and the "Weill Cornell" scale. The Sponsor's Clinical Rating Scale relies on parental report for scoring the language domain and investigator observation for the gait domain. The investigator also interviews caregivers with respect to gait, but the Sponsor claims this information is not used to rate the subject. Although the Division does not have the full clinician-reported outcome dossier for the Hamburg scale, based on the published literature, it appears that using the Hamburg scale, clinicians rated all scoring components based on more objective criteria without relying on parental or caregiver report,

¹ Kousi et al. "Update of the Mutation Spectrum and Clinical Correlations of over 360 Mutations in Eight Genes that Underlie the Neuronal Ceroid Lipofuscinoses." Human Mutation. 2011.

The Division has the following concerns regarding interpretation of the Sponsor's Clinical Rating Scale:

- Content validity and inter-observer reliability have not been established for either the gait or language components of either the original (Hamburg) or the Sponsor's new scale. Since different scales are used to evaluate the subjects in Study 190-201 versus the historical controls comparisons between the two populations are tenuous. In the current study, the domain elements have been significantly modified (two domains were left out and the remaining 2 domains used slightly different definitions). The Sponsor has not provided a rationale for the modifications made (the Division will seek further clarification).
- As currently designed, the Sponsor's scale might miss a clinically important deterioration in either the gait or language domains because the two domains are combined and changes occurring in opposite directions could cancel out and potentially conceal deterioration in one domain.
- The Sponsor's modified scale relies on caretaker subjective qualitative assessment of their child's language compared to a structured, more objectively measured evaluation of language skills. Preferably, outcome assessments should be based on clinicians' actual observations rather than caretakers' (i.e., parental) recollection of the subject's level of verbal functioning.
- It is unclear if the rating scale for language is accurate or reliable amongst children who speak a variety of primary languages given the international nature of the clinical development program, considering issues of cultural adaptation and translatability.

As noted in the outcome measurements presented in Table 1, it is not clear how the sponsor relates elements of their proposed scale to that used to analyze historical controls. For example:

- it is not clear whether a clinical score of 2 for the Hamburg versus the Sponsor's scale is comparable, given that the former uses a definition of "Frequent Falls, Clumsiness obvious," whilst the latter uses, "Walks 10 steps w/o support (can fall & have instability);"
- it is not clear if assessments of language are comparable across the two scales. It appears as though with the Hamburg scale clinicians rated children's language ability based on more objective criteria, whereas with the Sponsor's scale, language is rated based on subjective caregiver (parental) recall.

Table 1. Differences Between Scoring Scales Used by Sponsor for Natural History Controls and Prospectively Treated Subjects

Hamburg Scale (Natural History Data)			Sponsor's Scale: CLN2 Score (Prospective Trial Data)		
Language	3	Normal*	Language	3	No decline noted by parent
	2	Recognizably Abnormal		2	Abnormal, per parent "has become worse"
	1	Hardly Understandable		1	Hardly understandable, few intelligible words (worsening from prior skill level)
	0	No language or unintelligible		0	No intelligible words or vocalizations (worsening from prior skill level)
Motor	3	Normal [^]	Gait	3	Grossly normal (no pathologic falls, no prominent ataxia)
	2	Frequent Falls, Clumsiness obvious		2	Walks 10 steps w/o support (can fall & have instability)
	1	Crawls or walks with aid		1	Needs external assistance/only crawls
	0	Immobile, mostly bedridden		0	No Walking or Crawling
Visual	3	Recognizes objects & grabs at them	n/a		
	2	Uncoordinated grabbing of objects			
	1	Reacts to light			
	0	No response to visual stimuli			
Seizures (grand mal)	3	None in 3mo	n/a		
	2	1-2 in 3mo			
	1	1 per mo			
	0	>1 per mo			

* In some children, normal language development was never present. In such cases, the best performance ever achieved was taken as a starting point and rate 3; when language then became recognizably worse, it was rated 2.

[^] In some children, motor development was never normal

To summarize, the Sponsor presents interim results from a limited number of subjects (9) assessed with an instrument of uncertain accuracy and reliability. In addition, if one considers the natural history of the neurological decline in this disease, the duration of treatment (e.g., 9-12 months) is relatively short when compared to the natural history of the neurological decline in this disease. The accuracy of the control data (the Hamburg data) may be affected by the fact that it is based in major part on parental recall. It is therefore not clear how to draw valid conclusions when comparing the preliminary BMN 190 data and the control data.

4. Brief description of available therapies (if any)

There is no approved therapy available for CLN2; available treatment is geared towards symptomatic relief and palliative care. Products under development for the treatment of CLN2 include BMN 190 and gene therapy.

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

None.

6. Description of preliminary clinical evidence

The sponsor has enrolled 24 subjects into the ongoing single-arm, open-label, phase 1/2 clinical trial (Study 190-201). Study participants had an ICV catheter implanted surgically and received infusions of BMN 190 every 2 weeks through the catheter. The first six subjects were slowly dose escalated from 30mg or 100mg to 300mg every 2 weeks and then all subsequent subjects were treated with 300mg every 2 weeks which will continue for at least 48 weeks. Subjects are assessed with the rating scale every 8 weeks. (One subject was non-compliant and was withdrawn from the study).

This breakthrough designation request is based on interim data obtained from only 9 subjects who have been treated for at least 36 weeks; the Sponsor feels that this is an adequate duration to provide preliminary evidence of substantial improvement of BMN 190 treated subjects. Please note that in previous discussions the Division and Sponsor reached agreement that 1 year is a more reasonable time-point to detect a change; admittedly, even longer durations might be needed to detect a change. In this submission the Sponsor has not provided a convincing justification that an interim analysis based on 9 months of treatment is of adequate duration to expect a decline in clinical scores using their rating scale. Specifically, the Sponsor submitted a data-set using gait and language domains from a third scale (the Weill Cornell Scale) from a cross-sectional analysis of 46 children with CLN2 who had a decline <1 point/year in combined gait and language score. In the FDA's analysis of the Sponsor's longitudinal control data, separate subjects remained at each level (e.g., 2-5 on the Hamburg Scale) for up to 24-70 months. Therefore, these data suggest that a longer duration than 12 months may be necessary to demonstrate a substantial improvement.

Of the nine subjects studied for at least 36 weeks in Study 190-201, none had a decline from their baseline scores at the time of the final measurement (and no subject has had an improvement in their total score compared to their baseline score). The lack of deterioration in the CLN2 disease Rating Scale over a duration of 36 weeks is the basis for Sponsor's claim of substantial improvement. These data are illustrated graphically in Figure 1, below, which presents the overall and single domain (language and gait) scores for all 9 subjects who provided interim data.

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

7. Division's recommendation and rationale

Based on our review of the preliminary data provided by the Sponsor's interim analysis, the division recommends that a breakthrough therapy designation be denied for BMN 190 at this time. We agree that BMN 190 is intended to treat a serious and life-threatening disease; however, the preliminary evidence submitted to date has not demonstrated a substantial improvement on 1 or more clinically significant endpoints.

There remain a number of deficiencies in the data collection and analysis of that data submitted by the Sponsor for breakthrough designation.

- Data for 9 subjects treated with BMN-190 is of such short duration (9-12 months) that it is inadequate to demonstrate that the observed lack of decline in BMN-190 subjects represents a a substantial improvement compared to the natural history.
- The instrument used to measure clinical deterioration, the Sponsor's primary outcome endpoint, may not be reliable as content validity, inter-observer and intra-observer reliability have not been established. Without an accurate and reliable measurement tool, there is no discernible way to detect clinically meaningful changes.
- The Sponsor's comparison to control data is unreliable and difficult to interpret based on methodological flaws. A different measurement tool was used to assess controls than was used for BMN 190 treated subjects. The scales differ enough to expect that the same child rated on each scale could result in different scores based on which scale was used. The control data are further biased because it is based in part on parental recall. Lastly, the Sponsor's data analysis utilizing median duration at a score when multiple measurements exist for controls makes it appear as though the controls decline faster than they actually did.
- The open-label design increases the possibility of systematic bias by parents and raters.
- The sample size is very limited especially for a heterogeneous disease. The Sponsor only provided data from 9 children treated with BMN 190 and two of those children were asymptomatic and too young to expect a decline for years.
- Important confounders of disease progression, such as age, were not accounted for in the analysis.

8. Division's next steps and Sponsor's plan for future development

There is a face-to-face meeting scheduled with the Sponsor on 5/20/15 to gain clarification, discuss our recommendations and reach agreement on a path forward. The Division believes that the preliminary evidence provided by the Sponsor can be strengthened.

- In defining a clinically significant endpoint for any future Breakthrough Therapy Designation, the Division believes that the tool being used to measure change compared to natural history subjects must result in reliable and interpretable data. The Sponsor could possibly obtain additional prospective control data so that its proposed new rating scale could be applied to both populations. The Sponsor has videotaped and continues to videotape all clinician rater assessments of subjects on BMN 190, so the interval gait assessments can be rescored in a blinded fashion using a scoring scale that is deemed to be sensitive to change and reflects attention to measurement principles.

- The Division believes that the natural history data indicate a longer duration study is needed to detect a substantial improvement between subjects treated with BMN 190 and natural history subjects. The current protocol allows for subjects to receive full treatment doses of BMN 190 for a total of 48 weeks, and the Sponsor has submitted a protocol for an extension phase of the trial to follow eligible subjects on the same dosing schedule for an additional 239 weeks. Additional follow-up could provide data to support that there is a substantial improvement, including possibly a survival benefit.
- At this time, the Sponsor only has submitted interim data from 9 subjects, but has enrolled 24 subjects. If the Sponsor submits data from the larger number of subjects there might be adequate preliminary evidence to account for heterogeneity within the disease and assess substantial improvement.
- The analytical methods used by the Sponsor do not provide preliminary clinical evidence, but if the Sponsor uses a more rigorous methodology for making comparisons to the natural history data, i.e., not adjusting the control data and accounting for age, then there might be adequate preliminary data in the future. Additional control data may be available from an ongoing Cornell study.

DGIEP looks forward to further discussion with the Sponsor to develop a robust clinical program for this drug and indication.

Questions for Medical Policy Council

- 1) The Division believes that the interim analysis performed on the preliminary data submitted by the sponsor to conclude that BMN 190 results in a slower loss of motor and verbal abilities in children with CLN-2 is inadequate to support Breakthrough Therapy Designation. Does the Council agree?
 - 2) What additional steps are recommended by the MPC to develop a valid instrument for the measurement of change in clinically relevant endpoints in CLN-2?
 - 3) How would you recommend comparing BMN 190 subjects to historical control subjects given that this is a rare heterogeneous disease in which no controls were enrolled?
 - 4) Assuming the methodological flaws are addressed by the Sponsor, what duration of stabilization on BMN 190 treatment (relative to a decline in natural history controls) would constitute preliminary evidence of substantial improvement?
-

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

/s/

ELIZABETH S HART
04/29/2015

ROBERT FIORENTINO
04/29/2015
The End.