

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203568Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203568 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Kynamro Established/Proper Name: mipomersen Dosage Form: Injection, 200 mg/mL		Applicant: Genzyme Corporation Agent for Applicant (if applicable): N/A
RPM: Kati Johnson		Division: Division of Metabolism and Endocrinology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" 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>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></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 rely 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><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is January 29, 2013 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		X None

¹ 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.

² 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input 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</p> <p>NDA: 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 checked="" type="checkbox"/> Communication Plan <input checked="" 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>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. 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"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> 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> 	<input checked="" 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"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	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"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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> 	<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>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
❖ 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>)	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	AP 1/29/2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	We were told it was not necessary to include ANY labeling except that which is attached to the AP letter.
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Not included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Not included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Not included

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ 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>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Not included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Not included
<ul style="list-style-type: none"> Example of class labeling, if applicable 	Not included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	Not included
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 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. 	Not acceptable-7/6/2012 Acceptable-11/27/2012
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 5/24/2012 <input checked="" type="checkbox"/> DMEPA 12/17/2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 1/9/2013 <input checked="" type="checkbox"/> ODPD (DDMAC) 1/10/2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	5/24/2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>drug and indication designated as orphan</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
❖ 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

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	X
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	X No mtg 2/15/2008-no minutes were drafted
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	X N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 12/13/2010
• EOP2 meeting (<i>indicate date of mtg</i>)	X No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	N/A
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	10/18/2012
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	X
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/29/2013
Division Director Summary Review (<i>indicate date for each review</i>)	1/29/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	X None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1/24/2013 (4 PMRs)
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	5/14/2012; 11/26/2012
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	X 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>)	Page 35 of the 11/26/2012 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 1/9/2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	1/29/2013
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	<input type="checkbox"/> None
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	1/29/2013, 12/19/2012
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 12/3/2012

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None 5/21/2012; 7/2/2012; 11/13/2012
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None 5/23/2012; 11/30/2012
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		None 1/23/2013
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> None 12/4/2012
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None 12/3/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> No carc 1/10/2013
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None 8/3/2012 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None 5/14,2012; 9/11/2012; 12/7/2012; 1/4/2013
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 1/4/2013
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	X-see page 134 of 9/11/2012 CMC review
<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>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 10/11/2012 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<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) The information has been submitted.

⁷ 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

KATI JOHNSON
01/31/2013

EXCLUSIVITY SUMMARY

NDA # 203568

SUPPL #

HFD # 510

Trade Name Kynamro

Generic Name mipomersen sodium

Applicant Name Genzyme Corporation

Approval Date, If Known 1/29/2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Kati Johnson
Title: Senior Project Manager
Date: 1/15/2012

Name of Office/Division Director signing form: Eric Colman, MD
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

KATI JOHNSON
01/29/2013

ERIC C COLMAN
01/29/2013



mipomersen sodium
1.3.3 Debarment Certification

DEBARMENT CERTIFICATION

Genzyme Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

GENZYME CORPORATION

A handwritten signature in cursive script that reads "Jill P. Hillier".

Jill P. Hillier, PhD
Senior Director, Regulatory Affairs

01 March 2012

Date

Johnson, Kati

From: Jill.Hillier@genzyme.com
Sent: Tuesday, January 29, 2013 5:54 PM
To: Johnson, Kati
Subject: RE: NDA 203568, Kynamro (mipomersen) Injection, AP letter

Dear Kati,
CONFIRMED! Thank you!!
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443

(b) (4)

jill.hillier@genzyme.com

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Tuesday, January 29, 2013 5:43 PM
To: Hillier, Jill GZ/US
Subject: NDA 203568, Kynamro (mipomersen) Injection, AP letter

Hi Jill, please confirm receipt.

Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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

/s/

KATI JOHNSON
01/28/2013

From: [Johnson, Kati](#)
To: "Jill.Hillier@genzyme.com"
Cc: [Johnson, Kati](#)
Subject: RE: NDA 203568, Mipomersen, revised PI
Date: Monday, January 28, 2013 2:25:10 PM

We accept your revisions to the labeling (PI) sent to you via e-mail on 1/24/2012
Kati

From: Jill.Hillier@genzyme.com [mailto:Jill.Hillier@genzyme.com]
Sent: Thursday, January 24, 2013 6:02 PM
To: Johnson, Kati
Subject: NDA 203568, Mipomersen, revised PI

Dear Kati,
Apologies we missed the comment cited below. It came through on our version as 1 pt font probably due to differences in versions of Microsoft, and we didn't see it. In any event, Table 4 (page 19) has been corrected now.
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Thursday, January 24, 2013 12:47 PM
To: Hillier, Jill GZ/US
Cc: Johnson, Kati
Subject: FW: Mipomersen revised PI and MG to firm 1 22 2013 and again to firm 1 24 2013

see below. Please fix the PI and send it back.
We haven't looked at the MG yet.

Kati

From: Craig, Eileen
Sent: Wednesday, January 23, 2013 6:04 PM
To: Colman, Eric C
Cc: Johnson, Kati
Subject: FW: Mipomersen revised PI and MG to firm 1 22 2013

I looked over the label. In Table 4 we had asked them to change the HDL and TG numbers from mean to median values as that was what was presented in the NDA because the result of the Kolmogorov Smirnov test was <0.05 indicating non-normal distribution—so the data was presented as median and interquartile range. They did not make that change. They did make the other changes we requested.

From: Jill.Hillier@genzyme.com [mailto:Jill.Hillier@genzyme.com]
Sent: Wednesday, January 23, 2013 3:56 PM
To: Johnson, Kati
Cc: Craig, Eileen
Subject: RE: Mipomersen revised PI and MG to firm 1 22 2013

Dear Kati,

Thank you again for the opportunity to discussion the pediatric statement and inclusion of Lp(a). We have accepted all of yesterday's feedback for both the Medication Guide and the Package Insert. The clean documents are attached.

Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Tuesday, January 22, 2013 2:23 PM
To: Hillier, Jill GZ/US
Cc: Craig, Eileen; Johnson, Kati
Subject: Mipomersen revised PI and MG to firm 1 22 2013

Hopefully we are almost done with this!!
IFUs are still with Patient Labeling. But MY bad in that I was late in sending it over...
Will hear back from them fast, though.

I need to forward the REMS stuff to the group.
Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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/s/

KATI JOHNSON
01/28/2013

From: [Johnson, Kati](#)
To: "Jill.Hillier@genzyme.com"
Cc: [Johnson, Kati](#)
Subject: RE: Revised MG
Date: Monday, January 28, 2013 2:43:54 PM

We accept your revisions to the MG labeling sent to you on 1/22/2013
Thanks, Kati

From: Jill.Hillier@genzyme.com [mailto:Jill.Hillier@genzyme.com]
Sent: Wednesday, January 23, 2013 3:56 PM
To: Johnson, Kati
Cc: Craig, Eileen
Subject: RE: Revised MG

Dear Kati,

Thank you again for the opportunity to discuss the pediatric statement and inclusion of Lp(a). We have accepted all of yesterday's feedback for both the Medication Guide and the Package Insert. The clean documents are attached.

Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Tuesday, January 22, 2013 2:23 PM
To: Hillier, Jill GZ/US
Cc: Craig, Eileen; Johnson, Kati
Subject: Mipomersen revised PI and MG to firm 1 22 2013

Hopefully we are almost done with this!!
IFUs are still with Patient Labeling. But MY bad in that I was late in sending it over...
Will hear back from them fast, though.

I need to forward the REMS stuff to the group.
Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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/s/

KATI JOHNSON
01/28/2013

From: [Johnson, Kati](#)
To: ["Hillier, Jill GZ/US"](#)
Subject: RE: NDA 203568, Kynamro-revised container/cartons from firm
Date: Monday, January 28, 2013 3:30:15 PM

We accept your revisions to the following carton/container labeling submitted 1/14/2013:

Vial Container Label
Vial Carton Label (single- and 4-pack)
Prefilled Syringe Container Label
Prefilled Syringe Lid
Prefilled Syringe Carton Label (single- and 4-pack)

Thanks, Kati

From: Hillier, Jill GZ/US [mailto:Jill.Hillier@genzyme.com]
Sent: Monday, January 14, 2013 4:40 PM
To: Johnson, Kati
Subject: RE: NDA 203568, Kynamro-revised container/cartons from firm

Dear Kati,
Please see attached the revised packaging (7 pieces) per the feedback below.
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Hillier, Jill GZ/US
Sent: Monday, January 14, 2013 2:13 PM
To: Johnson, Kati
Subject: RE: NDA 203568, Kynamro, additional revisions, Section 2.2

Dear Kati,
Please see attached the revised IFUs addressing the requests below. I will be sending the packaging pieces in a separate mail.
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Thursday, December 20, 2012 1:13 PM
To: Hillier, Jill GZ/US
Subject: RE: NDA 203568, Kynamro, additional revisions, Section 2.2

glad to help out

From: Hillier, Jill GZ/US [mailto:Jill.Hillier@genzyme.com]
Sent: Thursday, December 20, 2012 12:57 PM
To: Johnson, Kati
Subject: RE: NDA 203568, Kynamro, additional revisions, Section 2.2

Yes, thank you!

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Thursday, December 20, 2012 12:51 PM
To: Hillier, Jill GZ/US
Subject: RE: NDA 203568, Kynamro, additional revisions, Section 2.2

we will need to see the packaging stuff, revised as requested in the e-mail I sent you yesterday (I think).
You can send them by e-mail, and we can look at them, and if they are OK, you can submit officially. Will that work??

From: Hillier, Jill GZ/US [mailto:Jill.Hillier@genzyme.com]
Sent: Thursday, December 20, 2012 12:46 PM
To: Johnson, Kati
Subject: RE: NDA 203568, Kynamro, additional revisions, Section 2.2

Dear Kati,
Could you please confirm that you would like to receive updated mock layouts of the packaging as soon as possible in advance of the action date? Thank you.
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, December 19, 2012 12:38 PM
To: Hillier, Jill GZ/US
Cc: Craig, Eileen; Johnson, Kati
Subject: NDA 203568, Kynamro, additional revisions, Section 2.2

I am also providing you the comments from the DMEPA folks regarding the various pieces of labeling:

A. All Labels and Labeling: Vial Container Label, Prefilled Syringe Label, Prefilled Syringe Lid Label, Prefilled Syringe Carton Labeling and Vial Carton Labeling

1. We note that the established name is ½ the size of the proprietary name however, lacks prominence commensurate with the proprietary name. Thus, we request you decrease the font size of the proprietary name “Kynamro” and revise the established name in accordance with 21 CFR 201.10 (g)(2), taking

into account all factors, including typography, layout, contrast and other printing features.

2. Revise the presentation of the proprietary name, KYNAMRO, from UPPERCASE to Title Case "Kynamro" to improve readability of the name.
3. Increase the prominence of the strength statement for improved readability.
4. Add the dosage form "Injection" immediately next to or immediately underneath the established name.

B. Prefilled Syringe Container Label

1. Relocate the NDC number to the top one-third of the PDP where the "Rx only" statement is currently located, as required by 21 CFR 207.35(3)(i).
2. Reduce the font size of the "Rx only" statement and relocate the statement to appear after the manufacturer's information "Genzyme Corporation." This will reduce clutter around the proprietary name, established name, and strength.

C. Prefilled Syringe Lid Label

1. On the prefilled syringe lid, increase the prominence of the statement "For subcutaneous injection only" so it is the same size as the "1 Single-use syringe" statement by increasing the font size of this statement since this is important information. This can be achieved by relocating the manufacturer's information "Manufactured by:.. For:...Cambridge, MA 02142" to the white panel as this information clutters the principal display panel containing the most important information such as proprietary and established names of the product, strength, and route of administration.
2. Add the statement "Discard unused portion" immediately next to "1 Single-use syringe" statement to prevent the potential for multiple-use thus increasing the risk of contamination, since this is a single-use formulation.

D. Prefilled Syringe Carton Labeling

1. Reduce the prominence or color intensity of the green and purple background to provide adequate color contrast between the texts and the background color. In addition, ensure that the proprietary name, the established name, and strength are in the same color block in accordance with 21 CFR 201.10 (a) which states that these important information should not be separated by placement of intervening matter such as tagline or other graphics.
2. Add the statement "Discard unused portion" immediately following or underneath the net quantity statement. For example,
1 Single-use syringe
Discard unused portion
3. Ensure that the proprietary and established names of the product, strength, and NDC number are prominent on the principal display panel and all side panels, so that this information is visible regardless of the way the product is placed in the refrigerator.
4. Increase the prominence of the statement "For subcutaneous injection only" and relocate to the middle portion of the principle display panel underneath the statement, "Each prefilled syringe..." similar to the vial carton labeling.
5. Decrease the prominence of the statements "1 Single-use syringe" and "4 Single-use syringes" in order to create room for the statement "For

subcutaneous injection only.”

6. Add the statement “each containing 1 mL” immediately after the net quantity statement for the 4 Single-use syringes packaging to read “4 Single-use syringes each containing 1 mL”

7. If feasible, consider adding a statement to the side panel advising to leave the product at room temperature for 30 minutes prior to administration.

E. Vial Container Label

1. If feasible, increase the prominence of the route of administration by using bigger font size. This can be achieved by deleting the name of the firm “Genzyme” from the label as manufacturer information appears immediately underneath this name.

2. The “Rx only” statement is more prominent than the route of administration. Thus, decrease the prominence of the “Rx only” statement by decreasing font size and debolding.

3. Revise the statement (b) (4) to read “Discard unused portion” to prevent the potential for multiple-use thus increasing the risk of contamination since this is a single-use formulation. Additionally, relocate this statement to appear immediately underneath “Single-use vial” statement.

F. Vial Carton Labeling

1. See D.1. through D.3. and revise vial carton labeling accordingly.

2. Delete all trailing zeroes that appear throughout the insert labeling. Trailing zeroes (e.g. ‘1.0’) are considered dangerous abbreviations (3). As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.

³ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 01/03/2012.

3. Revise the net quantity statement (b) (4) to read “4 Single-use vials each containing 1 mL” so that it is consistent with the net quantity statement presentation of the prefilled syringe carton labeling.

4. Decrease prominence of the net quantity by debolding.

5. Relocate the statement “See package insert for dosage and administration” to the side panel to reduce clutter of the PDP and increase readability of other important information.

6. Decrease the prominence of the “Rx only” statement by debolding and relocating to the bottom portion of the PDP (i.e. lower right or left hand corner). As currently presented, it is centrally located on the PDP and is as prominent as the route of administration s taking central location and as prominent as route of administration.

G. Instructions For Use

1. Delete all trailing zeroes that appear throughout the insert labeling. Trailing zeroes (e.g. ‘1.0’) are considered dangerous abbreviations. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.

2. Revise the bullet points to read Step 1, 2, etc., so that it is easier for patients to follow the instructions.

⁴ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

⁵ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 01/03/2012.

3. The figures do not clearly illustrate the instructions. We recommend using actual photos of the product or more prominent illustrations in color to demonstrate the actual step being performed.
4. There are multiple steps represented by a single bullet point and only some steps contain figures or illustrations. Thus, the IFU should be revised to contain relevant information clearly expressed with illustrations in color for each step for the preparation and administration process.
5. In section “Before you inject Kynamro,” revise the title to read “Supplies you will need before you inject Kynamro” so that patients are clear as to what supplies are needed prior to injection. In addition, consider adding illustration of the supplies or list the supplies in a bullet form so that it is easier to follow.
6. Under Section “How to prepare the syringe for injection,” patients are instructed to “Allow KYNAMRO to come to room temperature for at least 30 minutes. It is important that KYNAMRO be at room temperature prior to the injection” without stating the reason of importance. We recommend adding the reason for this instruction so that it emphasizes importance to patients.

My apologies for the funky format.

Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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/s/

KATI JOHNSON
01/28/2013

From: [Johnson, Kati](mailto:Johnson_Kati)
To: "Jill.Hillier@genzyme.com"
Subject: RE: Mipomersen IFUs to firm 1 24 2013
Date: Monday, January 28, 2013 4:15:33 PM

We accept your 1/25/2013 revisions to the IFUs forwarded to you on 1/24/2013
Thanks, Kati

From: Jill.Hillier@genzyme.com [mailto:Jill.Hillier@genzyme.com]
Sent: Friday, January 25, 2013 10:26 AM
To: Johnson, Kati
Subject: RE: Mipomersen IFUs to firm 1 24 2013

Dear Kati,
Please see attached the revised IFUs addressing yesterday's feedback. We have attached the Word documents as well as the revised PDF documents.
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Thursday, January 24, 2013 3:18 PM
To: Hillier, Jill GZ/US
Cc: Johnson, Kati
Subject: Mipomersen IFUs to firm 1 24 2013

The Patient labeling folks had to make the revisions to the PDF copy because the "arrows" that they wanted deleted did not show up in the WORD version. Please revise the WORD version and send it back.

Thanks, Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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/s/

KATI JOHNSON
01/28/2013

From: Jill.Hillier@genzyme.com
To: [Johnson, Kati](#)
Subject: RE: NDA 203568, Mipomersen, required PMRs-milestone dates from firm
Date: Wednesday, January 23, 2013 11:35:45 AM

Dear Kati,
Yes, we can accept these revised dates.
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Wednesday, January 23, 2013 9:02 AM
To: Hillier, Jill GZ/US
Subject: RE: NDA 203568, Mipomersen, required PMRs-milestone dates from firm

Hi Jill,
The immunogenicity folks have weighed in on your proposed dates for #1 and #2, and would like them revised to 12/31/2013 and 7/31/2014, respectively. Please let me know if that is feasible.
Thanks, Kati

From: Hillier, Jill GZ/US [<mailto:Jill.Hillier@genzyme.com>]
Sent: Tuesday, January 15, 2013 1:20 PM
To: Johnson, Kati
Subject: RE: NDA 203568, Mipomersen, required PMRs-milestone dates from firm

Dear Kati,
Please see our proposed milestone dates for the PMRs below in red.
Kind regards,
Jill

Jill P. Hillier, PhD
Vice President, Regulatory Affairs
Genzyme Corporation
O: 781-434-3443
M: 617-218-7807
jill.hillier@genzyme.com

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Wednesday, January 09, 2013 11:24 AM
To: Hillier, Jill GZ/US
Subject: NDA 203568, Mipomersen, required PMRs

Per our 1/7/2013 telephone conversation:

Postmarketing Requirements for Kynamro (mipomersen sodium):

1) Develop and validate a sensitive assay to assess for the presence of antibodies to double-stranded (ds) DNA. Your final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).

Submit date for Final Report Submission.

Final Report Submission	(b) (4)
-------------------------	---------

2) A study to assess for the presence of antibodies that bind native double-stranded (ds) DNA among patients treated with Kynamro (mipomersen sodium). The study may be conducted with stored serum samples from patients treated with Kynamro (mipomersen sodium) in the clinical development program, but should include samples from patients who test negative as well as patients who test positive for antibodies to mipomersen. Among patients who develop anti-drug antibodies, samples should be included from patients shortly after seroconversion as well as from sustained responders.

Submit date for Final Report Submission.

Final Report Submission	(b) (4)
-------------------------	---------

3) A long-term prospective observational study (product exposure registry) of patients with homozygous familial hypercholesterolemia (HoFH) treated with Kynamro (mipomersen sodium) to evaluate known and potential serious risk related to the use of Kynamro (mipomersen sodium). Known and potential safety concerns to be addressed include hepatotoxicity (including hepatic transaminase elevations, hepatic steatosis, (b) (4) malignancies (including hepatocellular adenomas or carcinomas, and fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis), and new diagnoses of autoimmune disorders (lupus erythematosus, anti-phospholipid syndrome, rheumatoid arthritis, glomerulonephritis). The registry will include a sample of patients prescribed Kynamro (mipomersen sodium) and followed for 10 years.

Submit dates for Final Protocol Submission*, Annual Interim Report Submissions, Study Completion, and Final Report Submission.

Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months).

Final Protocol Submission:	29 Oct 2013
Annual Interim Reports	29 Nov 2014
	29 Nov 2015
	29 Nov 2016
	29 Nov 2017
	29 Nov 2018
	29 Nov 2019
	29 Nov 2020
	29 Nov 2021
	29 Nov 2022
	29 Nov 2023
	29 Nov 2024
	29 Nov 2025

Study Completion	29 Nov 2026
Final Report Submission	29 May 2027

4) [REDACTED] (b) (4) reports of hepatic abnormalities, malignancy, and immune-mediated reactions in patients treated with Kynamro (mipomersen sodium) for a period of 10 years from the date of approval.

The enhanced pharmacovigilance program will include the following:

a) Active query of reporters to obtain additional clinical information related to serious reports of hepatic abnormalities, malignancy, and immune-mediated reactions. The sponsor should actively query reporters for the following information:

(i) For reports of hepatic abnormalities: liver-related laboratory, imaging and pathology results, duration of Kynamro (mipomersen sodium) exposure, and other risk factors for hepatic abnormalities

(ii) For reports of malignancy: cancer site, timing and duration of Kynamro (mipomersen sodium) exposure in relation to diagnosis, and other risk factors for the specific cancer.

(iii) For reports of immune-mediated reactions (such as severe cutaneous reactions, anaphylaxis, vasculitis, acute onset renal failure, and autoimmune disorders): nature of the defect, timing and duration of Kynamro (mipomersen sodium) exposure, and other risk factors for the immunologic responses.

b) Expedited reporting to FDA of all initial and follow-up reports of serious cases of hepatic abnormalities and malignancy. Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

c) Expedited reporting to FDA of all initial and follow-up reports of serious cases of potential immune-mediated adverse reactions. Interim analyses and summaries of new and cumulative safety information of reports of immune-mediated reactions with a serious outcome must be submitted semi-annually, followed by the final report at the conclusion of the monitoring period.

Submit dates for Final Protocol Submission*, Semi-Annual Assessment and Summary Report Submissions, Study Completion, and Final Report Submission.

Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months)

Final Protocol Submission:	29 Oct 2013
Semi-annual Reports*	28 Feb 2014
	29 Aug 2014
	28 Feb 2015
	29 Aug 2015
	28 Feb 2016
	29 Aug 2016
Annual Reports#	28 Feb 2017
	28 Feb 2018
	28 Feb 2019
	28 Feb 2020

	28 Feb 2021
	28 Feb 2022
	28 Feb 2023
	28 Feb 2024
Study Completion	29 Nov 2024
Final Report Submission	29 May 2025

* Please note semi-annual reports dates are those requested for item c). The date for the annual reports will be 28 Feb of each year.

Please note we are proposing Annual Reports rather than semi-annual reports after the third year since all serious cases will be expedited to FDA, and this allows alignment with the periodic report prepared and submitted as per 21 CFR 314.80,

*A protocol is not considered final until FDA and sponsor have reached agreement on it.

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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/s/

KATI JOHNSON
01/24/2013

Johnson, Kati

From: Johnson, Kati
Sent: Wednesday, January 09, 2013 11:24 AM
To: 'Hillier, Jill GZ/US'
Subject: NDA 203568, Mipomersen, required PMRs

Per our 1/7/2013 telephone conversation:

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Submit date for Final Report Submission.

2. A study to assess for the presence of antibodies that bind native double-stranded (ds) DNA among patients treated with Kynamro (mipomersen sodium). The study may be conducted with stored serum samples from patients treated with Kynamro (mipomersen sodium) in the clinical development program, but should include samples from patients who test negative as well as patients who test positive for antibodies to mipomersen. Among patients who develop anti-drug antibodies, samples should be included from patients shortly after seroconversion as well as from sustained responders.

Submit date for Final Report Submission.

3. A long-term prospective observational study (product exposure registry) of patients with homozygous familial hypercholesterolemia (HoFH) treated with Kynamro (mipomersen sodium) to evaluate known and potential serious risk related to the use of Kynamro (mipomersen sodium). Known and potential safety concerns to be addressed include hepatotoxicity (including hepatic transaminase elevations, hepatic steatosis, (b) (4) malignancies (including hepatocellular adenomas or carcinomas, and fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis), and new diagnoses of auto-immune disorders (lupus erythematosus, anti-phospholipid syndrome, rheumatoid arthritis, glomerulonephritis). The registry will include a sample of patients prescribed Kynamro (mipomersen sodium) and followed for 10 years.

Submit dates for Final Protocol Submission*, Annual Interim Report Submissions, Study Completion, and Final Report Submission.

Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months).

4. [REDACTED] (b) (4) reports of hepatic abnormalities, malignancy, and immune-mediated reactions in patients treated with Kynamro (mipomersen sodium) for a period of 10 years from the date of approval.

The enhanced pharmacovigilance program will include the following:

- a) Active query of reporters to obtain additional clinical information related to serious reports of hepatic abnormalities, malignancy, and immune-mediated reactions. The sponsor should actively query reporters for the following information:
- (i) For reports of hepatic abnormalities: liver-related laboratory, imaging and pathology results, duration of Kynamro (mipomersen sodium) exposure, and other risk factors for hepatic abnormalities
 - (ii) For reports of malignancy: cancer site, timing and duration of Kynamro (mipomersen sodium) exposure in relation to diagnosis, and other risk factors for the specific cancer.
 - (iii) For reports of immune-mediated reactions (such as severe cutaneous reactions, anaphylaxis, vasculitis, acute onset renal failure, and autoimmune disorders): nature of the defect, timing and duration of Kynamro (mipomersen sodium) exposure, and other risk factors for the immunologic responses.
- b) Expedited reporting to FDA of all initial and follow-up reports of serious cases of hepatic abnormalities and malignancy. Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.
- c) Expedited reporting to FDA of all initial and follow-up reports of serious cases of potential immune-mediated adverse reactions. Interim analyses and summaries of new and cumulative safety information of reports of immune-mediated reactions with a serious outcome must be submitted semi-annually, followed by the final report at the conclusion of the monitoring period.

Submit dates for Final Protocol Submission*, Semi-Annual Assessment and Summary Report Submissions, Study Completion, and Final Report Submission.

Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months)

*A protocol is not considered final until FDA and sponsor have reached agreement on it.

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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/s/

KATI JOHNSON
01/15/2013



NDA 203568

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Genzyme Corporation
153 Second Avenue
Waltham, MA 02451

Attention: Jill P. Hillier, PhD
Vice President, Regulatory Affairs

Dear Dr. Hillier:

Please refer to your New Drug Application (NDA), dated and received on March 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Mipomersen Sodium Solution for Injection, 200 mg/mL.

We also refer to:

- Your initial proprietary name submission, dated April 12, 2011, for the proposed name Kynamro;
- Our initial correspondence dated July 6, 2012, finding this proposed proprietary name unacceptable;
- Your submission dated and received September 6, 2012, requesting reconsideration of your proposed proprietary name, Kynamro.

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

The proposed proprietary name, Kynamro, will be re-reviewed 90 days prior to the approval of the NDA. 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 March 29, 2012, 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, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

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/

CAROL A HOLQUIST
11/29/2012



NDA 203568

GENERAL ADVICE

Genzyme Corporation
Attention: Jill P. Hillier, PhD
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Hillier:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mipomersen Injection 200 mg/mL.

Your application contained a protocol entitled [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

(b) (4)



If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ⁱ Hunt JR & White E. Retaining and tracking cohort study members. *Epid Rev* 1998;20(1):57-70.

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/s/

AMY G EGAN
10/17/2012



NDA 203568

DISCIPLINE REVIEW LETTER

Genzyme Corporation
Attention: Jill P. Hillier, PhD
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Hillier:

Please refer to your March 29, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KYNAMRO (mipomersen) Injection, 200 mg/mL.

We also refer to your amendments dated May 11 and June 20, 2012.

Our review of the chemistry, manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

1. Provide numerical values for a) melting temperature (T_m) for Sequence Determination, and b) m/z for Identity using IP-HPLC-UV-MS as part of the drug substance specifications.
2. Provide information regarding possible differences in efficacy among the mixture of (b) (4)
[REDACTED]
3. Provide details of the 9-month vial/stopper study, including tabulated experimental results, that support your conclusion of compatibility of mipomersen sodium injection, 200 mg/mL, with (b) (4) glass vials, as well as with both (b) (4) rubber stoppers.
4. Provide details of the 12-month prefilled syringe study, including tabulated experimental results that support your conclusion of a demonstration of compatibility of mipomersen sodium injection, 200 mg/mL, with any of the three conditions for the three syringe/plunger stopper configurations.
5. Provide a single drug product specification with one set of acceptance criteria for tests for a) identification, b) assay, c) degradation products, d) volume of injection in container, and e) osmolality in the drug product specifications. Your proposed specification currently has two sets of criteria, for release and for stability testing. The regulatory acceptance criteria

should be the same from release throughout shelf life; however, you may choose to have tighter in-house limits at the time of release to provide increased assurance that the product will remain within the regulatory acceptance criteria throughout its shelf life. See ICH Q6A for guidance.

6. Provide a description and technical details of the needle shield safety device as part of the container closure system for the prefilled syringe.
7. As part of the Postapproval Stability Protocol and Stability Commitment, updated stability results on the drug products in vials and prefilled syringes should be included either as a supplement or in the Annual Report pursuant to 21 CFR.314.81(b)(2).

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 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 Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Chief, Branch 7, Division 3
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
09/11/2012



NDA 203568

GENERAL ADVICE

Genzyme Corporation
Attention: Jill Hillier, PhD
Senior Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 0214

Dear Dr. Hillier:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mipomersen Injection, 200 mg/mL.

A risk evaluation and mitigation strategy (REMS) is being required for mipomersen because of the risk of increased hepatic transaminases and hepatic steatosis which has the potential to progress to steatohepatitis, cirrhosis, and liver failure. Because of the limited safety information available, the REMS is required to limit broader use of mipomersen in patients with less severe forms of hypercholesterolemia where the benefit-risk profile has not been established.

REMS Goals:

- To educate prescribers about the approved indication for use of mipomersen, the potential risk of hepatotoxicity associated with the use of mipomersen, and the need to monitor patients during treatment with mipomersen as per product labeling
- To limit access to therapy with mipomersen to patients in whom therapy with mipomersen is medically appropriate

REMS Elements:

- Elements to Assure Safe Use (ETASU)
 - (A) Health care professionals (HCP) who prescribe mipomersen are specially certified
 - (B) Pharmacies that dispense mipomersen are specially certified
 - (D) Mipomersen will be dispensed to patients with evidence or other documentation of safe-use conditions.
- Implementation System
- Timetable for Submission of Assessments of the REMS (6 months, 12 months, and then annually following approval)

In order for HCPs to be certified, they must undergo an educational program and enroll in the mipomersen REMS program by acknowledging understanding of the risks of mipomersen therapy; the need to monitor hepatic transaminases during treatment; and the indication for use. They must also agree to counsel patients about the risk of hepatotoxicity, the need to have regular blood tests performed to monitor for evidence of liver injury or dysfunction, and to attest that the patient is an appropriate candidate for mipomersen therapy prior to prescribing mipomersen.

Patient enrollment or patient acknowledgement of risks associated with the use of mipomersen is not being required. FDA propose the following safe use condition: the prescriber will need to attest on an authorized prescription form, for each prescription, that he/she is aware that mipomersen is indicated for patients with homozygous familial hypercholesterolemia and the drug is medically appropriate for the patient. The form does not require a patient signature.

A sample form is attached. The prescriber would fill out the form and send it directly to a certified pharmacy. (We acknowledge that you have proposed using specialty pharmacies to fill prescriptions.) You (Genzyme) would not directly receive patient specific information but would receive aggregate data from specialty pharmacies based on their contracts and information needed for assessments

Certified pharmacies would need to have systems in place to ensure that only certified prescribers prescribe mipomersen to patients in whom therapy with mipomersen is medically appropriate. The certified pharmacies do not need to ensure that the appropriate laboratory testing has been performed prior to dispensing mipomersen.

We ask that you consider how to incorporate into the REMS:

- e-prescribing
- closed medical care systems (for example, VA, large HMOs, DOD)
- inpatient use

A Medication Guide is not being required as part of the REMS. FDA is requiring a Medication Guide as part of labeling to mitigate other safety concerns associated with the use of mipomersen:

- Injection site reactions – patients should be informed of the possible occurrence of these reactions, how to alleviate symptoms, and concerning signs/symptoms to be aware of and report to their HCP.
- Flu-like symptoms – patients should be informed of the possible occurrence of these reactions, how to alleviate symptoms, and concerning signs/symptoms to be aware of and report to their HCP.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

Sample REMS Prescription Authorization Form

This form consists of two parts: 1) Prescription Authorization 2) Prescriber Statement of Medical Need
Instructions: Complete **both** sides of this form for each new prescription. This form must be sent to a certified pharmacy only. Contact the TRADENAME REMS Program for a list of certified pharmacies by phone at 1-XXX-XXX-XXXX, or at www.tradename.rems.com.

1) Prescription Authorization

Patient Information (Please Print) *indicates required fields

First Name *: _____ Middle Initial*: _____ Last Name*: _____

Gender*: Male Female Date of Birth*: _____

Address 1*: _____

Address 2*: _____

City*: _____ State*: _____ Zip code*: _____

Preferred Time to Contact: Day _____ Evening _____

Preferred Phone*: _____ Alternate Phone _____

Email: _____

Alternate Contact/Guardian: _____ Phone: _____

Patient Insurance Information

Primary Insurance: _____

Group #: _____ Policy #: _____

Insurance phone #: _____

Policy Holder/Subscriber: _____ Relationship: _____

Policy Holder Date of Birth: _____

Secondary Insurance: _____

Group #: _____ Policy #: _____

Insurance phone #: _____

Policy Holder/Subscriber: _____ Relationship: _____

Policy Holder Date of Birth: _____

Prescription Card: Yes (complete below) Not applicable

Carrier: _____

Identification #: _____

Policy/Group #: _____

Card Holder First Name: _____ Middle Initial: _____ Last Name: _____

Card Holder Date of Birth : _____

Shipping Information Ship to: Patient's Home Other (indicate below)

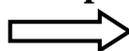
Name: _____

Address 1: _____

Address 2: _____

City: _____ State: _____ Zip code: _____

Please turn over and complete both sides of this form.



Tradename Prescription Information

Starting Dose: _____ Refills: _____

Dosing Instructions: _____

2) Prescriber Statement of Medical Need

Prescriber Statement of Medical Need

- I understand that TRADENAME is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B) and triglycerides (TG) in patients with homozygous familial hypercholesterolemia (HoFH).
- I certify that the TRADENAME is medically necessary for this patient and that the information provided above is accurate to the best of my knowledge.
- I attest that have obtained the aminotransferase levels (ALT, AST) for this patient as directed in TRADENAME’s prescribing information.

Prescriber Information

First Name: _____ Last Name: _____

Address 1*: _____

Address 2: _____

City*: _____ State*: _____ Zip code*: _____

Phone #*: _____ Fax #*: _____

NPI #*: _____

Prescriber Signature*: _____

Dispense as Written Substitution Allowed

Date*: _____

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/s/

AMY G EGAN
08/29/2012

Executive CAC

Date of Meeting: July 31, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHOT, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP, Team Leader
Ronald Wange, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Ronald Wange

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 203-568
Drug Name: Kynamro[®] (Mipomersen)
Sponsor: Genzyme

Background: Mipomersen (ISIS 301012) is a synthetic 20-base oligonucleotide with specific antisense activity towards human apolipoprotein (apo) B₁₀₀. Hybridization of mipomersen to the mRNA for apoB₁₀₀ results in selective degradation of this mRNA and reduced apoB₁₀₀ protein synthesis. In humans, apoB₁₀₀ is the principal apolipoprotein associated with very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and low density lipoprotein (LDL). ApoB₁₀₀ is also a principal component of lipoprotein (a) (Lp[a]). LDL-cholesterol (LDL-C), apoB, and Lp(a) are key risk factors for atherosclerosis. Sponsor is seeking to market mipomersen as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce LDL-C, apoB and Lp(a) in patients with homozygous familial hypercholesterolemia.

(b) (4)

Mipomersen was not genotoxic in the Ames, Mouse Lymphoma or *In Vivo* Micronucleus tests.

Mouse Carcinogenicity Study:

CD-1 mice (70 per sex and group) received weekly subcutaneous injections of 5, 20 or 60 mg/kg of mipomersen in phosphate buffered saline. A single control dose group (70 per sex) received weekly injections of vehicle at a volume that matched the high-dose group. Mipomersen is not pharmacologically active in the mouse because of sequence differences in the targeted region of the apoB₁₀₀ mRNA. Therefore, in order to assess the carcinogenic risk posed by exaggerated pharmacology, the study included an additional arm that received a weekly SC injection of ISIS 147764 (a pharmacologically active mouse surrogate; MS) at 60 mg/kg/week. An additional

dosing arm (MD2) with mipomersen given 80 mg/kg/month was tested, however this is not the intended clinical dosing interval.

Treatment with mipomersen was associated with a decreased rate of survival. This resulted in early discontinuation of dosing when the number of surviving animals declined to 20 and early sacrifice when the number of surviving animals decreased to 15:

Cessation of Dosing: HD♀ Week 83 HD♂ Week 95 MD♀ Week 98
 Early Sacrifice: HD♀ Week 88 HD♂ Week 96 MD♀ Week 103

Drug-Related Neoplasms in Male Mice

Organ Tumor	Incidence						Significance levels			
	C	LD	MD1	HD	MD2	MS	trnd1-4 trnd1-3	4vs1 5vs1	3vs1 3vs5	2vs1 6vs1
Liver										
CARCINOMA, HEPATOCELLULAR	1	2	8	2	1	4	.2512 .0038	.3747 .7366	.0153 .9983	.5000 .1938
Hepato. Adenoma/-carc.	13	10	18	12	11	25	.1826 .0767	.3964 .7218	.1937 .9500	.8421 .0303
Skin, subcutis										
FIBROSARCOMA	0	0	1	4	0	3	.0021 .3241	.0291 .	.4896 1	. .1250
Sarcoma/Fibro-/Lipo-	2	0	1	5	0	3	.0072 .6913	.1130 1	.8671 .5000	1 1

Drug-Related Neoplasms in Female Mice

Organ Tumor	Incidence						Significance levels			
	C	LD	MD1	HD	MD2	MS	trnd1-4 trnd1-3	4vs1 5vs1	3vs1 3vs5	2vs1 6vs1
Systemic										
HEMANGIOSARCOMA	2	8	6	11	9	2	.0025 .2073	.0012 .0416	.1250 .4075	.0482 .7660
Hemangioma/-sarcoma	3	8	7	12	9	4	.0024 .1879	.0022 .0940	.1471 .5272	.1050 .6163
Liver										
ADENOMA, HEPATOCELLULAR	4	0	5	11	5	23	<0.0001 .1623	.0095 .5722	.4844 .7148	1 .0003
CARCINOMA, HEPATOCELLULAR	0	0	0	2	0	2	.0306 .	.14963086
Hepato. Adenoma/-carcinoma	4	0	5	12	5	25	<0.0001 .1623	.0044 .5722	.4844 .7148	1 .0001

- Red indicates rare tumor, yellow highlight indicates statistical significance
- LD, MD1, HD refer to 5, 20, and 60 mg/kg/week of mipomersen
- MD2: 80 mg/kg/month of mipomersen
- MS: 60 mg/kg/week of mouse surrogate

An increased incidence of basophilic and/or eosinophilic foci of cellular alteration in the liver (a precursor to neoplastic change) was associated with administration of either mipomersen or the mouse surrogate.

Rat Carcinogenicity Study:

Sprague-Dawley rats (60/sex/group) received weekly subcutaneous injections of 0 (vehicle), 3, 10 or 20 mg/kg of mipomersen in phosphate buffered saline. As mipomersen is not pharmacologically active in the rat, the study included an additional arm that received a weekly SC injection of ISIS 147768 (a pharmacologically active rat surrogate; RS) at 10 mg/kg/week, in order to assess the carcinogenic risk posed by exaggerated pharmacology. Notably, high dose males initially received a dose of 30 mg/kg/week. This was reduced to 25 mg/kg/week in Week 2 on the basis of proteinuria observed in a concurrent rat toxicity study, and was further reduced to 20 mg/kg/week at Week 25 on the basis of proteinuria observed in the high dose males in this study. Similarly, high dose females were initially dosed at 25 mg/kg/week, and this dose was reduced to 20 mg/kg/week at Week 25 on the basis of proteinuria observed in the high dose females in this study.

Treatment with mipomersen was associated with a decreased rate of survival at all dose levels. This resulted in early discontinuation of dosing when the number of surviving animals declined to 20 and early sacrifice when the number of surviving animals decreased to 15:

Cessation of Dosing: HD♀ W88 HD♂ W70 MD♀ W98 MD♂ W94 LD♀ W96 LD♂ na
 Early Sacrifice: HD♀ W92 HD♂ W74 MD♀ W100 MD♂ W96 LD♀ W98 LD♂ na

Drug-Related Neoplasms in Male Rats

Organ Tumor	Incidence					Significance levels			
	C	LD	MD	HD	RS	trnd1-4/ trnd1-3	4vs1/ 5vs1	3vs1	2vs1
Skin, subcutis									
FIBROUS HISTIOCYTOMA	0	1	3	3	1	.0046 .0301	.0148 .4889	.0652	.4713

Drug-related Neoplasms in Female Rats

Organ Tumor	Incidence					Significance levels			
	C	LD	MD	HD	RS	trnd1-4/ trnd1-3	4vs1/ 5vs1	3vs1	2vs1
Skin, subcutis									
FIBROSARCOMA	0	1	4	5	1	.0046 .0215	.0098 .4810	.0491	.4533
FIBROUS HISTIOCYTOMA	0	0	3	4	0	.0053 .0370	.0259 .	.1067	.
Fibroma/Fibrosarcoma/ Fibr.Histiocytoma	1	2	9	10	1	.0003 .0016	.0007 .7275	.0058	.4203

- Red indicates rare tumor, yellow highlight indicates statistical significance
- LD, MD, HD refer to 3, 10, and 20 mg/kg/week of mipomersen
- RS: 10 mg/kg/week of rat surrogate

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee agreed that the study was adequate, noting prior FDA concurrence with the doses as well as with Sponsor's proposal for early termination of dosing and early sacrifice in the high-dose group of both sexes and in mid-dose females.

- The Committee concurred that the following neoplasms were drug related:
 - Hepatocellular adenomas and combined hepatocellular adenomas or carcinomas in females administered 60 mg/kg/week mipomersen.
 - Hepatocellular adenomas or carcinomas, combined, in both sexes administered 60 mg/kg/week ISIS 147764 (mouse surrogate).
 - Fibrosarcoma of the skin/subcutis in males administered 60 mg/kg/week mipomersen.
 - Hemangiosarcomas in female mice given 60 mg/kg/week mipomersen.

Rat:

- The Committee agreed that the study was adequate despite the absence of prior FDA concurrence with doses and a high intercurrent mortality rate in the clinical candidate treatment groups.
- The Committee concurred that the following neoplasms were drug related:
 - Fibrous histiocytoma of the skin/subcutis in males and females at ≥ 10 mg/kg/week.
 - Fibrosarcoma of the skin/subcutis in females at ≥ 10 mg/kg/week.
 - Combined fibroma/fibrosarcoma/fibrous histiocytoma of the skin/subcutis in females at ≥ 10 mg/kg/week.

It was noted that the above neoplasms of the skin/subcutis were not associated with the injection sites, and are therefore unlikely to be a consequence of the method of administration.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DMEP
/Karen Davis-Bruno, DMEP
/Ronald Wange, DMEP
/Kati Johnson, DMEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
08/03/2012

DAVID JACOBSON KRAM
08/03/2012



NDA 203568

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Genzyme Corporation
153 Second Avenue
Waltham, MA 02451

Attention: Jill P. Hillier, PhD
Vice President, Regulatory Affairs

Dear Dr. Hillier:

Please refer to your New Drug Application (NDA), dated and received on March 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Mipomersen Injection, 200 mg/mL.

We also refer to your correspondence, dated and received on April 12, 2012, requesting review of your proposed proprietary name, Kynamro.

We have completed our review of the proposed proprietary name, Kynamro, and have concluded that it is vulnerable to name confusion that could lead to medication errors with a pending proposed proprietary name due to orthographic similarity and shared product characteristics. Therefore, at this time, the acceptability of the proposed proprietary name, Kynamro, is dependent upon which application is approved first. If Kynamro is approved first, we will advise the second product to seek an alternative name. If the second name application is approved prior to your application then you will be requested to submit another name.

If you wish to withdraw Kynamro to avoid the potential confusion with the other pending name and submit an alternate name for review, please submit a request for withdrawal and submit a new proprietary name for review (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

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/

CAROL A HOLQUIST
07/06/2012



NDA 203568

FILING COMMUNICATION

Genzyme Corporation
Attention: Jill Hillier, PhD
Senior Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 0214

Dear Dr. Hillier:

Please refer to your New Drug Application (NDA) dated March 29, 2012, received March 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for KYNAMRO (mipomersen) Injection, 200 mg/ml.

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 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **January 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, midcycle, 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 commitment requests by **December 3, 2012**.

We request that you submit the following information:

Clinical Statistical

Provide the following with **discussion and conclusion** for the primary efficacy variable. If they are already in the NDA, please provide the location. The number of patients is an important part of the information.

1. A graph for the percent of patients discontinuing (or continuing) over time by treatment group and on the same page or graph, a similar graph for the percent of patients discontinuing over time due to adverse effects.
2. Graphs for responses over time for the **completer set**, by treatment arm.

3. **Investigation of effect of dropouts on statistical analyses**

Sensitivity analyses for the handling of missing data, in addition to the analyses you provided in the NDA.

The sensitivity analyses may be based on parametric models, for example, Mixed Model Repeated Measures or Multiple Imputation.

The effects of dropouts on observed cases (OC) and LOCF results should be investigated graphically. A simple tool is a plot of efficacy results over time for each (separate) cohort (depending on the interval of dropout) for (1) OC and (2) LOCF populations. Please make sure that the graph does not become clumsy (i.e., choose location and scale so that the curves are distinguishable and use different colors). However, you are always welcome to present additional graphs or methods which you think provide more reasonable depictions of the data. The number of patients for each case should be provided.

4. Provide summary results of a thorough investigation of confounding and interaction effects (but protocol-mentioned primary analysis remains the primary analysis), if you have not already done so. Also, include covariation and interaction p-values. Provide treatment comparison p-values for each level of important subgroups. The number of patients for each case should be provided.
5. For screening and exploratory purposes (not confirmatory), as reviewers, we would like to see (a) 2-sided p-values for all baseline pair-wise comparisons (between treatment groups) on baseline status, demographics, and other prognostic variables.

Microbiology

6. Provide protocols and final reports supporting aseptic processing operations for both the vial presentation and the prefilled syringe presentation. Include information on the sterilization (b) (4) of the primary containers/closures and filling equipment. Also, include information on the environmental monitoring program.
7. Provide protocols and final reports supporting container closure integrity testing for both the vial presentation and the prefilled syringe presentation.

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), Medication Guide, and patient

PI (as applicable). 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), Medication Guide, and patient PI (as applicable), 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.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
05/25/2012



NDA 203568

NDA ACKNOWLEDGMENT

Genzyme Corporation
Attention: Jill Hillier, PhD
Senior Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Hillier:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: KYNAMRO (mipomersen sodium) Injection 200 mg/mL

Review Priority Classification: Standard

Date of Application: March 29, 2012

Date of Receipt: March 29, 2012

Our Reference Number: NDA 203568

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **May 28, 2012**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

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 NDA 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 Metabolism and Endocrinology 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. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
04/09/2012



IND 70969

MEETING MINUTES

Genzyme Corporation
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
153 Second Avenue
Waltham, MA 02451

Dear Ms. Penhale-Unz

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

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2010. The purpose of the meeting was to discuss your proposed content for a future NDA submission.

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 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: DSI Request for Information
Summary Level Clinical Site Data for Data Integrity Review And Inspection
Planning in NDA and BLA Submissions

Meeting Minutes
Pre-NDA Meeting
December 13, 2010

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Monday, December 13, 2010
Meeting Location: FDA White Oak Campus
10903 New Hampshire Avenue
Building 22, Conference Room 1311
Silver Spring, MD 20993

Application Number: IND 70969
Product Name: Mipomersen Injection
Indication: 1. Homozygous Familial Hypercholesterolemia (HoFH)
(b) (4)

Sponsor/Applicant Name: Genzyme Corporation

Meeting Chair: Eileen Craig, MD
Meeting Recorder: Kati Johnson, Project Manager

FDA ATTENDEES

Division of Metabolism & Endocrinology Products

Mary Parks, MD-Director
Eric Colman, MD-Deputy Director, Lipid Team Leader
Amy Egan, MD-Deputy Director, Safety
Eileen Craig, MD-Clinical Reviewer
Karen Davis Bruno, PhD-Pharmacology/Toxicology Supervisor
Ron Wange, PhD-Pharmacology/Toxicology Reviewer
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology

Sally Choe, PhD-Clinical Pharmacology Team Leader
Jee Eun Lee, PhD-Clinical Pharmacology Reviewer

Office of Translational Sciences, Office of Biostatistics

Todd Sahlroot, PhD-Deputy Director, Division of Biometrics II
Japobatra Choudhury, PhD-Statistician

Office of New Drug Quality Assessment (ONDQA)

Suong Tran, PhD- CMC Lead - Division 3
Joseph Leginus, PhD-Reviewer

Meeting Minutes
Pre-NDA Meeting
December 13, 2010

SPONSOR ATTENDEES

Genzyme Corporation

Joanne Donovan, MD, PhD-VP Clinical Research
Scott Chasan-Taber, PhD-Sr. Dir., Biomedical Data Sciences and Informatics
Marjie Hard, PhD-Assoc. Dir., Clinical Research, Clinical Pharmacology
Richard Geary, PhD-Sr. V.P., Development
Tejdeep Singh, MD-Medical Dir., Global Patient Safety and Risk Management
Judith Marquis, PhD-Group V.P., Pharmacology & Preclinical Development
Nicole Oliynyk-Dir., Regulatory Affairs, Chemistry Manufacturing and Controls (CMC)
Jill Hillier, PhD-Sr. Director, Regulatory Affairs
Kathryn Penhale-Unz- Director, Regulatory Affairs
Pamela Williamson-Sr. V.P., Global Head, Regulatory Affairs and Compliance
John Nyland, MD-Sr. V.P., Global Therapeutic Group Head Renal, Cardiovascular,
Endocrine, Solid Organ Transplant, and Fibrotic Disease
Richard Moscicki, MD-Chief Medical Officer, Sr. V.P., Clinical Development and Medical
Affairs

Genzyme Consultants

Mary McGowan, MD-Medical Director, Cholesterol Treatment Center, Concord Hospital,
Concord, NH

Paul Ridker, MD-Eugene Braunwald Professor of Medicine, Harvard Medical School, Director
for Cardiovascular Disease Prevention, Divisions of Cardiovascular Diseases and Preventive
Medicine, Brigham and Women's Hospital, Boston, MA

1.0 BACKGROUND

ISIS 301012 (now called Mipomersen) is an antisense oligonucleotide targeted to apoB-100, the principal apolipoprotein of atherogenic LDL-C and its metabolic precursor, VLDL. ISIS Pharmaceuticals was the initial sponsor of the IND. They requested a pre-IND meeting in June 2005 to discuss their proposed Phase 3 protocol (C5) for HoFH [REDACTED] (b) (4). The firm was notified that, during the internal meeting, it became clear that the agency had insufficient information to be able to discuss their Phase 3 plans. There were concerns with the dose selection (200 mg), renal toxicity and inflammatory responses in animals. The firm was advised to instead conduct a small Phase 2 dose ranging study to determine the dose. The firm was also advised to submit the IND and request an End-of-Phase 2 (EOP2) meeting. See September 1, 2005 letter. The IND was submitted November 17, 2005. The initial IND contained Phase 2 dose-ranging studies in both HoFH (CS8) and HeFH (CS9). Fast Track Designation for HoFH was requested April 11, 2006, which was denied May 30, 2006 because the development program, as described, was not designed to determine a cardiovascular benefit.

The firm requested an EOP2 meeting on May 4, 2007, which was granted. An internal meeting was held on September 5, 2007. Again, it was determined that the clinical questions could not be addressed until some preclinical findings were resolved. On January 4, 2007, the firm submitted a draft 6-month interim report of a one-year cynomolgus monkey toxicity study (Study ISIS

Meeting Minutes
Pre-NDA Meeting
December 13, 2010

301012-AS15). The final interim report (through Week 52) of the one year toxicity study was submitted on June 8, 2007. The new finding after one year of dosing was that animals treated with drug (3, 10 and 30 mg/kg/week) developed arterial (peri)vasculitis and intimal hyperplasia (N=5 total affected). The vasculitis was observed in the GI tract in 3 monkeys (3, 10 or 30 mg/kg) and in multiple organs in another 2 monkeys (30 mg/kg). Coronary artery vasculitis and intimal thickening was present in 1 out of 4 monkeys treated with 10 mg/kg and euthanized on Day 185 of the study. Additional new findings in the 30 mg/kg group included renal tubule epithelial cell degeneration, thrombocytopenia and decreases in complement protein C3.

It has been the firm's position that the vasculitis is due to complement activation and this activation does not occur in humans at the proposed dose levels. In addition, complement and inflammatory markers will be monitored in the proposed Phase 3 studies. The division was not convinced that the firm's explanations are valid and remains concerned because, among other things, monitoring for vasculitis in clinical trials is not feasible.

On January 22, 2008, the sponsor was notified that the IND was on partial clinical hold and that only high-risk patients could be studied. This population was defined as:

- 10 year risk for CVD \geq 20%
- taking a maximum statin dose
- still not at LDL goal

The sponsor was notified that the information needed to get off partial clinical hold would be provided to the firm following the February 15, 2008 Regulatory Briefing. It does not appear that any information was provided to the firm, and the application remains on partial clinical hold.

On July 23, 2008, the sponsorship of the application was transferred to Genzyme Corporation.

A PreNDA meeting was requested September 24, 2010 and granted on September 29, 2010. Initial preliminary responses (without responses to the clinical questions) were forwarded to the sponsor on December 10, 2010. Revised preliminary responses, which included responses to the clinical questions, were forwarded to the sponsor on December 13, 2010. These questions were not addressed during the meeting. See the DISCUSSION section.

Nonclinical Question 1

The NDA for mipomersen will be supported by acute and repeat dose, genetic mutation, chromosomal damage, safety pharmacology, reproductive, juvenile, immune function and carcinogenicity studies.

Does the Agency agree the proposed package of nonclinical studies is sufficient to support the NDA?

FDA's Response: : It is acknowledged that Genzyme plans to submit a complete nonclinical development program as outlined in Table 1 Section 14 of the meeting briefing package with the NDA filing. There remains uncertainty about the clinical significance,

monitorability and mechanism of action by which mipomersen induced vascular lesions in monkeys (characterized as multi-focal intimal hyperplasia with mixed inflammatory infiltrates).

Please provide the validation report for detection of anti-mipomersen antibodies in human serum/plasma. This should be submitted and found acceptable by the Agency prior to submission of the NDA.

Clinical Question 1

The pharmacokinetics and pharmacodynamics of mipomersen have been characterized in healthy subjects, and in patients with non-familial and familial hypercholesterolemia (FH) over the dose range of 30 mg to 400 mg. A summary of key studies that will support the clinical pharmacology package is provided below:

- A total of 5 single and multiple-dose Phase 1 and Phase 2 dose escalation studies
- Determination of the bioavailability of s.c. mipomersen in a single Phase 1 study
- Three *in vitro* studies evaluating the induction and inhibition potential of mipomersen, and the involvement of human cytochrome P450 isoforms in the metabolism of mipomersen
- An *in vitro* evaluation of the p-glycoprotein substrate and inhibition potential of mipomersen
- Two dedicated drug-drug interactions studies conducted in healthy volunteers evaluating the potential for drug interactions between mipomersen and 2 oral lipid lowering medications (simvastatin and ezetimibe), and warfarin
- A healthy volunteer study comparing the pharmacokinetics of mipomersen following once weekly dosing to 2 alternative dose regimens
- A thorough QT/QTc study
- A population PK-PD analysis to include data from Phase 1, 2 and 3 studies

Mipomersen plasma concentrations have also been evaluated in 4 Phase 3 studies following 26 weeks of treatment, and in 2 open label extension studies being conducted with up to 104 weeks of treatment.

The presence of anti-mipomersen antibodies has been evaluated in several Phase 2 and all Phase 3 studies.

The NDA will include a comprehensive clinical pharmacology package that evaluates the pharmacokinetic and pharmacodynamic properties of mipomersen, as well as the intrinsic and extrinsic factors that may alter its behavior, to support the proposed dose regimen. Genzyme considers that the clinical pharmacology of mipomersen has therefore been well-characterized and that no further clinical pharmacology studies are needed to support the NDA for mipomersen.

Does the Agency agree that no further clinical pharmacology studies are required to support the NDA?

FDA Response: Yes, the clinical pharmacology program you have established appears to be sufficient for an NDA submission.

Clinical Question 2

The proposed indication for mipomersen is:

Mipomersen is an apo B synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce LDL-C, apo B, total cholesterol, non-HDL-C, and Lp(a) levels in patients with homozygous familial hypercholesterolemia (HoFH) (b) (4)

- a) Homozygous familial hypercholesterolemia, (HoFH), is a rare genetic defect characterized by elevated plasma cholesterol levels up to 10-fold higher than normal with untreated patients having LDL-C levels in the range of 650 – 1000 mg/dL. The prevalence of HoFH worldwide is approximately 1:1,000,000, which extrapolates to approximately 300 patients with HoFH in the United States and 455 patients with HoFH in the European Union. ISIS 301012-CS5, a Phase 3 pivotal study, met its primary objective by demonstrating that in this patient population, treatment with mipomersen 200 mg weekly for 26 weeks resulted in clinically meaningful and statistically significant decreases in LDL-C compared to placebo (24.7% reduction versus 3.3% reduction; $p < 0.001$) with an absolute mean change in LDL-C from baseline to the primary efficacy time point (PET) of -112.7 mg/dL for the mipomersen group and -12.0 mg/dL for the placebo group. This study also met all 3 secondary endpoints with significant reductions in apo B, non-HDL-C and total cholesterol, and demonstrated a significant reduction in Lp(a).

Twenty-eight of 34 (82%) mipomersen-treated patients completed treatment in this study versus 17/17 (100%) in the placebo group. Injection site reactions and flu-like symptoms were experienced by 26/34 (77%) and 10/34 (29%), respectively, of the mipomersen treated patients. Elevations in alanine transaminase (ALT) ≥ 3 times the upper limit of normal (ULN) were observed at least once in 4/34 (12%) of the mipomersen-treated patients versus none in the placebo group; 2 consecutive measures of ALT ≥ 3 times ULN at least 7 days apart occurred in 1/34 (3%) of mipomersen treated patients.

Genzyme considers that these data support a clear and defined benefit for patients with HoFH that outweighs potential risks.

Does the Agency agree that the Phase 3 study ISIS 301012-CS5, supports an indication for the treatment of patients with HoFH?

FDA Response: We note that there is six-month placebo-control data with mipomersen in 28 HoFH subjects. A total of thirty-nine patients from CS5 (i.e. HoFH patients) are enrolled in the ongoing open-label study CS6 and twenty-two of these HoFH subjects have been treated for 12-months with mipomersen. You estimate that at the time of the 120-safety update, data on 4 HoFH and 59 HeFH subjects in ongoing study CS6 will be submitted. Given the safety concerns with mipomersen, all HoFH subjects currently enrolled in CS6 should have at least one year of exposure to mipomersen prior to submitting the NDA.

Whether the Phase 3 study ISIS 301012-CS5, along with the open-label extension study CS6, supports an indication for the treatment of patients with HoFH will be determined

after a full review of the relevant data and, most likely, input from an FDA advisory committee.

(b) (4)

As described in this briefing package, Severe HeFH is defined as either LDL-C levels >200 mg/dL on a maximally tolerated lipid lowering regimen for patients with coronary heart disease (CHD) or other forms of clinical atherosclerotic disease, or LDL-C >300 mg/dL for patients without CHD or other forms of clinical atherosclerotic disease. Patients with Severe HeFH are a small subset of the HeFH population, with prevalence in the adult population estimated at 1:15,000. The overall size of the population of patients with Severe HeFH is estimated at 16,000 adult patients in the United States and 28,000 adult patients in the European Union; and is thus an orphan-sized population.

Mipomersen was assessed in the Severe HeFH population in the pivotal Phase 3 study MIPO3500108. This study met its primary objective in that treatment with mipomersen 200 mg weekly for 26 weeks resulted in a clinically meaningful and statistically significant reduction in LDL-C compared to placebo (35.9% reduction versus 12.5% increase; $p < 0.001$) at PET. This represented an absolute mean change in LDL-C in the mipomersen group from 276.1 mg/dL at baseline to 174.9 mg/dL at PET, and in the placebo group from 249.4 mg/dL to 263.9 mg/dL. This study also met all 3 secondary endpoints with significant reductions in apo B, non-HDL-C and total cholesterol, and demonstrated a significant reduction in Lp(a). Twenty-seven of 39 (69%) mipomersen patients completed treatment in this study versus 18 of 19 (95%) placebo patients. Injection site reactions and flu-like symptoms were experienced by 90% and 46% of the mipomersen-treated patients, respectively. Elevations in ALT $\geq 3 \times$ ULN were observed at least once in 31% of the mipomersen-treated patients versus none in the placebo group; 2 consecutive elevations $\geq 3 \times$ ULN at least 7 days apart were seen in 15% of mipomersen-treated patients. Six patients had both baseline and end of treatment magnetic resonance imaging (MRI) studies performed for-cause (increase in ALT), all of whom had increases in fat fraction versus baseline ranging from 13 to 39.5 percentage points.

(b) (4)

FDA Response: We note that there is limited patient exposure to mipomersen:

HoFH

- 6-month placebo-control data with mipomersen in 28 HoFH subjects
- 12-month data with mipomersen, none of which is placebo-controlled for 12 months, in 22 HoFH subjects

Severe HeFH

- 6-month placebo-control data with mipomersen in 33 Severe HeFH subjects
- 12-month data with mipomersen, none of which is placebo-controlled for 12 months, in 9 Severe HeFH subjects

A preliminary review of the safety database reveals one case of fulminant liver failure and subsequent death in a patient that had severe hepatic steatosis based on an MR imaging report, additional cases of hepatic steatosis, significant ALT elevations, increased incidence of hypertension adverse events, injection site reactions, flu-like symptoms, neuropsychiatric adverse events, intermittent hsCRP elevations, possible increase in renal laboratory abnormalities such as proteinuria and creatinine increases, and lack of any evidence of CV benefit.

This database is inadequate to support a thorough risk-benefit assessment for this patient population (b) (4)

Clinical Question 3

The requirements of an Integrated Summary of Efficacy (ISE) will be incorporated within Section 2.7.3.3 (“Comparison of Results Across Studies”) rather than as a separate ISE within Module 5. The NDA will include efficacy results from 1 Phase 3 pivotal study for each of the 2 subpopulations, HoFH (ISIS 301012-CS5) and Severe HeFH (MIPO3500108). The efficacy results of these Phase 3 studies, in addition to Phase 3 supportive studies, ISIS 301012-CS7 and ISIS 301012-CS12, will be presented individually in Section 2.7.3 and individual study data tables and listings will be provided as part of the CSRs in Module 5. These analyses include evaluation of the primary efficacy parameter in subgroups of age, gender, race, and baseline LDL-C.

Does the Agency agree with the plan to summarize the efficacy findings in Section 2.7.3 of the eCTD to meet the requirements of an ISE?

FDA response: Yes, we agree. The location in the NDA should not be a problem, if the components of the ISE are there. Please provide a graphical comparison of study results

with 95% confidence intervals. For other features, please provide the side-by-side comparisons by tables.

In your subgroup analyses, provide treatment by factor interaction p-values.

Clinical Question 4

The total clinical Phase 1, 2 and 3 exposure to support the NDA for the HoFH (b) (4) populations will include an estimated 800 mipomersen-treated subjects at all doses and durations, including an estimated 260 patients treated at the indicated dose (200 mg weekly s.c. injection) for a least 6 months and an estimated 100 patients treated for at least 12 months.

Does the Agency agree that the size of the clinical database is adequate to support approval in patients with HoFH (with a prevalence of 1:1,000,000) (b) (4) ?

FDA Response: Please refer to the response to Question #2.

Clinical Question 5

Based on the data that are available to date, including an estimated 260 patients exposed to mipomersen for 6 months, and an estimated 100 patients treated for at least one year, we consider there is an adequate benefit-risk profile for use of mipomersen in patients with HoFH (b) (4) who have a serious medical need. The conclusions regarding clinical benefit derive at this time from observed effects on LDL-C, a well established coronary heart disease risk factor, after 6 months of exposure. We acknowledge that additional data obtained after longer term exposure in larger numbers of patients will further inform the mipomersen risk benefit profile. Genzyme is considering that this may include limited and focused distribution of mipomersen, tools to educate and update prescribers and patients, as well as post-approval patient surveillance tools such as a group surveillance study or an observational cohort study, that would be able to provide additional and important information concerning longer term treatment and follow up.

Genzyme would appreciate any initial feedback or guidance that the Agency may have on the considerations and proposals presented in the briefing package. Additionally, we would appreciate reviewing the steps we can take to enable detailed discussions of risk management to take place before and during review of the NDA.

FDA Response: We agree with you that the conclusions regarding clinical benefit derive at this time from observed effects on LDL-C after 6 months of exposure and that additional data obtained after longer term exposure in larger numbers of patients will further inform the mipomersen risk benefit profile. Placebo-controlled cardiovascular outcome data in a more diverse population may be necessary to fully assess the risk-benefit profile of mipomersen, particularly if use is considered in lower risk individuals.

Whether there is an adequate benefit-risk profile for the use of mipomersen in patients with HoFH is a review issue. As previously noted, we have significant concerns regarding

the safety of this product outside of the HoFH population. We recommend that you strongly consider risk mitigation strategies that would ensure that the product would be used in the target population, including a risk evaluation and mitigations strategy (REMS) informing patients (Medication Guide) and healthcare providers (a Communication Plan) of the serious risks associated with the use of your product, and restricting the distribution of your product (Elements to Assure Safe Use) to the target population. While any REMS would be a review issue, we recommend you consider these elements of a REMS in your proposed NDA submission. Furthermore, we are interested in your proposal for an observational cohort study and/or a registry as a post-marketing requirement. We suggest that you provide details of these proposals in your NDA submission.

Clinical Question 6

The Integrated Summary of Safety (ISS) will be comprised of a synthesis of results from all individual studies along with 2 sets of pooled analyses from study designs of a similar nature as follows:

1. ISIS 301012-CS5, ISIS 301012-CS7, ISIS 301012-CS12, and MIPO3500108 for the 6 month Phase 3, double blind, placebo-controlled studies (mipomersen: 261 patients; placebo: 129 patients; total: 390 patients).
2. ISIS 301012-CS4, ISIS 301012-CS8, and ISIS 301012-CS9 for the Phase 2 short-term dose-ranging studies (mipomersen: 108 patients; placebo: 23 patients; total: 131 patients).

For these studies, data will be pooled for analyses of baseline characteristics and demographics, patient disposition, and safety data including exposure to study drug, adverse events (AEs), laboratory assessments, vital signs, electrocardiograms (ECGs), and MRI assessments of liver fat content. The 2 open label extension studies, ISIS 301012-CS6 (N=141; results will be integrated with the patient's experience in their index Phase 3 study) and ISIS 301012-CS17 (N=21), will not be pooled but key findings will be compared between studies.

Does the Agency agree with the pooling strategy for these safety data for the ISS?

FDA Response: Yes, provided that the safety data is also presented by each individual study.

Clinical Question 7

The ISS will include safety data as described in Clinical Question 6 from completed studies, as well as from the ongoing open label extension study, ISIS 301012-CS6 (N=141) with database cut-off for an interim study report approximately 8.5 months prior to NDA submission, and the ongoing open label extension study, ISIS 301012-CS17 (N=21), which has a database cut-off for all 2-year data in May 2010 (4 patients entered into a third year extension). Further, serious adverse events reported from all studies through 3 months prior to the NDA submission will also be included.

The 120-day safety update report will contain updated safety information for studies completed since the original submission and any new/ongoing studies, including new deaths,

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discontinuations due to AEs and other SAE data reported through a database cut-off date 4 months prior to the 120-day safety update submission.

Does the Agency agree with the plan for the ISS and 120-day safety update report?

FDA Response: All data that will be necessary for the approval consideration of mipomersen must be submitted at the time of the NDA submission. Please refer to our response to Clinical Question #2.

Clinical Question 8

Case Report Forms (CRFs) for all completed Phase 1, Phase 2 and Phase 3 as well as the 2 ongoing open label extension studies will be provided for all subjects who died or withdrew from the study due to an adverse event consistent with 21 CFR 314.50, as well as for all subjects who experienced a serious adverse event.

Does the Agency agree with this proposal for presentation of CRFs?

FDA Response: Yes. In addition, we would like Case Report Forms for patients who develop moderate or greater hepatic steatosis on any imaging study in any of the trials.

Clinical Question 9

CDISC compliant SAS datasets based on SDTM (Version 3.1.1) and the production ADaM model (“Analysis Data Model Version 2.0 Final”) will be included in the NDA only for studies that provide either substantial dose ranging information in a setting with background lipid lowering therapy, or provide substantial efficacy and safety data at the 200 mg once weekly dose. Additionally, CDISC compliant SAS datasets will be submitted for the thorough ECG study (MIPO2800209), the warfarin drug-drug interaction study (MIPO2900509), and the ISS. CDISC compliant SAS datasets as well as tables, listings and figures, will also be submitted for study ISIS 301012-CS19, the Phase 2 single center, placebo-controlled 26-week study in high risk patients intolerant to statins (N=34). These data will be described only in Section 2.7.3, 2.7.4 and the ISS, and not in a study report. Phase 1 and 2 studies in which monotherapy is used and/or the number of treated patients within a dose level is very small and/or treatment duration is very short will only have the study report and all appendices presented in eCTD format; no SAS datasets will be provided for these studies. In addition, a population PK dataset compatible with NONMEM as well as all models tested will be provided that will include data from all studies that include a PK component with the exception of the thorough ECG study (MIPO2800209) and the warfarin drug-drug interaction study MIPO2900509). Study design datasets are not planned to be submitted because the pivotal studies are simple and very consistent designs.

Does the Agency agree with this proposal for submission of datasets?

FDA Response (Clinical Pharmacology): Yes, but please specify what you mean by study design datasets.

Additional Statistical Requests for Study Reports:

Percent Of Patients Continuing Over Time (Table as well as graph)

Please provide “percent of patients continuing over time” for each treatment group separately (on the same page or graph).

Graph for efficacy over time

Please provide Graphs for the primary and key secondary efficacy measures over time for the set of patients who completed the study.

CDF (Table as well as graph)

Please provide cumulative Distribution Function (CDF) for primary efficacy variables at the primary time-point.

Sensitivity Analyses

1. With Respect to Missingness

- a. of patients excluded from the Randomized Set of Patients
- b. all other missingness

2. Consistency of results across different statistical methods, studies, sites, etc. should be studied and, if there are any inconsistencies, the reasons for the inconsistencies should be investigated.

FDA Response (Clinical Pharmacology): Yes.

With respect to your population PK-PD analyses, provide the following:

- 1. All datasets used for model development and validation as SAS transport files (*.xpt). Flag and maintain any concentrations and/or subjects that have been excluded from the analysis.**
- 2. All code files (R or S-plus scripts and NONMEM control streams) and output listings used for development of base structural model, covariate model, final model and model evaluation (VPC, QPC). These files should be submitted as ASCII files with *.txt format (e.g., myfile_ctl.txt, myfile_out.txt)**

Clinical Question 10

A Phase 1 thorough QT/QTc study was conducted entitled “A Randomized, Double-Blind Crossover Study to Define the ECG Effects of Mipomersen in Healthy Men and Women A Thorough ECG Study” (MIPO2800209). The raw ECG tracings will be uploaded to the ECG Warehouse.

Does the Agency agree with this proposal for posting the ECGs?

FDA Response: Yes, this is acceptable.

Additional FDA Requests:

Please address the following issues in your submission:

- 1. In-depth analysis of any elevations in blood pressure or pulse rate in the development program, to include discontinuations due to hypertension, hypertensive medications that were increased or added into the subject's regimen, cardiovascular adverse event rates in subjects that experienced an elevation in blood pressure or pulse rate as compared to those who did not experience an increase in pulse rate or blood pressure, etc. Provide analysis of blood pressure and pulse data that includes shift tables (based on JNC7 definitions) An example of a shift table and a categorical change table for systolic blood pressure is provided below. Similar tables should be provided for diastolic blood pressure and pulse.**

Table 1: Systolic Blood Pressure (mm Hg) Shift Table from Baseline to Trial Visit

SBP	Placebo				Study drug			
	<90 n (%)	Normal ≥90- <140 n (%)	≥140-<160 n (%)	≥160 n (%)	<90 n (%)	Normal ≥90-<140 n (%)	≥140-<160 n (%)	≥160 n (%)
Week 4								
Week 8								
Week 12								
Week 16								
Week 20								
Week 24								
Week 28								
Week 32								
Week 36								
Week 40								
Week 44								
Week 48								
Week 52								
Week 56								

JNC7 Stage 1 (systolic) HTN: 140-159 mm Hg

JNC7 Stage 2 (systolic) HTN: ≥ 160 mm Hg

Table 2: Incidence of Treatment-Emergent Increases in Systolic Blood Pressure

Category	Placebo (N=) n (%)	Study Drug (N=) n (%)
Subjects with ≥ 1 post-BL measurement		
≥ 2 values ≥ 140 mm Hg		
≥ 2 values ≥ 150 mm Hg ^a		
≥ 2 values ≥ 160 mm Hg ^a		
≥ 2 values ≥ 10 mm Hg over BL ^b		
≥ 2 values ≥ 15 mm Hg over BL ^b		
≥ 1 value ≥ 10 mm Hg over BL		
≥ 1 value ≥ 15 mm Hg over BL		

a At least two consecutive treatment-emergent values or a single treatment-emergent value if last (subjects with a value ≥ 150 or ≥ 160 mm Hg at baseline are excluded from the analysis).

b At least two consecutive treatment-emergent values or a single treatment-emergent value if last.

- 2. Include the number of patients, if any, who satisfy the criteria for Hy's Law: AST or ALT > 3x ULN, with ALP < 2x ULN and total bilirubin > 2x ULN. Each case should include a detailed narrative. An example of how to summarize ALT/AST data is provided below:**

Table 3: Potentially Clinically Significant Laboratory Values

	Placebo N=1515	Study drug dose 1	Study drug dose 2	Total Study drug
ALT > 3x ULN				
ALT > 5x ULN				
ALT > 10x ULN				
ALT > 20x ULN				
AST > 3x ULN				
AST > 5x ULN				
AST > 10x ULN				
AST > 20x ULN				
Total bilirubin > 2x ULN				
Hy's Law 1: ALT >3 x ULN and bilirubin >2 x ULN				
Hy's Law 2: AST >3 x ULN and bilirubin >2 x ULN				
<p>Hy's Law: (1)The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.</p> <p>(2) Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN). (3) No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Final, July 2009</p>				

3. In the laboratory value datasets please provide the lower and upper thresholds for normal and the ranges for “markedly abnormal”. Include a listing of abnormal values and markedly abnormal values for individual subjects that also include unscheduled lab values, length of time on study drug, and dose.
4. Please present the efficacy and safety data in conventional units
5. Please include length of time on study drug prior to SAE, AE leading to withdrawal, or significant clinical or laboratory AE

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 Exposure-Response Relationships - important exposure-response assessments.
3. Less common adverse events (between 0.1% and 1%).
4. Section 7.4.2 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.4.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.4.2 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.4.3 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.4.3 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.4.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.4.4 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.4.4. – Standard analyses and explorations of ECG data.
12. Section 7.6.4 – Overdose experience.
13. Section 7.5.1 - Explorations for dose dependency for adverse findings.
14. Section 7.5.2 - Explorations for time dependency for adverse findings.
15. Section 7.5.3 - Explorations for drug-demographic interactions.
16. Section 7.5.4 - Explorations for drug-disease interactions.
17. Section 7.5.5 - Explorations for drug-drug interactions.
18. Section 7.5.5 - Dosing considerations for important drug-drug interactions.
19. Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Chemistry Manufacturing and Controls Question 1

Genzyme intends to include the full chemistry, manufacturing and controls information for 2 drug product packaging configurations; a single use vial and a pre-filled syringe, both of the same formulation and strength (200 mg/mL). Each proposed configuration will have its own Product CTD section as required by *M4: The Common Technical Document for the Registration of Pharmaceuticals for Human Use*. Although the 2 container closure systems are different mechanically, the primary product contact components are similar (e.g., [REDACTED] (b) (4) stopper) between the pre-filled syringe and vial container closure systems. Given that the

strength and formulations are the same and the primary product contact components are similar Genzyme plans to compare the stability profiles of both of these presentations. At the time of submission, Genzyme plans to submit 18 months of real time data and 6 months of accelerated data for the vial configuration; and 6 months of real time and accelerated data will be included for the pre-filled syringe. If the stability profiles for each configuration are shown to be comparable (i.e., no significant differences in drug product quality attributes) Genzyme considers that the totality of stability data is sufficient to support inclusion of a pre-filled syringe as 1 of 2 container closures systems in the initial NDA for mipomersen 200 mg/mL drug product. Stability studies for both presentations are planned to be carried minimally to 24 months. *Does the Agency agree with this approach to support drug product stability in the NDA for both the vial and pre-filled syringe presentations of mipomersen?*

FDA Response: Your proposal to submit 18 months of real time data and 6 months of accelerated data for the drug product vial configuration, and 6 months of real time and accelerated data for the pre-filled syringe at the time of NDA submission is acceptable. However, the expiry of the drug product(s) will be independently determined based upon the available stability submitted to the NDA.

Chemistry Manufacturing and Controls Question 2

Genzyme intends to include SAS transport or Excel files and statistical analysis of all stability indicating quality attributes for both the pre-filled syringe and the vial configurations in the NDA.

Does the Agency agree with this proposal for submission of data files?

FDA Response: Extrapolation of data on the stability indicating quality attributes of the drug product by statistical analysis should be minimized as much as possible. If the sponsor maintains that statistical analyses of these data are necessary, the analyses should be clear, concise and unequivocal.

2. DISCUSSION

The firm wanted to focus their presentation on three areas:

[Redacted] (b) (4)

2. Clarify the available 1 year exposure to support (b) (4) HoFH (b) (4)
3. Explain their proposal to manage the risk by ensuring that the drug is only prescribed by the appropriate physicians for the appropriate patient population.

[Redacted] (b) (4)

The sponsor stated that while apheresis is a potential treatment for HeFH, it is not a readily available therapy. There are only 35 apheresis centers in the country and they service only approximately 400 patients. According to the firm, the treatment requires 3 to 4 hours every 2 weeks, and requires a surgically implanted port.

It was the firm's position that the 100 patients, across both populations treated with the proposed weekly dose of 200 mg s.c. injection, with treatments in some patients exceeding 12 months, would provide sufficient information to assess the risk of mipomersen treatment. According to the background package, 12-month exposure data with mipomersen will be available for 22 HoFH and 9 Severe HeFH patients. There will be an additional 3 Severe HeFH patients with 11, 11, and 8 months of therapy at the time of submission.

The firm stated that there were no discontinuations due to hypertension adverse events in Study MIPO035. The firm acknowledged the single patient with liver failure who died. The case was evaluated by two members of the Data Safety Monitoring Committee. Given the elapsed time between the last mipomersen dose and the adverse event, it was the opinion of both that the event was due to acetaminophen toxicity, not mipomersen.

Regarding the increase in hepatic fat, it is the firm's position that this is a pharmacological effect of mipomersen as a result of the inhibition of Apo B. It appears to occur in patients with the highest LDL-C, and is reversible upon discontinuation of mipomersen. Four patients had biopsies, showing fat, inflammation and minimal fibrosis. The firm characterizes this as "bland steatosis". The NDA will provide MRI data at baseline, and at 6, 12, 18, and 24 months in some subjects. Some subjects will have a liver fibrosis panel done for 1 year. It is the firm's position that a moderate increase in hepatic fat is not a problem in the short term, and can be monitored. This risk must be balanced against the CV risk of the diseases.

Regarding the inflammation concerns, according to the firm there is a small transient increase in hsCRP which is similar to what is observed in moderate infection and one needs to balance this with the large decrease in LDL-C. The firm has conducted a Phase 1 study to evaluate the effect of mipomersen on various inflammatory markers, and it was largely negative.

The firm said they were totally in agreement with the risk management program proposed in the preliminary responses.

With 16,000 severe HeFH patients in the US, the firm was asked why only 6-month studies were done. The firm responded that many of those 16,000 have not been diagnosed with severe

HeFH. It is their position that the 100 subjects treated at the proposed dose (200 mg weekly s.c. injection) for 1 year will provide representative data for efficacy across both the HeFH and HoFH populations. The agency agreed that they have positive lipid parameter changes but more cardiac disorder serious adverse events in the mipomersen-treated subjects vs placebo in Studies CS5 and MIPO035.

It was noted that the firm has studied more HoFH patients than severe HeFH patients, particularly with one-year of mipomersen exposure.

(b) (4)

The agency stated that we have limited outcomes data on patients on apheresis, whereas no information beyond 1 year is available for severe HeFH patients on mipomersen.

(b) (4)

In response to a question, the firm responded that the HOFH study (CS5) was conducted in 7 countries and the severe HeFH study (Mipo)35) was conducted in 6 countries.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

See Action Item below

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
FDA will notify Genzyme if the database presented would support an indication (b) (4)	FDA	Friday, December 17, 2010*

5.0 ATTACHMENTS AND HANDOUTS

(b) (4)

Johnson, Kati

From: Johnson, Kati
Sent: Thursday, December 16, 2010 9:39 AM
To: 'Penhale-Unz, Kathryn'
Subject: IND 70969, Mipomersen, [REDACTED]

(b) (4)

(b) (4)

I will archive this communication in our database. I am here today, then on leave Friday and Monday. I will be reading e-mail daily while on leave.

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
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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.

/s/

KATI JOHNSON
12/16/2010