

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125460Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

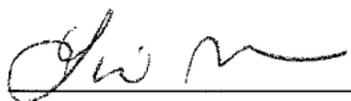
[Trade Name] (BMN 110)

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**1.3.3 Debarment Certification**

Certification Pursuant to Section 306 (k)(1) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. Section 335a (k)(1)].

BioMarin Pharmaceutical Inc. certifies that the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act [21 U.S.C Section 335a (a) or (b)] were not and will not be used in any capacity in connection with this application.



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Lisa Bell, Ph.D.  
Vice President, Regulatory Affairs  
BioMarin Pharmaceutical Inc.

3/11/2013

Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 125460	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Vimizim Established/Proper Name: elosulfase alfa Dosage Form: injection, for intravenous use		Applicant: Agent for Applicant (if applicable):
RPM: Elizabeth Ford		Division: Division of Gastroenterology and Inborn Errors Prducts
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2) Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(For additional information regarding 505(b)(2)s, please refer to <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm</a>)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not reply upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>February 28, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

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

<sup>2</sup> For resubmissions, (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).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  <input type="checkbox"/> Breakthrough Therapy designation       </p> <p>         NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)          Subpart I <input type="checkbox"/> Approval based on animal studies       </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request       </p> <p>         BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)          Subpart H <input type="checkbox"/> Approval based on animal studies       </p> <p>         REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required       </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input checked="" type="checkbox"/> Yes, dates 1/24/2014
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

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

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

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

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	2/14/2014
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ <b>Copies of all action letters (<i>including approval letter with final labeling</i>)</b>	Action(s) and date(s)
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	1/21/2014
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	3/29/2013
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	10/10/2013
<ul style="list-style-type: none"> <li>❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	7/25/2013 1/13/2014, 7/25/2013
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 5/22/2013 <input checked="" type="checkbox"/> DMEPA 10/22/2013, 9/16/2013, <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> OPDP (DDMAC) 9/23/2013 <input checked="" type="checkbox"/> SEALD 1/9/2014 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews OBP 9/18/2013
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	5/23/2013
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	2/12/2014, 1/17/2014, 1/10/2014, 12/20/2013, 12/13/2013, 11/27/2013, 11/25/2013, 11/4/2013, 10/30/2013, 10/29/2013, 10/28/2013, 10/18/2013, 10/17/2013, 10/8/2013, 9/24/2013, 9/20/2013, 9/11/2013, 8/29/2013, 8/16/2013, 8/7/2013, 8/7/2013, 8/2/2013, 7/15/2013, 7/10/2013, 6/7/2013, 5/28/2013, 5/22/2013, 5/3/2013, 5/1/2013, 4/16/2013,
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 11/13/2012 (CMC), 12/11/2012
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 7/28/2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	11/19/2013
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	12/10/2013
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2/14/2014
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2/13/2014
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/17/2014
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 2/14/2014
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL review
• Clinical review(s) <i>(indicate date for each review)</i>	11/26/2013, 5/16/2013
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See clinical review dated 11/26/2013, page 20.

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 1/15/2014 (OOPD), 12/4/2013 (DPARP), 10/21/2013 (PMHS), 9/13/2013 (DBRUP)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	<input checked="" type="checkbox"/> None 1/8/2014
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 2/8/2014, 10/25/2013, 10/18/2013, 9/26/2013
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/25/2013, 5/15/2013
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/30/2013, 10/28/2013, 5/26/2013
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/24/2013
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/31/2013
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/25/2013, 4/25/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
<b>❖ Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/26/2014
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/2/2014, 12/13/2013, 10/28/2013, 5/15/2013,
<b>❖ Microbiology Reviews</b>	<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	12/5/2013, 10/29/2013, 10/30/2013, 6/19/2013
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input type="checkbox"/> None
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See 10/28/2013 CMC review, pg 6.
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
<b>❖ Facilities Review/Inspection</b>	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: 2/14/2014 <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/  
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ELIZABETH A FORD  
02/14/2014

## Ford, Elizabeth

---

**From:** Ford, Elizabeth  
**Sent:** Wednesday, February 12, 2014 9:47 AM  
**To:** Brad Glasscock (BGlasscock@bmrn.com); Marjorie Tano (MTano@bmrn.com)  
**Cc:** Ford, Elizabeth (Elizabeth.Ford@fda.hhs.gov)  
**Subject:** BLA 125460/Vimizim/PMR-PMCs

Dear Ms. Tano,

The FDA has amended the post marketing requirements (PMRs) and post marketing commitments (PMCs) you have agreed to thus far in the review cycle. Please review this amended version of PMRs/PMCs and provide your acknowledgment and agreement to PMRs/PMCs 1- 16 as a submission to your BLA.

### POSTMARKETING REQUIREMENTS

- 1 Evaluate the long-term safety of Vimizim in adult and pediatric patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. Include incidence rate calculations as part of long-term safety evaluation assessments to monitor and characterize risk of exposure to Vimizim. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time to orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted every 6 months. Patients previously enrolled in clinical trials MOR-005 and MOR-007 may be rolled over to this study but will be monitored using the MOR-005 and MOR-007 protocols, respectively.

Final Protocol Submission:	09/2014
Final Protocol Submission (Updated Final Protocol for MOR-005)	12/2014
Final Protocol Submission (Updated Final Protocol for MOR-007)	03/2015
Interim Report Submission:	09/2017
Interim Report Submission (Report for MOR-007):	03/2018
Interim Report Submission:	09/2019
Interim Report Submission (Report for MOR-005):	03/2020
Study Completion:	09/2024
Final Report Submission:	03/2025

- 2 Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibits binding to the mannose-6-phosphate receptor. The final report will contain a summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay Standard Operating Procedure (SOP). This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs 1 3, and 6.

Final Report Submission: 03/2015

3 Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 3/2016

4 Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs 1, 5, and 6.

Final Report Submission: 3/2015

5 Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 3/2016

6 Evaluate the occurrence of serious infections associated with administration of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim (elosulfase alfa) who are at high risk of developing persistent neutralizing antibodies. This immune tolerance regimen will be implemented before or concomitant with the onset of Vimizim (elosulfase alfa) therapy.

Final Protocol Submission: 09/2016

Trial Completion: 03/2020

Final Report Submission: 09/2020

## POSTMARKETING COMMITMENTS

7 To develop and implement, as a release and stability test method, a potency assay that measures the  $K_m$  and  $k_{cat}$  of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

Study Completion: 06/2015

Final Report Submission: 09/2015

8 To revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between (b) (4) peak. The revised specification together with the validation report will be submitted to your BLA in accordance with 21 CFR 601.12.

Study Completion: 06/2015

Final Report Submission: 09/2015

9 To demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in a side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.

Study Completion: 09/2014  
Final Report Submission: 01/2015

- 10 To include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.

Study Completion: 06/2014  
Final Report Submission: 09/2014

- 11 To include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.

Study Completion: 06/2014  
Final Report Submission: 09/2014

- 12 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.

Final Report Submission: 04/2014

- 13 Conduct studies to understand the mechanism of low endotoxin recovery in the formulated bulk drug substance and drug product. These studies should investigate the endotoxin degradation or association pathway and determine whether or not depyrogenation is reversible (and if so, the conditions under which depyrogenation is reversible). Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods.

Study Completion: 09/2014  
Final Report Submission: 01/2015

- 14 Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC 1224 M.

Final Report Submission: 04/2014

- 15 Conduct an additional study comparing rabbit pyrogen and LAL test results. The study should include formulated bulk drug substance spiked with 20 EU/ml and 100 EU/ml endotoxin. The time points and controls should be the same as for the previous studies.

Study Completion: 11/2014  
Final Report Submission: 01/2015

16 Provide results from protocol PVP-101037 (b) (4) to be executed during the 2014 manufacturing campaign.

Study Completion: 03/2015  
Final Report Submission: 06/2015

Sincerely,

Elizabeth A.S. Ford, RN  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-0193

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/s/  
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ELIZABETH A FORD

02/13/2014

Cleared through level of CDTL

## Ford, Elizabeth

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**From:** Ford, Elizabeth  
**Sent:** Friday, January 17, 2014 4:35 PM  
**To:** Marjorie Tano (MTano@bmrn.com); Brad Glasscock (BGlasscock@bmrn.com)  
**Cc:** Ford, Elizabeth  
**Subject:** BLA 125460/Vimizim/Labeling Comments/PMR & PMCs

Dear Ms. Tano,

Please see the attached labeling comments for Vimizim and incorporate these revisions into the version of the package insert (PI) you sent on December 20, 2013. Submit the revised PI to your BLA.

1. The **bolded** Highlights Limitation Statement must include the following verbatim statement: **“These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”** The name of drug product should appear in UPPER CASE letters. For the HL Limitation Statement, the name of the drug product should appear as "VIMIZIM" (i.e., upper case letters), not "Vimizim."
2. In Highlights, the product title reads: (b) (4)  
The product title should read: **VIMIZIM (elosulfase alfa) injection, for intravenous use**
3. In the Table Of Contents (TOC), when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.” This statement must appear at the END of the TOC (i.e., right justified, below section 17). It appears left justified below subsection 6.2. "Right justify" statement so that it is correctly placed. Also, the words "Full Prescribing Information" should be "full prescribing information" (i.e., use lower case letters "f" "p" and "i").

In addition, we are sending an updated version of all the post marketing requirements and post marketing commitments you have agreed to thus far in the review cycle. There have been edits to the language in PMRs 1 - 4, and additional clarification was provided to PMC 7. Please review these and provide your acknowledgment and agreement to PMRs 1-8 and PMCs 1-10 as a submission to your BLA.

### Post Marketing Requirements:

- 1 Evaluate the long-term safety of Vimizim in patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. Include incidence rate calculations as part of long-term safety evaluation assessments to monitor and characterize risk of exposure to Vimizim. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time to

orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted every 6 months.

Final Protocol Submission: 09/30/2014  
Interim Trial Report Submission 09/30/2019  
Study/Trial Completion: 09/30/2024  
Final Report Submission: 03/31/2025

2



3

Evaluate the safety and clinical outcomes of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim who are at high risk of developing persistent neutralizing antibodies. This immune tolerance regimen will be implemented before or concomitant with the onset of Vimizim therapy.



Final Protocol Submission: 09/30/2016  
Study/Trial Completion: 03/31/2020  
Final Report Submission: 09/30/2020

4



- 5 Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibits binding to the mannose-6-phosphate receptor. The final report will contain a summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay Standard Operating Procedure (SOP). This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs (b) (4) and 6.

Final Report Submission: 03/2015

- 6 Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 3/2016

- 7 Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs (b) (4)

Final Report Submission: 3/2015

- 8 Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 3/2016

#### Post Marketing Commitments:

- 1 Develop and implement, as a release and stability test method, a potency assay that measures the  $K_m$  and  $k_{cat}$  of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

Study Completion: 06/2015

Final Report Submission: 09/2015

- 2 Revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between (b) (4) peak. The revised specification together with the validation report will be submitted to your BLA in accordance

with 21 CFR 601.12.

Study Completion: 06/2015

Final Report Submission: 09/2015

- 3 Demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in a side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.

Study Completion: 09/2014

Final Report Submission: 01/2015

- 4 Include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.

Study Completion: 06/2014

Final Report Submission: 09/2014

- 5 Include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.

Study Completion: 06/2014

Final Report Submission: 09/2014

- 6 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.

Final Report Submission: 04/2014

- 7 Conduct studies to understand the mechanism of low endotoxin recovery in the formulated bulk drug substance and drug product. These studies should investigate the endotoxin degradation or association pathway and determine whether or not depyrogenation is reversible (and if so, the conditions under which depyrogenation is reversible). Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods.

Study Completion: 09/2014

Final Report Submission: 01/2015

- 8 Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC 1224 M.

Final Report Submission: 04/2014

- 9 Conduct an additional study comparing rabbit pyrogen and LAL test results. The study should include formulated bulk drug substance spiked with 20 EU/ml and 100 EU/ml endotoxin. The time points and controls should be the same as for the previous studies.

Study Completion: 11/2014

Final Report Submission: 01/2015

- 10 Provide results from protocol PVP-101037 [REDACTED] (b) (4) to be executed during the 2014 manufacturing campaign.

Study Completion: 03/2015

Final Report Submission: 06/2015

Sincerely,

Elizabeth A.S. Ford, RN  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-0193

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/s/  
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ELIZABETH A FORD  
01/17/2014

# MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** December 11, 2013 11:30AM – 12:00PM EST

**Application Number:** BLA 125460

**Product Name:** Vimizim (elosulfase alfa)

**Sponsor/Applicant Name:** BioMarin Pharmaceutical, Inc.

## **FDA Participants:**

Emanuela Lacana, Ph.D., DTP  
Cristina Ausin, Ph.D., DTP  
Richard Ledwidge, Ph.D., DTP  
Lyndsay Hennessey, OBP

## **Sponsor/Applicant Participants:**

Lisa Bell, Ph.D., Vice President, Regulatory Affairs  
Art Blum, Vice President, Regulatory Affairs  
Victoria Sluzky, Ph.D., Group Vice President, Quality and Process Development  
Robert Baffi, Senior Executive Vice President, Technical Operations and Quality  
Erno Pungor, Ph.D., Staff Scientist, Quality  
Loc Vo, Ph.D., Senior Scientist 2, Quality Control  
Laurel Konkol, Director, Regulatory Affairs

## **1.0 BACKGROUND:**

To discuss the qualification of rhASB (b) (4) content in the (b) (4) content release specification

## **2.0 DISCUSSION:**

The Agency asked the sponsor about the stability of (b) (4) content in rhASB over time.

- The sponsor said they have data that demonstrates the (b) (4) content of rhASB does not change appreciably over time and that they would provide the data by 12/16/13.

The Agency asked the sponsor if they have established acceptance criteria for (b) (4) content in rhASB reference standard qualification.

- The sponsor stated that they have had internal discussions regarding the establishment of minimal (b) (4) content levels for rhASB reference standard qualification and that they would propose a value by Monday 12/16/13.

The Agency and sponsor had a conversation regarding administrative items.

- The sponsor asked if the agency agreed to their proposal for a 2 year expiry on drug product. The Agency replied that the discussion was ongoing and that we would get back shortly regarding our answer.
- The sponsor plans to set specific acceptance criteria for (b) (4) content in a qualification protocol currently being worked on
- The sponsor will provided updated data regarding the consistency of (b) (4) content

### **3.0 ACTION ITEMS:**

- The sponsor plans to submit the (b) (4) content data requested from the Agency on Monday, December 16, 2013

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/s/  
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LYNDSAY J HENNESSEY  
01/02/2014

EMANUELA LACANA  
01/10/2014



BLA 125460/0

**GENERAL ADVICE**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologics License Application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We also refer to your amendment submitted on November 26, 2013, received November 26, 2013.

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

To support a (b) (4) expiration date, you need to provide (b) (4) real time data. Without this information, the data you provided would support a 24 month expiration date.

If you have any questions, call Lyndsay Hennessey, Quality Regulatory Project Manager, at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Emanuela Lacana, Ph.D.  
Product Quality Team Lead  
Division of Therapeutic Proteins  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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EMANUELA LACANA  
12/20/2013

## Ford, Elizabeth

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**From:** Ford, Elizabeth  
**Sent:** Friday, December 13, 2013 5:02 PM  
**To:** Brad Glasscock (BGlasscock@bmrn.com); Marjorie Tano (MTano@bmrn.com)  
**Cc:** Ford, Elizabeth  
**Subject:** BLA 125460/Vimizim/PI, PMR, PMC Comments

Dear Brad and Marjorie,

Please review the attached document and comments regarding labeling changes and postmarketing requirements and commitments. These comments and revisions have been reviewed and cleared to the level of Cross Discipline Team Leader.

We have reviewed your responses, dated November 4, 2013, to the proposed post-marketing requirements. We agree with initiating a disease-based registry to collect long-term safety and efficacy data on Morquio A patients who are treated with Vimizim, and acknowledge the operational challenges associated with continuing separate clinical trials for this rare patient population. However, we believe that longitudinal data collected from patients who participated in the placebo-controlled trial (i.e., MOR-004) and subsequently transitioned to the extension trial (i.e., MOR-005) are essential for elucidating long-term safety, immunogenicity and efficacy of Vimizim. The importance of evaluating long-term data on these patients was also emphasized by the Committee members who participated in the Endocrinologic and Metabolic Drugs Advisory Committee meeting on November 19, 2013.

You have stated in your responses that all patients currently participating in the Vimizim clinical trial program will be invited to participate in the Morquio A registry and that you will endeavor to enroll as many MOR-005 patients into the registry as possible. It may be possible to conduct MOR-005 as a sub-trial under the Morquio A Registry, provided you collect prospective data on *each* enrolled patient for a minimum of 5 years, and analyze and summarize the MOR-005 data separately from the remaining registry data to fulfill the PMR requirement. This approach would allow assessments to occur at the local sites and reduce patient travel burden, while capturing information necessary to address the safety concerns and evaluate clinical outcome data. We believe that the pediatric trial MOR-007 should also remain under a separate protocol, as a sub-trial under the Morquio A Registry.

Based on the Late Cycle meeting, Advisory Committee meeting and internal discussions, we have revised the PMRs to as follows:

PMR 1: Evaluate the long-term safety of Vimizim in patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time to orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted at least every 6 months.

Final Protocol Submission:	09/30/2014
Interim Trial Report Submission:	09/30/2019
Trial Completion:	09/30/2024
Final Report Submission:	03/31/2025

PMR 2:



PMR 3:

Evaluate the safety and efficacy of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim who are at high risk of developing persistent neutralizing antibodies. This immune tolerance regimen will be implemented before or concomitant with the onset of Vimizim therapy.



Final Protocol Submission:	09/30/2016
Trial Completion:	03/31/2020
Final Report Submission:	09/30/2020

PMR 4:



PMR 5: Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibits binding to the mannose-6-phosphate receptor. The final report will contain a summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay Standard Operating Procedure (SOP). This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs 1- (b) (4) and 6.

Final Report Submission: 03/31/2015

PMR 6: Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 03/31/2016

PMR 7: Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs 1- (b) (4)

Final Report Submission: 03/31/2015

PMR 8: Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 03/31/2016



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We request a response to these comments by 4:00 PM EST on December 18, 2013.

Sincerely,

Elizabeth A.S. Ford, RN  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-0193

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ELIZABETH A FORD  
12/13/2013

**From:** [Ford, Elizabeth](#)  
**To:** [Marjorie Tano \(MTano@bmrn.com\)](#)  
**Cc:** [Ford, Elizabeth](#)  
**Subject:** BLA 125460 Labeling Comments  
**Date:** Wednesday, November 27, 2013 10:32:45 AM  
**Attachments:** [BLA 125460 Labeling FDA comments 11-27-2013.doc](#)

---

Dear Marjorie,

Please find enclosed FDA's comments for the package insert (PI). We request that you review this version of the PI, and respond by December 3, 2013.

Sincerely,

Elizabeth A.S. Ford, RN  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-0193

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ELIZABETH A FORD  
11/27/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We have reviewed the Quality Microbiology sections of your application and have determined that the following information is necessary to take a complete action on your application:

1. Report QC-1214-M showed that endotoxin standard added to formulated bulk drug substance was not consistently detected by the rabbit pyrogen test. To better understand the relationship between low endotoxin recovery and pyrogenicity, the study comparing the rabbit pyrogen test and LAL test results should be repeated. The study should include formulated bulk drug substance spiked with 20 EU/ml and 100 EU/ml endotoxin. The time points and controls should be the same as for the previous studies. The [REDACTED] (b) (4) [REDACTED] test reports should be provided along with the BioMarin study report. Please provide time frames for study completion and data submission. This study may be completed as a post-marketing commitment (PMC).
2. Please provide the following rabbit pyrogen test reports from [REDACTED] (b) (4) [REDACTED]

We also refer to FDA correspondence dated October 28, 2013, containing postmarketing requirement/postmarketing commitment (PMR/PMC) discussion comments, and your submission received November 5, 2013, provided in response to FDA's October 28, 2013 letter. We have the following comments, and revised language for Postmarketing Commitment (PMC) 1:

3. Measurement of the enzyme kinetic parameters ( $K_m$  and  $k_{cat}$ ) provides more robust information on the enzymatic activity of enzymes than the activity assays usually conducted at a single substrate concentration.

In addition, measurements of enzyme kinetic parameters using physiologically relevant substrates are likely to provide valuable information on the subtle enzyme conformational changes that may affect product potency. We noted that you use galactose-6-sulfate instead of a physiological substrate for testing of elosulfase alfa. According to the literature (Bielicki et al, Biochem J. 1995, 311, 333-339), the affinity of GALNS for trisaccharide substrates (b) (4) than what you report for galactose-6-sulfate (b) (4). Thus, the use of the lower affinity substrate for elosulfase alfa may lead to a lack of sensitivity in detecting meaningful changes in the conformation of elosulfase alfa, which may have a negative effect on its in vivo potency.

Therefore, we recommend that you conduct a study aimed at the determination of elosulfase alfa kinetic parameters using an adequate physiologically relevant substrate. As part of your postmarketing study, you should evaluate different substrates in order to make a determination regarding their adequacy, and compare them to the substrate you are currently using. The study should include the use of elosulfase alfa subjected to forced degradation conditions.

With these comments in mind, please consider our proposed language for postmarketing commitment 1:

Revised PMC 1: To develop and implement, as a release and stability test method, a potency assay that measures the  $K_m$  and  $k_{cat}$  of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA.

If you have any questions, please contact the Regulatory Project Manager, Elizabeth Ford, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Brian K. Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
11/25/2013



BLA 125460/0

**DISCIPLINE REVIEW LETTER**

BioMarin Pharmaceutical, Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologics License Application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN 110 (elosulfase alfa).

We also refer to your amendments dated April 25, 2013, June 11, 2013, June 17, 2013, June 19, 2013, August 12, 2013, August 19, 2013, August 26, 2013, September 9, 2013, October 1, 2013, and October 16, 2013.

Our review of the Quality section of your submission is complete. We have identified the following deficiencies:

- a) You provided stability studies on drug product manufactured at different sites and stored under a variety of conditions. We noted that under accelerated and stressed storage conditions, the enzyme specific activity of drug product manufactured at the proposed commercial site (b) (4) exhibited a significantly higher degradation rate than drug product manufactured at (b) (4) the site that manufactured clinical trial material. A difference in degradation rates between drug products indicates a change in a quality attribute(s) that rendered the proposed commercial material less stable than its clinical counterpart. We conclude that drug products manufactured at the two sites are not physico-chemically comparable. Therefore, the real-time stability data generated at the (b) (4) cannot be used to establish the shelf-life of product manufactured at the (b) (4) facility. Potential paths forward include manufacturing at (b) (4)
- b) As part of the demonstration of comparability between Novato and Shanbally testing sites for the specific activity test method, you extrapolated the degradation profile of Vimizim DP lot BSKB01. Because determination of specific activity is a stability indicating test method, you should have performed the testing at both sites at the same time, to ensure that the age of the DP lot did not affect the results. We conclude that the transfer of this method to Shanbally is not appropriate and the method should

not be performed at the site for release of drug product in the United States. Potential paths forward include delaying the assay transfer for specific activity to Shanbally until the aforementioned issues are resolved.

We are providing these comments to you before completing our review of your 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.

If you have any questions, call Lyndsay Hennessey, Regulatory Project Manager, at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Amy Rosenberg, M.D.  
Director  
Division of Therapeutic Proteins  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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AMY S ROSENBERG  
10/30/2013



BLA 125460/0

**INFORMATION REQUEST**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We are reviewing your application and have determined that the following information is necessary to take a complete action on your application:

1. Clarify whether the Polysorbate 20 is tested for endotoxin and specify the established limits and test methods.
2. Include the endotoxin specification and results from the (b) (4) in the formulated bulk drug substance (FBDS) Certificate of Analysis (COA) until an alternative method for endotoxin testing is developed for the FBDS.
3. Provide the following information regarding the endotoxin test study performed under protocol QC-1214-M.
  - a. Provide the rabbit pyrogen test report for the 1-month time point (formulated drug substance lot P40152-13103).
  - b. Provide summary data and the associated study reports for tests done with the second lot of formulated bulk drug substance.
4. For (b) (4) of BMN 110 performed at (b) (4) clarify whether an upper pressure limit validated by the microbial retention study has been implemented.
5. The (b) (4) showed that the test can consistently detect vials with a (b) (4). However, the study report indicates that the positive control used for the (b) (4) will have (b) (4). Justify use of a positive control with (b) (4) instead of (b) (4).

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact the Regulatory Project Manager, Elizabeth Ford, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Brian K. Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
10/29/2013



BLA 125460/0

**LABELING PMR/PMC DISCUSSION COMMENTS**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologics License Application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We also refer to our May 28, 2013, letter in which we notified you of our target date of October 28, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.”

On June 10, 2013, we received your June 7, 2013 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader. We request that you resubmit labeling (Microsoft Word format) by November 4, 2013. The resubmitted labeling will be used for further labeling discussions.

We are proposing postmarketing requirements (PMRs) and postmarketing commitments (PMCs) for BLA 125460/0, below. Please review these PMRs/PMCs and provide your response by November 4, 2013. With your response, provide milestone dates as requested (PMR 3 and PMCs 1-9) or your concurrence with the dates proposed by FDA (PMRs 1-2 and 4-7). The proposed PMRs have been reviewed and cleared to the level of Office Director.

**Postmarketing Requirements**

PMR 1:



(b) (4)



PMR 2: Evaluate the safety and efficacy of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with VIMIZIM who are at high risk of developing persistent neutralizing antibody. This immune tolerance regimen will be implemented before or concomitant with onset of VIMIZIM therapy.

(b) (4)



Final Protocol Submission:	03/31/2015
Trial Completion:	03/31/2020
Final Report Submission:	09/30/2020

PMR 3:

(b) (4)



PMR 4: Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibit binding to the mannose-6-phosphate receptor. A summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to the FDA. This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs 1 (b) (4)

Final Report Submission: 03/31/2015

PMR 5: Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 03/31/2016

PMR 6: Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs 1 (b) (4)

Final Report Submission: 03/31/2015

PMR 7: Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 03/31/2016

### Postmarketing Commitments

PMC 1: Develop and implement a potency assay that measures the  $K_m$  and  $k_{cat}$  of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

Final Protocol Submission: MM/DD/YYYY

Study Completion: MM/DD/YYYY

Final Report Submission: MM/DD/YYYY

PMC 2: Revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between (b) (4) -peak. The revised specification together with the validation report will be submitted to your BLA in accordance with 21 CFR 601.12.

Final Protocol Submission: MM/DD/YYYY

Study Completion: MM/DD/YYYY

Final Report Submission: MM/DD/YYYY

PMC 3: Demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in a side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 4: Include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 5: Include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 6: Add cellular uptake as a release assay for DP and establish an appropriate acceptance criterion when a statistically significant number of DP lots is tested.

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 7: Conduct studies to understand the mechanism of low endotoxin recovery in the FBDS and DP. Modify the endotoxin release test accordingly as new information on low endotoxin recovery becomes available.

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 8: Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC-1224-M.

Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 9: Provide results from protocol PVP-101037 (intermediate hold time validation study) to be executed during the 2014 manufacturing campaign.

Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

If you have any questions, call me, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Elizabeth A.S. Ford, R.N.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE: Revised Draft Labeling

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

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/s/  
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ELIZABETH A FORD  
10/28/2013



BLA 125460/0

**INFORMATION REQUEST**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We are reviewing your application and have determined that the following information is necessary to take a complete action on your application:

1. Using data obtained from the MOR-004 trial, provide the following analyses by treatment group (elosulfase alfa 2 mg/kg QW, elosulfase alfa 2 mg/kg QOW, and placebo). Include both tabular and graphical presentations, and provide correlation analyses.
  - Change in the 6MWT from baseline to week 24 by baseline FVC % predicted
  - Change in the 6MWT from baseline to week 24 by baseline FEV1 % predicted
  - Change in the 6MWT from baseline to week 24 by baseline MVV % predictedSpecify the reference standards used to calculate the % predicted value for each pulmonary function test.
2. Based on the pulmonary function test results, determine whether each patient has restrictive and/or obstructive lung disease. Specify the method used to determine this clinical status. Provide a subgroup analysis by treatment group that evaluates change in the 6MWT from baseline to week 24 by type of lung disease (none, restrictive, obstructive, combined restrictive and obstructive disease).
3. We held a teleconference with the European Medicines Agency on October 16, 2013. The EMA informed us that additional clinical data were requested, which may strengthen the evidence to support clinical benefit of elosulfase alfa in Morquio A patients. Provide the same information to your pending BLA, as was submitted to the EMA in response to their request for additional clinical data.
4. Please submit the clinical and analysis datasets which were the basis for the September 27, 2013 submission (eCTD sequence 0017).

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact the Regulatory Project Manager, Elizabeth Ford, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Brian K. Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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ELIZABETH A FORD  
10/18/2013  
Signing for Brian Strongin



BLA 125460/0

INFORMATION REQUEST

BioMarin Pharmaceutical, Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

- 1) You propose to report the results of the (b) (4) as ratio of rhGALNS

(b) (4)  
Your proposal is based on the assumption that (b) (4)  
(b) (4) However, you did not  
provide evidence to demonstrate that there is (b) (4)  
We are concerned that (b) (4)  
Additionally, we are also concerned that (b) (4)  
Please provide data  
supporting your claim that there is (b) (4)

- 2) You provided a method validation report for the measurement of Polysorbate 20 (PS20), an excipient in final drug product formulation. PS20 content is determined by RP-HPLC (b) (4). You also provided RP-HPLC chromatographs generated during the validation exercise. While the (b) (4) the PS20 standard exhibited (b) (4)

(b) (4)

- 3) In amendment 0012 (dated August 19, 2013), you provided Qualification and validation protocols for generation of a new working cell bank for the Vimizim manufacturing process (report PVP-100685). In this document, you propose to

(b) (4)

. In order to assure product quality, we recommend that all new working cell banks should include testing of at least one drug substance batch at commercial scale operations. In addition, all new working cell banks should include analysis of gene copy number in the characterization testing. Please amend your qualification protocol for new working cell bank to include these items.

- 4) Please submit the SOP's to the application for in-process tests rhGALNS concentration by RP-HPLC,

(b) (4)

We request a written response to the items enumerated above by November 7, 2013 in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
10/17/2013



BLA 125460/0

**INFORMATION REQUEST**

BioMarin Pharmaceutical, Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

You revised several acceptance criteria for FBDS and DP; however, you did not update your specifications tables. Please provide updated versions of Table 3.2.S.4.1.1 Specification and Tests for Release of FBDS and Table 3.2.P.5.1.1 Drug Product Test Methods and Specifications.

We request a written response to the item above by October 16, 2013 in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
10/08/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical, Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

On September 6<sup>th</sup>, 2013 you provided a response to our information request from May 28, 2013 to account for the observed differences in degradation slopes between clinical and commercial material stored at (b) (4). Whereas the degradation rates of commercial lots manufactured at (b) (4) are in-line with clinical lots, lots manufactured at (b) (4) degrade significantly faster than lots manufactured at (b) (4) (See Appendix 1). Based on our reanalysis, we cannot determine whether the differences noted are due to drug substance or drug product manufacturing. To address our concerns please conduct a thermal degradation study similar to the study submitted on September 6<sup>th</sup>, using drug substance lots manufactured at (b) (4). Drug substance lots from (b) (4) should include a sufficient number of lots that were used for drug product manufacturing at both (b) (4).

### Appendix 1

Using the data from Table 2 of your September 6<sup>th</sup> submission (excluding Clinical Phase 3 lot BSJJ03) we performed a degradation slope analysis (See Figure 1). We agree with your interpretation that there is no statistical significant difference in the degradation slopes between the Clinical Phase 3 and Commercial drug product lots (slopes for Phase 3 and Commercial lots are (b) (4), respectively, with a T-test p value = (b) (4)).

However, additional analysis of your data showed a statistical significant difference in degradation slopes when comparing commercial lots manufactured at (b) (4) (slopes for (b) (4) were (b) (4) respectively, with a T-test p value = (b) (4) Figure 2) and when we compared all drug product lots manufactured at (b) (4) (Phase 3 and Commercial) and (b) (4) (slopes for (b) (4) were (b) (4) and (b) (4) respectively, with a T-test p value = (b) (4) Figure 3).

It is the Agency's conclusion that the thermal stress study conducted at 50°C is not sufficient to conclude that there are no differences between product filled at VLA5 and product filled at RSV2.

FIGURE 1

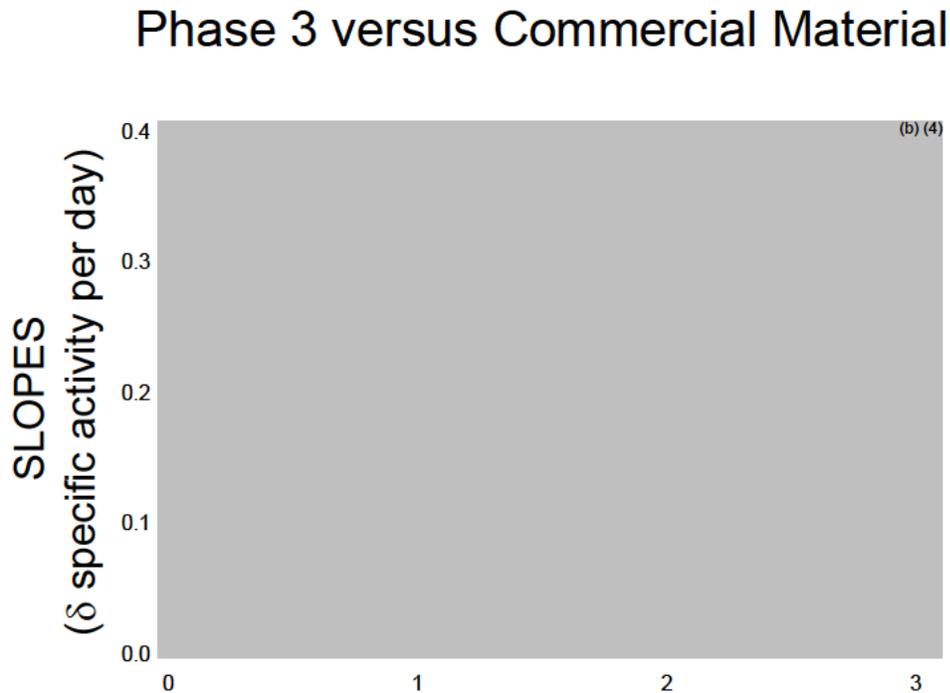


FIGURE 2

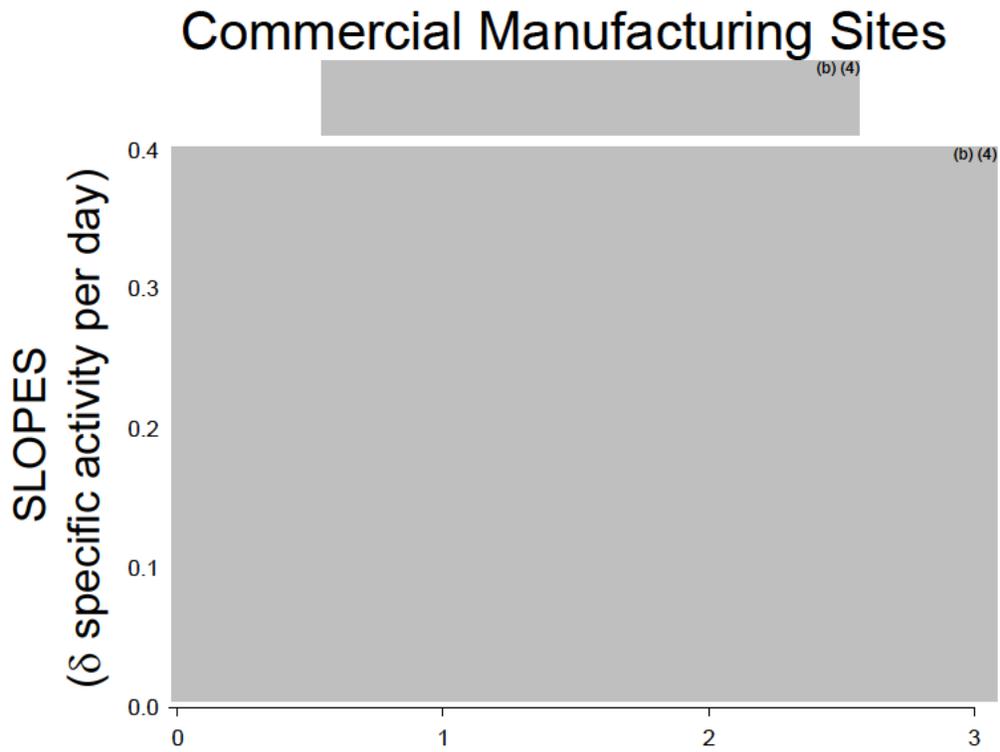
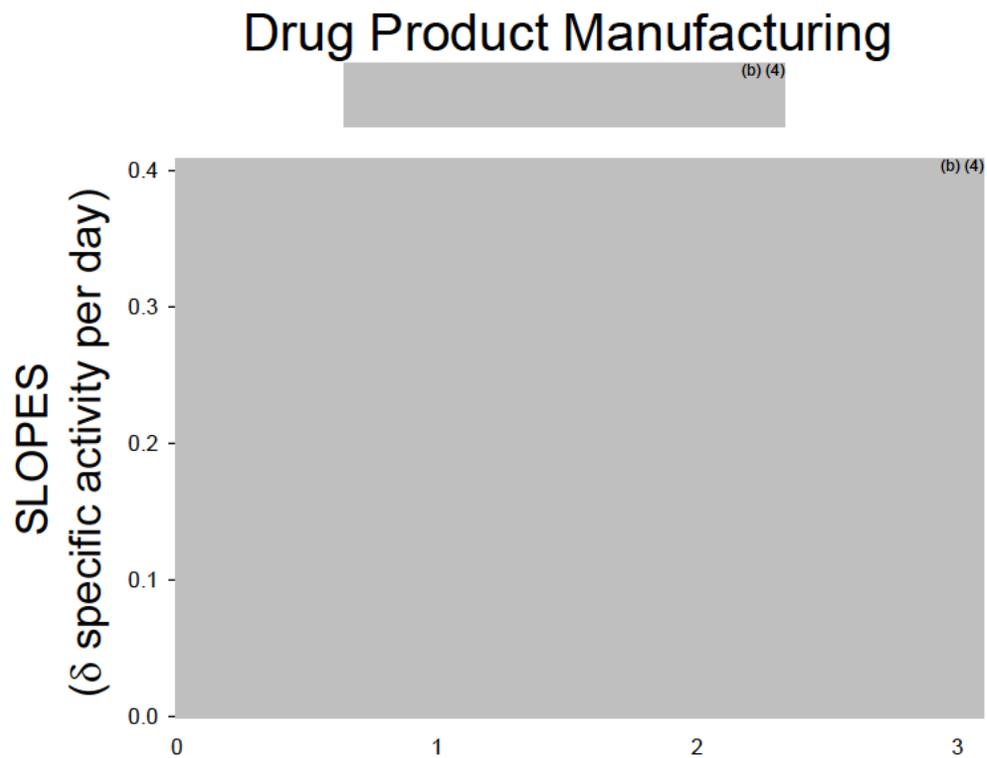


FIGURE 3



We request a written response to the item above by October 16, 2013 in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
09/24/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We are reviewing your application and have determined that the following information is necessary to take a complete action on your application:

### QUALITY MICROBIOLOGY

1. (b) (4) for in-process intermediates were validated using two commercial scale batches based on biochemical stability; however, no evidence of microbial control was provided.

Submit data from three successful product (b) (4) runs at manufacturing scale. Include bioburden and endotoxin levels before and after the maximum allowed (b) (4). Provide established bioburden and endotoxin limits for (b) (4)

If these data are not available, submit a protocol for a study to demonstrate microbial control at the start and end of the established (b) (4) for all in-process intermediates.

### CLINICAL

2. During the Midcycle Communication Meeting held on July 31, 2013, we discussed the possibility of obtaining additional endurance test results (i.e. six-minute walk test and three-minute stair climb) from all patients currently receiving the proposed dosing regimen, elosulfase alfa 2 mg/kg once per week, in Trial MOR005 so that we can better understand the long-term clinical benefit of elosulfase alfa. You stated during the teleconference that additional long-term data may be available from the September data cut, and that you would inform the Agency regarding the possibility of providing these data after evaluation. Please inform us whether these additional long-term data from Trial MOR 005 could be provided to

the Agency during this review cycle. If possible, provide endurance test and immunogenicity results for any patient who has received elosulfase alfa 2 mg/kg once per week for 48 weeks or more.

### CONTAINER LABEL and CARTON LABELING

3. Revise the presentation of the proprietary name to title case (i.e., from ‘VIMIZIM’ to ‘Vimizim’) and revise the (b) (4) color on the left side of the letter ‘V’ to the color of the other letters to improve the readability of the proprietary name. See recommended format provided under item 5 below.
4. Revise the dosage form (b) (4) to “injection” to comply with the United States Pharmacopeia 8/1/13-11/30/13, USP 36/NF 31, General Chapter, Injection <1>, Nomenclature and Definitions. Relocate the dosage form to appear after the active ingredient and just outside of the parenthesis. See recommended format below.

**Vimizim**  
(elosulfase alfa)  
Injection  
**5 mg/5 mL**  
1 mg/mL  
for Infusion

5. Ensure the presentation of the active ingredient (elosulfase alfa) and the dosage form (injection) have a prominence that is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
6. Increase the prominence of the total drug statement (5 mg/5 mL) so that it is more prominent than the strength statement (1 mg/mL).
7. Revise the statement (b) (4) to read “Usual dosage: see package insert.”

### CONTAINER LABEL

8. Remove the (b) (4) from around the manufacturer’s name and relocate the manufacturer’s name to the bottom of the principal display panel. Ensure that this information is less prominent than the proprietary, established names, and strength.
9. If space permits, relocate the statement “For single use only” to the principal display panel and follow it with the statement “Discard unused portions.”
10. Please indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60 (e).

**CAP and OVERSEAL**

11. Please comment on if there is any text on the ferrule and cap overseal. A revised USP standard will go into effect on December 1, 2013. We refer you to the following address:

[http://www.usp.org/sites/default/files/usp\\_pdf/EN/USPNF/genChapter1Labeling.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf)

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact the Regulatory Project Manager, Elizabeth Ford, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Brian K. Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
09/20/2013



BLA 125460/0

**INFORMATION REQUEST**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We are reviewing the Non-clinical sections of your application and have determined that the following information is necessary to take a complete action on your application:

Upon review of your pre-/post-natal developmental study in rats (study # BMN 110-12-013), we noted an increased incidence of pup mortality and the detection of elosulfase alfa in milk from the nursing mothers. Provide information to clarify whether the increase in pup mortality was due to *in utero* exposure to drug or the oral exposure to drug in milk.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact the Regulatory Project Manager, Elizabeth Ford, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Brian K. Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
09/11/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical, Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

In your BLA submission, you propose acceptance criteria for the CEX-HPLC peaks relative to the corresponding peaks in the reference material. We noted that the %CV for these measurements is high and the results are too variable to establish relevant limits. To address this issue, we recommend that you revise your acceptance criteria and establish appropriate limits for Peaks 1-6 in terms of percentage of the total peak area and not relative to the reference material.

Alternatively, provide a justification as to why it would be more appropriate to report the results in percentages of relative peak areas to the corresponding peaks in the reference material.

We request a written response by the end of September at the latest to the item above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
08/29/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

In the validation report for the GALNS Specific IgE in Human Serum by RIA (DocNo PS-1334-VP1) assay you mention that you used a GALNS specific human IgE-positive control during assay validation. However, you did not include any additional information about this control in your submission. At a minimum, please provide the following information to better understand its performance during assay validation:

- Was the control sample obtained from plasma or serum?
- Was the positive control made from samples that were:
  - obtained at different times from the same patient and/or obtained from individual samples from different patients?
  - obtained from patient(s) who had anaphylactic responses to BMN110?
- Did the positive control contain anti-BMN110 IgG? If so, what was the IgG titer of the positive control?
- Was the positive control used to determine assay sensitivity?

We request a written response to the items enumerated above by September 6, 2013 in order to continue our evaluation of your BLA. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
08/16/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We are reviewing the Clinical Pharmacology, Clinical, and Immunogenicity sections of your application and have determined that the following information is necessary to take a complete action on your application:

### **Clinical Pharmacology**

1. Elosulfase alfa clearance (CL) appears to be lower in Asians than in Whites, and the majority (12 of 15) of non-White patients in the PK dataset are Asians. Therefore, we request that you replicate the analyses presented in Figures 2.7.2.2.1.1.1, 2.7.2.2.1.1.2, and 2.7.2.2.1.1.3 (see pages 16, 17 and 18 in Summary of Clinical Pharmacology) using Asians instead of non-Whites to explore the differences in CL values between Asians and Whites at Weeks 0 and 22. Present the results in both scatter plots and box-and-whisker plots.

### **Clinical**

2. During review of hypersensitivity reactions identified by the Angioedema SMQ and Anaphylactic Reaction SMQ (Integrated Summary of Safety Patient Listings 1.19.2 and 1.19.3), there were several cases that appeared potentially to meet the NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H *et al.*, 2006). Provide case narratives for all patients listed in the ISS Patient Listings 1.19.2 and 1.19.3. Case narratives should include the following information:
  - Premedication(s) given prior to the event
  - Specify whether the event occurred during or after infusion. If the event occurred after infusion, specify the number of hours after infusion the event occurred.

- Detail of the event -- specify affected body location/distribution, duration of the event, changes in vital signs, and concurrent symptoms
- Medications and medical interventions administered to treat the event
- Outcome of the event
- If the patient resumed treatment, specify how soon after the event he/she resumed treatment. Indicate whether any changes were made to premedication(s) with the restart of treatment and whether symptoms recurred.

In addition, review the adverse event database and provide narratives for all patients who meet the NIAID/FAAN 2006 criteria for anaphylaxis, regardless of IgE antibody status.<sup>1</sup>

### **Immunogenicity**

3. Because all patients had high titer anti-BMN110 antibodies, it is difficult to assess the impact of antibodies on efficacy. For some products, e.g. (b) (4) You did not assess titer in your NAb assay. However it is possible that % inhibition in the NAb assay may be a useful surrogate for titer. Assess whether % inhibition in the NAb assay is correlated with 6-minute walk test results over time. Provide separate analyses for data up to 24 weeks and up to 48 weeks.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact the Regulatory Project Manager, Elizabeth Ford, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Brian K. Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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<sup>1</sup> Sampson H et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

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/s/  
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BRIAN K STRONGIN  
08/07/2013



BLA 125460/0

**MID-CYCLE COMMUNICATION**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 31, 2013. 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) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.  
Senior 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

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** July 31, 2013, 12:30-1:30 PM

**Application Number:** BLA 125460

**Product Name:** Vimizim (elosulfase alfa)

**Indication:** Mucopolysaccharidosis IV type A (Morquio A syndrome, MPS IVA).

**Sponsor/Applicant Name:** BioMarin Pharmaceutical Inc.

**Meeting Chair:** Jessica Lee, M.D.

**Meeting Recorder:** Elizabeth Ford, R.N.

**FDA ATTENDEES**

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

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D., Director  
Andrew Mulberg, M.D., Deputy Director  
Jessica Lee, M.D., Clinical Team Leader  
Tamara Johnson, M.D., Clinical Reviewer  
Elizabeth Ford, R.N., Senior Regulatory Health Project Manager

Office of Biotechnology Products/Division of Therapeutic Proteins

Susan Kirshner, Ph.D., Review Chief  
Emanuela Lacana, Ph.D., Associate Lab Chief, Laboratory of Chemistry  
Cristina Ausin, Ph.D., Staff Fellow  
Richard Ledwidge, Ph.D., Chemist  
Jinhai Wang, M.D., Medical Officer

Office of Compliance/Biotech Manufacturing Assessment Branch

Patricia Hughes, Ph.D., Team Leader, Microbiology  
Colleen Thomas, Ph.D., Microbiologist

Office of Translational Sciences

Office of Clinical Pharmacology/Division of Clinical Pharmacology 3

Christine Hon, PharmD., Clinical Pharmacology Reviewer  
Yow-Ming Wang, Ph.D., Biologics Team Leader

Office of Biostatistics/Division of Biometrics III

Behrang Vali, M.S., Statistics Reviewer  
Stephen Wilson, Dr. P.H., Director

Office of Surveillance and Epidemiology

Phong Do, PharmD, Regulatory Health Project Manager

Office of Executive Programs

Division of Advisory Committee and Consultant Management

Karen Abraham-Burrell, PharmD, CDR, United States Public Health Service

**EASTERN RESEARCH GROUP**

SoHyun Kim, Independent Assessor

**APPLICANT ATTENDEES**

Kris Antonsen, Senior Director, Process Development  
Robert Baffi, Executive Vice President, Technical Operations  
Art Blum, Vice President, Regulatory Affairs  
Brian Chipman, Associate Director, Quality Assurance Validation  
Dan DiPrimeo, Director, Statistical Programming  
Wolfgang Dummer, Vice President, Clinical Sciences  
Pamela Farmer, Senior Medical Director, Pharmacovigilance  
Henry Fuchs, Executive Vice President, Chief Medical Officer  
Brad Glasscock, Senior Director, Regulatory Affairs  
Christine Haller, Senior Medical Director, Clinical Sciences  
Chito Hernandez, Vice President, Biometrics  
Scott Jordan, Director, Contract Manufacturing  
Laurel Konkol, Director, Regulatory Affairs  
James Nickas, Executive Director, Pharmacovigilance  
Chuck O'Neill, Vice President, Pharmacological Sciences  
Yulan Qi, Senior Scientist 1, Pharmacokinetics  
Becky Schweighardt, Principal Scientist, Immunogenicity Assessment  
Peter Slasor, Director, Biostatistics  
Victoria Sluzky, Group Vice President, Quality and Process Development  
Gary Taniguchi, Senior Director, Bioanalytical Sciences  
Marjorie Tano, Associate Director, Regulatory Affairs  
Loc Vo, Senior Scientist 2, Quality Control

**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

**Product Quality Microbiology:** Product Quality Microbiology review issues were included in the July 10, 2013 information request letter. The proposed response date of August 9, 2013 is acceptable. Additional information requests may be sent after the response has been reviewed.

**Product Quality:** We remind you that your response to the review issue communicated in the filing letter is still pending.

**Clinical Pharmacology:** We have reviewed the pharmacokinetic data from Study MOR-004 in your BLA submission. The data showed that elosulfase alfa clearance (CL) was inversely correlated with age and body weight at Week 0, but the trend was not observed at Week 22. The clinical significance of age and weight effects on elosulfase alfa pharmacokinetics (PK) at Week 22 remains to be further evaluated. We remind you that your response to item #4 of the July 10, 2013 information request is needed to complete our evaluation of the impact of immunogenicity and intrinsic factors on elosulfase alfa PK.

Based on our review, elosulfase alfa CL appears to be lower in Asians than in Whites at Weeks 0 and 22, and non-Whites have less improvement in 6MWT compared to Whites. These results may be related to the literature finding of a higher incidence of severe genetic defects (large structural rearrangements) in Japanese than in Whites<sup>1</sup> and, therefore, we are concerned that genotype may have an impact on elosulfase alfa PK and efficacy. As such, the proposed dosage may not be appropriate for non-Whites or patients with certain genotypes. Further assessment of the associations of genotype with elosulfase alfa PK, efficacy, and safety is needed. Conceivably, such evaluations could be done based on the data collected in MOR-004 with additional genotyping data in patients who continue onto Study MOR-005. Alternatively, it could be done in future PMR/PMC studies.

**Clinical: Efficacy.** Upon review of the efficacy data, we are concerned about the small treatment effect seen in the six-minute walk test and its clinical meaningfulness, as well as the lack of clinically or statistically significant change in the three-minute stair climb results. Further, long-term durability of treatment effect and impact of persistent anti-drug antibodies on efficacy are not clear. Additional data are needed to support the long-term durability of treatment effect, since the treatment benefit seems to decline after 36 months.

1. FDA stated that additional data point on endurance testing (i.e., six-minute walk test and three-minute stair climb) from all patients currently receiving the proposed dose

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<sup>1</sup> Tomatsu S, Fukuda S, Cooper A, et. al. Mucopolysaccharidosis IVA: Structural Gene Alterations Identified by Southern Blot Analysis and Identification of Racial Differences. *Hum Genet* 1995;95:376-81.

(2 mg/kg/week) in Part 2 of Trial MOR005 may help demonstrate long-term durability of clinical benefit. FDA inquired whether BioMarin thought this additional data point is feasible to obtain during the current application review timeline (goal date of November 1, 2013 to allow adequate time for review).

BioMarin stated that it is not feasible to amend the protocol at this time in order to obtain a new interim 6-month assessment and provide the information by November 1, 2013. However, BioMarin agreed to provide the number of patients that could be added to long-term efficacy data from the September 2013 data cutoff for Trial MOR005.

BioMarin pointed out that after completion of the randomized controlled trial (MOR004), patients were permitted to have orthopedic surgery, which could impact the efficacy analysis of the extension trial (MOR005) due to missing assessments.

2. Because almost all patients developed high titers of anti-drug antibodies, it is difficult to assess the impact of antibodies on efficacy. FDA stated that BioMarin may be asked to evaluate whether patients should undergo tolerance induction.

**Clinical: Anaphylaxis, Hypersensitivity, and Infusion Associated Reactions.**

1. Upon review of the adverse events identified as hypersensitivity per the Angioedema SMQ and Anaphylactic Reaction SMQ, there were several cases that appeared potentially to meet the NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H *et al.*, 2006). We are concerned that more cases of anaphylaxis are present than were reported in the application. In order to correctly assess the incidence of anaphylaxis, additional case narratives are required for review.
2. Because the term (b) (4) is considered ambiguous due to the wide range of clinical events it encompasses, the term will no longer be included in product labeling. Refer to the new draft guidance, “Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products”, which does not recommend using the term (b) (4) to categorize adverse events.<sup>2</sup> The adverse events that have been described as infusion-associated reactions will be incorporated into the appropriate sections of the product labeling.

### 3.0 INFORMATION REQUESTS

**The following information requests are outstanding:**

1. Filing Communication Letter issued May 28, 2013: Response to Quality review issue pending. BioMarin’s proposed response date of August 31, 2013 is acceptable.

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<sup>2</sup> Draft Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, February 2013.  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf>

2. Letter issued July 10, 2013: Included 22 requests for information from Clinical Pharmacology and Quality Microbiology. BioMarin's proposed response dates are acceptable:
  - 4 Clinical Pharmacology requests will be submitted on August 1, 2013.
  - 18 Product Quality Microbiology requests will be submitted on August 9, 2013
3. Letter issued July 15, 2013: Included 13 requests for information from Product Quality. BioMarin's proposed response date of August 16, 2013 is acceptable.

**New Information Requests the team plans to send in the near future:**

• **Product Quality:**

1. Conduct in-use stability studies, specifically:
  - a. testing for particulate and subvisible particulates;
  - b. characterization of impurity peaks that are present in the drug product sample diluted in the saline bag; and
  - c. microbiological studies in support of the 24-hour post-dilution storage time at 2-8°C.

2.  (b) (4)

- **Clinical Pharmacology:** Elosulfase alfa clearance (CL) appears to be lower in Asians than in Whites, and the majority (12 of 15) of non-White patients in the PK dataset are Asians. Therefore, we request that you replicate the analyses presented in Figures 2.7.2.2.1.1.1, 2.7.2.2.1.1.2, and 2.7.2.2.1.1.3 (see pages 16, 17 and 18 in Summary of Clinical Pharmacology) using Asians instead of non-Whites to explore the differences in CL values between Asians and Whites at Weeks 0 and 22. Present the results in both scatter plots and box-and-whisker plots.

• **Clinical:**

1. During review of hypersensitivity reactions identified by the Angioedema SMQ and Anaphylactic Reaction SMQ (Integrated Summary of Safety Patient Listings 1.19.2 and 1.19.3), there were several cases that appeared potentially to meet the NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H *et al.*, 2006). Provide case narratives for all patients listed in the ISS Patient Listings 1.19.2 and 1.19.3. Case narratives should include the following information:
  - Premedication(s) given prior to the event
  - Specify whether the event occurred during or after infusion. If the event occurred after infusion, specify the number of hours after infusion the event occurred.
  - Detail of the event -- specify affected body location/distribution, duration of the event, changes in vital signs, and concurrent symptoms
  - Medications and medical interventions administered to treat the event
  - Outcome of the event

- If the patient resumed treatment, specify how soon after the event he/she resumed treatment. Indicate whether any changes were made to premedication(s) with the restart of treatment and whether symptoms recurred.

In addition, you should review the adverse event database to ensure that you are providing narratives for all patients who meet the NIAID/FAAN 2006 criteria for anaphylaxis, regardless of IgE antibody status.<sup>3</sup>

- **Immunogenicity:**

1. Because all patients had high titer anti-BMN110 antibodies, it is difficult to assess the impact of antibodies on efficacy. For some products, e.g. (b) (4)

You did not assess titer in your NAb assay. However it is possible that % inhibition in the NAb assay may be a useful surrogate for titer. Please assess whether % inhibition in the NAb assay is correlated with 6-minute walk test results over time. Provide separate analyses for data up to 24 weeks and up to 48 weeks.

2. Depending on the results of the analysis described above, additional assays may be needed to characterize the impact of NAb on efficacy. This may include an assay to measure the titer of NAb, a cell-based assay to evaluate uptake inhibition, or both.

#### 4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time, and there is currently no need for a REMS.

#### 5.0 ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is planned for Tuesday, November 19, 2013, and the application will be reviewed by the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC). FDA is in the process of identifying additional experts in clinical and biochemical genetics, pulmonology, cardiology, neurology, neurosurgery, and orthopedic surgery to supplement the standing committee. FDA encouraged BioMarin to communicate types of subspecialists they would like to see represented in the panel, and stated that BioMarin could recommend names of experts for consideration.

Preliminary topics of discussion include the extent to which changes in 6-minute walk test (6-MWT) from baseline to Week 24 assess treatment benefit in patients with Morquio A syndrome and whether the data presented in the application support the effectiveness of Vimizim for

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<sup>3</sup> Sampson H et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

treatment of MPS IVA. FDA will work with BioMarin to reduce unnecessary overlap in presentations, and is amenable to reviewing the presentations in a conceptual way approximately 4 weeks prior to the AC meeting.

FDA stated that any interested party can participate in the open public hearing during the AC meeting, but they would need to disclose any potential conflict of interest.

## **6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

The proposed date for the late cycle meeting (LCM) is November 12, 2013. In addition, please note the following projected milestone dates:

Labeling, PMR/PMC to Applicant:	October 28, 2013
Discipline Review Letters:	November 4, 2013
LCM Background Package:	October 30, 2013
Advisory Committee Meeting:	November 19, 2013
PDUFA Goal Date:	February 28, 2014

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/s/  
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ELIZABETH A FORD  
08/07/2013



BLA 125460/0

**INFORMATION REQUEST**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

1. In section 3.2.A.2.1 of your BLA, you specify that [REDACTED] (b) (4) The master file you reference, [REDACTED] (b) (4) does not provide sufficient information to assess the adequacy of virus testing of this human sourced component and your master cell bank has not been tested for the presence of any human viruses. This raises a concern that human virus may be present in your cell bank and this could impact the safety of your final drug product. Therefore, provide a risk assessment and relevant data (literature reference, etc.) on human virus infection and propagation in your CHO-K1 cell line. Specific human viruses that you should consider in your evaluation include hepatitis A, B, C viruses, enteroviruses, human HIV-1, HIV-2, HTLV-1, HTLV-2, circoviruses, parvovirus B19, papillomaviruses, human polyomaviruses, human adenoviruses, Epstein-Barr virus, human cytomegalovirus, human herpes viruses 6, 7, 8, and simian viruses that could potentially infect humans (SV40, SFV, SIV, SRV, STLV). Based on this information, you should provide a risk assessment and propose and justify a strategy to test your master cell bank for the most relevant human viruses, or justify why testing for the presence of human viruses is not necessary.

2. In regard to your in-use studies, we have the following comments and request for information:

a.

b.

c.

(b) (4)

We request a written response by August 24, 2013, or provide a timeline for when the studies will be completed for the items enumerated above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
08/02/2013



BLA 125460

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

BioMarin Pharmaceutical Inc.  
105 Digital Drive  
Novato, CA 94949

ATTENTION: Marjorie Tano  
Associate Director, Regulatory Affairs

Dear Ms. Tano:

Please refer to your Biologics License Application (BLA) dated and received March 29, 2013, submitted under section 351 of the Public Health Service Act, for Elosulfase Alfa, 1 mg/mL.

We also refer to your April 29, 2013, correspondence, received April 29, 2013, requesting review of your proposed proprietary name, Vimizim. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your April 29, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Elizabeth Ford at (301) 796-4795

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
07/25/2013



BLA 125460/0

**INFORMATION REQUEST**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

1. In order to understand the release and stability methods system suitability and reporting of results, provide the SOPs for all FBDS and DP release and stability test methods.
2. The cellular uptake method validation you submitted did not contain sufficient information regarding specificity. Provide relevant assay development data that demonstrate that mannose-6-phosphate inhibits cellular uptake, while other molecules, such as mannose-1-phosphate, do not.
3. You provided [REDACTED] (b) (4)
4. Provide the process development reports [REDACTED] (b) (4)
5. You have not provided a protocol for the qualification of a new working cell bank. Be advised that without an approved qualification protocol, you will need to submit a prior approval supplement to the Agency before the implementation of a new cell bank into

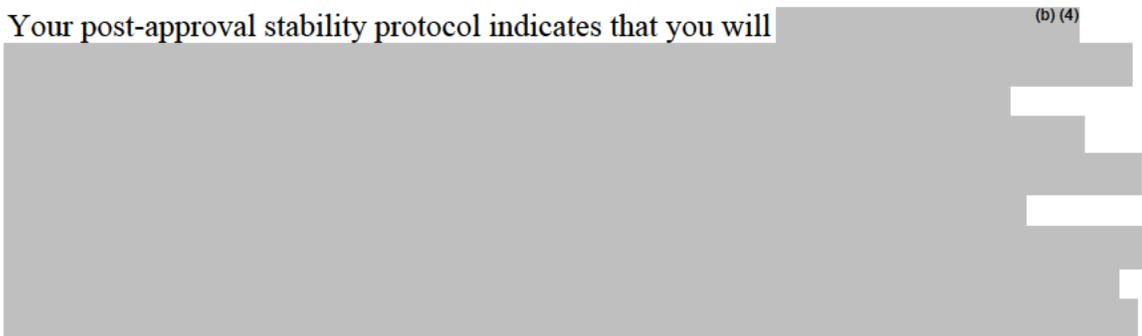
your manufacturing process. We recommend that you provide a protocol for the qualification of a new working cell bank as part of your BLA submission.

6. You provided a list of tests and acceptance criteria supporting the qualification of the reference material. However, there is no detailed information on number of samples used for each test. Please provide your qualification protocol for reference material, including the above information. Additionally, provide the protocols that will be used to qualify new primary and working reference materials. These protocols should include the number of samples tested for each assay and acceptance criteria that should be tighter than the release acceptance criteria, in particular for those assays where results are expressed as percentage of the reference standard, to avoid drift on product quality attributes over time.
7. Provide the technical transfer reports for all the test methods to be transferred to your Shanbally, Ireland facility.
8. Regarding rhGALNS lot P401420-12105, we noted that the total protein/rhGALNS ratios are (b) (4)  

9. In order to understand how the (b) (4)  

10. Provide your validation report for the (b) (4)  

11. You provided validation data to support (b) (4)  

12. Your post-approval stability protocol indicates that you will (b) (4)  


(b) (4)

With this comment in mind, please update your annual stability protocol to incorporate these suggestions, or provide a scientifically valid justification as to why these updates are not necessary.

13. You proposed acceptance ranges and limits for the assay used to monitor quality of the product at release and during shelf life storage. We find that some of the rhGALNS FBDS and DP release and stability acceptance criteria you propose are not justified by the method capabilities and your clinical and manufacturing experience. Please revise the following:

(b) (4)

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the remaining sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
07/15/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for elosulfase alfa.

We are reviewing the Clinical Pharmacology and Quality sections of your application and have determined that the following information is necessary to take a complete action on your application:

### CLINICAL PHARMACOLOGY

1. In your response to FDA information request dated May 10, 2013, you provided long-term stability (LTS) data for elosulfase alfa samples in (b) (4)

Provide a list of these 57 samples including the subject ID, treatment arm, dosing week, elapsed sampling time relative to the start of infusion, the date and time of sample collection, the date and time of sample analysis. Alternatively, the requested information can be incorporated into the requested dataset as described in item 2 below, with a separate column to flag the stability status of each sample.

2. In the pre-BLA Meeting Minutes dated January 10, 2013, we requested that, in addition to the Summary of Pharmacology Findings, you submit all datasets including the original pharmacokinetic (PK) and pharmacodynamic (PD) datasets, PK/PD analysis datasets, and PK/PD parameter datasets for the completed studies. We have received the original PK and

PD datasets. However, we did not find the analysis-ready PK dataset that corresponds to your PK analysis results. We request that you submit one analysis-ready PK dataset containing the following information for Study MOR-004. The dataset should be formatted in a way that it can be imported directly for non-compartmental analysis.

- a. Subject ID
- b. Demographic information including age, sex, and race
- c. Treatment arm (i.e., QOW or QW)
- d. Dosing Week (i.e., Week 0/Week 22) and the corresponding body weight
- e. Actual dose of elosulfase alfa that the patient received
- f. Date and time of each dosing events (including but not limited to start and completion of elosulfase alfa infusion) and PK sample collection to determine elosulfase alfa concentration at Weeks 0 and 22
- g. Elapsed times relative to the start of infusion for each of the dosing events and PK sample collection for elosulfase alfa concentration determination during Weeks 0 and 22

Provide a separate analysis-ready PK/PD dataset, which contains elosulfase alfa PK parameters, along with the corresponding PD, efficacy, and safety measurements that were analyzed to evaluate the exposure-response relationship of elosulfase alfa described in Section 2.7.2 Summary of Clinical Pharmacology Studies.

3. For the non-compartmental analysis, provide information on the time points that were used to determine the elimination rate constant, which was used subsequently to calculate the elosulfase alfa half-life. If these time points differed among subjects, provide the specific time points that were used for each subject.

According to Table 1 of your proposed product label, elosulfase alfa infusion volumes and infusion rates varied according to the patient's body weight and tolerability, respectively. Clarify whether the variable infusion rates were used to determine PK parameter values for each subject in the non-compartmental analysis. If so, provide the specific dosing information for each subject as described in item 2, above.

4. In Section 2.7.2 (Summary of Clinical Pharmacology Studies) of Study MOR-004, we noted that mean  $AUC_{0-t}$ ,  $C_{max}$ , and  $t_{1/2}$  values were greater at Week 22 compared to those at Week 0. You indicated that these differences were possibly attributed to the formation of neutralizing antibodies capable of interfering with the cellular uptake of elosulfase alfa. This hypothesis suggests that the bioanalytical assay (a ligand binding assay) for determination of elosulfase alfa concentration cannot differentiate the Nab-elosulfase alfa complex (i.e., complexed elosulfase alfa) from the uncomplexed elosulfase alfa. In other words, the assay measures the total sum of uncomplexed and complexed elosulfase alfa. Provide supportive data to show that, in addition to uncomplexed BMN 110, the ligand binding assay for detection of elosulfase alfa in human  $K_3EDTA$  plasma can also detect the elosulfase alfa-Nab complex in plasma.

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/s/  
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BRIAN K STRONGIN  
07/10/2013



BLA 125460/0

## INFORMATION REQUEST

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your biologics license application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351 of the Public Health Service Act for BMN110 (elosulfase alfa).

We have reviewed the CMC section of your application and have determined that the following information is necessary to take a complete action on your application:

1. Process Characterization and Risk Assessment (PCRA) document

We request a written response by June 11, 2013 to the item enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me, at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Quality Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Lyndsay.Hennessey@fda.hhs.gov

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/s/  
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LYNDSAY J HENNESSEY  
06/07/2013



BLA 125460/0

**EXTENSION USER FEE GOAL DATE**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologics License Application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351(a) of the Public Health Service Act for elosulfase alfa.

On May 10, 2013, we received your May 10, 2013 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 February 28, 2014.

As per the filing communication dated May 28, 2013, if major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 28, 2013.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Andrew E. Mulberg, M.D., F.A.A.P.  
Deputy Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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ANDREW E MULBERG  
05/28/2013



BLA 125460/0

**FILING COMMUNICATION**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologics License Application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351(a) of the Public Health Service Act for elosulfase alfa.

We also refer to your amendments dated April 25, 2013, April 30, 2013, and May 10, 2013.

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**. 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> . Therefore, the user fee goal date is November 29, 2013.

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 28, 2013. In addition, the planned date for our internal mid-cycle review meeting is July 18, 2013. 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. The Division is concerned about the level of evidence to establish the effectiveness of your drug product in the target patient population. Your evidence includes a single 24-week Phase 3 randomized, placebo-controlled trial (MOR-004), with a supporting

uncontrolled extension study (MOR-005) that demonstrates a “continuing upward trajectory in [6 minute walk test] improvement.” At the Pre-BLA meeting held on December 11, 2012, the Division had recommended that a longer (1-2 year long) placebo-controlled trial be conducted to evaluate the efficacy of elosulfase alfa. Without a controlled trial, we cannot be sure that the trends toward improvement in the primary efficacy endpoint (6 minute walk test) and the secondary efficacy endpoint (3 minute stair climb test) seen in the extension study are related to a BMN 110 treatment effect. In addition, it is not clear whether the extent of improvement seen on the primary efficacy endpoint in the placebo-controlled trial (MOR-004) represents a clinically meaningful benefit to patients with Morquio A syndrome. Therefore, the Division will carefully review these issues over the course of the review period and convene an advisory committee meeting to discuss this application.

2. You provided stability data under accelerated ( $25 \pm 2$  °C/  $60 \pm 5\%$  relative humidity) and stressed ( $40 \pm 2$  °C/  $75 \pm 5\%$  relative humidity) storage conditions for both phase 3 and commercial material. The specific activity data you provided indicate that, under both conditions, (b) (4)

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.

We request that you submit the following information:

**Chemistry, Manufacturing, and Controls (CMC):**

1. Provide certificates of analysis for your formulated bulk drug substance (FBDS) and drug product (DP) process qualification lots.
2. Provide representative certificates of analysis for raw materials used in the manufacturing process.
3. Provide your risk assessment report (V11-075) for raw materials used in the production process. Describe your rationale for monitoring (b) (4)
4. Provide a linear regression analysis of  $k_{cat}$  vs. specific activity within the specification range of (b) (4) Include both graphic and tabular data for all lots of rhGALNS used in this study.

5. Justify the discrepancies in (b) (4) between Table 3.2.S.2.4.3.1 and Table 3.2.S.2.5.8.2.1 or Table 9.4.1 in GLNS-PV-4004.
6. Provide the results of in-process testing performed as part of the validation of the manufacturing process of (b) (4).
7. Provide a justification for the acceptance criteria of the in-process tests performed during the manufacture of FBDS.
8. Submit an update on stability data available for Bulk Drug Substance (BDS) lots P40142-12105, P40142-1103, and P4014-10005 and FBDS rhGALNS lots P40152-12008, P40152-12009, P40152-12010, P40152-12112, D40012-12101, and P40152-11101.
9. Provide the risk assessment you performed to determine the suitability of (b) (4) bags, and (b) (4) used during the manufacture of rhGALNS. Additionally, submit the risk assessment for (b) (4) for all materials in contact with the product, and the results of all relevant (b) (4) studies performed.
10. You provided Table 3.2.S.4.4.3.1, Table 3.2.S.4.4.3.2, and Table 3.2.P.5.4.1 reporting FBDS, BDS and DP lot numbers, respectively, and their use. However, these lot numbers do not correlate with the lot numbers used in clinical trials. Provide an updated table containing lot traceability for phase 3 and commercial processes. This table should include BDS, FBDS, and DP lot numbers, and the corresponding lot numbers used in clinical trials.
11. Clarify if you used rhGALNS drug product lot BSJJ03 in your safety and efficacy studies.

12. (b) (4)

13. (b) (4)

14

15

(b) (4)

16. Clarify whether release testing and batch release for BMN 110 drug product distributed in the U.S. is performed only at the BioMarin site in Novato, CA or if this function may also be performed at the BioMarin site located in Ireland.

**Pharmacology and Toxicology (non-clinical):**

17. Provide justification for not performing evaluations of behavior, locomotor activity, sensory functions, and reflex development in the F1 generation in the study entitled “A Developmental and Perinatal/Postnatal Reproduction Study of BMN 110 by Intravenous Injection in Rats, Including a Postnatal Behavioral/Functional Evaluation”. These parameters are routinely included in pre- and postnatal developmental studies (see ICH guidance S5(R2)).
18. Describe the method used for measuring the specific activity of the following lots used in the 52-week toxicity study in monkeys: 11428P95, 11541P04, and 11541P73.

**Immunogenicity**

19. Provide a description of how you qualify the critical reagent (b) (4) that was used in your neutralization assay. The description should include, but not be limited to, identification methods and results, molecular weight, storage condition, and whether it is a monomer or a dimer.
20. Provide a detailed assay protocol for your IgE assay that includes a description of the secondary detecting reagent(s) and positive controls.
21. Provide a detailed justification for why you are unable to develop and validate an assay to assess for inhibition of enzymatic activity by anti-BMN110 antibodies.
22. Provide individual patient data for each treatment group in Study MOR004. Include the patient identification number and genotype and/or residual enzyme levels.
23. You measured antibodies that interfere with receptor binding at seven time points and report the data as positive or negative. Provide the percent inhibition for individual patients who tested positive at each time point for each treatment group in Study MOR004.

24. Provide anti-drug antibody data for each patient during 25 to 48 weeks of treatment in the MOR004/MOR005 study as soon as they are available.

During our preliminary review of your submitted labeling, we have identified the following labeling issues:

### **Highlights**

1. Propose an established pharmacologic class (EPC) to be included in the Highlights section, and provide a rationale for your proposal. The EPC should be scientifically valid and clinically meaningful (see FDA guidance, “Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information”).
2. White space must be present before each major heading in HL.
3. Initial U.S. Approval in HL must be placed immediately beneath the product title, bolded, and include the verbatim statement “Initial U.S. Approval:” followed by the 4-digit year. Therefore, there must not be a space between the product title and initial U.S. approval lines.
4. Under Adverse Reactions, for drug products other than vaccines, the verbatim bolded statement must be present: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).” An email address, fax number, or general link to a company’s website does not meet the requirement to have AR reporting contact information in HL. Delete the (b) (4) inserted into this statement, or provide the web address of the direct link to the site.
5. Bolded revision date (i.e., “Revised: MM/YYYY or Month Year”) must be at the end of HL. Change the revision date from MM/2013 to MM/YYYY.

### **Contents: Table of Contents (TOC)**

6. All section headings must be **bolded** and in UPPER CASE.

### **Full Prescribing Information (FPI)/Adverse Reactions**

7. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the*

*clinical trials of another drug and may not reflect the rates observed in clinical practice.*"

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by June 10, 2013. The resubmitted labeling will be used for further labeling discussions.

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:

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

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.

You submitted establishment information that is not required as part of a BLA for specified products. Please refer to the CMC guidance document, *Guidance for Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In-Vivo Use*, for the information you should include in your application. We will assess this information during the pre-license inspection of your establishment, but not as part of your application. Its inclusion in the file does not constitute approval.

**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, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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ANDREW E MULBERG  
05/28/2013

## Ford, Elizabeth

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**From:** Ford, Elizabeth  
**Sent:** Friday, May 03, 2013 5:09 PM  
**To:** Marjorie Tano (MTano@bmrn.com)  
**Cc:** Ford, Elizabeth  
**Subject:** FW: BLA 125460/elosulfase alfa/Discussion points for May 3, 2013 teleconference

Dear Ms. Tano,

Please refer to the Clinical Pharmacology comment listed as item 2 in the attached message, and to today's 12:30-1:00 PM (EDT) teleconference with BioMarin. As per the discussion, the Clinical Pharmacology team would like to provide the following additional information:

There are two places in which results for matrix effect are stated to be pending.

1. It is stated that the report is pending for matrix effect in Table 2.7.1.1.1.1.1, on page 6 of the Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods.
2. It is also stated that matrix effect "will be performed in-study when samples are available" in Table 9, Assay Performance Characteristics, on page 17 of the validation report BMN110-12-017.

Please provide a date by which this information can be submitted to the BLA.

Sincerely,

Elizabeth A.S. Ford, RN  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-0193

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**From:** Ford, Elizabeth  
**Sent:** Thursday, May 02, 2013 2:56 PM  
**To:** Marjorie Tano (MTano@bmrn.com)  
**Cc:** Ford, Elizabeth (Elizabeth.Ford@fda.hhs.gov)  
**Subject:** BLA 125460/elosulfase alfa/Discussion points for May 3, 2013 teleconference

Dear Ms. Tano,

Please see the below list of information identified as required for the review of BLA 125460/elosulfase alfa. This information is being provided to you in preparation for the May 3, 2013 teleconference between BioMarin and the Division of Gastroenterology and Inborn Errors Products.

## **Clinical Pharmacology**

1. Long-term stability data for frozen BMN 110 in human K<sub>3</sub>EDTA plasma samples beyond the (b) (4) data.
2. Matrix effect on the BMN 110 in human K<sub>3</sub>EDTA plasma assay to verify the selectivity and specificity of the BMN 110 analytical assay.
3. Incurred sample reanalysis results to verify the performance of the BMN 110 in human K<sub>3</sub>EDTA plasma assay during study sample analysis.

## **Quality Microbiology**

(b) (4)

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/s/  
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ELIZABETH A FORD

05/22/2013

cleared through clinical pharmacology team (including team leader) and CDTL prior to issue to the applicant.

## Ford, Elizabeth

---

**From:** Laurel Konkol <LKonkol@bmrn.com>  
**Sent:** Tuesday, May 07, 2013 10:40 PM  
**To:** Ford, Elizabeth  
**Subject:** Progress report following May 3 2013 teleconference with BioMarin

Dear Elizabeth,

We appreciate the feedback received from the Agency on May 3<sup>rd</sup> with respect to items that are needed to enable review of the application. To this end, we have been diligently pursuing all items with the intent of submission of the majority of the items on May 10, 2013. At this time we'd like to ensure our plan to address the requests focused on the Quality section is adequate pending review of the submission. We are open to discussing any or all of these items should there be any questions. Clinical Pharmacology items 1, 2, and 3 will be submitted on May 10. Regarding the Quality items, our plan to provide the information is summarized below:

To be provided by May 10, 2013

- [Redacted] (b) (4)
- [Redacted] (b) (4)
- [Redacted] (b) (4)
- Summary of Rabbit Pyrogen Test Results for a BMN 110 drug product lot (testing performed on May 9, 2013) – Item 11  
(A final report will be available within 2 working days)
- Updated DMF Letter of Authorization - Item 12

[Redacted] (b) (4)

BioMarin would like to ask the Agency to confirm that by providing the items listed above by May 10, 2013 and performing the additional container closure integrity test studies as described above, that the Agency will find the application suitable for acceptance. We look forward to working with you on this BLA.

Thank you very much,

Laurel Konkol  
415 506 6597

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/s/  
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ELIZABETH A FORD  
05/22/2013

## **Ford, Elizabeth**

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**From:** Ford, Elizabeth  
**Sent:** Thursday, May 02, 2013 2:56 PM  
**To:** Marjorie Tano (MTano@bmrn.com)  
**Cc:** Ford, Elizabeth (Elizabeth.Ford@fda.hhs.gov)  
**Subject:** BLA 125460/elosulfase alfa/Discussion points for May 3, 2013 teleconference

Dear Ms. Tano,

Please see the below list of information identified as required for the review of BLA 125460/elosulfase alfa. This information is being provided to you in preparation for the May 3, 2013 teleconference between BioMarin and the Division of Gastroenterology and Inborn Errors Products.

### **Clinical Pharmacology**

1. Long-term stability data for frozen BMN 110 in human K<sub>3</sub>EDTA plasma samples beyond the (b) (4) data. (b) (4) verify the validity of the pharmacokinetic data.
2. Matrix effect on the BMN 110 in human K<sub>3</sub>EDTA plasma assay to verify the selectivity and specificity of the BMN 110 analytical assay.
3. Incurred sample reanalysis results to verify the performance of the BMN 110 in human K<sub>3</sub>EDTA plasma assay during study sample analysis.

### **Quality Microbiology**

(b) (4)

11. Rabbit pyrogen test data as required in 21CFR610.13(b) was not provided for BMN110 drug product. The rabbit pyrogen test should be performed at least once to demonstrate that the drug product does not contain (b) (4)
12. The Letter of Authorization for West DMF (b) (4) does not reference the most recent update to the DMF. Please provide an updated letter that references the 2012 update to the DMF.

Sincerely,

Elizabeth A.S. Ford, RN  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-0193

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ELIZABETH A FORD

05/03/2013

Cleared through each discipline (including TL), and DGIEP Chief, Project Management Staff prior to issue to the applicant.

## Ford, Elizabeth

---

**From:** Ford, Elizabeth  
**Sent:** Wednesday, April 24, 2013 10:37 PM  
**To:** Marjorie Tano (MTano@bmrn.com)  
**Cc:** Ford, Elizabeth (Elizabeth.Ford@fda.hhs.gov)  
**Subject:** BLA 125460/elosulfase alfa

**Importance:** High

Dear Marjorie,

In reference to BLA 125460, submitted on March 29, 2013, the Reviewer's Guide 0000 in Section 1.2 states that the drug substance manufacturing campaign at the [REDACTED] (b) (4) will begin early April 2013 and continue through the end of October 2013. Provide a more detailed production schedule which lists specific manufacturing activities for the May through July timeframe. We request a written response to the item outlined above by May 2, 2013.

Please submit your proprietary name review as per the Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names. As noted in the guidance, the proprietary name review should be submitted as a separate submission (or cover letter if provided on the same day as the BLA submission). Provide a separate cover letter requesting the proprietary name review. The proprietary name review should include all labels and labeling, including carton and container, or reference the submission date in the cover letter for the name request.

Your FDA form 356h does not include an IND cross reference number. If you wish to cross-reference an IND number as part of the review of this BLA, update this section of FDA form 356h.

Sincerely,

Elizabeth A.S. Ford, RN  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-0193

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ELIZABETH A FORD

05/01/2013

Cleared through the review team and through DGIEP Chief, Project Management Staff prior to issue.



BLA 125460/0

**BLA ACKNOWLEDGEMENT**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

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:** elosulfase alfa

**Date of Application:** March 29, 2013

**Date of Receipt:** March 29, 2013

**Our Secondary Tracking Number (STN):** BLA 125460/0

**Proposed Use:** Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)

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/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

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

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

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

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](mailto: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 me, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Elizabeth A.S. Ford, R.N.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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ELIZABETH A FORD  
04/16/2013



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** December 11, 2012, 10:00-11:00 AM  
**Meeting Location:** White Oak Building 22, Room 1419

**Application Number:** IND 101234  
**Product Name:** BMN 110 (recombinant human N-acetylgalactosamine-6-sulfatase)  
**Indication:** Mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA)  
**Sponsor/Applicant Name:** BioMarin Pharmaceutical Inc.

**Meeting Chair:** Melanie Blank, M.D.  
**Meeting Recorder:** Elizabeth A.S. Ford, R.N.

**FDA ATTENDEES**

Office of Drug Evaluation III

Julie Beitz, M.D., Director

Victoria Kusiak, M.D., Deputy Director

Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Error Products (DGIEP)

Donna Griebel, M.D., Director

Andrew E. Mulberg, M.D., Deputy Director

Melanie Blank, M.D., Acting Clinical Team Leader

Nancy Snow, M.D., Clinical Reviewer

David Joseph, Ph.D., Nonclinical Team Leader

Fang Cai, Ph.D., Nonclinical Reviewer

Elizabeth A.S. Ford, R.N., Senior Regulatory Health Project Manager

Office of Translational Sciences

Office of Clinical Pharmacology/Division of Clinical Pharmacology 3

Yow-Ming Wang, Ph.D., Biologics Team Leader

Office of Biotechnology Products/Division of Therapeutic Proteins

Cristina Ausin, Ph.D., Staff Fellow

Emanuela Lacana, Ph.D., Associate Chief, Laboratory of Chemistry

IND 101234  
Meeting Minutes  
Pre BLA Meeting

Laura Salazar-Fontana, Ph.D., Immunogenicity Team Leader

Office of Biostatistics/Division of Biometrics III

Freda Cooner, Ph.D., Statistics Reviewer

Office of New Drugs/Immediate Office

Anne Pariser, M.D., Acting Associate Director for Rare Diseases

Larry Bauer, R.N., M.A., Regulatory Health Project Manager

Office of Orphan Products Development

Jeff Fritsch, Regulatory Review Officer

Office of Surveillance and Epidemiology

Phong Do, Pharm.D., Project Manager, Project Management Staff

Thang La, Safety Reviewer, Division of Pharmacovigilance I

Denise Baugh, Safety Evaluator, Division of Medication Error Prevention and Analysis

PDUFA V Program Assessment

Kim Taylor, OPI/OPA/PES, Operations Research Analyst

(b) (4)

**SPONSOR ATTENDEES**

Diane Androvich, M.S., Senior Manager, Statistical Programming

Wolfgang Dummer, M.D., Ph.D., Vice President, Clinical Sciences

Pamela L. Farmer, M.D., FAAFP, Senior Medical Director, Pharmacovigilance

Henry Fuchs, M.D., Executive Vice President, Chief Medical Officer

Brad Glasscock, Pharm.D., Senior Director, Regulatory Affairs

Christine Haller, M.D., Senior Director, Clinical Sciences

Laurel Konkol, M.S., Associate Director, Regulatory Affairs

Debra Lounsbury, R.N., M.S., Principal Scientist, Clinical Sciences

Gary Taniguchi, Ph.D., Senior Director, Bioanalytical Science

Marjorie Tano, Associate Director, Regulatory Affairs

Amy Waterhouse, Vice President, Regulatory Affairs

Paul Harmatz, M.D., Principal Investigator, Children's Hospital Oakland

## 1.0 BACKGROUND

BioMarin is developing Recombinant N-acetylgalactosamine-6-sulfatase (BMN 110) as an enzyme replacement therapy (ERT) for the treatment of mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA). BMN 110 is produced in a genetically engineered Chinese Hamster Ovary mutant cell line that over-expresses the cDNA encoding for the full human GALNS protein.

On July 28, 2010, FDA and BioMarin met at a Pre-IND meeting to discuss a proposed phase 3 clinical study design and the adequacy of the clinical, nonclinical, and CMC programs for BMN

110. FDA provided comments regarding BioMarin's proposed study design and endpoints, including specific information that would be necessary to justify the use of the 6 Minute Walk Test (6MWT) as an acceptable clinical endpoint in clinical trials for MPS IVA.

As recommended by FDA at the Pre-IND meeting, BioMarin submitted a request for a special protocol assessment (SPA) of clinical protocol MOR-004 on December 3, 2010. FDA issued a SPA No-Agreement Letter on January 1, 2011. FDA agreed that the 6MWT could be used as a primary endpoint for the pivotal study in MPS IVA patients but did not agree with the proposed null hypothesis for the primary statistical analysis.

BioMarin submitted a Type C meeting request on April 11, 2012, seeking agreement with the Agency on clinical and statistical aspects of the clinical development plan. The meeting was granted, and scheduled for July 10, 2012. Preliminary comments issued by FDA articulated continued concerns regarding the proposed study dose and dose regimen as well as proposed study endpoints and trial duration for the pivotal trial. Following receipt of the preliminary comments, the meeting was cancelled by BioMarin.

BioMarin requested a pre-BLA meeting on August 20, 2012. The meeting was granted, and scheduled for December 11, 2012. BioMarin plans to submit a BLA for BMN 110 in March 2013.

## 2.0 DISCUSSION

### 2.1 Introductory Comments

**We are concerned that the extent of safety and efficacy data that you are proposing to include in this BLA may not be sufficient to make an adequate assessment of the safety and efficacy of BMN110 at the proposed dose of 2.0 mg/kg/wk.**

**The proposed BLA will be subject to "the Program" under PDUFA V. Under "the Program," all major components of the application are expected**

to be included in the original application and are not subject to agreement for late submission (please see section 3.0). Therefore, you will need to submit the complete safety and efficacy analysis (except for the 120-day update) at the time of original submission. We strongly recommend that you submit a larger body of safety and efficacy data than what you have proposed. In general, to assess adequately the safety of enzyme replacement therapies (ERT), FDA needs to have at least one year of safety data on at least 50 patients who have taken a dose of ERT that is at least as high as what is proposed to be marketed. In your submission, it appears that only 13 patients have completed 48 weeks of treatment with the proposed dose of 2.0 mg/kg/wk. It is essential to establish long-term safety for this product as it is likely that patients will need to be on this product for their entire lives. For this reason, we request that you strongly consider collecting more long-term data on the dose you plan to market prior to submitting your BLA.

In addition, the lack of an improvement shown on the 3 minute stair climbing test (3MSCT) in your pivotal trial casts doubt on the efficacy of BMN110. We highly recommend that you conduct a longer (1-2 year-long) placebo-controlled trial to evaluate the efficacy of BMN110 in patients with Mucopolysaccharidosis IV (MPS- IV) because it appears from your extension study that there could be continued improvement in 3 MSCT and 6 minute walk test (6MWT) that may be attributable to a treatment effect. Without a controlled trial, we cannot be sure that the trends toward improvement in the 3MSCT and 6MWT seen in the extension study are related to a BMN 110 treatment effect.

Additional Discussion: *The sponsor agreed to FDA's outlined requirements.*

## 2.2 Meeting Questions

### Question 1:

Does the Agency agree that the proposed nonclinical and clinical data package will provide an adequate basis for submission of a BLA for BMN 110 to treat patients with MPS IVA (refer to Section 6 and Section 7)?

### FDA Response to Question 1:

#### *Non Clinical*

To support a BLA submission, your nonclinical data package should also include a carcinogenicity assessment of BMN 110, in accordance with the addendum to ICH S6 (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals). Aside from this deficiency, the completed and ongoing nonclinical studies appear to be adequate to support a BLA submission.

*Clinical and Clinical Pharmacology*

**In addition to Summary of Clinical Pharmacology Findings in the eCTD submission, provide a Clinical Pharmacology Summary as a review aid, according to the format provided in the appended document. It can be submitted under eCTD section 1.11.4. As indicated in the appendix, all datasets should be provided, including the original pharmacokinetic (PK) and pharmacodynamic (PD) data, PK/PD analysis datasets, and PK/PD parameter datasets for the studies.**

**In your BLA submission, provide justifications for the selection of 2 mg/kg as the appropriate dose of BMN 110 for the treatment of patients with MPS IVA. We are concerned that the appropriate dose may not have been investigated as your data suggested that a higher dose than what you tested in MOR-004 may have better efficacy. We refer you to previous Agency advice provided in association with your August 2012 Pre-IND meeting, and July 2012 Type C meeting (meeting minutes dated August 27, 2012 and July 9, 2012 respectively) which recommended conducting a dose-ranging study.**

*Clinical*

**As mentioned in the introductory paragraph, we have concerns that the extent of the safety and efficacy data will be inadequate to assess the safety and efficacy of BMN110 at the dose that you are proposing to market.**

**Additional Discussion: See additional discussion under introductory comments.**

**Question 2:**

**Does the Agency find the proposed structure, format, and content of the BLA acceptable (refer to Section 9), including:**

- a. **the provision of final full clinical study reports (CSRs) in Module 5 for the completed Phase 1/2 study (MOR-002) and completed Phase 3 study (MOR-004)?**

**FDA Response to Question 2a:**

**We agree with your proposal to provide the final full clinical study reports in Module 5 for the completed Phase 1/Phase 2 study (MOR-002) and completed Phase 3 study (MOR-004). However, because of insufficient safety and efficacy data, we do not think that these studies alone are sufficient for supporting a marketing application.**

**Additional Discussion: None**

- b. the provision of abbreviated CSRs in Module 5 for the two ongoing extension studies (MOR-100 and MOR-005) and the two ongoing ancillary Phase 2 studies (MOR-007 and MOR-008), as recommended in the ICH E3 Guidance on "Structure and Content of Clinical Study Reports"?

**FDA Response to Question 2b:**

**We do not agree with your proposal to provide abbreviated CSRs in Module 5 for the two ongoing extension studies (MOR-100 and MOR-005) and two ongoing ancillary phase 2 studies (MOR-007 and MOR-008). We highly recommend that you submit the CSRs of these studies when there is substantially more accumulated data. As noted in the introductory comments, we need to see complete data and analyses on at least 50 patients who have completed at least 52 weeks of treatment with BMN 110 at the dose you plan to market before we can conduct an adequate assessment of the safety and efficacy of BMN110.**

**Additional Discussion: BioMarin provided clarification regarding the content of the abbreviated CSRs (see slide deck). FDA agreed to the sponsor submitting "abbreviated" CSRs because the contents will include a summary of the complete safety data and efficacy data up until the cut point when at least 50 patients will have completed a year on study drug at the dose that the sponsor is planning to label. The sponsor also agreed that the "abbreviated" CSRs will include a discussion and presentation of the available exploratory efficacy endpoint data and analyses at the same cut point.**

- c. BioMarin's proposal for the clinical summary documents in Module 2 and the Integrated Summary of Safety in Module 5.3.5.3?

**FDA Response to Question 2c:**

**See FDA introductory comments. We do not believe that you have collected an adequate extent of safety information for FDA to conduct a thorough review of the safety of BMN 110 at 2.0 mg/kg/day. When a sufficient extent of safety data have been collected, analyzed and summarized, as explained in the introductory statement, you may submit a Summary of Clinical Safety that will include both a summary of data from the individual studies in Module 2 and an integrated analysis of safety with information from multiple clinical studies in Module 5.3.5.3.**

**Additional Discussion: None**

**Question 3: With respect to the data tabulation datasets and analysis datasets for the BLA (refer to Section 10):**

- a. Is the proposed plan to submit data in SDTM and ADaM datasets for MOR-002, MOR-100, MOR-004, and MOR-005 acceptable to the Agency?

**FDA Response to Question 3a:**

**We agree with the proposed plan to submit data in SDTM and ADaM datasets for MOR-002, MOR-100, MOR-004 and MOR-005. Provide a well commented and organized software program written for each analysis dataset and efficacy table created.**

**Additional Discussion: None**

b. Is the proposed plan to submit (b) (4) acceptable to the Agency?

**FDA Response to Question 3b:**

**We do not agree with your proposal (b) (4)  
(b) (4) Provide these datasets as separate datasets.**

**Additional Discussion: FDA agrees to the sponsor's plan to submit a combined dataset, subject to FDA's review of the sample dataset that the sponsor agreed to provide to FDA in early January.**

c. Is the proposed plan to submit (b) (4) data from MOR-007 and MOR-008 with the (b) (4)

**FDA Response to Question 3c:**

**All data, including the data for studies MOR-007 and MOR-008 should be provided in electronic format upon submission. We are interested in being able to explore the safety data in subjects under 5 years of age (study MOR-007). We are also interested in exploring both safety and efficacy data of the higher-dosed patients in MOR-008.**

**Additional Discussion: (See BioMarin slide deck) FDA agreed to BioMarin's plan to submit as much safety and efficacy data from 007 and 008 as possible at the time of submission. BioMarin understands this may have labeling and/or REMS ramifications.**

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

**FDA Response to Question 3d:**

**We would be amenable to meeting with BioMarin post-BLA submission to orient the review team to the programs and datasets provided.**

**Additional Discussion: None**

**Question 4:** Does the Agency agree with the proposed content for the 120-day safety update (refer to Section 11)?

**FDA Response to Question 4:**

See FDA introductory comments and our response to question 1. If there are acceptable data submitted at the time of submission, a 120-day safety update of the extension studies in the format that you propose in Section 11 will be acceptable.

**Additional Discussion:** None

**Question 5:** Does the Agency agree with BioMarin's proposal to perform antibody analysis using BMN 110-specific total antibodies, receptor binding neutralizing antibodies, and IgE to assess immunogenicity for safety and efficacy (refer to Section 9.3.2)?

**FDA Response to Question 5:**

**Clinical Pharmacology**

Almost all subjects developed anti-drug antibodies by the end of the treatment period. Therefore, it may be difficult to assess the impact of anti-drug antibody on PK/PD, efficacy and safety using results from a single time point. Devise an alternate strategy to assess the impact of anti-drug antibodies on PK/PD, safety and efficacy. For example, the appearance of anti-drug antibody in a given study subject may affect the PD measurements such as urine keratan sulfate to creatinine ratio. We recommend that you evaluate antibody status and titers with PD, safety and efficacy results over time. Provide all immunogenicity data at the time of submission.

**Additional Clinical Comments:**

1. **Submit electronic copies of all CRFs at the time of submission even for patients in ongoing trials.**
2. **At the time of submission, provide graphs in which you have delta uKS (from baseline to 24 weeks) on the y-axis and the delta in the various clinical measures (6MWT, 3MSCT, and maximum voluntary ventilation) at 24 weeks on the x-axis to provide us with a better understanding of the relationship between changes in this biomarker and the clinical outcomes measures.**
3. **Figure 7.2.3.2.1.3 on p. 65 shows a histogram of change from Baseline to Week 24 in the 6 MWT (m) in the ITT population. This histogram does not include patients who had decrements in performance. At the time of submission of your BLA, provide a similar histogram with categorical**

**intervals of improvements (and decrements) on the X-axis, as opposed to a cumulative grouping on the X-axis (groupings were for  $\geq$  to a certain level of improvement). We request you do the same for the 3 MSCT and the MVV.**

*Additional Comments about the Assays*

1. **Provide data to document that the [REDACTED] (b) (4) BMN110 is comparable to the native receptor on human cells with regard to binding affinity for the drug and for antibody blocking by the neutralizing antibodies.**
2. **Provide the protocol and validation report for the IgE ADA assay.**
3. **Provide neutralizing antibody inhibition data in percent inhibition for each tested sample.**

**2.3 Post Meeting Comments, Office of Scientific Investigations**

**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 the inspections (Item I and II).**

**The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will 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 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).**

- I. **Request for general study related information and specific 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 Phase 3 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. **Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)**

2. **Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:**
  - a. **Number of subjects screened for each site by site**
  - b. **Number of subjects randomized for each site by 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 Phase 3 clinical trials:**
  - a. **Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]**
  - b. **Name, address and contact information of all CROs used in the conduct of the clinical trials**
  - c. **The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies**
  - d. **The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)**
  
4. **For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).**
5. **For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).**

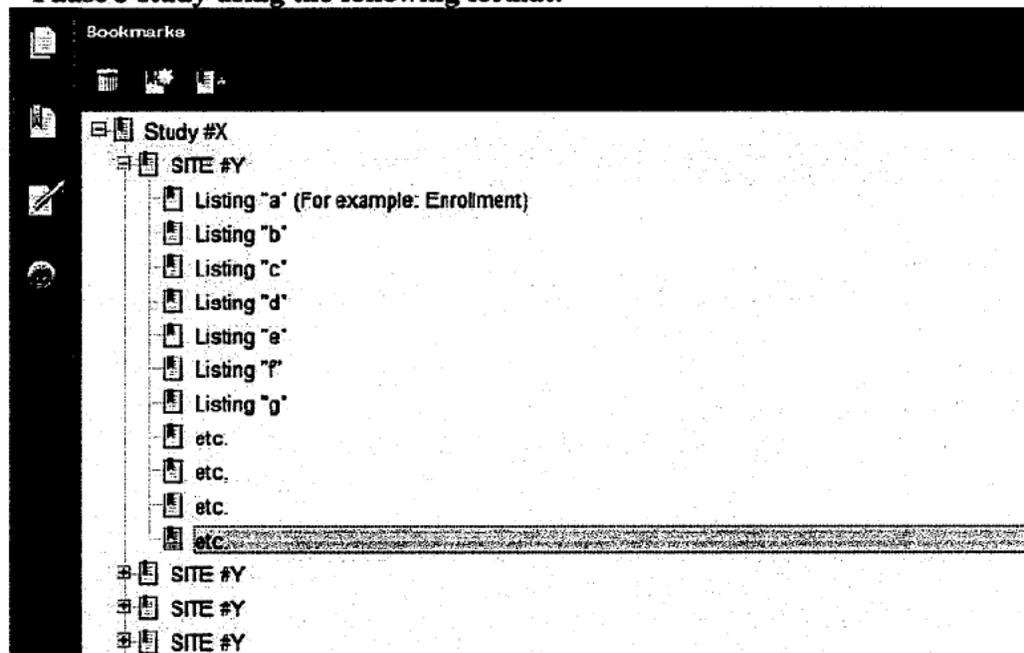
**II. Request for Subject Level Data Listings by Site**

1. **For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:**
  - a. **Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements**
  - b. **Subject listing for treatment assignment (randomization)**
  - c. **Subject listing of drop-outs and subjects that discontinued with date and reason**
  - d. **Evaluable subjects/ non-evaluable subjects and reason not evaluable**
  - 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, 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 laboratory tests 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. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.**

### **3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. The FDA and the sponsor reached several agreements on the contents and format of the proposed BLA submission. See FDA responses and "Additional Discussion" in Sections**

2.1 and 2.2. for a detailed description of the agreements that were made at the time of the meeting.

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

- A preliminary discussion on the need for a REMS was held. It was concluded that the totality of the safety and efficacy data available for review from MOR-007 and MOR-008 may impact the need for a REMS, particularly as it relates to the pediatric patients studied under 5 years of age (please see question 3c). Specifically, if insufficient data are available at time of BLA submission to evaluate the safety and efficacy in pediatric patients under 5 years of age, a REMS may be required.
- 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.

#### **4.0 PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

#### **5.0 PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

**6.0 MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests 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.				

**7.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

IND 101234  
Meeting Minutes  
Pre BLA Meeting

## **8.0 ACTION ITEMS**

None.

## **9.0 ATTACHMENTS AND HANDOUTS**

**Attachment 1, Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions**

**Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

**Clinical Pharmacology Summary**

**BioMarin Slides "Type\_B\_pre-BLA\_Meeting\_Slides\_Dec\_11\_2012\_FINAL.pdf"**

## Attachment 1

### 1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

#### 1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### 1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- **Treatment Efficacy Result (TRTEFFR)** – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- **Treatment Efficacy Result Standard Deviation (TRTEFFS)** – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- **Site-specific Efficacy Effect Size (SITEEFFE)** – the effect size should be the same representation as reported for the primary efficacy analysis
- **Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS)** – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- **Endpoint (endpoint)** – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- **Treatment Arm (ARM)** – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- **Censored Observations (CENSOR)** –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- **Discrete Endpoints** – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- **Continuous Endpoints** – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- **Time-to-Event Endpoints** – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- **Other** – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com.
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)**

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

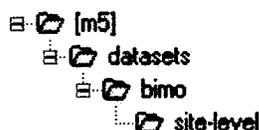
## Attachment 2

### 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 <sup>1</sup>	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.

<sup>1</sup> Please see the OSI Pre-NDA 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](mailto:ESUB@fda.hhs.gov)

# CLINICAL PHARMACOLOGY SUMMARY

## 1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a stand-alone word document, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

## 2. Question Based Review

### 2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

### 2.2 General Attributes of the Drug

#### 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for

**all formulations used in all *in vivo* studies and indicate corresponding study report numbers.**

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

**2.2.3 What are the proposed dosages and routes of administration?**

**2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?**

### **2.3 General Clinical Pharmacology**

**2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?**

**Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.**

**2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

**Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.**

**2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

**Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t<sub>1/2</sub> and AUC.**

## 2.4 Exposure-Response

### 2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate proportion of responders, if applicable.

Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

### 2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Of major interest are safety endpoints determining the therapeutic range. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C<sub>max</sub> and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

**2.4.3 Does this drug prolong QT/QTc Interval?**

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

**2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?**

Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the exposure-response relationship for both efficacy and safety of the drug.

**2.5 What are the PK characteristics of the drug?**

**2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?**

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [ $C_{max}$ ,  $t_{max}$ , AUC,  $C_{max,ss}$ ,  $C_{min,ss}$ ,  $C_{max,ss}/C_{min,ss}$ ,  $t_{max,ss}$ ,  $AUC_{0-\tau}$ , CL/F, V/F and  $t_{1/2}$  (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

**2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

**2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C<sub>max</sub>, C<sub>min</sub>, CL/F and t<sub>1/2</sub> of the parent drug and relevant metabolites after single doses and at steady-state.

**2.5.4 What are the characteristics of drug absorption?**

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, t<sub>max</sub>, t<sub>max,ss</sub>, C<sub>max</sub>, C<sub>max,ss</sub> and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

**2.5.5 What are the characteristics of drug distribution?**

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

**2.5.6 What are the characteristics of drug metabolism?**

**2.5.7 What are the characteristics of drug elimination in urine?**

**2.5.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C<sub>max</sub> and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

**2.5.9 How do the PK parameters change with time following chronic dosing?**

Indicate whether the mean ratio of AUC<sub>0-r</sub> at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly

from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

## **2.6 Intrinsic Factors**

### **2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in patients with the target disease and how much of the variability is explained by the identified covariates?**

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C<sub>max</sub>, clearance, volume of distribution and t<sub>1/2</sub> for pairs studied: elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

### **2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?**

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

#### **2.6.2.1 Severity of Disease State**

#### **2.6.2.2 Body Weight**

#### **2.6.2.3 Elderly**

#### **2.6.2.4 Pediatric Patients**

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is

available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

#### **2.6.2.5 Race/Ethnicity**

#### **2.6.2.6 Renal Impairment**

#### **2.6.2.7 Hepatic Impairment**

#### **2.6.2.8 What pregnancy and lactation use information is available?**

#### **2.6.3 Does genetic variation impact exposure and/or response?**

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

#### **2.6.4 Immunogenicity**

**2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

**2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

**2.6.4.3 Do the anti-product antibodies have neutralizing activity?**

**2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?**

**2.6.4.5 What is the impact of anti-product antibodies on clinical safety?**  
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

## **2.7 Extrinsic Factors**

**2.7.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?**

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

**2.7.2 What are the drug-drug interactions?**

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

**a) Drug of interest is impacted by co-administered other drugs**

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

**b) Drug of interest impacts other co-administered drugs**

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> of each of the co-administered drugs in the presence and absence of the drug of interest.

- 2.7.3 Does the label specify co-administration of another drug?**
- 2.7.4 What other co-medications are likely to be administered to the target population?**
- 2.7.5 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

## **2.8 General Biopharmaceutics**

- 2.8.1 *Was the manufacturing process changed during the development program? (Include a table listing all the products used throughout the clinical development programs.)***
- 2.8.2 *Was the proposed to-be-marketed formulation comparable to the formulation used in the pivotal clinical trials with respect to pharmacokinetics and/or pharmacodynamics?***

## **2.9 Analytical Section**

- 2.9.1 What bioanalytical methods are used to assess therapeutic protein concentrations?  
Briefly describe the methods and summarize the assay performance. Please provide tables for each assay to address the below questions**
  - 2.9.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?  
For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit-type of the calibration curves.**
  - 2.9.1.2 What are the lower and upper limits of quantitation?  
For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.**

- 2.9.1.3 What are the accuracy, precision, and selectivity at these limits?**  
For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).
- 2.9.1.4 What is the sample stability under conditions used in the study?**  
For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at  $\leq -20^{\circ}$  C.
- 2.9.1.5 What is the plan for the QC samples and for the reanalysis of the incurred samples?**  
For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.
- 2.9.2 What bioanalytical methods are used to assess the pharmacodynamic markers?**  
Briefly describe the methods and summarize the assay performance.
- 2.9.3 What bioanalytical methods are used to assess the immunogenicity? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference (including drug interference) and matrix, etc.**
- 2.9.3.1 What is the performance of the binding anti-product antibody assay(s)?**
- 2.9.3.2 What is the performance of the neutralizing assay(s)?**

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/s/

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ELIZABETH A FORD  
01/10/2013



IND 101234

MEETING MINUTES

BioMarin Pharmaceutical Inc.  
Attention: Laurel Konkol  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Konkol:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMN 110 (Recombinant N-acetylgalactosamine-6-sulfatase).

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2012. The purpose of the meeting was to discuss CMC topics related to a potential BLA submission.

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) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Elizabeth A.S. Ford, R.N.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

Meeting Type: C  
Meeting Category: Other

Meeting Date and Time: November 13, 2012, 12:00-1:00 PM  
Meeting Location: White Oak Building 22, Room 1419

Application Number: 101234  
Product Name: BMN 110 (Recombinant N-acetylgalactosamine-6-sulfatase)  
Indication: Mucopolysaccharidosis IV type A (Morquio A syndrome, MPS IVA).  
Sponsor/Applicant Name: BioMarin Pharmaceutical Inc.

Meeting Chair: Melanie Blank, M.D.  
Meeting Recorder: Elizabeth A.S. Ford, R.N.

**FDA ATTENDEES**

**Division of Gastroenterology and Inborn Errors Products**

Andrew Mulberg, M.D., Deputy Director  
Melanie Blank, M.D., Acting Team Leader  
Elizabeth Ford, R.N., Senior Regulatory Health Project Manager  
Matthew Brancazio, Regulatory Health Project Manager

**Office of Biotechnology Products/Division of Therapeutic Proteins**

Emanuela Lacana, Ph.D., Associate Chief, Laboratory of Chemistry  
Cristina Ausin-Moreno, Ph.D., Staff Fellow

**Office of Compliance/Biotech Manufacturing Assessment Branch**

Kalavati Suvarna, Microbiologist  
Colleen Thomas, Microbiologist

**SPONSOR ATTENDEES**

Kris Antonsen, Ph.D., Director, Purification Process Development  
Robert Baffi, Ph.D., Executive VP, Technical Operations  
Art Blum, Vice President, Regulatory Affairs  
Wolfgang Dummer, M.D., Ph.D., Vice President, Clinical Sciences  
Brad Glasscock, Pharm.D., Senior Director, Regulatory Affairs  
Laurel Konkol, Associate Director, Regulatory Affairs

**IND 101234**  
**Type C, CMC Meeting**

**Erno Pungor, Ph.D., Staff Scientist, Analytical Chemistry**  
**Tabitha Santoso, Senior Associate, Regulatory Affairs**  
**Victoria Sluzky, Ph.D., Group Vice President, Quality and Process Development**

## 1.0 BACKGROUND

On July 25, 2012, BioMarin Pharmaceutical Inc. submitted a CMC meeting request with the Division of Gastroenterology and Inborn Errors Products to discuss CMC topics related to a potential BLA submission in March 2013. The meeting was granted as a Type C meeting, and scheduled for November 13, 2012. The Clinical pre-BLA meeting is scheduled for November 28, 2012.

## 2. DISCUSSION

### 2.1. Questions

#### Question 1:

BioMarin is proposing to perform bulk release testing at the 1 mg/mL formulated bulk drug substance (FBDS) (b) (4) (b) (4)

(b) (4) Proposed FBDS specifications have been established based upon historical experience.

1a. Does the Agency agree with this approach for bulk release testing? (Refer to Section 6.1)

#### FDA Response to Question 1a:

Yes, we agree that your proposal to perform bulk release testing at the 1 mg/mL formulated bulk drug substance (FBDS) stage and in-process testing at the (b) (4) (b) (4) stage is acceptable.

Your marketing application should include the validation of all steps involved in the manufacture of FBDS, including the optional ones. (b) (4) for each (b) (4) is necessary and should be in place at the time of submission of the marketing application.

Please clarify the site(s) where the dilution of the (b) (4) 1 mg/mL FBDS will be performed for the commercial process, i.e., can this step be performed at the drug product (DP) manufacturing site?

(b) (4)

Discussion, Question 1a: None

1b. Does the Agency agree with the (b) (4) for FBDS and DP and limits for the (b) (4) (Refer to Section 6.4)

**FDA Response to Question 1b:**

No. It is premature to make a decision regarding the (b) (4) This is a review issue and a final decision on the (b) (4) will be made upon the evaluation of the data for all relevant lots of drug substance and drug product.

Additionally we have the following comments:

1. You did not provide data to confirm that the (b) (4) is suitable to monitor for (b) (4). Therefore, your proposal to (b) (4) from the release testing is not acceptable.
2. Regarding the RP-HPLC and SEC-HPLC specifications, establish acceptance limits for all peaks detected in the chromatograms, in addition to the main peak.
3. Include the cellular uptake assay in your drug substance stability testing and drug product release and stability testing.
4. Include a determination of the kinetic parameters  $K_m$  and  $k_{cat}$  in the drug substance and drug product release and stability testing.
5. Include qualification data for bioburden and endotoxin test methods performed for in-process intermediates and drug substance in the BLA.
6. Include qualification data for sterility and endotoxin test methods performed for drug product in the BLA.

7. (b) (4) d

8. (b) (4)

**Discussion, Question 1b: (comments 1, 3, 4)**

*The Sponsor agrees to add  $K_m$  and  $K_{cat}$  parameters required for DS and DP and to include the results of forced degradation studies (including  $K_m$  and  $K_{cat}$ ) in the BLA. FDA will consider the usefulness of  $K_m$  and  $K_{cat}$  for release and stability upon review of the BLA.*

*Biomarin provided clarification regarding the suitability of the CE oligosaccharide profiling method for the detection of sialic acid. FDA will make a determination of the suitability of the assay upon the review of the BLA.*

**Question 2:**

(b) (4)

(b) (4)

**FDA Response to Question 2:**

No, we do not agree. In addition to the proposed determination of comparability of BMN 110 lots manufactured from the

(b) (4)

(b) (4)

**Discussion, Question 2:**

*FDA recommends the sponsor evaluate the stability program for the master and working cell banks, and submit it to the BLA. FDA agreed, in general, with the approach proposed to determine the adequacy of the WCB, which consists of using a combination of one full scale and two small scale drug substance batches. However, this will ultimately be a review issue.*

**Question 3:**

(b) (4)

**FDA Response to Question 3:**

(b) (4)

The CMC Drug Product section of your BLA (Section 3.2.P) should include validation data summaries supporting the (b) (4). For guidance on the types of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for (b) (4), in Applications for Human and Veterinary Drug Products."

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- 1.
- 2.

(b) (4)

3. In-process microbial controls and (b) (4) should be validated at manufacturing scale at each of the drug product manufacturing sites. Studies should be performed to determine whether endotoxin recovery is (b) (4) (b) (4)
4. (b) (4) if applicable.
5. (b) (4) including summary environmental monitoring data obtained during the runs. (b) (4) procedures should be described.
6. Shipping validation studies.

The following method validation information should be provided:

1. (b) (4)

**Discussion, Question 3: (container closure integrity)**

*BioMarin clarification (see slides). FDA agreed to use sterility testing at release as the time zero for the stability program.*

**Question 4:**

BioMarin plans to present up to (b) (4) of stability data on ten lots of representative DP in the BLA. We propose to (b) (4)

(b) (4) Does the Agency agree that the proposed timeframe for providing additional drug product stability data is acceptable without extending the PDUFA action date? (Refer to Section 7.4)

**FDA Response to Question 4:**

No. According to PDUFA V, sponsors can submit agreed-upon amendments no later than 30 calendar days after the submission of the original application. Please submit all available stability data at the time of original submission. If we deem it necessary, we will request additional stability data during the review process. However, it is premature to decide if any submission containing updated stability data would constitute a major amendment, therefore an extension of the review clock cannot be excluded. In your BLA submission, you may also include a protocol to support extension of the shelf-life. Once the protocol is approved, you may extend the shelf-life of the product and submit the data to the Agency as they become available.

**Discussion, Question 4:**

*FDA agreed to accept 6-month stability data for the drug product within 30 days of the BLA. FDA reminded BiMarin that stability data reviewed as part of the inspection would have to be submitted to the BLA. The data will be requested by the FDA if necessary.*

**Question 5:**

BioMarin plans to present (b) (4) (b) (4) Type 1 (b) (4) glass vials for BMN 110 with supportive stability data (b) (4) in the BLA. Does the Agency agree with the approach for (b) (4) (Refer to Section 7.5)

**FDA Response to Question 5:**

No. Your background package did not contain sufficient information for us to answer your question. Data from at least three vial lots is usually necessary to qualify each source of vials.

(b) (4)

**Discussion, Question 5:**

*BiMarin provided additional clarification regarding the glass vial (see slides). FDA agreed to evaluate data from one full-scale lot. Additional lots of product under full-scale drug production would not be necessary to support the use of the (b) (4) glass vial as long as data from two small scale lots using different lots of vials will be provided. FDA agreed to consider historical data from currently approved products during the review of the appropriateness of the proposed glass vial together with a risk assessment for BMN-110.*

*Container closure integrity data from the two vials should be included in the BLA.*

**Question 6:**

BioMarin has found development of a (b) (4) technically challenging, but is actively working towards an (b) (4) Does the Agency agree that the (b) (4) is acceptable to support licensure of BMN 110 while BioMarin continues efforts to develop a (b) (4) to characterize the potency and enzyme kinetics of rhGALNS? (Refer to Section 7.6)

**FDA Response to Question 6:**

Your proposal to use a (b) (4) to measure enzymatic activity until you are able to develop a (b) (4) to characterize potency and enzyme kinetics of rhGALNS is generally acceptable. However, a final decision on the adequacy of the test methods will be made upon review of the validation information included in the marketing application.

**Discussion, Question 6:** None

**Question 7:** BioMarin will be evaluating the potential for introducing a (b) (4) after licensure to simplify dose preparation. A Comparability Protocol will be provided in the BLA to describe the qualification strategy. Does the Agency agree that if this approach is taken to introduce the (b) (4) after approval, the change can be filed as a CBE-30 or annual report submission? (Refer to Section 7.7)

**FDA Response to Question 7:**

No. Your background package did not contain sufficient information for us to answer your question. A final determination on the appropriate reporting category necessary to support the introduction of the (b) (4) will be made upon review of the Comparability Protocol.

Include the following information in your BLA submission:

1. (b) (4)
2. (b) (4)
3. (b) (4)

If there are changes to the aseptic process validation, a CBE-30 will be required.

**Discussion, Question 7:**

*Biomarin provided additional information regarding the glass vial to use (see slides). See additional discussion, question 5. FDA recommended considering a prior approval supplement (PAS) post-approval. Information from small-scale lots (bulk drug substance relative to the number of vials filled) may be acceptable. FDA further recommended submitting a type C meeting in advance of the submission of the PAS.*

**Question 8:**

BioMarin plans to file the BLA in March 2013. BioMarin underwent a comprehensive GMP inspection by FDA in October 2011, including the rhGALNS manufacturing areas. (b) (4) sites associated with BMN 110 manufacture have also been inspected by FDA regularly, with the most recent inspections occurring in 2012. (b) (4)

**FDA Response to Question 8:**

(b) (4)

Include the FEI numbers for the various sites used in the manufacture, release and stability testing of drug substance and drug product along with contact information. All facilities should be ready for inspection. For the purposes of pre-license inspection, please include a manufacturing schedule for the drug substance and drug product sites in the application. You should be in operation and manufacturing BMN110 during the review cycle so that an inspection can occur 3-5 months after BLA submission.

**Additional Comment**

1. We recommend that you generate a two-tier system for your reference material (i.e. standard). The two-tier system should consist of a primary and a working (secondary) reference material of which, the working reference is calibrated against the primary reference material. Ideally, the primary reference material should be derived from pivotal clinical trial batches. Creation of a working standard used in the testing of production lots calibrated against a single primary reference standard provides assurance that the test samples results are representative of the clinical trial material. The qualification protocol for new reference materials should consist of release and additional characterization testing. We expect tighter acceptance criteria for the qualification of a new reference material, when compared to those of release testing, in order to prevent a drift in product quality. Submit all relevant data to support use of the primary reference standard and a protocol for the qualification of secondary reference material in your marketing application.
2. In your BLA submission, provide a risk assessment for the formation of (b) (4) (b) (4) The risk assessment should include an evaluation of delamination over time and if necessary, a risk mitigation and control strategy.

***Discussion, Question 8:*** (Additional Agency comment 1, reference standard)  
*BioMarin provided additional information regarding the reference standard (see slides). FDA recommended the sponsor explore storage conditions for the reference standard such that it would not degrade over time. This would allow establishment of a two tier reference standard.*

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

**4.0 ACTION ITEMS**

None

**5.0 ATTACHMENTS AND HANDOUTS**

Sponsor slides: "Type C Meeting Slides Nov 13 2012 LK Nov 12.pdf"

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH A FORD  
12/04/2012



PIND 101234

**MEETING MINUTES**

BioMarin Pharmaceutical, Inc.  
Attention: Gina Capiiaux, Ph.D.  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Dr. Capiiaux:

Please refer to your Pre-Investigational New Drug Application (PIND) file for BMN 110 (recombinant human N-acetylgalactosamine-6-sulfatase).

We also refer to the meeting between representatives of your firm and the FDA on July 28, 2010. The purpose of the meeting was to discuss your proposed phase 3 clinical study design and the adequacy of the clinical, nonclinical, and CMC programs for BMN 110.

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

If you have any questions, call me at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-IND

**Meeting Date and Time:** July 28, 2010 / 1:00 – 2:00 pm EST  
**Meeting Location:** FDA White Oak Campus, Building 22, Room 1315

**Application Number:** PIND 101234  
**Product Name:** BMN 110 (recombinant human N-acetylgalactosamine-6-sulfatase)  
**Indication:** Treatment of MPS IVA  
**Sponsor/Applicant Name:** BioMarin Pharmaceutical, Inc.

**Meeting Chair:** Lynne Yao, M.D., Medical Officer, Acting Team Leader  
**Meeting Recorder:** Todd Phillips, Pharm.D., Regulatory Project Manager

**FDA ATTENDEES**

Donna Griebel, M.D., Director, Division of Gastroenterology Products  
Andrew Mulberg, M.D., Deputy Director, Division of Gastroenterology Products  
Lynne Yao, M.D., Medical Officer, Acting Team Leader, Division of Gastroenterology Products  
Erica Wynn, M.D., Medical Officer, Division of Gastroenterology Products  
Wen-Jen Chen, Ph.D., Acting Statistical Team Leader, Division of Biometrics III  
Hae-Young Ahn, Ph.D., Deputy Director, Division of Clinical Pharmacology III  
Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III  
David Joseph, Ph.D., Acting Pharmacology Team Leader, Division of Gastroenterology Products  
Yuk-Chow Ng, Ph.D., Pharmacology Reviewer, Division of Gastroenterology Products  
Serge Beaucage, Ph.D., Supervisory Research Chemist, Division of Therapeutic Proteins  
Cristina Ausin, Ph.D., Research Chemist, Division of Therapeutic Proteins  
Christine Mueller, M.D., Medical Officer, Office of Orphan Products Development  
Anne Pariser, M.D., Acting Associate Director for Rare Diseases, Office of New Drugs, Immediate Office  
Todd Phillips, Pharm.D., Regulatory Project Manager, Division of Gastroenterology Products

PIND 101234  
Meeting Minutes  
Type B / Pre-IND

**SPONSOR ATTENDEES**

Gina Capiaux, Ph.D., Associate Director, Regulatory Affairs  
Celeste Decker, M.D., Director, Clinical Sciences  
Cori Leonard, Senior Director, Regulatory Affairs  
Marjorie Tano, Manager, Regulatory Affairs  
Henry Fuchs, M.D., Executive Vice President, Chief Medical Officer  
Charles O'Neill, Ph.D., DABT, Vice President, Pharmacological Sciences  
Eugen Koren, M.D., Ph.D, Senior Director, Bioanalytical Sciences  
Jackie Walling, MBChB, Ph.D., Vice President, Clinical Development  
Sun Kim, MS, Senior Director, Biometrics, Development Sciences  
Robert Baffi, Ph.D., Executive Vice President, Technical Operations  
Art Blum, Senior Director, Regulatory Affairs  
Laurel Konkol, Senior Manager, Regulatory Affairs  
Erno Pungor, Ph.D., Staff Scientist, Analytical Chemistry  
Kris Antonsen, Ph.D., Director, Purification Process and Development  
Paul Harmatz, M.D., Consulting Medical Expert  
Amy Waterhouse, Vice President, Regulatory Affairs

## **1.0 BACKGROUND**

On April 16, 2010, BioMarin Pharmaceutical Inc. requested a type B (Pre-IND) meeting with the Division of Gastroenterology Products to discuss the proposed phase 3 clinical study design and the adequacy of the clinical, nonclinical, and CMC programs for BMN 110. The clinical development plan for BMN 110 includes an ongoing non-interventional longitudinal clinical assessment study (MOR-001), an ongoing phase 1/2 study (MOR-002), and a phase 3 pivotal study (MOR-004) to be conducted in the future. The conduct of studies MOR-001 and MOR-002 takes place outside of the United States.

## **2. DISCUSSION**

### **2.1. Clinical**

#### **1. Question**

Does the Agency agree that the design of the proposed Phase 3 clinical study, including selected endpoints, dose, and study duration, is adequate to demonstrate the efficacy of BMN 110?

#### **FDA Preliminary Response**

**Study MOR-002 was designed as a dose-escalation study rather than as a dose finding study. Because the dose escalation scheme in Study MOR-002 was sequential within patients, the major efficacy findings could be due either to the length of treatment time or dose. In addition, there was limited dose-safety response relationship data submitted in the package for review. Therefore, the proposed phase 3 study dose of 2 mg/kg is not adequately justified based on results from Study MOR-002. We recommend you conduct an additional, adequate phase 2 dose finding study with a parallel group design in order to optimize the dose before the initiation of the proposed phase 3 study. Furthermore, it appears that major differences may be present between lots produced for phase 1/2 trials and the proposed phase 3 trial (see response to question 2.3.2). We recommend that the product proposed for use in phase 3 trials be used in the recommended phase 2 dose finding study. Otherwise, additional clinical and/or clinical pharmacology studies may be required to demonstrate comparability between the phase 2 and phase 3 clinical trial material.**

**Additionally, we have concerns regarding the proposed endpoint measurements. You have provided some justification for the use of 6MWT and 3MSC as clinically meaningful endpoints. However, it is unclear that any statistically significant difference between the baseline and end of study between the treatment and placebo groups could be considered clinically meaningful. Therefore, we recommend that you define a clinically meaningful definition of response and analyze the primary endpoint utilizing a responder analysis. A responder analysis should be considered**

**the primary analysis for each of the primary endpoints considered (i.e., 6MWT, 3MSC, pulmonary function). Clear justification of a response that is clinically meaningful should be provided based on phase 1/2 trials and from the literature. Additionally, if a clinically meaningful response to treatment may not be achieved at 26 weeks, we recommend that you consider alternative study designs. Such studies could be designed as active-controlled studies that could be conducted over a longer period of time.**

**We recommend that you submit a Special Protocol Assessment (SPA) for your proposed phase 3 study, and include for our review in the SPA submission the clinical data obtained in your phase 2 program, including the urinary KS results, efficacy assessments based on dose ranging studies, and other relevant data, such as any published literature or other information available to you regarding the clinical meaningfulness of any proposed endpoint measurements.**

**Meeting Discussion**

*The Agency and the sponsor reviewed a variety of potential designs for the phase 3 clinical study (e.g., adaptive, parallel group, single dose (2mg/kg) with a concurrent dose-finding arm). In addition, the sponsor reviewed the safety and pharmacodynamic data (urinary KS) from the ongoing phase 1/2 study. The Agency reiterated its position that, given the currently available data for BMN 110, the optimal dose for the phase 3 clinical study cannot be determined. The Agency recommended the sponsor conduct an adequate dose-ranging study prior to initiating phase 3 clinical development.*

**2. Question**

Does the Agency agree with the sample size and statistical analyses proposed for the Phase 3 clinical study?

**FDA Preliminary Response**

**No, we do not agree (see response to question 2.1.1). In addition, we note that the determination of the sample size appears to be**

(b) (4)

(b) (4)

(b) (4)

**We recommend that you provide clear justification for your proposed sample size based on an appropriate study design as part of a SPA.**

**It is premature to comment on the adequacy of the proposed statistical analysis plan until agreement is reached on the measurement of the primary efficacy endpoints.**

### **3. Question**

Are BioMarin's plans to assess immune response to BMN 110 treatment in the Phase 3 clinical study adequate from the Agency's point of view?

#### **FDA Preliminary Response**

**Your plan to analyze serum samples for total binding antibodies, anti-BMN110 IgG, anti-BMN110 IgM, anti-BMN IgE and for neutralizing receptor binding antibodies appears acceptable. The proposed immunogenicity sampling time points appear to be acceptable. At the time of IND submission, please provide all available information regarding the immunogenicity assays you plan to use.**

**You will need to provide a plan for monitoring patient immune response and potential sequelae to immune responses. Additionally, you will need to clearly define infusion reactions, allergic reactions, and anaphylactic reactions as part of your safety monitoring plan. We recommend that you consider using the clinical definition of anaphylaxis as proposed by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network.<sup>1</sup>**

#### **Meeting Discussion**

*The sponsor stated they would define infusion reactions, allergic reactions, and anaphylactic reactions in the safety monitoring plan. The sponsor stated a Data Monitoring Committee would be convened to oversee the phase 3 study.*

### **4. Question**

Does the Agency agree that the proposed clinical program would be adequate to demonstrate safety and efficacy for product licensure for the treatment of all MPS IVA patients?

#### **FDA Preliminary Response**

**No we do not agree (see our responses to questions 2.1.1 and 2.1.2). We again recommend that you submit a Special Protocol Assessment for your proposed phase 3 study.**

#### **Meeting Discussion**

*The Agency reiterated its recommendation to submit a SPA for the phase 3 study prior to initiation of the clinical trial.*

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<sup>1</sup> Sampson HA, Munoz-Furlong A, Campbell RL, et al., Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis network symposium, J Allergy Clin. Immunol., 2006, 117(2),391.;397

## 2.2. Nonclinical

### 1. Question

Does the Agency agree that the nonclinical program completed to date, along with the ongoing fertility and early embryonic development study in the rat and embryo-fetal developmental toxicology studies in the rat and rabbit, is sufficient to initiate the proposed Phase 3 clinical study?

### FDA Preliminary Response

**The nonclinical program appears to be adequate to support the initiation of studies under IND. However, determination of whether the nonclinical studies provide a reasonable assurance of safety for the proposed clinical study will be based on our review and evaluation of the nonclinical study reports. Full reports of the general toxicology studies will need to be reviewed before initiating studies under the IND. The combined fertility and embryo-fetal developmental study in rats and the embryo-fetal developmental study in rabbits will need to be reviewed prior to initiation of phase 3 studies.**

**We note that the product used in the nonclinical studies is not physicochemically comparable to the product intended for use in future clinical studies (see response to question 2.3.2). Therefore, you should conduct a toxicity study in which the products of the phase 1/2 and phase 3 manufacturing processes are tested, to allow for a head-to-head comparison of toxicity. This study should include weekly dosing for at least 4 weeks, and toxicokinetic measurements in all treatment groups.**

### Meeting Discussion

*The sponsor stated that they will provide a comparative toxicology study characterizing the phase 1/2 and phase 3 products in the BLA submission. The Agency agreed with this approach. The sponsor also stated that the phase 3 product was being tested in the ongoing reproductive and developmental toxicity studies.*

### 2. Question

Does the Agency agree that the nonclinical program completed to date along with the ongoing fertility and early embryonic development study in the rat and embryo-fetal developmental toxicology studies in the rat and rabbit and the planned pre- and postnatal developmental toxicology study in rats will be adequate for product licensure?

**FDA Preliminary Response**

**It is premature to comment on whether the completed, ongoing, and proposed nonclinical studies will be sufficient for product licensure, since this determination will be based on our review and evaluation of the full reports. In addition to your proposed nonclinical program, the BLA submission should include a comparative toxicity study of the phase 1/2 and phase 3 products (see response to question 2.2.1) and information for assessment of any carcinogenic potential of the product (BMN 110).**

**2.3 Chemistry, Manufacturing and Controls (CMC)**

**1. Question**

Does the Agency agree that the proposed assays and specifications provided in the briefing package are acceptable for release testing and stability monitoring of BMN 110 being used in the Phase 3 clinical study, and will be adequate for product licensure?

**FDA Preliminary Response**

**No. The proposed release testing assays do not fully evaluate identity, purity and potency of BMN 110.**

- a. In regard to bulk drug substance (BDS), please consider adding tests, which include but are not limited to:**

(b) (4)  
(b) (4)



- b.**  
**c.**

**In regard to stability monitoring:**

- a. Please be aware that BDS, FBDS and DP stability studies should be performed under the recommended storage, accelerated and stress conditions.**
- b. Please confirm the sterility of the DP during your stability testing protocol.**
- c. When sufficient information is collected, please perform a risk assessment using the results obtained while monitoring the presence of**

(b) (4)  
(b) (4)



- d. Potency measurements of the kinetic parameters  $K_m$  and  $k_{cat}$  should be included at every time point of the DP stability testing protocol.
- e. Please be aware that additional stability studies should be performed to confirm that the quality attributes of the DP are unchanged under the conditions used during the course of the administration by infusion.

**In regard to both release and stability specifications:**

- a. Please provide an upper limit for the following tests: enzyme activity, specific activity and potency (% bis-mannose-6-phosphate oligomannose<sub>7</sub>).
- b. Please provide a detailed definition of “Comparable to Reference”.
- c. Please set upper and lower limits as an acceptance criterion for the SDS-CGE analysis.
- d. Please include an upper limit for the DP’s “Volume in Container” release specification.

**It is premature at this point to make final determinations on the adequacy of the methods and specifications in regard to product licensure.**

## **2. Question**

Does the Agency agree that the comparability presented is appropriate to support the formulation and process changes (scale and order of purification steps), and to demonstrate product quality for use in the Phase 3 clinical study and will be adequate for product licensure?

### **FDA Preliminary Response**

**No. The major differences between phase 1/2 and phase 3 lots include the**

(b) (4)

(b) (4)

(b) (4)

**As stated above it is premature to make final determinations with regard to product licensure.**

**In addition, you need to conduct a pharmacokinetic (PK) and pharmacodynamic (PD) comparability study to compare the phase 1/2 and phase 3 products because they are not considered to be physicochemically comparable. However, if you are to adequately characterize the PK and PD of BMN 110 in the phase 2 dose finding study recommended in question 2.1.1, the additional PK and PD comparability study may not be needed.**

*Meeting Discussion*

*The Agency stated that the proposed manufacturing changes may affect overall drug exposure which could impact dose selection for BMN 110. Therefore, the Agency recommended that the sponsor provide data demonstrating that the phase 1/2 and the phase 3 lots are clinically equivalent. The sponsor stated that they will provide further characterization data supporting the comparability of the two lots in the initial IND submission. The Agency agreed with this approach.*

**ADDITIONAL PRELIMINARY CLINICAL PHARMACOLOGY  
RECOMMENDATION**

**In the proposed phase 3 study, MOR-004, we recommend that you collect the PK blood samples longer than 2 hours post-infusion until predicted BMN 110 concentrations reach the lower limit of quantitation (e.g., 3 and 4 hours post dose) for an adequate PK characterization of BMN 110. In addition,  $AUC_{\infty}$  values need to be calculated and used for the determination of BMN 110 clearance.**

*Meeting Discussion*

*The sponsor stated that the initial IND submission will contain all relevant CMC, nonclinical, and clinical data. In addition, the IND will include CMC characterization data supporting the comparability of the phase 1/2 and phase 3 material, and comparative toxicology studies characterizing the phase 1/2 and phase 3 study material. The Agency stated that, if the sponsor elected to submit an IND, the IND would be evaluated according to applicable regulations and could be placed on hold if safety issues are identified.*

**3.0 ATTACHMENTS AND HANDOUTS**

The following attachment was provided by the sponsor and used as a tool to guide the meeting discussion.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

IND-101234

GI-1

BIOMARIN  
PHARMACEUTICA  
L INC

BMN 110

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/s/

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TODD D PHILLIPS  
08/27/2010

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 125460/0

**LATE-CYCLE MEETING MINUTES**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Vimizim (elosulfase alfa).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 12, 2013.

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 Elizabeth Ford, Regulatory Project Manager at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Late Cycle Meeting Minutes



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

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** November 12, 2013, 10:00-11:30 AM  
**Meeting Location:** White Oak Building 22, Room 1315

**Application Number:** BLA 125460  
**Product Name:** Vimizim (elosulfase alfa)  
**Sponsor/Applicant Name:** BioMarin

**Meeting Chair:** Jessica Lee, M.D.  
**Meeting Recorder:** Elizabeth Ford, R.N.

**FDA ATTENDEES**

Office of Drug Evaluation III

Julie Beitz, M.D., Director

Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D., Director

Andrew Mulberg, M.D., Deputy Director

Jessica Lee, M.D., Clinical Team Leader

Tamara Johnson, M.D., Clinical Reviewer

Elizabeth Ford, R.N., Senior Regulatory Health Project Manager

David Joseph, Ph.D., Nonclinical Team Leader

Fang Cai, Ph.D., Nonclinical Reviewer

Office of Biotechnology Products/Division of Therapeutic Proteins

Susan Kirshner, Ph.D., Review Chief

Emanuela Lacana, Ph.D., Associate Lab Chief, Laboratory of Chemistry

Cristina Ausin, Ph.D., Staff Fellow

Office of Compliance/Biotech Manufacturing Assessment Branch

Patricia Hughes, Ph.D., Team Leader, Microbiology

Colleen Thomas, Ph.D., Microbiologist

Candace Gomez-Broughton, Microbiologist

Office of Translational Sciences

Office of Clinical Pharmacology/Division of Clinical Pharmacology 3

Christine Hon, PharmD., Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics III

Behrang Vali, M.S., Statistics Reviewer

Freda Cooner, Acting Team Leader

Office of Surveillance and Epidemiology

Phong Do, PharmD, Regulatory Health Project Manager  
Carolyn McCloskey, M.D., Physician Epidemiologist  
David Shih, Epidemiology  
Eileen Wu, Team Leader, Pharmacovigilance

Office of Planning and Informatics

Kim Taylor, Operations Research Analyst

**EASTERN RESEARCH GROUP ATTENDEES**

So Hyun Kim, Independent Assessor

**APPLICANT ATTENDEES**

Robert Baffi, Executive Vice President, Technical Operations  
Lisa Bell, Vice President, Regulatory Affairs  
Art Blum, Vice President, Regulatory Affairs  
Pamela Farmer, Senior Medical Director, Pharmacovigilance  
Henry Fuchs, Executive Vice President, Chief Medical Officer  
Brad Glasscock, Senior Director, Regulatory Affairs  
Christine Haller, Senior Medical Director, Clinical Sciences  
Laurel Konkol, Director, Regulatory Affairs  
Chuck O'Neill, Vice President, Pharmacological Sciences  
Becky Schweighardt, Principal Scientist, Immunogenicity Assessment  
Peter Slasor, Director, Biostatistics  
Victoria Sluzky, Group Vice President, Quality and Process Development  
Gary Taniguchi, Senior Director, Bioanalytical Sciences  
Marjorie Tano, Associate Director, Regulatory Affairs

**1.0 BACKGROUND**

BLA 125460 was submitted on March 29, 2013 for Vimizim (elosulfase alfa).

Proposed indication(s): Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)

PDUFA goal date: February 28, 2013

FDA issued a Background Package in preparation for this meeting on November 4, 2013.

**2.0 DISCUSSION**

1. Introductory Comments

**The late-cycle meeting was intended to share information, identify deficiencies, plan for the AC in order to avoid redundancy, and plan the rest of the review. BioMarin was reminded that: the meeting was not intended to focus on the final regulatory decision for the application, no new data should be discussed in detail at the late cycle meeting (however, FDA would consider whether new information presented would be adequate for review).**

2. Discussion of Substantive Review Issues

a) Quality

- i) Comparability between drug product lots filled at (b) (4)
- ii) (b) (4) to Shanbally

**Discussion: Reference is made to the Quality Discipline Review Letter dated October 30, 2013. Regarding the comparability between drug product lots filled at (b) (4) BioMarin proposed a 24-month shelf life and enhanced stability testing program with determination of specific activity every 3 months during the second and third years of the stability studies (BioMarin handout, Slide 5). FDA requested that BioMarin provide the plan in writing with additional information: distribution plan, plans for recall, and updated stability data (17- and 18-month stability pulls for the first technical lot).**

**Regarding the (b) (4) to Shanbally, BioMarin stated that the head-to-head study has already been conducted, and they will submit the information post-approval (BioMarin handout, slide 7).**

b) Clinical

- i) Efficacy Results
- ii) Immunogenicity Results

**Discussion: Regarding the efficacy results, BioMarin agreed to submit the 72-week data graphical presentation for the QW-QW patients assessed at 48 weeks of treatment (BioMarin handout, slide 11).**

**Regarding the immunogenicity results, BioMarin was reminded that development of a cellular uptake neutralizing antibody assay may still be needed post-approval if results from the assay to determine the titer of receptor binding neutralizing antibodies are not sufficient to elucidate the impact of anti-drug antibodies on safety and efficacy (BioMarin handout slide 14).**

3. Discussion of Minor Review Issues

a) Clinical

- i) We have reviewed the case narratives for all patients identified as having hypersensitivity reactions and selected anaphylaxis cases based on the NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H *et al.*, J Allergy Clin Immunol 2006;117:391-7). We have identified two additional cases of anaphylaxis (MOR004-

1017-4016 and MOR004-1075-4050), in addition to the 16 cases you identified using the same criteria. Therefore, we consider the final incidence of anaphylaxis to be 7.7% (18 of 235 patients) for the safety population.

**Discussion: BioMarin accepted FDA's 2 additional cases of anaphylaxis for an overall event rate of 7.7%.**

b) Quality Microbiology

- i) The proposed strategy for [REDACTED] (b) (4)

**Discussion: BioMarin agreed to the proposed testing of [REDACTED] (b) (4)**

**FDA acknowledged this plan.**

4. Information Requests

a) Quality

- i. FDA letter dated October 17, 2013: Requested additional qualification information for [REDACTED] (b) (4) and [REDACTED] (b) (4) and a revised working cell bank qualification protocol.

**Discussion: BioMarin submitted a response to the above noted IR on November 8, 2013. FDA to review as submitted.**

b) Quality Microbiology

- ii. FDA letter dated October 29, 2013: Requested additional information regarding endotoxin testing of polysorbate, the endotoxin specification on the Certificate of Analysis for the formulated bulk drug substance, endotoxin test and rabbit pyrogen test data from the study described in protocol QC-1214-M, [REDACTED] (b) (4)

**Discussion: BioMarin submitted a response to the above-noted IR on November 8, 2013. FDA will review the submitted information and data. FDA intends to provide an additional IR to request rabbit pyrogen testing of another lot of material spiked with 20 EU/mL and 100 EU/mL in addition to the positive and negative controls.**

5. Discussion of Upcoming Advisory Committee Meeting

**Discussion: There was a general discussion regarding topics that will be covered at the Advisory Committee Meeting on November 19, 2013.**

6. Postmarketing Requirements/Postmarketing Commitments

**Discussion: BioMarin submitted a response to FDA's October 28, 2013 Labeling PMR/PMC Discussion Comments letter. FDA will review BioMarin's response. In addition, BioMarin clarified that all ongoing clinical studies would transition into a 10-year registry study after marketing approval.**

**Regarding PMC 1, FDA indicated that BioMarin's proposal would require additional discussion and FDA will provide revised language and a rationale for the revision.**

7. Major Labeling Issues

**Discussion: BioMarin responded to FDA's labeling proposals on November 5, 2013. FDA will review this proposal.**

8. Review Plans

**Discussion: An Advisory Committee Meeting will be convened on November 19, 2013, and the review team plans to complete the review in accordance with the PDUFA goal date.**

9. Wrap-up and Action Items

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

**Please see the action items listed under sections 2a, 2b, 3b, 4b, and 6.**

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/s/  
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JESSICA J LEE  
11/25/2013



BLA 125460/0

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

BioMarin Pharmaceutical Inc.  
Attention: Marjorie Tano  
Associate Director, Regulatory Affairs  
105 Digital Drive  
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Vimizim (elosulfase alfa).

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 12, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** November 12, 2013, 10:00-11:30 AM  
**Meeting Location:** White Oak Building 22, Room 1315

**Application Number:** BLA 125460  
**Product Name:** Vimizim (elosulfase alfa)  
**Indication:** Mucopolysaccharidosis IV type A (Morquio A syndrome)  
**Sponsor/Applicant Name:** BioMarin

### 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, 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, 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

In addition to the contents of this background document, please refer to the following Discipline Review Letter already provided to you:

Quality-October 30, 2013

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

1) Quality

- a) You provided stability studies on drug product manufactured at different sites and stored under a variety of conditions. We noted that under accelerated and stressed storage conditions, the enzyme specific activity of drug product manufactured at the proposed commercial site (b) (4) exhibited a significantly higher degradation rate than drug product manufactured at (b) (4) the site that manufactured clinical trial material. A difference in degradation rates between drug products indicates a change in a quality attribute(s) that rendered the proposed commercial material less stable than its clinical counterpart. We conclude that drug products manufactured at the two sites are not physico-chemically comparable. Therefore, the real-time stability data generated at the (b) (4) cannot be used to establish the shelf-life of product manufactured at the (b) (4) facility. Potential paths forward include manufacturing at (b) (4), or manufacturing at (b) (4) with an expiry based on real time data generated at (b) (4).
- b) As part of the demonstration of comparability between Novato and Shanbally testing sites for the specific activity test method, you (b) (4). Because determination of specific activity is a stability indicating test method, you should have performed the testing at both sites at the same time, to ensure that the age of the DP lot did not affect the results. We conclude that the transfer of this method to Shanbally is not appropriate and the method should not be performed at the site for release of drug product in the United States. Potential paths forward include delaying the assay transfer for specific activity to Shanbally until the aforementioned issues are resolved.

2) Clinical

- a) During this review cycle, you submitted additional endurance testing results (i.e., six-minute walk test [6MWT] and three-minute stair climb test [3MSCT]) from all patients currently receiving the proposed marketing dose of Vimizim (2 mg/kg once weekly) in Part 2 of Trial MOR005. While these data might suggest no overall decline in walking abilities with continued treatment, we are concerned about the decline in the 6MWT seen in a cohort of patients who were assessed at 48 weeks of treatment. Therefore, additional evaluation of the 72-week data obtained from this cohort of patients is needed. In addition, we remain concerned about the small treatment effect seen on the 3MSCT. We plan to discuss the modest treatment effect observed on the 6MWT and 3MSCT and their clinical meaningfulness in MPS IVA patients at the upcoming Advisory Committee Meeting.
- b) All patients treated with elosulfase alfa 2 mg/kg once weekly in MOR-004 developed anti-elosulfase alfa antibodies by Week 4. By Week 16, approximately 96% of the weekly-treated patients developed neutralizing antibodies capable of inhibiting the drug from binding the mannose-6-phosphate receptor. Based on MOR005 Part 2 data, patients continued to experience elevated titers of anti-drug antibodies after treatment

with Vimizim for 72 weeks. It is not clear whether MPS IVA patients treated with Vimizim will experience immune tolerance with continued therapy, and the impact of these anti-drug antibodies on long-term efficacy and safety is unknown. Post-marketing studies will be required to address these concerns.

## **ADVISORY COMMITTEE MEETING**

**Date of AC meeting:** November 19, 2013

**Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management:** October 24, 2013

### **Potential questions and discussion topics for AC Meeting are as follows:**

1. Discuss whether a change in 6MWT from baseline to Week 24 adequately evaluates treatment benefit in patients with MPS IVA.
2. Discuss other measures of treatment benefit that could be assessed in patients with MPS IVA.
3. Discuss whether the totality of clinical data supports the effectiveness of elosulfase alfa for treatment of MPS IVA.
  - a. Consider whether the magnitude of treatment difference observed in the 6MWT and 3MSCT represent a clinically meaningful benefit in this patient population.
  - b. Discuss whether an exploratory analysis based on baseline walking ability provides clinical support that elosulfase alfa treatment might be more effective in patients with more limitations in mobility.
4. Discuss whether the application raises concerns about safety findings in MPS IVA patients, taking into consideration the incidence of neutralizing antibodies and anaphylaxis.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

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

## LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 20 minutes (FDA Review Team)

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

a) Quality

- i) Comparability between drug product lots filled at [REDACTED] (b) (4)
- ii) Specific activity method transfer to Shanbally

b) Clinical

- i) Efficacy Results
- ii) Immunogenicity Results

3. Discussion of Minor Review Issues – 10 minutes (Clinical and Quality Microbiology)

a) Clinical

- i) We have reviewed the case narratives for all patients identified as having hypersensitivity reactions and selected anaphylaxis cases based on the NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H *et al.*, J Allergy Clin Immunol 2006;117:391-7). We have identified two additional cases of anaphylaxis (MOR004-1017-4016 and MOR004-1075-4050), in addition to the 16 cases you identified using the same criteria. Therefore, we consider the final incidence of anaphylaxis to be 7.7% (18 of 235 patients) for the safety population.

b) Quality Microbiology

- i) The proposed strategy for ensuring that the [REDACTED] (b) (4)

4. Additional Applicant Data – 10 minutes (BioMarin)

5. Information Requests – 10 minutes (FDA Review Team)

a) Outstanding Information Request Letters

i. Quality

- i. FDA letter dated October 17, 2013: Requested additional qualification information for [REDACTED] (b) (4) and a revised working cell bank qualification protocol.

ii. Quality Microbiology

- i. FDA letter dated October 29, 2013: Requested additional information regarding (b) (4) and rabbit pyrogen test data from the study described in protocol QC-1214-M, the pressure limit for sterile filtration, and the positive control for the dye ingress test method.

6. Discussion of Upcoming Advisory Committee Meeting – 10 minutes (FDA Review Team/BioMarin)
7. Postmarketing Requirements/Postmarketing Commitments – 10 minutes (FDA Review Team/BioMarin)

The following postmarketing requirements/commitments were communicated to you on October 28, 2013:

### **Postmarketing Requirements**

PMR 1:



PMR 2: Evaluate the safety and efficacy of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with VIMIZIM who are at high risk of developing persistent neutralizing antibody. This immune tolerance regimen will be implemented before or concomitant with onset of VIMIZIM therapy. (b) (4)

(b) (4)

(b) (4)

PMR 3:

(b) (4)

PMR 4: Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibit binding to the mannose-6-phosphate receptor. A summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to the FDA. This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs (b) (4)

Final Report Submission: 03/31/2015

PMR 5: Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 03/31/2016

PMR 6: Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE in the presence of high titers of IgG. This assay will be used to assess

for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs (b) (4)

Final Report Submission: 03/31/2015

PMR 7: Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

Final Report Submission: 03/31/2016

### Postmarketing Commitments

PMC 1: Develop and implement a potency assay that measures the  $K_m$  and  $k_{cat}$  of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

Final Protocol Submission: MM/DD/YYYY

Study Completion: MM/DD/YYYY

Final Report Submission: MM/DD/YYYY

PMC 2: Revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between (b) (4) peak. The revised specification together with the validation report will be submitted to your BLA in accordance with 21 CFR 601.12.

Final Protocol Submission: MM/DD/YYYY

Study Completion: MM/DD/YYYY

Final Report Submission: MM/DD/YYYY

PMC 3: Demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in a side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.

Final Protocol Submission: MM/DD/YYYY

Study Completion: MM/DD/YYYY

Final Report Submission: MM/DD/YYYY

PMC 4: Include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.

Final Protocol Submission: MM/DD/YYYY

Study Completion: MM/DD/YYYY

Final Report Submission: MM/DD/YYYY

PMC 5: Include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 6: Add cellular uptake as a release assay for DP and establish an appropriate acceptance criterion when a statistically significant number of DP lots is tested.

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 7: Conduct studies to understand the mechanism of low endotoxin recovery in the FBDS and DP. Modify the endotoxin release test [REDACTED] (b) (4).

Final Protocol Submission: MM/DD/YYYY  
Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 8: Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC-1224-M.

Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC 9: Provide results from protocol PVP-101037 [REDACTED] (b) (4) to be executed during the 2014 manufacturing campaign.

Study Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

8. Major labeling issues – 9 minutes (FDA Review Team/BioMarin)

9. Review Plans – 1 minute (FDA Review Team)

We plan to convene an Advisory Committee meeting on November 19, 2013, and complete the review in accordance with the PDUFA goal date.

10. Wrap-up and Action Items – 5 minutes (FDA Review Team/BioMarin)

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/s/  
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ANDREW E MULBERG  
11/04/2013