

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125559Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 125559	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Praluent Established/Proper Name: alirocumab Dosage Form: liquid for subcutaneous injection		Applicant: Sanofi Aventis, U.S. LLC Agent for Applicant (if applicable):
RPM: patricia madara		Division: DMEP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p style="margin-left: 20px;"> <input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)                      Date of check:                 </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>7/24/15</u></li> </ul>		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		XX None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		NA
❖ Application Characteristics <sup>3</sup>		

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

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

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

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

- |   |   |
|---|---|
| <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 type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments: Priority review because Applicant purchased a Pediatric Priority Review Voucher

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

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	7/24/15
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	XX Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	XX Included
❖ 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 type="checkbox"/> Medication Guide XX Patient Package Insert XX Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	XX Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	XX Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	Attached to approval letter
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	Acceptable letter 12/17/14 Reviews: 12/15/14 11/17/14
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: 1/19/15 DMEPA: 5/22/15 DMPP/PLT: 7/16/15 OPDP: 7/16/15 SEALD: XXNone CSS: XX None Product Quality 7/15/15 Other:
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	1/19/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	XX Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included NA
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	XX No

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

<ul style="list-style-type: none"> <li>• This application is on the AIP                             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<p>XX No</p> <p><input type="checkbox"/> Not an AP action</p>
<p>❖ Pediatrics (<i>approvals only</i>)</p> <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>5/27/15</u> If PeRC review not necessary, explain: _____</li> </ul>	
<p>❖ Breakthrough Therapy Designation</p>	N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<p>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</p>	included
<p>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</p>	N/A
<p>❖ Minutes of Meetings</p>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	9/4/14
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	2/21/12
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	Mtg 3/11/15
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	Mtg 5/28/15
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	EOP2 CMC: 5/9/12
<p>❖ Advisory Committee Meeting(s)</p>	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	6/9/15
<b>Decisional and Summary Memos</b>	
<p>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</p>	7/24/15
<p>Division Director Summary Review (<i>indicate date for each review</i>)</p>	7/24/15
<p>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</p>	NA – see division director memo
<p>PMR/PMC Development Templates (<i>indicate total number</i>)</p>	10 templates – 7/24/15
<b>Clinical</b>	
<p>❖ Clinical Reviews</p>	



<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	7/14/15
• Supervisory Review(s) <i>(indicate date for each review)</i>	None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	5/4/15; 1/7/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	X None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	X No carc
❖ ECAC/CAC report/memo of meeting	XX None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	X None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	XX None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	7/23/15 + 4/30/15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	OBP: 7/14 + 5/1(filing) 4/24/15 Micro, drug substance: 4/22/15 Micro, drug product: 7/1 + 4/24/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	CDRH facilities review: 12/18/14(into Dartrts 6/8/15) CDRH engineering review: 6/22/15+5/5/15 (into Dartrts 7/15 and 6/8/15)
❖ Environmental Assessment (check one) (original and supplemental applications)	
XX Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	7/23/15
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	NA
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	NA
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	XX Acceptable 7/20/15 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done NA
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<b>XX</b> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<b>XX</b> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<b>XX</b> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done BLA = pediatric page
❖ Send approval email within one business day to CDER-APPROVALS	<b>XX</b> Done

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/s/  
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PATRICIA J MADARA  
07/27/2015



BLA 125559

## INFORMATION REQUEST

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Senior Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated and received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for Praluent (alirocumab) injection, 75 mg and 150 mg.

We are requesting your assistance in populating the attached tables for Praluent.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly approved drugs and biologics will be made publicly available on [www.fda.gov/drugtrialsnapshot](http://www.fda.gov/drugtrialsnapshot).

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

1. Information written in consumer-friendly language
2. "MORE INFORMATION" sections that provide more technical, data-heavy information
3. Information that focuses on subgroup data and analyses
4. Links to the PI for the product and to the FDA reviews at [Drugs@FDA](mailto:Drugs@FDA)

We are requesting you submit this information no later than ten days after receipt of this letter. Thank you in advance for your cooperation.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

With respect to the request for completion of the shell table for LDL-C by subgroup, please complete the table for each of the following based on the pattern mixture model.

- (1.) Each of studies 1 thru 5 individually
- (2.) Studies 1 thru 5 combined in an analysis adjusted or stratified by study
- (3.) Studies 3, 4, and 5 combined in an analysis adjusted or stratified by study
- (4.) Studies 1 and 2 combined in an analysis adjusted or stratified by study
- (5.) Studies 3 and 4 combined in an analysis adjusted or stratified by study

For the analysis described in (5.) and for studies 2, 3 and 4 described in (1.), please complete the table twice, once each for the week 12 and 24 result. For all analyses, please report least square means rather than raw means.





**Table 7.2.1-a. Baseline Demographics for 5 pooled trials (double-blind, placebo-controlled trials)**

Demographic Parameters	PRALUENT	N=	Placebo	N=
<b>Sex</b>				
Male	25 (50.0)		30 (60.0)	
Female	25 (50.0)		20 (40.0)	
<b>Age</b>				
Mean years (SD)				
Median (years)				
Min, Max (years)				
<b>Age Group</b>				
below 65 years				
65 years and above				
<b>Race (may modify according to program)</b>				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
<b>Ethnicity</b>				
Hispanic or Latino				
Not Hispanic or Latino				
<b>Region (please populate all countries included below)</b>				
United States				

Source:

\* Percentages are calculated based on the total number of subjects in the respective arm. For example, percentage of males in Treatment Group 1 = 25/50



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/s/  
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JAMES P SMITH  
07/27/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** Proposed revised PI  
**Date:** Thursday, July 23, 2015 2:40:00 PM  
**Attachments:** [FDA to Sanofi 23July\\_annotated\\_proposedpi.doc](#)  
**Importance:** High

---

Hi Jana;

I have attached the package insert you sent yesterday at 5:38 PM. We are essentially in agreement. The clinical team made a couple of minor edits for consistency and the stats team requested a revision to text associated with a table.

Please review. I hope these minor revisions are acceptable. Confirm Receipt.

Also, please note that I will need to be offline from about 4:30 – 8 PM.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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/s/  
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PATRICIA J MADARA  
07/27/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** FDA response to IFUs submitted by Sanofi on 7/22  
**Date:** Thursday, July 23, 2015 1:44:00 PM  
**Attachments:** [FDA to Sanofi 23July 75mg PFS markup response to Sanofi 22Jul.doc](#)  
**Importance:** High

---

Hi Jana;

We have reviewed the revised Instructions for Use (IFUs) submitted by email on July 22, 2015. We find your proposed changes acceptable so I am not returning all the documents.

Please submit identical clean WORD and PDF versions to your BLA.

However, there was one error we ask that you correct. On the IFU for the 75 mg PFS only, the "clock" has been deleted in strike out track changes. Please retain the clock in the document. I am attaching this IFU only.

Sincerely;

Patricia Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Phone: 301-796-1249  
[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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/s/  
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PATRICIA J MADARA  
07/27/2015

**From:** Madara, Patricia  
**To:** ["Jana.Bodorova@sanofi.com"](mailto:Jana.Bodorova@sanofi.com)  
**Subject:** RE: Praluent BLA 125559 - PPI - we forgot to add a comment in the annotated version....  
**Date:** Wednesday, July 22, 2015 4:13:00 PM  
**Attachments:** [FDA to Sanofi 22Jul PPI response to sanofi PPI received 22Jul2015.doc](#)

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Hi Jana;

I did not send this latest comment but I don't think it matters. The Patient Labeling Team was quite adamant. See their comment. I accepted all the revisions with which we agree.

Please let me know if you want to pursue this farther. If you do not wish to discuss further, you may submit the PPI officially to the BLA.

Also, note that I will be unavailable, without access to email from 4:30 – 8:30 PM.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [mailto:[Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com)]  
**Sent:** Wednesday, July 22, 2015 3:53 PM  
**To:** Madara, Patricia  
**Subject:** RE: Praluent BLA 125559 - PPI - we forgot to add a comment in the annotated version....

Hi Pat,

Apologies again, but we forgot to add the comments on the side that we talked about during the TC today: The Sponsor proposes text to clarify that these are (b) (4) allergic reactions. We would like this to be provided to the other divisions who were not on the call so that they would understand our proposed text. This is the only change from the annotated document I sent at 3:13 pm. No contents text changed. The "clean" version did not change, so I am not resending it again.

I'm sorry. Thank you!

Best,

---

**From:** Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]  
**Sent:** Wednesday, July 22, 2015 3:13 PM  
**To:** Bodorova, Jana R&D/US  
**Subject:** RE: Praluent BLA 125559 - PPI - updated with the approval date at the end

Got them. Thanks.

---

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [<mailto:Jana.Bodorova@sanofi.com>]  
**Sent:** Wednesday, July 22, 2015 3:12 PM  
**To:** Madara, Patricia  
**Subject:** RE: Praluent BLA 125559 - PPI - updated with the approval date at the end  
**Importance:** High

Hi Pat,

Apologies! I just got updated versions of the PPI. The only change from the ones I sent you in the e-mail below is the approval date at the very end. It was “**Month 201X**”, now it’s “**July 2015**”. That’s the only change.

Best,  
Jana

---

**From:** Bodorova, Jana R&D/US  
**Sent:** Wednesday, July 22, 2015 2:45 PM  
**To:** 'Madara, Patricia'  
**Subject:** Praluent BLA 125559 - PPI  
**Importance:** High

Hi Pat,

Attached please find the revised PPI, both in tracking changes mode and a clean version. The IFUs will be coming under a separate e-mail shortly.

Please confirm receipt.

Best,  
Jana

---

**From:** Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]  
**Sent:** Tuesday, July 21, 2015 9:33 AM  
**To:** Bodorova, Jana R&D/US  
**Subject:** Revision to the PPI  
**Importance:** High

Hi Jana;

After more internal discussion with the patient labeling team, we need to request a small revision to the PPI.

In the “**What are the possible side effects of PRALUENT?**” section, the sentence:

“The most common side effects of PRALUENT include:  ” (b) (4)

Should be revised to read:

"The most common side effects of PRALUENT include: redness, bruising, itching, swelling, or pain at the injection site, symptoms of the common cold, and flu or flu-like symptoms"

In track changes:

"The most common side effects of PRALUENT include: [REDACTED] (b) (4)

I hope making this change is not a problem. I will be sending the PI very shortly. The IFUs will also come soon.

Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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/s/  
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PATRICIA J MADARA  
07/27/2015

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com)  
**To:** [Hanan, Elisabeth](#)  
**Cc:** [Madara, Patricia](#)  
**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's Revised Response  
**Date:** Thursday, July 23, 2015 4:52:11 PM

---

Dear Elisabeth,

We concur with the revisions.

Best,  
Jana

---

**From:** Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]  
**Sent:** Thursday, July 23, 2015 4:47 PM  
**To:** Bodorova, Jana R&D/US  
**Cc:** Madara, Patricia  
**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's Revised Response

Sounds good, thank you for confirming receipt.

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

---

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [<mailto:Jana.Bodorova@sanofi.com>]  
**Sent:** Thursday, July 23, 2015 4:43 PM  
**To:** Hanan, Elisabeth  
**Cc:** Madara, Patricia  
**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's Revised Response

Dear Elisabeth,

I confirm receipt and will get back to you very soon to confirm our agreement to the edits (just awaiting response from Regeneron).

Best,  
Jana

---

**From:** Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]  
**Sent:** Thursday, July 23, 2015 4:13 PM  
**To:** Bodorova, Jana R&D/US  
**Cc:** Madara, Patricia

**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's Revised Response

Dear Jana,

We have reviewed your revised PMR/PMC list and proposed milestones that were submitted on July 20, 2015, following our teleconference discussion that afternoon. We agree with your proposed PMR/PMC descriptions and milestones with the minor editorial revisions shown in the attached revised document.

Please confirm receipt of this email and your concurrence with the revisions as soon as possible.

Thank you,

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

---

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [<mailto:Jana.Bodorova@sanofi.com>]

**Sent:** Monday, July 20, 2015 5:05 PM

**To:** Hanan, Elisabeth

**Cc:** Madara, Patricia

**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's Revised Response

Hi Elisabeth,

Thank you very much for arranging the teleconference this afternoon, it was very helpful for us. As agreed, please find our revised response to the FDA PMR/PMC requests.

Please let me know if you need anything else if you have any questions.

Best,

Jana

---

**From:** Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]

**Sent:** Monday, July 20, 2015 2:39 PM

**To:** Bodorova, Jana R&D/US

**Cc:** Madara, Patricia

**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's response

Hi Jana,

This is to confirm receipt of your dial-in information. We look forward to speaking with you at 3:15.

Thank you,

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Phone: 240-402-0350  
Fax: 301-796-9712  
[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

---

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [<mailto:Jana.Bodorova@sanofi.com>]  
**Sent:** Monday, July 20, 2015 2:35 PM  
**To:** Hanan, Elisabeth  
**Cc:** Madara, Patricia  
**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's response

Hi Elisabeth,

Yes, we will be able to do this call. Here are the call in numbers.

**US & Canada:** (b) (4)  
US Toll: (b) (4)

**Conference code:** (b) (4)

I will provide you with the list of our people as soon as possible, it may be after the call, though I will try before.

Thanks,  
Jana

---

**From:** Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]  
**Sent:** Monday, July 20, 2015 2:31 PM  
**To:** Bodorova, Jana R&D/US  
**Cc:** Madara, Patricia  
**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's response

Hi Jana,

Here is the planned list of attendees for the conference call this afternoon:

Dr. Jennifer Rodriguez-Pippins, Deputy Director for Safety, DMEP

Dr. Stephanie Leuenroth-Quinn, Nonclinical Team Leader (Acting), DMEP  
Dr. Patricia Bright, Division of Epidemiology  
Dr. Ali Niak, Division of Pharmacovigilance  
Dr. Lynne Yao, Division of Pediatric and Maternal Health

We'll look for your confirmation as to whether your team can attend at 3:15 and the call-in numbers.

Thank you,

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Phone: 240-402-0350  
Fax: 301-796-9712  
[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

---

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [<mailto:Jana.Bodorova@sanofi.com>]  
**Sent:** Monday, July 20, 2015 12:48 PM  
**To:** Hanan, Elisabeth  
**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's response

Thank you, Elisabeth.

Best,  
Jana

---

**From:** Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]  
**Sent:** Monday, July 20, 2015 12:25 PM  
**To:** Bodorova, Jana R&D/US; Madara, Patricia  
**Subject:** RE: BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's response

Dear Jana,

Thank you for your prompt reply. Your response has been forwarded to management and we will get back to you as soon as we can.

Regards,

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

---

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [<mailto:Jana.Bodorova@sanofi.com>]

**Sent:** Monday, July 20, 2015 11:44 AM

**To:** Hanan, Elisabeth; Madara, Patricia

**Subject:** BLA 125559 (alirocumab) PMRs/PMCs - Sponsor's response

**Importance:** High

Dear Elisabeth and Pat,

Attached please find our response to FDA request of 17-July-2015 for an additional PMR (pregnancy study). Please note that in the attached response we propose to list it as a PMC in order to provide the Sponsor time to develop a protocol that will address the Agency's request.

We note that this new request was communicated only recently and it will be difficult to provide accurate detail in terms of protocol and study submission dates. Given the request, we will need to assess a number of protocol design elements including, but not limited to, appropriate "outcomes of interest" and statistical assumptions. Also, please note that we expect the pregnancies will be rather rare events given that Praluent will not be recommended for patients use during pregnancy and many HCPs will likely take patients intending to become pregnant off all lipid lowering therapies. In addition, the mean age of the non-FH patient population enrolled in our trials was ~60 years. If the proposal is not acceptable to the FDA, we respectfully request a TC today to understand what the Agency is specifically looking for in this study such that we can more accurately estimate the milestone dates.

Please confirm receipt and let me know whether the Agency agrees with our proposal.

Best,

Jana

**Jana Bodorova, M.Sc.**

Senior Director, Global Regulatory Affairs

Sanofi US

[jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)

TEL.: 908-981-6050 - CELL.: (b) (6)

55 CORPORATE DRIVE - BRIDGEWATER - New Jersey 08807



Please consider the environment before printing this email!

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**From:** Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]

**Sent:** Friday, July 17, 2015 5:24 PM

**To:** Bodorova, Jana R&D/US

**Cc:** Madara, Patricia

**Subject:** BLA 125559 (alirocumab) PMRs/PMCs

Good evening,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We also refer to your submission sent via email on July 15, 2015, containing your responses to our revised draft PMR/PMC list that was sent to you on July 14, 2015.

FDA has compiled the attached comments for your draft PMR/PMC list and milestones submitted via email on July 15, 2015. Note that we have added an additional PMR to this list, which will need your proposed milestone dates to be added as indicated in the document.

We request that you accept all proposed changes that you agree with and return a revised version as soon as possible, but no later than close of business on **Monday, July 20, 2015**. Any proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

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/s/  
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ELISABETH A HANAN  
07/24/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** Praluent revised IFUs - FDA to Sanofi  
**Date:** Tuesday, July 21, 2015 4:00:00 PM  
**Attachments:** [FDA to Sanofi 21July\\_Marked\\_Praluent\\_IFU\\_75mg\\_PFP.doc](#)  
[FDA to Sanofi 21July\\_Marked\\_Praluent\\_IFU\\_75mg\\_PFS.doc](#)  
[FDA to Sanofi 21July\\_Marked\\_Praluent\\_IFU\\_150mg\\_PFP.doc](#)  
[FDA to Sanofi 21July\\_Marked\\_Praluent\\_IFU\\_150mg\\_PFS.doc](#)  
**Importance:** High

---

Hi Jana;

Please find attached the marked up (track changes) versions of the Praluent IFUs. Please review and incorporate the revisions. If you propose alternative language, please provide a robust justification.

Also, please note that I emailed Drs. Smith and Parks but have not received a response. As mentioned earlier, I do not believe they have access to email. Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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PATRICIA J MADARA  
07/21/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** Praluent PI  
**Date:** Tuesday, July 21, 2015 10:02:00 AM  
**Attachments:** [FDA to Sanofi 21July\\_annotated\\_proposedpi response to comments received 17Jul.doc](#)  
**Importance:** High

---

Hi Jana;

Please review. We have a couple of questions related to data; please respond to these. Obviously, the faster you can turn this around, the better.

Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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PATRICIA J MADARA  
07/21/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** Revision to the PPI  
**Date:** Tuesday, July 21, 2015 9:32:00 AM  
**Importance:** High

---

Hi Jana;

After more internal discussion with the patient labeling team, we need to request a small revision to the PPI.

In the **"What are the possible side effects of PRALUENT?"** section, the sentence:

"The most common side effects of PRALUENT include: [REDACTED] (b) (4)

Should be revised to read:

"The most common side effects of PRALUENT include: redness, bruising, itching, swelling, or pain at the injection site, symptoms of the common cold, and flu or flu-like symptoms"

In track changes:

"The most common side effects of PRALUENT include: [REDACTED] (b) (4)

I hope making this change is not a problem. I will be sending the PI very shortly. The IFUs will also come soon.

Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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PATRICIA J MADARA  
07/21/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** Praluent PPI  
**Date:** Monday, July 20, 2015 10:50:00 AM  
**Attachments:** [FDA to Sanofi\\_20July\\_PPI.doc](#)  
**Importance:** High

---

Hi Jana;

I am attaching the revised PPI for Praluent. (It has been edited by the review team, DMEPA, patient labeling and OPDP.) It contains revisions to content and formatting. I am sending the clean copy only. If there are any revisions with which you do not agree, please use track changes and provide a very robust justification.

It is important to retain the formatting changes made by the patient labeling team. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please note that revising and harmonizing PPIs is the central job of the patient labeling team. Also, know that there is a current initiative to transition patient labeling documents into a boxed format. We will be using this new format for all new NDAs/BLAs and supplements.

I expect to send the IFUs sometime today. Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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PATRICIA J MADARA  
07/20/2015

**From:** [Hanan, Elisabeth](#)  
**To:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com)  
**Cc:** [Madara, Patricia](#)  
**Subject:** BLA 125559 (alirocumab) PMRs/PMCs  
**Date:** Friday, July 17, 2015 5:23:50 PM  
**Attachments:** [BLA 125559 PMRs and PMCs - FDA Comments 17Jul2015.doc](#)

---

Good evening,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We also refer to your submission sent via email on July 15, 2015, containing your responses to our revised draft PMR/PMC list that was sent to you on July 14, 2015.

FDA has compiled the attached comments for your draft PMR/PMC list and milestones submitted via email on July 15, 2015. Note that we have added an additional PMR to this list, which will need your proposed milestone dates to be added as indicated in the document.

We request that you accept all proposed changes that you agree with and return a revised version as soon as possible, but no later than close of business on **Monday, July 20, 2015**. Any proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

Fax: 301-796-9712

[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

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ELISABETH A HANAN  
07/17/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - revised package insert  
**Date:** Wednesday, July 15, 2015 10:11:00 PM  
**Attachments:** [FDA to sanofi 15July\\_sanofi to FDA 11July.doc](#)  
**Importance:** High

---

## **BLA 125559**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection.

I have attached the package insert containing FDA revisions. Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

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PATRICIA J MADARA  
07/16/2015

**From:** [Hanan, Elisabeth](#)  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Cc:** [Madara, Patricia](#)  
**Subject:** BLA 125559 (alirocumab) PMRs/PMCs  
**Date:** Tuesday, July 14, 2015 8:27:47 PM  
**Attachments:** [BLA 125559 PMRs and PMCs - FDA Comments 14Jul2015.doc](#)

---

Good evening,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We also refer to your submission sent via email on July 13, 2015, containing your responses to our revised draft PMR/PMC list that was sent to you on July 10, 2015.

FDA has compiled the attached comments for your draft PMR/PMC list and milestones submitted via email on July 13, 2015. We request that you accept all proposed changes that you agree with and return a revised version as soon as possible, but no later than close of business on **Wednesday, July 15, 2015**. Any proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

**Elisabeth A. Hanan, M.S.**

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-0350

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[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

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ELISABETH A HANAN  
07/14/2015

**From:** [Hanan, Elisabeth](mailto:Hanan.Elisabeth@sanofi.com)  
**To:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com)  
**Cc:** [Madara, Patricia](mailto:Madara.Patricia@sanofi.com)  
**Subject:** BLA 125559 (alirocumab) PMRs/PMCs  
**Date:** Friday, July 10, 2015 3:50:01 PM  
**Attachments:** [BLA 125559 PMRs and PMCs - FDA Comments 10Jul2015.doc](#)

---

Good afternoon,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We also refer to your submission sent via email to Ms. Pat Madara on July 2, 2015, containing your responses to our initial draft PMR/PMC list that was sent to you on June 26, 2015.

FDA has compiled the attached comments for your draft PMR/PMC list and milestones submitted via email on July 2, 2015. We request that you accept all proposed changes that you agree with and return a revised version by close of business on **Monday, July 13, 2015**. Any proposed changes from this version should be marked via tracked changes.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,

**Elisabeth A. Hanan, M.S.**  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Phone: 240-402-0350  
Fax: 301-796-9712  
[elisabeth.hanan@fda.hhs.gov](mailto:elisabeth.hanan@fda.hhs.gov)

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/s/  
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ELISABETH A HANAN  
07/10/2015

**From:** Madara, Patricia  
**To:** ["Jana.Bodorova@sanofi.com"](mailto:Jana.Bodorova@sanofi.com)  
**Cc:** [Nia.Tatsis@sanofi.com](mailto:Nia.Tatsis@sanofi.com)  
**Subject:** RE: Praluent PMR - Sponsor follow up clarifying question  
**Date:** Wednesday, July 01, 2015 9:55:00 AM  
**Importance:** High

---

Hi Jana;

Your request for revision of the postmarketing required studies was forwarded to FDA management. Your proposals would be acceptable with the following revisions:

PMR (b) (4)  
(b) (4) of new-onset diabetes mellitus, injection site reactions, hypersensitivity, and immunogenicity with alirocumab (b) (4)

(no FDA edits)

PMR (b) (4)  
A (b) (4) randomized, controlled, long-term trial that (b) (4), prospectively evaluates (b) (4) changes in neurocognitive function with alirocumab treatment (b) (4). The trial (b) (4) must be adequately powered to exclude a clinically meaningful effect.

Please incorporate the revisions into the PMR/PMC template and provide the milestone dates.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

---

**From:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com) [mailto:[Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com)]

**Sent:** Tuesday, June 30, 2015 5:46 PM

**To:** Madara, Patricia

**Cc:** [Nia.Tatsis@sanofi.com](mailto:Nia.Tatsis@sanofi.com)

**Subject:** Praluent PMR - Sponsor follow up clarifying question

Dear Pat,

We acknowledge the response that the (b) (4) will not be adequate to fulfill postmarketing requirement (b) (4). We plan to address all of the requests under this PMR except the one for prospective neurocognitive function evaluation (b) (4).

In order to meet the latter requirement we will propose to prospectively assess neurocognitive function as part of a long term study (b) (4).

[Redacted] (b) (4)

We would like to ask that the requirement be re-written to allow us to fulfill the requirement in a study separate from [Redacted] (b) (4) will use to fulfill the other requirements:

Current wording of PMR [Redacted] (b) (4):

A large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity, and immunogenicity [Redacted] (b) (4)

We ask that you change to:

PMR [Redacted] (b) (4)  
A large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity, and immunogenicity with alirocumab treatment will be evaluated.

PMR [Redacted] (b) (4)

We would like to secure your agreement to this approach before providing the requested protocol submission, study completion, and CSR submission dates. Please confirm this is acceptable.

Best,  
Jana

---

**From:** Bodorova, Jana R&D/US  
**Sent:** Tuesday, June 30, 2015 1:19 PM  
**To:** 'Madara, Patricia'; Tatsis, Nia R&D/US  
**Subject:** RE: Praluent PMR

Hi Pat,

Many thanks for getting us the response quickly.

Best,  
Jana

**From:** Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]  
**Sent:** Tuesday, June 30, 2015 1:07 PM  
**To:** Tatsis, Nia R&D/US; Bodorova, Jana R&D/US  
**Subject:** RE: Praluent PMR  
**Importance:** High

Hi Nia and Jana;

Your question below was forwarded to FDA management and we provide the following response:

- **Regarding PMR** (b) (4) **we note your request to change the language from** (b) (4) **" to** (b) (4) **We cannot agree with this proposal given the this safety issue.** (b) (4)

Please confirm receipt of this email.

Sincerely;  
Patricia Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Phone: 301-796-1249  
[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

---

**From:** [Nia.Tatsis@sanofi.com](mailto:Nia.Tatsis@sanofi.com) [<mailto:Nia.Tatsis@sanofi.com>]  
**Sent:** Monday, June 29, 2015 11:50 AM  
**To:** Madara, Patricia  
**Cc:** [Jana.Bodorova@sanofi.com](mailto:Jana.Bodorova@sanofi.com)  
**Subject:** Praluent PMR

Dear Pat,

As per our earlier conversation, please see some additional information that may be helpful when reviewing the attached slide.

With regard to the CVOT, there will be 50,000 double-blind patient years if the study runs to completion. (b) (4)

[Redacted] (b) (4)  
[Redacted]  
[Redacted] :

[Redacted] (b) (4)  
[Redacted]

If the answer is affirmative, then further discussion is not necessary from our standpoint.

Best,  
Nia

*Nia Tatsis PhD  
AVP, Global Regulatory Affairs  
Global Head of PCSK9 and Specialty Care 1 Products*

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/s/  
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PATRICIA J MADARA  
07/01/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** RE: BLA 125559 (Praluent) - PMR / PMC list for completion  
**Date:** Wednesday, July 01, 2015 3:31:00 PM  
**Importance:** High

---

Hi Jana;

Please reference the PMR / PMC list sent to you on June 26, 2015. We now have an additional PMC. Please add this to the original list and return it with proposed milestone dates:

Additional PMC:

- Revise the (b) (4) bioburden limit for (b) (4) after data from additional drug product batches has been analyzed.  
Activity Completion:  
Final Report Submission:

Sincerely;  
Patricia Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Phone: 301-796-1249  
[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

---

**From:** Madara, Patricia  
**Sent:** Friday, June 26, 2015 3:33 PM  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - PMR / PMC list for completion  
**Importance:** High

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have a request for information.

- **Please refer to the attached PDF document containing a list of postmarketing required studies (PMRs) and postmarketing commitments (PMCs).**

Please read the instructions and complete the form by adding proposed milestone dates for each PMR and PMC and any additional information requested.

Please respond by COB on July 2<sup>nd</sup> or early on July 3<sup>rd</sup>.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
07/01/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - PMR / PMC list for completion  
**Date:** Friday, June 26, 2015 3:33:00 PM  
**Attachments:** [26June15\\_BLA\\_125559\\_PMR-PMC\\_List\\_FINAL.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have a request for information.

- **Please refer to the attached PDF document containing a list of postmarketing required studies (PMRs) and postmarketing commitments (PMCs).**

Please read the instructions and complete the form by adding proposed milestone dates for each PMR and PMC and any additional information requested.

Please respond by COB on July 2<sup>nd</sup> or early on July 3<sup>rd</sup>.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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PATRICIA J MADARA  
06/26/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - URGENT REQUEST FOR INFORMATION  
**Date:** Tuesday, June 23, 2015 10:35:00 AM  
**Attachments:** [23June15 clinical Information Request.pdf](#)  
**Importance:** High

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**BLA 125559**

**URGENT INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have another urgent request for information.

- **Please refer to the attached PDF document.**

Please provide your responses as soon as possible. It is very important to provide a timeline for sending the responses, especially if all information will not be submitted at the same time.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

Information Request June 23, 2015

1. Regarding MedWatch Report 2015 SA 028033 please provide the following:
  - a. Anti-Hepatitis E IgM antibody titers
  - b. Name of the laboratory that conducted the Hepatitis testing (please designate if this is a local lab or the sponsor's central lab), information regarding the Hepatitis E antibody assay used, its controls, and other measures of test validity.
  - c. Confirmatory repeat measurement of Hepatitis E antibodies on the tested sample, or another, if available
  - d. Was testing performed for Hepatitis E IgG on March 5, 2015 or subsequently?
  - e. Request that the investigator obtain a convalescent serum test for Hepatitis E antibodies (IgM and IgG) now, and again 6 months after the patient's presentation. Submit these results when available.
2. Regarding the patient reported in MedWatch report 2014 SA 054543 diagnosed with ischemic stroke and thrombotic thrombocytopenic purpura on concomitant clopidogrel, please provide the patient's anti-drug antibody status during treatment and follow-up. As part of this patient's work up were auto-antibodies that inhibit ADAMTS13, which have been implicated in thienopyridine-associated TTP, evaluated?

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/s/  
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PATRICIA J MADARA  
06/23/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Cc:** [Madara, Patricia \(Patricia.Madara@fda.hhs.gov\)](mailto:Madara.Patricia.(Patricia.Madara@fda.hhs.gov))  
**Subject:** BLA 125559 - URGENT REQUEST FOR INFORMATION  
**Date:** Saturday, June 20, 2015 12:36:00 AM  
**Attachments:** [19June15 Information request clinical.pdf](#)  
**Importance:** High

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**BLA 125559**

**URGENT INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have an urgent request for information.

- **Please refer to the attached PDF document.**

Please provide your responses as soon as possible. It is very important to provide a timeline for sending the responses, especially if all information will not be submitted at the same time. Please submit by email prior to official submission to the BLA and IND.

-

If possible, please respond by COB on Monday, June 22<sup>nd</sup>.

**Please confirm receipt of this email.!**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

Information request 19 June 2015

We are very concerned regarding the case of hepatotoxicity accompanied by jaundice reported for Patient ID 710408-007 in MedWatch report # 2015 SA 028033 (“drug-induced liver injury”) submitted to your IND 105574. This appears to be a well-documented case of hepatotoxicity accompanied by jaundice for which you do not seem to offer an alternative explanation despite a hepatology evaluation, imaging, and serologies for autoimmune hepatitis (not specified), hepatitis A, B, or C, HSV type 1 and 2, EBV, and copper and ceruloplasmin. In response to this case we have the following requests for information:

1. Regarding MedWatch report # 2015 SA 028033:
  - a. Was Hepatitis E tested for? If not, are reserve samples available to perform this testing?
  - b. Was immunogenicity tested in this patient? If not, are reserve samples available to perform this testing (e.g., ADA both binding and neutralizing)?
  - c. Please provide all gastroenterology/hepatology consultation reports for this case.
  - d. Please provide all lipid values in this patient.
  - e. Clarify whether dosing of simvastatin and/or ezetimibe was continued throughout this event, temporarily held, or permanently discontinued.
  - f. Please provide further explanation for the Company comment on June 11, 2015: “Further internal review, a relationship with the investigational product could be excluded based on the chronological factor (long time to onset) and the poor documentation of the case.”

Submit this information to IND 105574 as well as to BLA 125559.

2. In the 4-month safety update, you provided an update from the outcomes trial that included a case report of a suspected unexpected serious adverse reaction of “liver function test abnormal” (Patient 11570-348-010-008). Provide follow-up including the results of the hepatology consultation and laboratory findings for this patient.
3. Query your entire clinical trial database (including ongoing open-label and blinded studies) for patients treated with alirocumab and those on blinded study medication who have developed:
  - Serum ALT  $\geq 3x$  ULN with total bilirubin  $\geq 2x$  ULN
  - Serum ALT  $> 5x$  ULN in association with a serious event or leading to interruption of therapy

Highlight cases that were not submitted with the original BLA (i.e., cases not submitted at all, cases submitted with the 4 month safety update or cases only submitted to the IND).

For cases that were submitted with the original BLA provide a link to those narratives. For all cases not submitted with the original BLA, provide a detailed narrative including baseline and follow-up liver test results and reference values. In your summaries provide clinical information and justification needed to include or exclude alternate etiologies, including the following.

- Acute viral hepatitis
- Alcoholic hepatitis
- Autoimmune hepatitis
- Hepatobiliary or pancreatic disorders
- Cardiovascular etiology
- Concomitant treatments

If any of the above listed alternative etiologies were not worked-up please state so and explain. In addition to the full clinical history, please describe the dose, timing and the effect of de- or re-challenge.

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/s/  
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PATRICIA J MADARA  
06/20/2015

**PeRC Meeting Minutes  
May 27, 2015**

**PeRC Members Attending:**

Lynne Yao

Wiley Chambers

George Greeley

Ruthanna Davi (Did not review [Non Responsive] )

Belinda Hayes

Kristiana Brugger

Tom Smith

Daiva Shetty

Andrew Mulberg (Non Responsive review only)

Adrienne Hornatk (Non Responsive review only)

Barbara Buch (Did not review [Non Responsive]

Peter Starke (Did not review [Non Responsive] )

Hari Cheryl Sachs

Lily Mulugeta

Dianne Murphy

Maura O'Leary ([Non Responsive] reviews only)

**Agenda**

9:00	IND	Non Responsive	
9:20	IND	Non Responsive	
9:40	BLA	Non Responsive	
9:50	BLA	Non Responsive	
10:10	IND	Non Responsive	
10:30	IND	Non Responsive	
10:50	BLA	125559	Praluent (alirocumab) Partial Waiver/Deferral/Plan (w/Agreed iPSP)   Treatment of dyslipidemia
11:00	NDA	Non Responsive	
11:10	NDA	Non Responsive	
11:20	IND	Non Responsive	
	<i>IND</i>	Non Responsive	
	<i>IND</i>	Non Responsive	
	<i>IND</i>	Non Responsive	

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Non Responsive

**Praulent (alirocumab) Partial Waiver/Deferral/Plan**

- Proposed Indications: Treatment of non-familial hypercholesterolemia with CHD or CHD risk equivalent; treatment of pediatric patients with mixed dyslipidemia (defined as elevated LDL-C and elevated TG); treatment of patients with heterozygous familial hypercholesterolemia
- The Division noted that the plan is the same as the one agreed upon in the Agreed iPSP for this product.
- The PeRC agreed with the plan as established in the Agreed iPSP.
- PeRC Recommendations:

○

○

- For treatment of patients with heterozygous familial hypercholesterolemia: the PeRC agreed to waivers in patients less than <sup>(b)</sup><sub>(4)</sub> years of age because studies would be impossible or highly impractical because the standard of care, which is highly effective, is based on diet and lifestyle modification and to the deferral of studies in patients <sup>(b)</sup><sub>(4)</sub> to less than 17 years of age. These studies are described in the Agreed iPSP.

(b) (4)

Non Responsive

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/s/  
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GEORGE E GREELEY  
06/16/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (alirocumab) Urgent Request for Information  
**Date:** Wednesday, June 03, 2015 8:19:00 AM  
**Importance:** High

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**BLA 125559**

**URGENT INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have an additional request for information.

- **It was noted on page 94, Table 30 of the briefing book a total of 5 neurocognitive events in patients with 2 LDL-C less than 25 mg/dL. The additional event is coded as memory impairment. This is different from the 4 neurocognitive events in patients with 2 LDL-C less than 25 mg/dL described in the ISS appendix table 1.4.5.7.**
- **Please explain the discrepancy and provide additional information about this patient with memory impairment and low LDL-C**

Please provide your response, at least informally, by tomorrow.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
06/03/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (alirocumab) Urgent request for information #2  
**Date:** Wednesday, June 03, 2015 9:39:00 AM  
**Importance:** High

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**BLA 125559**

**URGENT INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have an additional request for information.

- **Are the preferred terms listed in the cardiac disorders SOC in ISS appendix 1.4.9.7 and 1.4.10.1 the investigator reported adverse events before adjudication? If not, please explain how this table was populated.**

Please provide your response, at least informally, by tomorrow.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
06/03/2015

**Note:** The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

**Complete the section(s) of this template that are relevant to your *current submission*.**

***Definitions:***

***Deferral*** – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

***Full Waiver*** – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

***Partial Waiver*** – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

**Pediatric Assessment** – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

**Pediatric Plan** – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

**Pediatric Population/Patient**- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

**PREA Pediatric Record/Pediatric Page** – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

## Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

### BACKGROUND

Please check all that apply:  Full Waiver  Partial Waiver  Pediatric Assessment  Deferral/Pediatric Plan

**BLA/NDA#: 125559**

**PRODUCT PROPRIETARY NAME: PRAULENT**

**ESTABLISHED/GENERIC NAME: Alirocumab**

**APPLICANT/SPONSOR: Sanofi/Regeneron**

### PREVIOUSLY APPROVED INDICATION/S:

(1) Not Applicable

(2) \_\_\_\_\_

(3) \_\_\_\_\_

### PROPOSED INDICATION/S:

(1) PRALUENT is indicated for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (Apo A-1)

PRALUENT is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT).

PRALUENT is indicated as monotherapy, or as add-on to other non-statin LMT, including in patients who cannot tolerate statins.

(2) \_\_\_\_\_

(3) \_\_\_\_\_

**BLA/NDA STAMP DATE: 24 November 2014**

**PDUFA GOAL DATE: 24 July 2015**

**SUPPLEMENT TYPE: NA**

**SUPPLEMENT NUMBER:**

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

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

*Did the sponsor submit an Agreed iPSP? Yes*  *No*

*Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes*  *No*

*Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)*

*Yes*  *No*

*Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes*  *No*

*If Yes, PMR # \_\_\_\_\_ NDA # \_\_\_\_\_*

*Does the division agree that this is a complete response to the PMR? Yes*  *No*

*If Yes, to either question Please complete the Pediatric Assessment Template.*

*If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.*

## WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record (This is a BLA so including a pediatric page.)*

1.

(b) (4)

*Partial waiver (0 to (b) (4) years old) requested for treatment of patients with heterozygous familial hypercholesterolemia*

2. Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)

Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

•

(b) (4)

The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

•

(b) (4)

- *Grounds for partial waiver request for treatment of pediatric patients with HeFH*

- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. ***(This reason is for Partial Waivers Only)***

3. *Provide justification for Waiver:*

(b) (4)

*A partial waiver is requested for the treatment of patients with HeFH. Guidelines recommend treatment of children with HeFH starting at <sup>(b)</sup><sub>(4)</sub> years old with statin therapy as first-line pharmacological treatment after lifestyle/behavior modification based on the efficacy and safety in pediatric clinical trials. For children with HeFH who are less than <sup>(b)</sup><sub>(4)</sub> years of age, management focuses on diet and lifestyle modification.*

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*  
*Not applicable*

**Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics**

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

    basal cell and squamous cell skin cancer

    bladder

    breast

    cervical

    colorectal

    endometrial

    esophageal

cancer (continued):

    follicular lymphoma

    gastric

    hairy cell leukemia

    hepatocellular

    indolent non-Hodgkin lymphoma

    lung (small & non-small cell)

    multiple myeloma

    oropharynx (squamous cell)

    ovarian (non-germ cell)

    pancreatic

    prostate

    refractory advanced melanoma

    renal cell

    uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)  
dry eye syndrome (keratoconjunctivitis sicca)  
erectile dysfunction  
essential thrombocytosis  
Huntington's chorea  
infertility & reproductive technology  
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke  
memory loss  
menopause and perimenopausal disorders  
mesothelioma  
myelodysplasia  
myelofibrosis & myeloproliferative disorders  
osteoarthritis  
overactive bladder  
Parkinson's disease  
paroxysmal nocturnal hemoglobinuria  
plasma cells and antibody production disorders  
polycythemia vera  
postmenopausal osteoporosis  
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis  
reduction of thrombotic cardiovascular events in patients with coronary artery disease  
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone  
retinal vein occlusions  
stress urinary incontinence  
temporary improvement in the appearance of caudal lines  
treatment of incompetent great saphenous veins and varicosities  
type 2 diabetic nephropathy  
vascular dementia/vascular cognitive disorder/impairment

## DEFERRAL REQUEST

Please attach:

*Pediatric Record (This is a BLA so attaching pediatric pages.)*

1. **Age groups included in the deferral request:**  to <18 years old
2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**  
*Requesting partial waiver in children 0 to  years old. See above for partial waiver request.*
3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)**
  - a. **Adult studies are completed and ready for approval**
  - b. Additional safety or effectiveness data needed (**describe**)
  - c. Other (**specify**)
4. **Provide projected date for the submission of the pediatric assessment (deferral date):**  
*Deferred pediatric safety and efficacy studies will be conducted after approval in the adult population. Dates for delivery of final report will be negotiated with the Division. See the following page for the sponsor's proposed timeline.*
5. **Did applicant provide certification of grounds for deferring assessments?**  Yes  No
6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?**  Yes  No  
Statement included in application

## SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?**  Yes  No

2. Does the division agree with the sponsor's plan?  Yes  No

We agree with the plan, but will reword it such that it is a single postmarketing requirement with several parts. This will allow for the submission of a single complete study report that can support labeling, as required by PREA.

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?  Yes  No

a. Protocol Submission: Study 1 (dose finding study) Q3 2016; Study 2 (efficacy/safety) Q1 2018

b. Study Completion: Study 1 Q4 2016; Study 2 Q2 2018

c. Study Submission: BLA supplement Q4 2022

4. Has a Written Request been issued?  Yes  No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)

5. Has a PPSR been submitted?  Yes  No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

***Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.***

#### **DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL**

*Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.*

#### **Types of Studies/Study Design:**

Study 1 [REDACTED] <sup>(b) (4)</sup>: Phase 2 randomized, open-label, 8-week, ascending repeated dose-finding study of alirocumab with an optional open-label extension study

Study 2 [REDACTED] <sup>(b) (4)</sup>: Phase 3 randomized, 6 month, double-blind, placebo-controlled, parallel-group, multicenter, [REDACTED] <sup>(u) (4)</sup> efficacy and safety study followed by an 18-month open-label extension

#### **Nonclinical Studies:**

*Not applicable*

**Clinical Studies:**

*Part A: phase 2 dose finding study*

*Part B: phase 3 efficacy/safety study*

**Age group and population (indication) in which study will be performed:**

*Part A: patients <sup>(b)</sup><sub>(4)</sub> to <18 years with HeFH on stable lipid modifying therapy (LMT) with LDL-C  $\geq$  130 mg/dL*

*Part B: patients <sup>(b)</sup><sub>(4)</sub> to <18 years HeFH on stable LMT with LDL-C  $\geq$  130 mg/dL (patients treated in study 1, the phase 2 dose finding study will be offered enrollment in study 2, the phase 3 study)*

**Number of patients to be studied or power of study to be achieved:**

(b) (4)

**Entry criteria:**

(b) (4)

<b>Clinical endpoints:</b>	
<i>Part A: Percent change in LDL-C from baseline to 8 weeks and pharmacokinetic (PK)/pharmacodynamic(PD, e.g., PCSK9) parameters</i>	
<i>Part B: Percent change in LDL-C from baseline to 6 months compared to placebo and safety will be the primary endpoints</i>	
<b>Timing of assessments:</b>	
<i>Part A: Baseline, 8 weeks (end of double-blind period), 16 weeks (end of follow-up period)</i>	
<i>Part B: Baseline, 6 months (end of double-blind period), (b) (4) months (additional assessments during and at end of open-label period)</i>	
<b>Statistical information (statistical analyses of the data to be performed):</b>	
(b) (4)	
<b>Division comments on product safety:</b>	
<i>Are there any safety concerns currently being assessed?</i> <input checked="" type="checkbox"/> <b>Yes</b> <input type="checkbox"/> <b>No</b>	
<i>Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies?</i> <input type="checkbox"/> <b>Yes</b> <input checked="" type="checkbox"/> <b>No</b>	
<i>Will a DSMB be required?</i> <input checked="" type="checkbox"/> <b>Yes</b> <input type="checkbox"/> <b>No</b>	
<i>Other comments:</i>	
(b) (4)	

*Study protocols will be submitted to the FDA for review prior to start of pediatric studies.*

**Division comments on product efficacy:**

*Alirocumab has established statistically significant LDL-C lowering in the range of 45-60% as compared to placebo in adult patients with HeFH and/or at high risk for atherosclerotic cardiovascular disease. Patients on a range of statin doses (as well as on no statin) with or without other lipid modifying drugs were studied in phase 3. Alirocumab is currently being evaluated for cardiovascular benefit in a large outcomes trial; complete enrollment is projected to occur (b) (4)*

**Division comments on sponsor proposal to satisfy PREA:**

*The proposed studies should satisfy PREA.*

**PeRC ASSESSMENT TEMPLATE**

*Please attach:*

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

**Date of PREA PMR:**

**Description of PREA PMR:** *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC?  Yes  No If yes, did sponsor follow plan?

**If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.**

**Indication(s) that were studied:**

This section should list the indication(s) exactly as written in the *protocols*.

*Example:*

*DRUG for the treatment of the signs and symptoms of disease x.*

**Number of Centers** \_\_\_\_\_

**Number and Names of Countries** \_\_\_\_\_

**Drug information:**

*Examples in italics*

- **Route of administration:** *Oral*
- **\*Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

*\*If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

**Types of Studies/ Study Design:**

*Example:*

*Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.*

*Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.*

<p><b>Age group and population in which study/ies was/were performed:</b></p> <p><i>Example:</i>  <i>Study 1: patients aged X to Y years.</i>  <i>Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.</i></p>
<p><b>Number of patients studied or power of study achieved:</b></p> <p><i>Example:</i>  <i>Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.</i>  <i>Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .</i></p>
<p><b>Entry criteria:</b></p> <p>This section should list pertinent inclusion/exclusion criteria.</p> <p><i>Example:</i>  <i>Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs</i>  <i>Patients had a negative pregnancy test if female.</i></p>
<p><b>Clinical endpoints:</b></p> <p><i>Example:</i>  <i>Study 1: Clinical outcome and safety were the primary endpoints.</i></p> <p><i>Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F</i></p>

**Statistical information (statistical analyses of the data performed):**

This section should list the statistical tests conducted.

*Example:*

*Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.*

*Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.*

**Timing of assessments:**

*Example:*

*Baseline, week 2, week, 6, and end of treatment*

**Division comments and conclusions (Summary of Safety and Efficacy)**

**Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PATRICIA J MADARA  
06/02/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 Praluent high level labeling comments - please incorporate and resubmit  
**Date:** Friday, May 29, 2015 8:23:00 PM  
**Attachments:** [29May15 FDA to sanofi container and carton labels.pdf](#)  
[29May15 FDA to sanofi PI\\_23March15.doc](#)  
[29May15 FDA to sanofi OSE.pdf](#)  
**Importance:** High

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Hi Jana;

I am attaching three documents providing high level labeling revisions requested by FDA

1. **29May15 FDA to Sanofi container and carton labels**: Revisions recommended by the Office of Biotechnology Products and the Office of Surveillance and Epidemiology (OSE); Office of Medication Error Prevention and Risk Management(OMEPRM); Division of Medication Error Prevention and Analysis (DMEPA). Please incorporate the requested revisions. If you disagree with any of the recommendations, please provide a robust explanation.
2. **29May15 FDA to Sanofi PI\_23March15 (WORD)**: High level and formatting revisions requested by the Office of Biotechnology Products and by the DMEP Associate Director for Labeling. We acknowledge the later version of the package insert (PI) submitted on May 8<sup>th</sup>. Incorporate the requested revisions into the May 8<sup>th</sup> version and resubmit. If you disagree with any of the recommendations, please provide a robust explanation. Use track changes to identify those FDA revisions you do not accept and provide your alternative language. Also identify the FDA revisions you have accepted.
3. **29May15 FDA to Sanofi OSE**: Revisions to the PI and Instructions for Use provided by Office of Surveillance and Epidemiology (OSE); Office of Medication Error Prevention and Risk Management (OMEPRM); Division of Medication Error Prevention and Analysis (DMEPA). Please incorporate the requested revisions. If you disagree with any of the recommendations, please provide a robust explanation.

Resubmit the PI officially to your BLA. It will be used as the basis for additional revisions. Resubmit the container and carton labels and the IFUs by email, for further review by FDA. Remember to include a robust explanation for any revision you do not incorporate.

Please contact me if you have any questions. Please confirm receipt of this email.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Phone: 301-796-1249

[Patricia.madara@fda.hhs.gov](mailto:Patricia.madara@fda.hhs.gov)

**BLA 125559/0**  
**Praluent (alirocumab)**  
**Container Label and Carton Labeling Comments**

**A. General Comments**

1. We recommend changing any reference to (b) (4) prefilled syringe or prefilled pen on all container label and carton labeling to “Single-Dose” to ensure that the entire dose is delivered and the injectable device is not reused. “Single-Dose” is the appropriate term per United States Pharmacopeia USP 38/NF 33, 5/1/15 – 7/31/15, General Chapters: <659> Packaging and Storage Requirements.
2. We consider the prefilled syringe (PFS) container label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations for the PFS container label below are intended to improve the prominence of the required and critical information on the label.

**B. Prefilled Syringe Label**

1. Rotate the placement of the syringe label on the syringe by 90 degrees (label is parallel to the length of the syringe) so the information is readable without having to turn or rotate the syringe.<sup>1</sup>
2. Revise the strength in the upper right hand corner from (b) (4)” to “75 mg/mL” or “150 mg/mL”, respectively, in accordance with USP General Chapter <1>. The strength per total volume should be the primary and prominent expression on the principal display panel for single-dose injectable products. Ensure the “mg/mL” has the same prominence as “75” and “150”.
3. De-bold the Rx only statement and ‘Pre-filled Syringe’ as the text competes in prominence with other important information on the labels and labeling and appears more prominent than the established name on the Principal Display Panel (PDP).<sup>2</sup>
4. Bold the statements “For subcutaneous injection only. Single-dose.” to draw attention to how the medication should be safely handled and used.

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<sup>1</sup> See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. “FDA recommends that the text on the container label and carton labeling should be...(2) placed in the same field of vision (i.e., readable without having to turn or rotate the container.”

<sup>2</sup> See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. “Other information on the PDP such as the Rx-only statement...should not compete in size and prominence with the important information listed above.”

5. Add the U.S. License Number to appear with the manufacturer information. For example, revise “Mfd. by: sanofi aventis U.S. LLC to read “sanofi-aventis US Lic. # 1752”.

### C. Prefilled Syringe Tray Labeling

1. See Recommendations B.2., B.3., B.4.
2. Add the statement “Do not shake” to appear next to “Do not freeze”.

### D. Prefilled Syringe Carton Labeling

1. See Recommendations B.3 and B.4.
2. Revise the strength in the upper right hand corner of the Principal Display Panel and other side panels of the carton from (b) (4) to “75 mg/mL” or “150 mg/mL”, respectively, in accordance with USP General Chapter <1>. Ensure the “mg/mL” has the same prominence as “75” and “150”.
3. Include the finished dosage form on the line below the proper name.<sup>3</sup> For example:

**Praluent**

alirocumab

Injection

4. Add the statement “Do not shake” with the storage and handling information.
5. Revise the inactive ingredients to comply with USP Official 5/1/2015 –7/31/2015, USP 38/NF 33, <1091> Labeling of Inactive Ingredients by listing the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). For example, revise: Each (b) (4) prefilled pen contains: 75 mg alirocumab, 8mM histidine..., water for injection (USP) to read:  
Each 1 mL prefilled pen contains: 75 mg alirocumab, histidine (8mM), polysorbate 20 (0.1mg), sucrose (100 mg), and Water for Injection, USP.
6. Revise the manufacturer information to comply with 21 CFR 600.3, 21 CFR 610.61, and 21 CFR 610.64. The Applicant/licensee should be listed as “Manufactured by:”. Additionally, relocate the US License Number to appear directly under the manufacturer information. For example:

Manufactured by:

sanofi-aventis U.S. LLC, Bridgewater, NJ 08807

US License No. # 1752

A SANOFI COMPANY

“Distributed by” or “Marketed by”: Sanofi and

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<sup>3</sup> See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

“For biological products, the proper name for biological products should not include the finished dosage form. The finished dosage form can appear on the line below the proper name.”

Regeneron Pharmaceuticals

[Fill in address ]

7. Relocate the QR code to a side panel away from the required bar code in a size that does not compete with, distract from the presentations of the required bar code and any other required or recommended information on the label.<sup>4</sup>

**E. Prefilled Pen Label**

1. Revise the strength on the right side from [REDACTED]<sup>(b) (4)</sup> to "75 mg/mL" or "150 mg/mL", respectively, in accordance with USP General Chapter <1>. Ensure the "mg/mL" has the same prominence as "75" and "150".
2. De-bold the Rx only statement and 'Pre-filled Pen' as the text competes in prominence with other important information on the labels and labeling and appears more prominent than the proper name on the PDP.<sup>5</sup>
3. Bold the statements "For subcutaneous injection only." to draw attention to how the medication should be safely handled and used.

**F. Prefilled Pen Carton Labeling**

1. See Recommendations B.3 and B.4.
2. Revise the strength in the upper right hand corner of the Principal Display Panel and other side panels of the carton from [REDACTED]<sup>(b) (4)</sup> to "75 mg/mL" or "150 mg/mL", respectively, in accordance with USP General Chapter <1>. Ensure the "mg/mL" has the same prominence as "75" and "150".

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<sup>4</sup> See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. "If a manufacturer uses a QR code, we recommend that it appear on the side or back panel of the container label or carton labeling, away from the bar code and in a size that does not compete with, distract from the presentation of other required or recommended information on the label.

<sup>5</sup> See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. "Other information on the PDP such as the Rx-only statement...should not compete in size and prominence with the important information listed above."

3. Include the finished dosage form on the line below the proper name.<sup>6</sup> For example:

**Praluent**

alirocumab

injection

4. See Recommendations D.4, D.5, D.6, and D.7.

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

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<sup>6</sup> See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

“For biological products, the proper name for biological products should not include the finished dosage form. The finished dosage form can appear on the line below the proper name.”

## Labeling Recommendations

### Full Prescribing Information

#### 1. Section 2 Dosage and Administration

To ensure that all end users, including caregivers, receive training prior to use of Praluent, we recommend revising the statement [REDACTED] (b) (4)

to as follows:

[REDACTED] (b) (4)

Additionally, we recommend relocating the statement to the beginning of Section 2.2 Administration.

#### 2. Section 3 Dosage Forms and Strengths

To reduce redundancy and improve readability, we recommend revising [REDACTED] (b) (4) to:

*75 mg/mL mg Praluent single-dose pre-filled pen*

Consider the above recommendation for all strengths and dosage forms (i.e., 150 mg/mL prefilled pen, 75 mg/mL and 150 mg/mL prefilled syringe)

#### 3. Section 17 Patient Counseling

Include the following statement to ensure that patients/caregivers are aware of the longer than usual injection time:

“Instruct patients and caregivers to read the Patient Information and Instructions for Use (IFU) before the patient starts using PRALUENT, and each time the patient gets a refill as there may be new information they need to know.

Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique and how to use the prefilled pen or prefilled syringe correctly (see Instructions for Use leaflet).  
*Inform patients that it takes 20 seconds to inject Praluent.”*

## Instructions for Use:

A. We recommend changing any reference to (b) (4) prefilled syringe or prefilled pen in the Instructions for Use labeling to “single dose” to ensure that the entire dose is delivered and the injectable device is not reused.

### B. PraluentPrefilledSyringe

1. Under the section titled “Important Information”, we recommend to:

- i. Include a subsection that discusses statements related to the storage of Praluent, to mitigate the errors seen in the Human Factors study, so that end users do not overlook this information.
- ii. If possible, revise the statements in the “Do Not” section to positive/affirmative statements as the negation “NOT” can be overlooked.<sup>5</sup> For example, revise the statement “Do not freeze (b) (4).” to “Avoid freezing (b) (4).”
- iii. Include the following statement to ensure that patients and caregivers receive training by their health care provider prior to the use of the prefilled syringe to mitigate errors seen in your Human Factors study, in which trained participants performed better than untrained participants:

*“It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.”*

For Example:

#### **Important Information**

- The device is a single dose pre-filled syringe. It contains 75 mg of Praluent (alirocumab) in 1 mL.
- The Praluent syringe contains medicine prescribed by your (b) (4).
- The medicine is injected under your skin and can be given by yourself or someone else (caregiver).
- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.
- This syringe can only be used for one single injection, and must be discarded after use.
- ...Include other important information located in this section here.

#### **Storage of Praluent:**

- Store unused syringes in the refrigerator (b) (4) 36 °F to 46 °F (2 °C to 8 °C).
- (b) (4)
- Keep the Praluent syringe out of the reach of children.
- (b) (4)

2. In “Step A: Getting ready for (b) (4) injection”, we recommend:

- i. In Step A.1, relocate the statement about checking the expiration date to a separate bullet point and revising (b) (4) to “expiration date” as this may be a term that end users are more familiar with.
- ii. In Step A.3, explain the importance of waiting the recommended amount of time before delivering the injection, in order to mitigate the errors seen in the Human

<sup>5</sup> Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

Factors study. For example, we recommend including the following statement:

“Let the syringe warm up at room temperature for 30 to 40 minutes.

- *This is important due to the viscosity of Praluent and for a more comfortable injection.”*

iii. In Step A.4, relocate the statement “Clean skin in the injection area with an alcohol wipe” to after the statement regarding washing hands for better readability.

3. In “Step B: How to <sup>(b) (4)</sup>”, we recommend:

i. In Step B.1, label the needle cap and plunger in the image to mitigate the errors seen in the Human Factors study.

ii. In Step B.4, we recommend including the following statement as a separate bullet point to mitigate the errors seen in the Human Factors study, so end users understand that the increased resistance may be related to the nature of the drug product:

*“Due to the viscosity of Praluent, you may experience more resistance compared to most medications administered subcutaneously.”*

iii. In Step B.5, we recommend including the following statement as a separate bullet point to mitigate the errors seen in the Human Factors study, so end users understand that the increased resistance may be related to the nature of the drug product:

*“Due to the viscosity of Praluent, the time required for injection may be longer than most medications administered subcutaneously.”*

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<sup>6</sup> Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

C. PraluentPrefilledPen

1. Under the section titled “Important Information”, we recommend to:

- i. Include a subsection that discusses statements related to the storage of Praluent, to mitigate the errors seen in the Human Factors study, so that end users do not overlook this information.
- ii. If possible, revise the statements in the “Do Not” section to positive/affirmative statements as the negation “NOT” can be overlooked.<sup>6</sup> For example, revise the statement “Do not freeze (b) (4).” to “Avoid freezing (b) (4).”
- iii. Include the following statement to ensure that patients and caregivers receive training by their health care provider prior to the use of the prefilled pen, to mitigate errors seen in your Human Factors study, in which trained participants performed better than untrained participants:

*“It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.”*

For Example:

<p><b>Important Information</b></p> <ul style="list-style-type: none"><li>• The device is a single dose disposable pen. It contains 150 mg of Praluent (alirocumab) in 1 mL.</li><li>• The Praluent pen contains medicine prescribed by your (b) (4).</li><li>• This pen can only be used for one single injection, and must be discarded after use.</li></ul> <p><b>Storage of Praluent:</b></p> <ul style="list-style-type: none"><li>• Store unused pens in the refrigerator (b) (4) 36°F to 46°F (2°C to 8°C).</li><li>• (b) (4).</li><li>• Keep the Praluent pen out of the reach of children.</li><li>• (b) (4).</li></ul>	<ul style="list-style-type: none"><li>• It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.</li><li>• <i>...Include other important information located in this section here.</i></li></ul>
--	---

<sup>6</sup> Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

2. In “Step A: Getting ready for (b) (4) injection”, we recommend:
  - i. In Step A.1, relocate the statement about checking the expiration date to a separate bullet point and revising (b) (4) to “expiration date” as this may be a term that end users are more familiar with.
  - ii. In Step A.3, explain the importance of waiting the recommended amount of time before delivering the injection, in order to mitigate the errors seen in the Human Factors study. For example, we recommend including the following statement:
    - *“Let the pen warm up at room temperature for 30 to 40 minutes.*
    - *This is important due to the viscosity of Praluent and for a more comfortable injection.”*
  - iii. In Step A.4, relocate the statement “Clean skin in the injection area with an alcohol wipe” to after the statement regarding washing hands for better readability.
3. In “Step B: How to (b) (4)”, we recommend:
  - i. In Step B.1, label the cap in the image to mitigate the errors seen in the Human Factors study.
  - ii. In Step B.3, we recommend including the following statement so end users understand that the increased amount of force required to activate the device may be related to the nature of the drug product:
    - *“Due to the viscosity of Praluent, you may experience more resistance compared to most medications administered subcutaneously.”*
  - iii. In Step B.4, we recommend providing a clearer image to separate the two steps of pushing the button and immediately releasing the button. For example, circle the area around the green button in order to emphasize to users that the difference between the two images is that they lift their thumb off the green button.
  - iv. In Step B.5, include a downward-facing arrow stemming from the hand to emphasize that end users need to *continue* to push the autoinjector down onto the skin. Additionally, include an image of a clock showing 20 seconds to visually emphasize the injection time to end users.
  - v. In Step B.5, we recommend including the following statement so end users understand that the so end users understand that the long injection time may be related to the nature of the drug product:
    - *“Due to the viscosity of Praluent, the time required for injection may be longer than most medications administered subcutaneously.”*
  - vi. In Step B.6, include a “click” image (see Step B.4), so end users are aware of the auditory notification that their injection is complete.

APPEARS THIS WAY ON  
ORIGINAL

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/s/  
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PATRICIA J MADARA  
06/01/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Monday, May 18, 2015 4:24:00 PM  
**Importance:** High

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have an additional request for information.

- **We encourage you to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with Praluent following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please submit it to the BLA application in the appropriate module so it can be reviewed accordingly.**

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
05/24/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Friday, May 22, 2015 8:06:00 PM  
**Importance:** High

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional requests for information.

- **In the Response to the FDAIR dated March 13, 2015, we note in Appendix 2 that the number of events in the alicumab group LDL  $\geq 25$  mg and alicumab group 2 LDL-C  $< 25$  mg/dL do not necessarily equal the total number of events in the alicumab group.**

**For example, in Table 15, the total number of alicumab events is 115. The events in the 2 LDL  $< 25$  group is 15 and the  $\geq 25$  mg/dL is 91, which equals 106 events. Please explain the discrepancy.**

You may provide your response informally, via email, but also submit your response officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
05/24/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com); [Lisa.Pruss@sanofi.com](mailto:Lisa.Pruss@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Monday, May 18, 2015 12:40:00 PM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have an additional request for information.

- **In the CSR for your phase 3 trials you included results from a pattern-mixture model (PMM) fit to the primary efficacy endpoint but not for the key secondary efficacy endpoints. For each phase 3 trial, please provide results for weeks 12 and 24 from an analysis fitting the PMM to each of your key secondary efficacy endpoints (i.e., ApoB, non HDL-C, total-C, Lp(a), HDL-C, ApoA-1, and TG).**
- **We request you provide the analysis results in a SAS transport file; the format you used for LDL-C in the initial BLA submission would be an acceptable format.**
- **Please provide the requested material by May 26, 2015.**

You may provide your response informally, via email, but also submit your response officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
05/18/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Monday, May 11, 2015 5:18:00 PM

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have an additional request for information.

- **Patient 011569-348-908-005 was noted to have an increase in LDL-C to concentrations above baseline during treatment with alirocumab coincident with high-titer neutralizing antibodies. LDL-C decreased after cessation of therapy. It did not appear that there were any confounding factors that would explain the LDL-C increase. Please provide your interpretation of this case and describe whether any follow-up ADA testing has been conducted.**

You may provide your response informally, via email, but also submit your response officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
05/14/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Monday, May 11, 2015 12:30:00 PM  
**Attachments:** [11May15\\_Information\\_Request.pdf](#)  
**Importance:** High

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

Information Request 5/11/15

1. For Pt ID 001112-528-201-009 was statin treatment continued while she experienced elevations in liver enzymes? If it was discontinued please provide an updated narrative describing the management of the patient's statin therapy during this TEAE.
2. Please provide an update, if available, regarding Patient ID 11717-840-150-016 for the event of idiopathic progressive polyneuropathy – resolved, latest diagnoses, etc. It is unclear from the narrative if the patient had symptoms of paresthesia prior to randomization and treatment with alirocumab, please clarify if the patient had pre-existing symptoms or conditions that may be relevant.

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/s/  
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PATRICIA J MADARA  
05/11/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Friday, May 08, 2015 5:25:00 PM  
**Attachments:** [8May15\\_DSI\\_IR.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

1. We were made aware of a tool provided to LONG TERM investigators to extrapolate off-treatment LDL-C values in order to confirm a clinical diagnosis of HeFH when there was no off-treatment LDL-C available. It is our understanding that this tool was not described in the LONG TERM protocol or CSR. We are curious whether this tool is validated or published and what role it plays in the diagnosis of HeFH in the clinical setting. We are also concerned about the extent to which this tool was relied on in the alirocumab program. How many patients were diagnosed with HeFH by LDL-C criteria utilizing this tool in the trials that enrolled patients with HeFH (LONG TERM, FH I, FH II, and HIGH FH)?
2. We understand that there were 108 patients who were re-screened for possible HeFH prior to enrollment in the OLE portion of LONG TERM, and 51 patients who met criteria. Please provide information about the 51 patients: what criteria allowed them to be initially eligible, how they were identified for additional testing, what new criteria met the definition of HeFH, and why they weren't originally identified as HeFH patients. To some extent this raises issues regarding the reliability of diagnostic criteria for HeFH, specifically for over-diagnosis in the event that alirocumab is approved with an HeFH indication.
3. We were given a list of 48 patients (by our manual count, please confirm) from LONG TERM that had lipid testing done through local laboratories and reported to the site and/or the patient. This could potentially lead to unblinding. Were any sensitivity analyses done to explore the impact that this disclosure could have had on efficacy? Did this issue occur in any other trial? Have any new procedures been implemented to ensure that lipid values are not disclosed in the future?
4. Please provide additional information regarding the extent to which calcium scoring criteria were used to identify patients for trial eligibility. In which trials was it implemented, what criteria/cut-offs were used, how frequently were patients identified for eligibility with calcium scores, and what additional CV risks did these patients have?
5. Provide a table of all stratification and drug dose allocation errors due to IVRS problems in the phase 3 program.

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PATRICIA J MADARA  
05/08/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Friday, May 01, 2015 4:36:00 PM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have an additional request for information.

- **For patient 001308-840-174-018 (anaphylactic reaction) please supply the results of allergy/immunology workup done as a result of this adverse event on this patient including assessment of ADA.**

You may provide your response informally, via email, but also submit your response officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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PATRICIA J MADARA  
05/01/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Thursday, April 23, 2015 3:03:00 PM  
**Attachments:** [23April15 information request #1 device control.doc](#)  
[23April15 information request #2 labeling.docx](#)  
**Importance:** High

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional requests for information.

- Please refer to the attached PDF documents.
- Please note the requested response date for information request #2

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

1. Within the original BLA submission, and within your response to several information requests, you have described the following changes to the to-be-marketed PFP versions with respect to the PFP versions for which there is clinical experience:

- a) The to-be-marketed 75mg/ml PFP presentation will have (b) (4) while (b) (4) versions of the 75mg/ml PFP used within clinical studies
- b) The to-be-marketed versions of the 75mg/ml and 150mg/ml PFP will be produced (b) (4)

Please state how the changes described in a and b, above have been evaluated to ensure that they will not introduce unexpected and undesirable effects on the following device attributes: container closure integrity of the PFS, mechanical degradation of the drug product.

2. In addition, please clarify whether the (b) (4) in-process control for syringe and plunger stopper lots applies to all bulk PFS or only to PFS that are destined for PFP manufacturing. Describe any additional changes (such as increased (b) (4)) that are being considered by the component suppliers (b) (4).

**BLA 125559**  
**Praluent™ (alirocumab)**  
**Manufacturer Information Request**

We have the following information request for your labeling submitted on November 24, 2014.

Your proposed carton labeling for Praluent™ (alirocumab) displays the following manufacturer information:

Manufactured (b) (4) by:  
sanofi-aventis U.S. LLC, Bridgewater, NJ 08807  
A SANOFI COMPANY  
Marketed by Sanofi and Regeneron Pharmaceuticals, Inc.  
PRALUENT is a trademark of Sanofi  
©201X Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC  
U.S. License # 1752

It is unclear which regulation(s) you are using to display the manufacturer information on your proposed carton labeling. Please cite the regulation(s) you are using to display your manufacturer information. Your response to this inquiry will inform our forthcoming labeling comments.

Please respond by COB April 29, 2015.

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PATRICIA J MADARA  
04/23/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - Request for Information  
**Date:** Wednesday, April 15, 2015 9:11:00 PM  
**Importance:** High

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

Information request 4/15/15

1. In Table 3 submitted in response to our March 13, 2015 information request, we note 20 total deaths. Were these deaths included in Table 42 of the ISS titled TEAEs leading to permanent discontinuation?
2. Given the 37 on-study deaths reported in the initial submission and only 20 deaths listed in the disposition table, please clarify into which group the other 17 patients would have been categorized.
3. Please clarify in ISS appendix 1.4.5.6 through 1.4.5.8, did these events occur after the first LDL <25 mg/dL in patients with 2 consecutive LDL-C <25 mg/dL or at any time in patients with 2 consecutive LDL-C <25 mg/dL?
4. Please provide in tabular form a listing of patients with memory impairment, confusional state, and amnesia and include patient ID, age/sex, treatment group, verbatim term, day study event occurred, outcome, action taken with alirocumab or control, whether this patient had 2 consecutive LDL-C <25 mg/dL, last LDL-C value before the event, and additional comments for example, hospitalized for stroke when event occurred, any relevant concomitant medications.
5. Please submit the laboratory methodology utilized in the phase 3 program for calculated and directly measured LDL-C (or provide a location in the BLA if already submitted).

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/s/  
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PATRICIA J MADARA  
04/20/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - request for information  
**Date:** Saturday, April 18, 2015 12:00:00 AM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following request for information.

- **In Table 4 of the response to the IR dated March 13, 2015, the number of subjects in the alirocumab group with impaired glucose control is 283. In Table 6 the total is 267. Please explain the discrepancy.**

You may respond informally, via email, but also submit your responses officially to the BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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PATRICIA J MADARA  
04/20/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) Request for Information  
**Date:** Tuesday, April 14, 2015 10:54:00 AM  
**Attachments:** [14April15 Information Request.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

## Information request

1. We noted that patient number 01110-840-590-006 death was adjudicated as sudden cardiac death, but not as a CHD death in the ADAJ dataset. The narrative suggests that this patient's death was reviewed again and changed to CHD death. The narrative states, "The patient's death was initially adjudicated to be a non-CV death. However, after database lock, the CEC re-reviewed this death and the final adjudication as determined by the committee was CHD death = yes"

Please explain how the re-review of this patient's death occurred.

Do the tables in the ISS and 4 month safety update regarding adjudicated deaths (Table 16, Table 59, respectively), and analyses of treatment emergent MACE events reflect this change?

Provide a breakdown of the events that comprise the CHD death row in Table 16 in ISS and 4-month safety update Table 59.

Provide a listing of the patients that comprise the CHD death row in Table 16 and Table 59 in 4 month safety update.

2. As an add-on to our information request from 3/11/15 regarding the disposition of patients, please update any tables and Kaplan-Meier curves related to permanent discontinuation due to an adverse event that may be affected by the re-categorization of discontinuations. For example, Table 42 in the ISS and ISS appendix 1.4.1.2.4, etc.

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PATRICIA J MADARA  
04/14/2015



BLA 125559

**MID-CYCLE COMMUNICATION**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 11, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** March 11, 2015 at 12:30 PM  
**Application Number:** BLA 125559  
**Product Name:** Praluent (alirocumab)  
**Indication:** Treatment of dyslipidemia  
**Applicant Name:** Sanofi Aventis  
**Meeting Chair:** James P. Smith, M.D., M.S.  
**Meeting Recorder:** Patricia Madara

**FDA ATTENDEES**

**Office of the Commissioner; Office of Combination Products**

Bindi Nikhar, M.D. Associate Clinical Director

**Office of Drug Evaluation II (ODE II)**

Mary H. Parks, M.D. Deputy Director

**ODE II; Division of Metabolism and Endocrinology Products**

Jean-Marc Guettier, M.D. Director  
James P. Smith, M.D., M.S. Deputy Director  
Mary Roberts, M.D. Medical Officer  
Julie Golden, M.D. Medical Officer  
Kati Johnson, R.Ph. Regulatory Project Manager  
Patricia Madara, M.S. Regulatory Project Manager

**Office of Translational Sciences (OTS); Office of Biostatistics; Division of Biometrics II**

Mark Rothmann, Ph.D. Team Leader  
Bradley McEvoy, Ph.D. Reviewer

**Office of Clinical Pharmacology; Division of Clinical Pharmacology II**

Jaya Vaidyanathan, Ph.D. Clinical Pharmacology Team Leader (Acting)

**Office of Process and Facilities, Division of Microbiology Assessment (DMA):**

Patricia Hughes, Ph.D. Team Leader, Biotech Manufacturing Team  
Colleen Thomas, Ph.D. Microbiologist

**Office of Biotechnology Products, Division of Monoclonal Antibodies; Division of Biotechnology Research and Review III**

Amy Rosenberg, M.D.	Director
Susan Kirshner, Ph.D.	Laboratory Director
Howard Anderson, Ph.D.	Team Leader
Richard Ledwidge, Ph.D.	Quality Reviewer

**Center for Devices and Radiological Health (CDRH); Office of Device Evaluation**

Alan M. Stevens	Engineer
Janice Polacek, RN, BSN, CRNI	Nurse Consultant

**Eastern Research Group**

Christopher Sese	Independent Assessor
------------------	----------------------

**APPLICANT ATTENDEES**

**Sanofi attendees:**

Barry Sickels, PhD,	Vice President, Head, Global Regulatory Affairs
Nia Tatsis, PhD,	Associate Vice President, Head, Global Regulatory Affairs
Jana Bodorova, MSc,	Senior Director, Global Regulatory Affairs
Lisa Pruss, PharmD,	Assistant Director, Global Regulatory Affairs
Jay Edelberg, MD, PhD,	Vice President, Head, PCSK9 Development and Launch Unit
Laurence Bessac, MD, MSc,	Associate Vice President, Head, Clinical Development, PCSK9 Development and Launch Unit
Corinne Hanotin, MD,	Lead Clinical Research Director, Clinical Development, PCSK9 Development and Launch Unit
Howard Surks, MD,	Senior Director, Clinical Pharmacology
Leslie Dondey-Nouvel, MD,	Head of Safety Surveillance Risk Management Strategic Development, Global Pharmacovigilance and Epidemiology
Michel Scemama, MD,	Global Safety Officer, Global Pharmacovigilance and Epidemiology
Heather Schiappacasse, PharmD, MBA,	Senior Director, US RISC, North America Medical Affairs
Christelle Lorenzato, MSc,	Biostatistics
Guillaume Lecorps, MSc	Biostatistics
Pascal Minini, PhD,	Biostatistics
Aurelie Brunet, PharmD,	Drug Disposition Expert, Disposition Safety and Animal Research
Frances Crofts, PhD,	Director, Toxicology, Disposition Safety and Animal Research
James Collins, P.E., MBA,	Vice President, Devices Development Unit, Medical Devices
Alex Zuyev,	Sr. Director, Auto-Injector Platforms, Medical Devices
Stephen Fitzpatrick, PhD,	Senior Director, Global Regulatory CMC Biologic Products
Martine De-Luis, PharmD,	Global Regulatory CMC Biologic Products
Catherine Dubuisson-Brengel, PhD,	Associate Director, Global Regulatory CMC Biologic Products

Serge Mathonet, MSc, John Schalago, MSc, RAC,	Site Leader, Global Regulatory CMC Biologic Products Associate Vice President, Head of CMC/Devices, Global Regulatory Affairs
Deborah Thomas, MA,	Senior Director, CMC Devices/Combination Products, Global Regulatory Affairs
Marie-Therese David-Comte, PhD,	Director, Biotherapeutics
Danielle Grelet, PhD,	CMC Development and Coordination
Thierry Colin, PharmD,	CMC Dossier Development and Coordination
Aaron Wirscham,	Assistant Director, Sites Quality Operations, Alliance & Partners Quality Management
Gloria Garcia Palacios, PharmD,	EU Regulatory Head Alirocumab, Global Regulatory Affairs
Véronique Sabot, PharmD,	EU Regulatory Team Alirocumab, Global Regulatory Affairs
Christian Morello, PhD,	Head, Program Management Office, PCSK9 Development and Launch Unit

**Regeneron attendees:**

Ned Braunstein, MD,	Senior Vice President, Regulatory Affairs
Mary Alice Raudenbush, MSc,	Senior Director, Regulatory Affairs
Bill Sasiela, PhD,	Vice President, Program Direction, Cardiovascular & Metabolism Therapeutics
Kathryn Miller, MSc,	Director, Biostatistic
Jennifer McNay, PhD,	Senior Director, Process Science
Sundari Ravindran, MSc, MBA,	CMC Project Management
Anne Pirozzi, PhD,	Sr. Specialist, CMC Regulatory Sciences

## 1.0 INTRODUCTION

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

## 2.0 SIGNIFICANT ISSUES

### A. Center for Devices and Radiological Health (CDRH)

Significant review issues identified to date include:

1. **Clinical acceptability of relatively long injection times as allowed within the product specification**
2. **Significant delays in injection times and underdose events observed within stability assessments of the pre-filled pen device**

#### Discussion:

*The applicant asked if there was an acceptable range for injection times. FDA responded that there was no set acceptable time for injection; it is reviewed as part of the benefit / risk assessment. The applicant noted that they would like to know as soon as possible if FDA anticipated problems since they would need to make adjustments in preparation for marketing.*

*FDA asked for confirmation if the new configuration of the 75 mg auto injector (b) (4) component) had been tested in clinical trials. The applicant replied that only the 150 mg/ml autoinjector with the (b) (4) component had been used in clinical trials and confirmed that the new 75 mg/ml configuration had not been used in any clinical trials.*

*FDA asked if the (b) (4) resulted in a change in injection time. The firm stated there was a shift of about two seconds, leading to more consistency in injection times, but that overall there had not been much impact on injection time .*

*FDA noted that the Agency had clinical concerns related to the device stability and the increase in injection times as storage times increased. In actual use situations, the auto injector may be stored by the patient for up to three months, which could lead to increased injection times. Also, there are limitations since there are no data that compare performance of the prefilled syringe and auto injector delivering the same dose in the same clinical trial. FDA has concerns about an interaction between the drug and device.*

*The applicant stated they would submit a white paper, providing additional information on what devices were used in the pivotal clinical trials, their performance, etc. FDA noted that would be helpful. The Agency needed to know which devices were used in clinical trials, what changes were made, the number of patients exposed to changes, and the clinical implications of those changes.*

### B. Division of Microbiology Assessment

The microbiology assessment review team has the following significant review issues for product quality microbiology:

1. **The microbial retention study was performed with (b) (4)**
2. **Dose setting, dose mapping, and dose audit data was not provided for the (b) (4)**

**Discussion:**

*The microbiology assessment team noted they would be sending additional information requests shortly.*

**3.0 INFORMATION REQUESTS**

**A. Clinical**

The clinical reviews for safety and efficacy are ongoing and FDA has no major issues to discuss at this time. It was noted that additional IRs might be forthcoming.

**B. Biometrics**

The statistical reviewer also noted that the review was ongoing and information requests would be sent shortly.

**C. Clinical Pharmacology**

The reviewer stated the review was ongoing and there were no major issues at this point.

**D. Nonclinical**

The nonclinical review team did not attend the meeting. Their reviews are ongoing and they had no major issues at this time.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

You did not submit a REMS with your application and at this time, the Office of Surveillance and Epidemiology is not proposing a REMS for alirocumab. However, this recommendation may change. FDA noted that it was too early to discuss postmarketing requirements (PMRs).

**Discussion:**

*The company asked if they could expect to receive a letter on 4/22/15. The review team stated they would check with OSE.*

**Post Meeting Comment**

At this point in time DMEP does not anticipate the need for a REMS; however, the review of safety remains ongoing. A final decision will be made upon completion of the review and after the June advisory committee meeting.

## **5.0 ADVISORY COMMITTEE MEETING**

At this time, the Advisory Committee Meeting (AC) is TENTATIVELY scheduled for June 9, 2015.

### **Discussion:**

*The applicant noted that they would like to submit their briefing document for the Advisory Committee Meeting about two weeks prior to the actual “due” date. They would like feedback from FDA. The Agency stated that they could not make any promises regarding the ability to provide comments. The FDA briefing document would be provided to the company through the Advisory Committee staff.*

*The company asked if there were any specific topics already identified for discussion at the AC that FDA could share. FDA stated that the discussion would focus, as expected, on the efficacy and safety of alirocumab. FDA stated that one topic that will need to be discussed is whether alirocumab-induced lowering of LDL-C lowering is sufficient to support approval before the availability of results from a cardiovascular outcomes trial.*

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

FDA reminded the applicant that the late cycle meeting had been scheduled for May 28, 2015. The briefing document for this meeting would be provided by FDA no later than May 20, 2015.

## **7.0 APPLICANT QUESTIONS / DISCUSSION**

*See discussion above.*

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/s/  
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JAMES P SMITH  
04/10/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - request for information  
**Date:** Sunday, April 05, 2015 11:51:00 PM  
**Importance:** High

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following request for additional information.

- **Please update Table 1 (Treatment-emergent ADA in Phase 3 Studies) from the document, Response to Agency Request #2 – Additional Information on Clinical Topics requested on 03 March 2015, with data from the first 6 months of treatment only overall and by study. Please also include 95% confidence intervals with the percentages.**

You may respond informally, via email, but also submit your responses officially to the BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
04/07/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - Request for Information  
**Date:** Tuesday, April 07, 2015 10:21:00 PM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection.

1. As of March 2015, you reported stability data from 3 months of aging at 5°C and 1 month of aging at (25°C) for 75 mg/mL presentation batches which were manufactured under the [REDACTED] (b) (4) ”.
- a. Please state the next time-point which will be assessed for injection time for these products. If Sanofi has planned for any assessments prior to a 6 month time-point, please provide the Agency with updated stability information for those time points, once testing is completed and approved.
- b. For product stored at 25°C, please state if Sanofi considers these samples to be “accelerated aged samples” representative of an equivalent real time 5°C storage time-point. If so, please indicate the equivalent real-time 5°C storage time-point and provide supporting information based on accelerated aging methods.

You may respond informally, via email, but also submit your responses officially to the BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
04/07/2015



BLA 125559

**INFORMATION REQUEST**

Sanofi-Aventis US LLC  
Attention: Jana Bodorva, M.Sc.  
Director, Global Regulatory Affairs  
55 Corporate Drive  
Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated November 24, 2014, received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for PRALUENT (alirocumab).

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by April 17, 2015 in order to continue our evaluation of your BLA.

1. With regard to your response to question 1.a, (b) (4)  
(b) (4)
2. With regard to your response to question 2.a, question 2.b requesting (b) (4)  
(b) (4)
3. With regard to your response to question 2.b, clarify when bioburden qualification results will be submitted to the BLA and when the new bioburden test volumes will be implemented.
4. With regard to your response to question 8.b, indicate when the new endotoxin recovery study will be submitted to the BLA. (b) (4)  
(b) (4)

FDA Information Request 9

Release samples for bioburden and endotoxin should be taken  
justification should be provided.

(b) (4)

Alternatively, a valid

If you have any questions, please contact me at (301) 796-2066 or Anita.Brown@fda.hhs.gov

Sincerely,

Howard A.  
Anderson -  
A

Digitally signed by Howard A.  
Anderson -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=CDER,  
ou=2342.1922090.1001.1-2000,  
email=605528.comHoward.A.Anderson  
-A  
Date: 2015.04.07 11:55:35 -0400

Howard Anderson, Ph.D.  
Product Quality, Team Lead  
Division of Biotechnology Review & Research III  
Office of Biotechnology  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - Request for additional information\_01April15 #2  
**Date:** Wednesday, April 01, 2015 4:23:00 PM  
**Attachments:** [01April15\\_Information request.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- 1. Please refer to the attached PDF document.**
- 2. In addition we reference your response to our March 3, 2015, information request, which you submitted to the BLA on March 11, 2015. (This is our second info request related to the 3/3/15 response document.)**
  - a. In appendix 2, in your response to Agency Request #2, for patient number 001112-528-202-003, we note the patient's dosing was interrupted: 3 doses till day 30 then resumption of dosing day~260. Please provide an explanation for this interruption.**

You may respond informally, via email, but also submit your responses officially to the BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

Information request 4/1/15

1. We are interested in the concordance/discordance between investigator adverse event reporting and adjudicated events in the alirocumab program. For each component of MACE (CHD death, nonfatal MI, fatal/non-fatal stroke, hospitalization for unstable angina) and total MACE, complete the following table by treatment group (alirocumab and control):

		CEC		
		YES	NO	TOTAL
Investigator reported	YES			
	NO			
	TOTAL			

2. We note that a total of 48 patients had serious unstable angina events captured by the MedDRA PT 'angina unstable' (ISS appendix, table 1.4.10.1), but only 3 patients had positively adjudicated unstable angina requiring hospitalization (tables 30 and 31 in the ISS). Please explain the discrepancy.
3. We note the 104 patients with positively-adjudicated events of ischemia driven revascularization procedure, but could not identify a MedDRA PT in the adverse event tables that specified revascularization ('coronary revascularization', for example). Therefore, please describe which PTs were reported by the investigators in the event of adjudicated revascularization.
4. In the 4 month safety update patient 011717-840-117-008 described as a patient with "positive Ab – RNA not available" in the initial BLA submission is now classified as negative since the RNA test returned with negative results (Patient No. 011717-840-117-008). We did not find this patient in the ISS section 5.3.3 Hepatitis C antibody. Please explain the discrepancy and update this section if needed.

Please describe the procedure for "reflexive testing" of patients with a positive Hepatitis C antibody. Please explain why the RNA was "not available" in 5 patients with a positive Hep C antibody.

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/s/  
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PATRICIA J MADARA  
04/02/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - Request for Information  
**Date:** Tuesday, March 31, 2015 2:39:00 PM  
**Attachments:** [31March15 clinical information request.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

Information request 3/31/15

1. Provide graphical patient profiles of the 7 patients with normal/missing baseline eGFR with moderate decreases in eGFR. Include changes in eGFR, BUN, Creatinine, urine albumin (all in US conventional units) over time. Include start and stop of IMP, other concomitant medications, and TEAEs.
2. Provide in tabular and graphical format the change over time in eGFR, BUN, Creatinine, urine albumin (all in US conventional units) in patients with a normal/missing baseline eGFR who displayed a mild decrease in eGFR while on treatment divided by treatment group in the placebo controlled pool and ezetimibe controlled pools.
3. Please provide a shift table of hsCRP using the following median hsCRP categories <1, 1-3, >3 mg/L
4. Please provide the change over time in total testosterone levels in US conventional units. Please include the number of patients which comprise these post-baseline assessments.
5. Please provide a review of the TEAEs that may be associated with low testosterone in the patients in LONG TERM that experienced a shift from normal total testosterone at baseline to TT < LLN.
6. Provide in tabular and graphical format the mean change in total testosterone from baseline over time in the patients that shifted from a normal/missing total testosterone level to a TT <LLN by treatment groups.
7. Please provide a review of the TEAEs that may be associated with low Vitamin K (<LLN) in the patients in LONG TERM that experienced a shift from normal Vitamin K at baseline to < LLN.
8. Please provide narratives for the patients who demonstrated a shift in either QTcF or QTcB from normal at baseline to  $\geq 500$  msec
9. In the response dated 23 January 2015, please provide the codes used to comprise the SMQs in Tables 2 and 3. In particular please explain the use of LLT in the SMQs versus PT, particularly for presyncope.

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/s/  
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PATRICIA J MADARA  
04/01/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - Request for additional information  
**Date:** Wednesday, April 01, 2015 10:33:00 AM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection.

In addition we reference your response to our March 3, 2015, information request, which you submitted to the BLA on March 11, 2015. We are reviewing your response and have the following request for additional information.

- **In your "Response Document #2," in your response to Agency question 2, you list data for patient 001565-840-511-005 in Table 2. However we cannot find this patient's data in Appendix 1 "Profiles of Antibody Positive Patients. Please provide this data.**

**We are requesting a response within one week of receipt.**

You may respond informally, via email, but also submit your responses officially to the BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
04/01/2015



BLA 125559

**INFORMATION REQUEST**

Sanofi-Aventis US LLC  
Attention: Jana Bodorva, M.Sc.  
Director, Global Regulatory Affairs  
55 Corporate Drive  
Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorva:

Please refer to your Biologics License Application (BLA) dated November 24, 2014, received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for PRALUENT (alirocumab).

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by April 3, 2015 in order to continue our evaluation of your BLA.

You state in your approach to setting specifications that acceptance criteria were set based on, in order of consideration: (b) (4)

(b) (4) However there are a number of proposed acceptance criteria that are outside your clinical experience and confidence intervals. Please justify how limits beyond clinical experience process capability and stability data were set. This information will allow the agency to determine the appropriateness of your proposed acceptance criteria.

You provided control charts that include data from clinical and proposed commercial lots to establish acceptance criteria. However it is unclear in the charts which lots were used in clinical trials. Provide control charts for drug substance and drug product that distinguishes lots used in clinical trials from lots manufactured by the proposed commercial process. In the control charts distinguish the clinical lots used in the phase I & II studies, pivotal phase III studies, and phase III extension studies. This information will allow the agency to determine the appropriateness of your proposed acceptance criteria for all specifications but in particular specifications that monitor impurities and degradation products.

If you have any questions, please contact me at (301) 796-2066 or [Anita.Brown@fda.hhs.gov](mailto:Anita.Brown@fda.hhs.gov)

Sincerely,

**Anita N.  
Brown -S**

Digitally signed by Anita N. Brown -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Anita N. Brown -  
S,  
0.9.2342.19200300.100.1.1=2000546085  
Date: 2015.03.18 16:39:02 -04'00'

Anita N. Brown  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (alirocumab) - request for information  
**Date:** Tuesday, March 17, 2015 4:07:00 PM  
**Importance:** High

---

**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following requests for information related to your devices.

- 1. For study number LTS11717, protocol amendment 1 (dated 11/29/2011) specifies that LDL-C values derived from the Friedewald equation (calculated) and beta quantification (measured) will done at baseline. All 2341 randomized subjects had a calculated value, but only 1999 had a measured value. There did not appear to be any discussion in the clinical study report why 342 subjects did not have a measured value. Additionally, the protocol amendment preceded the enrollment of the first subject into the trial (1/6/2012). Please clarify why 342 subjects did not have a measured value at baseline. In addition, confirm whether this discrepancy occurred at other follow-up visits and in other trials that collected both calculated and measured values, and if so, clarify why.**
- 2. Study number LTS11717 specified that if TG values exceed 400 mg/dL (4.52 mmol/L) then the central lab will reflexively measure (via the beta quantification method) the LDL-C rather than calculating it. In the analysis dataset most subjects with TG > 400 mg/dL did not have a calculated value, while some did. For example, subject 011717-032-010-015 had at week 24 a TG value of 842 mg/dL, a calculated LDL-C value of 71 mg/dL and a measured LDL-C value of 60 mg/dL. It is unclear why subjects with TG values exceeding 400 mg/dL had LDL-C values included in the analysis dataset. Please clarify.**
- 3. Please clarify whether your analysis of calculated LDL-C excluded observations when TG values exceeded 400 mg/dL. Also clarify when TG exceed 400 mg/dL whether calculated LDL-C values were or were not supposed to be included in the analysis.**

**We are requesting a response within one week of receipt.**

You may respond informally, via email, but also submit your responses officially to the BLA.

**Please confirm receipt of this email.**

Thanks for your help.

Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
03/17/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - Request for Information  
**Date:** Friday, March 13, 2015 1:51:00 PM  
**Attachments:** [13March15\\_Information Request.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

## Information Request 3/13/15

1. Provide a time to event analysis including Kaplan-Meier curve of first anti-diabetic medication use in patients without use of any anti-diabetic medication or diagnosis of diabetes at baseline divided by treatment group in the global pool, and separately in the placebo and ezetimibe pools.
2. Provide a time to event analysis including Kaplan-Meier curve of time to new onset of impaired fasting glucose (combining data from both AEs and laboratory values): (1) by treatment group and (2) within alirocumab-treated patients only, by two consecutive LDL-C values  $<25$  mg/dL vs. others. Provide these plots for both the global pool as well as separately for the placebo and ezetimibe pools.

Please provide this same analysis with time to new onset of diabetes (by AE or laboratory values).

3. Provide separate graphs plotting the on-treatment mean change in glucose and HbA1c over time in patients with impaired fasting glucose, normal glucose control, and diabetes at baseline (defined either by medical history or laboratory data) by treatment group in the global pool and in the placebo and ezetimibe-controlled pools
4. Please provide in tables using the format in ISS appendix 1.4.5.4 (global pool) and 1.4.5.5 (placebo pool) TEAEs by HLGT, HLT, and PT in control patients, alirocumab patients, alirocumab-treated patients with LDL-C  $\geq 25$  mg/dL and patients with 2 consecutive LDL-C  $<25$  mg/dL. Please provide the p-values for the following comparisons of interest 2 LDL-C  $<25$  mg/dL versus  $\geq 25$  mg/dL within the alirocumab group; 2 LDL-C  $<25$  mg/dL alirocumab versus control or placebo; and LDL-C  $\geq 25$  mg/dL versus control or placebo. (We recognize that this post hoc hypothesis testing is exploratory and that the comparisons being made are not randomized comparisons since the subgroups are defined by post-randomization data.)

Please provide a table using this same format and analyses described above listing AEs of special interest (e.g. diabetic CMQ, neurologic, neurocognitive, hepatic, etc.)

5. Please provide a table similar to ISS appendix 1.4.1.10.10 and forest plot similar to that shown in ISS appendix 1.4.1.10.9 plotting the HR and CI for each study within the placebo and ezetimibe controlled pools and overall risk estimate of shifting from normal glucose control at baseline to impaired fasting glucose (using AE and laboratory data) between treatment groups.

Please provide a similar analysis evaluating risk of shifting from impaired fasting glucose to diabetes.

Provide an analysis evaluating the risk of shifting to a worsening diabetic status by baseline disease condition (non-FH versus FH)

6. Please provide the location within the BLA or submit graphical profiles of the 3 patients that went from normal glucose control to diabetes. Include glucose and HbA1C levels, changes in concomitant medications. Provide a brief summary narrative for these patients
7. Provide the baseline demographics of patients that had worsening shift in diabetes status (normal to impaired; impaired to diabetes) versus patients without a change in diabetic status.
8. Please provide the location within the BLA or submit a table that provides the number (%) of patients who reported local injection site reactions, discontinuations due to injection site reactions and the symptoms associated with these reactions, according to the device and the treatment administered (alirocumab or placebo of alirocumab).
9. From the 19 February 2015 information request response, in Table 33 of patients within the subcategory "Other reasons/Other" there are several examples of patients that could be categorized as withdrawing consent and discontinuing due to an AE, including several deaths. Please submit a revised disposition table which accurately represents the disposition of all subjects in Table 32 (specifically the patients listed in Table 33). For example, patients that discontinued because they died should be listed as deaths, not as an Other reasons/other. As another example, patients that discontinue because "the subject did not want to continue study without being able to see his cholesterol levels" should be recoded as a withdrawal of consent. Create another category that captures the patients that completed the planned duration of treatment but had a final visit outside the pre-specified visit window.
10. From the 19 February 2015 information request response, please clarify if within the Other reasons subcategories patients could be listed more than once. For example there are 220 patients that discontinued due to "other reasons" in the placebo-controlled alirocumab treatment group; however, there are 236 patients which appear (the row indentation does not clearly indicate what subcategories comprise the main category) to comprise this group. In the table you construct in response to request #9, please ensure that the table formatting makes clear what rows are subtotals of other rows.

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/s/  
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PATRICIA J MADARA  
03/16/2015



BLA 125559

**INFORMATION REQUEST**

Sanofi-Aventis US LLC  
Attention: Jana Bodorva, M.Sc.  
Director, Global Regulatory Affairs  
55 Corporate Drive  
Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated November 24, 2014, received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for PRALUENT (alirocumab).

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by March 25, 2015 in order to continue our evaluation of your BLA.

1. The BLA indicates that the Alirocumab proposed mechanism of action involves binding to PCSK9 and redirecting the LDL receptor from lysosomal degradation to a sorting of the receptor back to the cell surface. The proposed potency assay measures uptake and accumulation of fluorescently labeled LDL inside liver carcinoma cells. The control strategy does not include a potency assay that directly measures LDL receptor levels on the cell surface or an assay that quantifies LDL receptor recycling. Provide data or published literature regarding the effect of Alirocumab on LDL receptor levels on the plasma membrane or the effect of Alirocumab on LDL receptor recycling. This information will allow the FDA to better assess the suitability of the proposed potency assay.
2. Comparability report REGN727-MX-10080 states (b) (4) between REGN727 produced by (b) (4) processes (b) (4), (b) (4) are not expected to have a negative impact on clinical performance. This information will allow the FDA to

INFORMATION REQUEST

better assess comparability for REGN727 manufactured by the (b) (4) processes.

3. The production parameters for the (b) (4) are not clearly indicated in section 3.2.P.3.5. Please address the following comments.
  - a. Describe the (b) (4) used for production of the drug product.
  - b. Describe the maximum batch sizes for production of the 150 mg/ml and 75 mg/ml drug products in terms of (b) (4)
  - c. Indicate the (b) (4) during production.
  - d. The time limit for (b) (4) Please clarify.

4. The microbial retention study was performed with (b) (4)  
(b) (4)

5. Please respond to the following comments regarding (b) (4)  
(b) (4)

- a. Provide a copy of the Certificate of Analysis for (b) (4)
- b. (b) (4)
- c. (b) (4)
- d. (b) (4)
- e. Summarize data from the last three quarterly dose audits performed at the (b) (4) site and provide the dose audit reports.

6. Please clarify whether the bioburden sample is taken (b) (4)  
(b) (4)

If you have any questions, please contact me at (301) 796-2066 or [Anita.Brown@fda.hhs.gov](mailto:Anita.Brown@fda.hhs.gov)

Sincerely,

**Anita N.  
Brown -S**

Digitally signed by Anita N. Brown -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Anita N. Brown -S,  
0.9.2342.19200300.100.1.1=20005460  
85  
Date: 2015.03.11 15:14:01 -04'00'

Anita N. Brown  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 Request for Information  
**Date:** Saturday, March 07, 2015 12:53:00 PM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following requests for information related to your devices.

1. Please confirm if the final to-be-marketed combination product involving both the prefilled syringe and the autoinjector were used in the pivotal clinical trials. If not, please specify what changes were made, when they were made, and how many patients were exposed to each version of the change.
2. Also, if changes were made to the combination product during the conduct of the clinical trials, what was the incidence of adverse events, such as injection site reactions, device malfunction, etc. before and after the change.

You may respond informally, via email, but also submit your responses officially to the BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
03/09/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - Request for Information  
**Date:** Tuesday, March 03, 2015 11:58:00 AM  
**Attachments:** [3March15 information request #1.pdf](#)  
[3March15 information request #2.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- Please refer to the attached PDF documents.

**We request that you submit responses within one week of receipt.**

You may provide responses informally, via email, but also submit your them officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

1. In each phase 3 trial, provide the proportion of patients per group who required
  - a. Rescue LMT for TG  $\geq$  500 mg/dL
  - b. Rescue LMT for LDL-C > 25% on 2 consecutive visits
  - c. Increase in dose of background LMT for any reason
  - d. Addition of new background LMT for any reason
  - e. Decrease in dose or stopping background LMT for any reason
2. For LTS11717, provide an analysis for mean % change from baseline LDL-C by baseline LDL-C subgroups at week 12.
3. For LTS11717, provide mean (SD) percent LDL-C change at week 24 by development of treatment-emergent anti-drug antibodies (yes/no), development of ADA titer > 240 (yes/no) and development of neutralizing ADA (yes/no) in the alirocumab group.
4. For LTS11717, update the primary efficacy data by gender subgroup (figure 7 in the CSR) by including pre- and post-menopausal women subgroups (or if not available, women by age subgroups (< 50 yrs,  $\geq$  50 yrs)).
5. For patient 01112-528-202-003 shown on page 1912 of the ISE (figure 4.10.4.1), describe the clinical scenario during which the patient was off of drug, including any changes in concomitant medications and adverse events. It is noted that LDL-C increased to over twice baseline coincident with NABs, and then decreased coincident with loss of neutralizing activity while the patient was still off of drug.

With regard to the immunogenicity of your anti-PCSK9 mAb, Praluent, we have the following requests for additional information; please provide this information for trials in phases 2 and 3:

1. Incidence of antibody responses to product:
  - a. Stratify by treatment protocol as patients treated with Praluent alone may have a different incidence of immune responses to product than those co-treated with either statins or ezetimibe, which have immunomodulatory properties.
2. For each antibody positive patient, document the following:
  - a. Course of the antibody response from development to disappearance including titers
  - b. Effects of the antibody response on the clinical endpoints, PK/PD, or biomarkers of efficacy
  - c. The presence or absence of neutralizing antibody (NABs), the time course of development and disappearance, whether such patients experienced an impact on clinical endpoints, PK/PD, or biomarkers of efficacy, and whether drug was discontinued following development of NABs
  - d. Concomitant medications
3. Follow up on all patients with positive binding and neutralizing antibody at end of study as some had sustained titers. The response should be followed until it is back to baseline; if it is maintained, patients should continue to be monitored.
4. The epitope specificity of the neutralizing antibody should be defined. If specific for determinants in the Complementarity Determining Region (CDR), follow up with assessment of catalytic activity on LDLR in low pH setting.
5. Scrutiny of individual patient data in the ISE (pages 1910 to 1945) reveals that in patients with very transient antibody responses, there appears, as you assert, to be no or little effect on efficacy, as judged by LDL-C levels. However, in patients with more sustained binding and neutralizing antibody responses, two patterns are observed. In some patients, the persistence of antibodies appears to diminish efficacy, with increases in LDL back to baseline (patients on pages 1910, 1912, 1923, 1926, 1937, 1941, 1944) while in some patients with sustained NABs, efficacy is maintained or enhanced suggesting that antibodies to alirocumab are acting as carriers and prolonging the PD of the mAb (patients on pages 1916, 1928, 1930, 1936, 1940, and 1942). In the face of these striking patterns, please provide additional data regarding the PK/PD of alirocumab in the latter two categories as well as correlations with clinical adverse events such as injection site reactions, etc.
6. For patients with general allergic (SMQ) events
  - a. Provide in tabular form, the number and frequency of general allergic (SMQ) events by preferred term divided by presence or absence of ADA
  - b. For patients with positive ADA and a general allergic event, provide a table listing the following, pt ID, treatment, general allergic PT, whether patient was positive for ADA at the time of the event, the antibody titer closest to the time of the event, peak antibody titer and week of peak titer, if antibody response was transient or persistent, presence of neutralizing antibodies the isotype, including results of testing for IgE and whether drug administration was discontinued based on such reactions;
  - c. If antibody negative, identify the cause of the hypersensitivity response

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/s/  
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PATRICIA J MADARA  
03/03/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - Request for Information  
**Date:** Friday, February 27, 2015 3:23:00 PM  
**Attachments:** [27Feb15 Information Request clinical.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

Clinical Information Request 2/27/15

1. If available, please submit a representative sample of photos taken of patients with local injection site reactions.
  - a. Include reactions of varying degrees of severity/seriousness in the control and alirocumab treated populations
  - b. Include photos of injection site reactions in patients with positive ADA and negative ADA
  - c. Include photos of reactions with the pre-filled syringes and autoinjectors.
  - d. If available, provide photos of the 2 bruising events, referenced in the ISS associated with stalled autoinjector devices.
  - e. Please provide follow-up photos, if available, of these reactions
2. If available, please submit a representative sample of photos of general allergic events
  - a. Include reactions of varying degrees of severity/seriousness in the control and alirocumab treated populations
  - b. Include photos of general allergic reactions in patients with positive ADA and negative ADA responses
3. Please provide the number and frequency of patients with any fracture overall and by preferred term in the placebo-controlled and ezetimibe-controlled studies
4. In the ISS, page 159, it states: "Among the 8 serious hepatic disorders TEAEs, in 6 cases the events recovered while patients continued on alirocumab." Please confirm, as it appears that of the 8, 3 patients permanently discontinued alirocumab, 3 patients temporarily discontinued alirocumab, and 2 recovered without corrective treatment (12492-840-415-006 and 1171-710-005-031).
  - a. In tabular form for each SAE in the hepatic disorder SMQ, please list the pt ID, hepatic related PT, statin therapy, action taken with statin therapy, action taken with alirocumab, outcome of the event

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/s/  
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PATRICIA J MADARA  
02/27/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - Request for Information  
**Date:** Friday, February 27, 2015 3:07:00 PM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following requests for information.

- 1. Within BLA submission section 3.2.P.7 for the pre-filled pen product, you have provided a listing of system-level requirements for the combination product.**
  - a. This listing does not appear to contain a complete list of essential product requirements. Examples of essential system requirements not included within this listing are: the presence and descriptive information for audible/visual feedback related to injections and biocompatibility of the product. Please provide a revised listing of product requirements which contains each essential performance requirement for the product.**
  - b. The submission does not appear to contain information which justifies pre-filled pen system requirements/specifications in the context of the clinical use of the product. For each system-level requirement please provide rationale supporting clinical acceptability of the selected requirement.**
- 2. Within BLA submission section 3.2.P.7 for the pre-filled pen product, you have provided a description of pre-filled pen activation steps. Based on your description, (b) (4)**  
(b) (4)  
**Please state if the activation sequence must occur in a particular order.**
- 3. Within BLA submission section 3.2.P.7 for the pre-filled pen product, you state that the pre-filled pen has been designed with a (b) (4)**  
(b) (4)  
**Please provide an enhanced description of this design feature.**
- 4. Within BLA submission section 3.2.P.7, for the pre-filled pen product, you have provided a "batch analysis" section which provides certain verification performance information for the 150mg/ml and 75mg/ml product.**
  - a. Please contrast the information presented within this section with product verification activities conducted under MAF (b) (4).**

- b. Please provide the individual test report documents used to generate the summary information provided within the "batch analysis" section.
  - c. The summary results shown within the "batch analysis" section appear to show a large degree in variability both intra- and inter-batch. Please provide an analysis of the causes of the observed variability.
  - d. Please describe the type of product used to generate the "batch analysis" section within the context of your February 20th 2015 pre-filled pen stability update (b) (4)  
[REDACTED]
5. You have provided an injection time requirement for the pre-filled pen which ranges from (b) (4) seconds.
- a. Please provide justification for this (b) (4) range in acceptance criteria for injection time.
  - b. Provide clinical acceptability of an allowable injection time of (b) (4) seconds
  - c. The injection time specification appears to be stated with the assumption that the injection will be completed at room temperature with a pre-filled pen which has been permitted to warm to room temperature. Provide an analysis of how injection time and deliverable dose may change when the injection takes place within a cool environment or with a pre-filled pen which has not been permitted to warm to room temperature. Testing should be conducted exactly as labeled.
  - d. According to the current injection time requirement for the pre-filled pen, a pre-filled pen provided to a user/customer would be considered acceptable if it delivered the dose of medication up to but not greater than (b) (4) seconds. Please characterize the performance of pre-filled pen test units used as part of human factors validation activities, within respect to injection time and provide assurance that such validation testing used pre-filled pens which were representative of the upper bounds of injection time acceptability.
6. After review of the BLA submission, the Agency was unable to locate risk analysis documentation for the device constituent parts of the final finished pre-filled pen or pre-filled syringe products. Please provide risk analysis information for these device constituent parts of the combination product. Note that risk analysis information as composed by third party suppliers will not be sufficient unless such documentation contains risks which have been analyzed in the context of the delivery of the specific medication to be delivered

through the device constituent part.

- 7. After review of the BLA submission, the Agency was unable to locate information comparing the pre-filled pen and pre-filled syringe components to device constituent parts used to deliver medication within clinical studies. Provide an analysis comparing the pre-filled pen and pre-filled syringe components to device constituent parts used to deliver medication within clinical studies**
  
- 8. On February 20, 2015, you provided a stability update to the Agency for the pre-filled pen product. This stability update provided an analysis of the failure of certain stability lots of pre-filled pen product to meet stated performance requirements after aging. The Agency has the following questions related to this stability update:**
  - a. Your firm appears to conclude that the root cause of the observed increased injection times and under-deliveries of medication are due to (b) (4). Please state how you have eliminated the potential contributing cause of (b) (4)**
  
  - b. Your firm appears to conclude that the root cause of the observed increased injection times and under-deliveries of medication is (b) (4). Please provide support for this position given that no failures appear to occur at the time of manufacturing (time point 0).**
  
  - c. You appear to focus improvement efforts on the 75mg/ml pre-filled pen presentation, however the stability results show that the 150 mg/ml pre-filled pen presentation also showed failures after aging. Provide rationale for your decision to eliminate the 150 mg/ml pre-filled pen presentation from your analysis.**
  
  - d. You have not provided a comprehensive plan for demonstrating that the pre-filled pen and pre-filled syringe products will perform as specified after aging to the desired expiration point. The Agency expects that you will provide sufficient information in the form of real-time and/or accelerated aging studies to substantiate that pre-filled pen and pre-filled syringe products will perform as specified after aging to the desired expiration point.**
  
  - e. You have included prospective control of (b) (4). Provide an analysis of how this change could affect other performance requirements.**
  
  - f. You have included prospective control of an (b) (4) test to determine (b) (4) during manufacturing. Provide an enhanced description of the (b) (4) as well as information which validates this test and identify any product quality risks associated with the additional processing step.**

**9. It is observed that you are proposing to use a syringe as your container closer system for the delivery of alirocumab solution. In the information provided to the Agency, it is not clear whether the final finished product will be sterilized. Please clarify whether the combination product will be sterilized. If the final finished combination product is sterilized then please provide the type of sterilization and the residuals from that sterilization process.**

Please submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
02/27/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 (Praluent) - Request for Information  
**Date:** Thursday, February 19, 2015 11:30:00 PM  
**Attachments:** [clinical Information Request 2\\_19\\_15.pdf](#)  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have additional clinical requests for information.

- Please refer to the attached PDF document.

You may provide responses informally, via email, but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

## Clinical Information Request 2/19/15

1. In Table 6 of the ISS, please explain why there are a smaller number of patients included in the drug exposure calculations, than the total of patients treated. For example, 2476 patients in the placebo-controlled alicumab group were treated but only 2470 patients are included in the duration of exposure calculations.
2. Provide a table defining the CV risk categories (moderate, high, very high) for each of the Phase 3 studies
3. Please explain why there is a difference in the number of patients who discontinued due to an AE in Table 5 and Table 42 in the placebo-controlled pool. Please provide a listing of the patients that are excluded from Table 42.
4. In the ISS appendix Table 1.4.1.6.4 and any other Tables similar to it (Table 1.4.1.7.4, 1.4.1.9.4 etc.) please provide the preferred terms for the SAEs, fatalities, and discontinuations.
5. Please provide the preferred terms for the TEAES which led to permanent treatment discontinuation which have an outcome of “not recovered” in Tables in the ISS appendix such as 1.4.19.8.
6. In the narrative for patient 11717-380-001-003 please clarify if the patient’s simvastatin was also stopped and restarted; please provide the corresponding dates if this occurred.
7. Please provide a breakdown of the individual components comprising “Other reasons” for not completing the study treatment period (as per CRF) in Table 5 in the ISS.
8. Provide the definitions for “strict CRF criteria for study treatment period completion” for all the phase 2/3 trials

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/s/  
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PATRICIA J MADARA  
02/19/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - Request for Information  
**Date:** Saturday, February 14, 2015 11:17:00 PM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following request for information.

- Regarding the Human Factors studies for Praluent, you state in the report:  
***“As a part of the training, participants performed their first simulated self-injection (into a skin pad) under the supervision and guidance of a health care professional, in a simulated setting”***
- Please provide the results of this injection or tell us where the information is located within your application.

You may provide a response, informally, via email but also submit your response officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
02/14/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - Request for Information  
**Date:** Monday, February 09, 2015 9:56:00 AM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following requests for information.

- 1. Two patients 011717-826-006-123 and 011717-840-193-008 experienced trigeminal neuralgia. The ISS states for these cases of trigeminal neuralgia the “demyelination” is secondary to the external compression of blood vessels due to vertebro-basilar atherosclerotic disease. Did these patients have MRI imaging to rule out other causes of trigeminal neuralgia such as multiple sclerosis or tumor. If so, please provide this documentation.**
- 2. Pt 011717-380-002-004. The narrative states a consulting neurologist recommended discontinuation of IMP. Please provide an update on this patient’s neurological condition – please include whether alirocumab was continued and if this patient has been formally diagnosed with multiple sclerosis.**
- 3. In the phase 2/3 trials, treatment emergent period, please provide the number and frequency of patients with intracranial hemorrhage fatal and non-fatal overall and by preferred term divided by treatment group.**
- 4. Please include listing of patients with any intracranial hemorrhage. Please include the study ID, verbatim term, preferred terms, adjudicated outcome, treatment assignment, treatment period, event outcome, LDL levels over time, and any other relevant information.**
- 5. Was patient 001118-840-487-001’s event of right cerebellar hemorrhagic stroke sent for adjudication? If not, please explain or provide the adjudicated outcome of this event.**

You may provide a response, informally, via email but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
02/09/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - Request for Information  
**Date:** Wednesday, January 28, 2015 4:21:00 PM  
**Importance:** High

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**BLA 125559**

**INFORMATION REQUEST**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection. We are reviewing your application and have the following request for information.

- 1. Please provide baseline demographics and characteristics of patients treated with alirocumab that achieved two consecutive LDL-C <25 mg/dL versus alirocumab-treated patients that did not in the global pool. As part of this description include adherence to study medication, statin therapy, average dose of statin therapy, duration of exposure to study medication.**
- 2. Please provide the number and percentage of patients that had their medication temporarily discontinued or reduced due to LDL-C <25 mg/dL.**

You may provide a response, informally, via email but also submit your responses officially to your BLA.

**Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
01/28/2015



BLA 125559

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated and received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for Praluent (alirocumab) injection.

We also refer to your amendments dated December 17 and 19, 2014, and January 12, 13, and 20, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is **July 24, 2015**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 28, 2015.

In addition, the planned date for our internal mid-cycle review meeting is February 25, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

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

- As we have stated previously, it will be a review issue whether this application could be approved based on effects on lipid parameters such as LDL-C before cardiovascular (CV) outcomes data are available. Uncertainty is greater with regard to net clinical benefit when benefit of a drug is assessed solely by effects on a biomarker, regardless of whether the biomarker is considered a valid surrogate endpoint for a given patient population.

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

We request that you submit the following information:

1. Please submit or provide the location of the following analysis that was requested in the End-of-Phase 2 (EOP2) meeting written comments:  
“You should perform a categorical analysis and submit it to the BLA. The analysis should include the number and percentage of individuals with :
  - Absolute QT/QTc values > 450ms, > 480 ms, and > 500 ms; as well as the number and percentage of individuals with change from baseline > 30 ms and > 60 ms.
  - PR changes from baseline  $\geq$  50% if absolute baseline value was < 200 ms and  $\geq$  25% if absolute baseline value was > 200 ms.
  - QRS changes from baseline  $\geq$  50% if absolute baseline value was < 100 ms and  $\geq$  25% if absolute baseline value was > 100 ms.
  - Number and percentage of individuals with abnormal ECG findings.
  - Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.”
2. Please submit or provide the location of the assessment of skeletal muscle-related withdrawal rates between alirocumab and ezetimibe in the ezetimibe-controlled pool referred to in the EOP2 meeting minutes.
3. Please submit or provide the location of non-fatal SAEs summarized in tabular form by SOC and preferred term in the placebo-controlled and ezetimibe-controlled pools.
4. We note in LONG TERM there were 5 patients with the preferred term “amnesia” (840-204-002, 840-083-004, 710-009-013, 826-006-080, and 124-006-008). Only two of these patients have narratives describing this event (840-083-004 and 124-006-008). Please submit narratives for the other 3 patients and clarify why they were not included in the original application.

5. For each phase 3 trial, utilizing the ITT analysis, fill in the mock table for the following targets (the right 2 columns will only be applicable in the trials that utilized alirocumab up-titration; studies that have more than one comparator should have those data presented in separate comparator columns):
  - a. Among very high risk patients only, LDL-C < 70 mg/dL
  - b. Among moderate-to-high risk patients only, LDL-C < 100 mg/dL
  - c. LDL-C < 70 mg/dL among very high risk patients or LDL-C < 100 mg/dL among moderate to high CV risk patients
  - d. Among very high risk patients only, LDL-C < 70 mg/dL and/or  $\geq 50\%$  reduction in LDL-C
  - e. LDL-C reduction  $\geq 50\%$  (all pts)
  - f. LDL-C reduction  $\geq 50\%$  (very high risk pts only)

Time		Comparator N=	Alirocumab		
			All N=	Up-titrate: No (75 mg) N=	Up-titrate: Yes (75/150 mg) N=
Week 12	Observed	n (%)	n (%)	n (%)	n (%)
	Missing	N	N	N	N
Week 24	Observed				
	Missing				
Week 52*	Observed				
	Missing				

\*if applicable

6. Clarify why the dose change at week 12 was based on week 8 data (as opposed to week 10 or week 12 data, for example). Clarify how missing data from week 8 were handled with respect to dosing decisions at week 12.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

**Comments for All Patient Labeling:**

1. Assure that the document is organized according to the format and style described in this document, in the CMI Guidance document (<http://www.fda.gov/cder/guidance/7139fnl.htm>), and in 21 CFR 208.20 (a).
2. Information concerning the drug product should be included in the Patient Package Insert (PPI). Information concerning the device should be included in the Instructions for Use (IFU). For brevity and reading ease avoid duplication of information across all patient labeling materials.
3. Patient labeling materials should meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
4. Patient labeling materials should utilize simple wording and clear concepts where possible and should be consistent with the Prescribing Information. Do not use complex medical terminology.
5. Although not regulated like Medication Guides (MGs), for consistency across patient labeling we recommend PPIs include the same headings and sections as MGs per 21 CFR 208.20. For example, the proposed section “(b) (4)?” is not included in patient labeling practice and should be deleted in the PPI.
6. Optimally, PPIs and MGs should have a reading ease score of 60% to 100% or a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, if possible.
7. Patient labeling materials should be in fonts such as Verdana, Arial or APFont at font size 11 or greater to make medical information more accessible for patients with vision loss. We recommend Verdana 11 point font.
8. The purpose of the patient information is to enhance appropriate use and provide important information to patients about the medication. Preferably, disease specific information should be placed at the end of the patient labeling after the section, “What are the ingredients in TRADENAME?”
9. Use bolded text instead of underlining and text boxes to highlight important information. Text that is underlined or placed in a text box is difficult to read for patients with vision loss.

**Comments for the Instructions for Use:**

10. The Instructions for Use (IFU) should be titled as such and appear at the end of the PPI after the list of ingredients. The IFU may also be provided as a separate document.
11. IFUs are generally organized as follows:
  - a. Standard header
  - b. Bulleted list of all the supplies needed to complete the task, including an illustration of all supplies needed.

- c. Patient instructions that are not sequential should be bulleted.
- d. Patient instructions that are sequential should be labeled as “**Step 1, Step 2**” etc.
- e. Figures should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related text. The figures should be labeled as “**Figure A, Figure B**” etc.
- f. Within the figures there should be detailed labeling for each part of any device that the patient expected to become familiar with.
- g. Refer to each figure at the end of each numbered step. For example, at the end of **Step 1**, say (**See Figure A**).
- h. Storage information as stated in the Prescribing Information (PI) should appear at the end of the IFU if the IFU will be a separate document. If the PPI and IFU are combined, the storage information should appear in the PPI only.
- i. Disposal information. If needles, syringes or injectable Pens are used to prepare or deliver the drug, disposal language should be consistent with the FDA “Safe Sharps Disposal” website language.
- j. Other pertinent miscellaneous instructions to the patient
- k. Manufacturer name and address
- l. If the IFU is a stand-alone document, add the statement “These Instructions for Use have been approved by the U.S. Food and Drug Administration.”
- m. If the IFU is attached to a PPI, add the statement “This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.”
- n. “Approved” Month/Year5:30 still

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **February 13, 2015**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form

with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JAMES P SMITH  
01/22/2015

**From:** Madara, Patricia  
**To:** [jana.bodorova@sanofi.com](mailto:jana.bodorova@sanofi.com)  
**Subject:** BLA 125559 - Request for Information  
**Date:** Friday, January 16, 2015 9:10:00 AM  
**Importance:** High

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**BLA 125559  
REQUEST**

**INFORMATION**

Dear Jana;

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for alirocumab injection. We are beginning to review your application and have the following request for information.

- **Please submit the manufacturing schedule for Praluent (alirocumab), BLA 125559, at the Sanofi Winthrop Industrie (EIN 2977302488) drug product manufacturing facility in LeTrait, France.**

You may provide a response, informally, via email but also submit your responses officially to your BLA. **Please confirm receipt of this email.**

Thanks for your help.  
Sincerely;

Pat Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
Phone: 301-796-1249

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/s/  
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PATRICIA J MADARA  
01/16/2015



BLA 125559

**INFORMATION REQUEST**

Sanofi-Aventis US LLC  
Attention: Jana Bodorva, M.Sc.  
Director, Global Regulatory Affairs  
55 Corporate Drive  
Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated November 24, 2014, received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for PRALUENT (alirocumab).

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by February 15, 2015 in order to continue our evaluation of your BLA.

1. Description of the Manufacturing Process and Process Controls

a. For each step of the manufacturing process indicate the following and clarify at which point it take place:

i. [Redacted] (b) (4)

ii. [Redacted] (b) (4)

iii. [Redacted] (b) (4)

The information may be provided as a diagram similar to Figure 1 of section 3.2.S.2.2 and should indicate the sequence between [Redacted] (b) (4)

b. [Redacted] (b) (4)

c. [Redacted] (b) (4)

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

(b) (4)



Please do not reply to this email. Send your submission through the Electronic Submission Gateway <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**RESPONSE TO INFORMATION REQUEST  
QUALITY**

INFORMATION REQUEST

Kindly provide a PDF copy of your official submission to Anita.Brown@fda.hhs.gov. If you have any questions, please contact me at 301-796-2066 or the email address above.

Sincerely,

Anita N.  
Brown -A

Digitally signed by Anita N. Brown -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Anita N. Brown -  
A  
0.9.2342.19200300.100.1.1=2000546085  
Date: 2015.01.16 02:52:20 -0500

Anita N. Brown  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

---

Food and Drug Administration  
Silver Spring, MD 20993

BLA 125559  
INFORMATION REQUEST

Sanofi-Aventis US LLC  
Attention: Jana Bodorva, M.Sc.  
Director, Global Regulatory Affairs  
55 Corporate Drive  
Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated November 24, 2014, received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for PRALUENT (alirocumab).

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by February 4, 2015 in order to continue our evaluation of your BLA.

1. In section 3.2.S.3.2 you describe (b) (4) and provide a corresponding control strategy for this potential process impurity. However, in section 3.2.S.2.3 we were unable to find (b) (4) listed as a raw material. Update section 3.2.S.2.3 accordingly and if (b) (4) is a component of the production media please describe the (b) (4) type, source, manufacturing and control. The information will allow the agency to assess the impact of supplementing Alirocumab manufacturing with (b) (4)

2. In section 3.2.S.3.1 you provide CE-SDS electropherograms under non-reducing conditions with an estimated Alirocumab molecular weight of approximately (b) (4) kDa. However, when analyzed by SEC-MALLS under native conditions the estimated Alirocumab molecular weight is approximately 147 kDa. Provide information and/or data that accounts for the discrepancy. The information will allow the agency to assess the accurate molecular

weight of the monomeric form of Alirocumab.

Please do not reply to this email. Send your submission through the Electronic Submission Gateway

<http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**RESPONSE TO INFORMATION REQUEST  
QUALITY**

Kindly provide a PDF copy of your official submission to [Anita.Brown@fda.hhs.gov](mailto:Anita.Brown@fda.hhs.gov). If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at 301-796-2066.

Sincerely,

Anita N. Brown  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



BLA 125559

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

sanofi-aventis U.S. LLC  
55 Corporate Drive  
Mail stop: 55D – 215A  
Bridgewater, NJ 08807

ATTENTION: Jana Bodorova, M.Sc.  
Director, Global Regulatory Affairs

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated and received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for Alirocumab, 75 mg/mL and 150 mg/mL.

We also refer to your correspondence, dated and received November 24, 2014, requesting review of your proposed proprietary name, Praluent.

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

If any of the proposed product characteristics as stated in your November 24, 2014, 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 Terrolyn Thomas, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2981. For any other information regarding this application, contact Patricia Madara, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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TODD D BRIDGES  
12/17/2014



BLA 125559

**BLA ACKNOWLEDGMENT**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

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

Name of Biological Product: alirocumab subcutaneous injection, 75 mg or 150 mg administered once every 2 weeks.

Date of Application: November 24, 2014

Date of Receipt: November 24, 2014

Our Reference Number: BLA 125559

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 January 23, 2015, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [per 21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

The BLA 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](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

Patricia Madara  
Regulatory Project Manager  
Division of Metabolism and Endocrinology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA J MADARA  
12/02/2014



IND 105574

**MEETING MINUTES**

Sanofi US Services Inc.  
Attention: Jana Bodorova, M.Sc.  
Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for alirocumab (SAR236553) injection.

We also refer to the meeting between representatives of your firm and the FDA on September 4, 2014. The purpose of the meeting was to discuss submission of a BLA for alirocumab.

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

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** PreBLA  
**Meeting Date and Time:** September 4, 2014 at 10:00 AM  
**Meeting Location:** Building 22, Rm 1415; White Oak Campus, Silver Spring, MD  
**Application Number:** IND 105574  
**Product Name:** alirocumab  
**Indication:** adjunct therapy to diet, for long-term use in adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia (corresponding to Type IIa and Type IIb hyperlipidemia in the Fredrickson classification), including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1).  
**Meeting Chair:** James P. Smith, M.D., M.S.  
**Meeting Recorder:** Patricia Madara

**FDA Attendees**

**Office of Drug Evaluation II (ODE II)**

Mary H. Parks, M.D. Deputy Director

**ODE II; Division of Metabolism and Endocrinology Products**

Jean-Marc Guettier, M.D.	Director
James P. Smith, M.D., M.S.	Clinical Team Leader
Eileen Craig, M.D.	Medical Officer
Mary Roberts, M.D.	Medical Officer
Julie Golden, M.D.	Medical Officer
Karen Davis Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
Lee Elmore, Ph.D.	Pharmacology/Toxicology Reviewer
Julie Van der Waag, MPH	Chief, Project Management Staff
Kati Johnson, R.Ph.	Regulatory Project Manager
Patricia Madara, M.S.	Regulatory Project Manager

**Office of Clinical Pharmacology; Division of Clinical Pharmacology II**

Immo Zadezensky, Ph.D.	Clinical Pharmacology Team Leader
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer

**Office of Compliance, Division of Manufacturing and Product Quality, Manufacturing Assessment & Pre-Approval Compliance Branch**

Patricia Hughes, Ph.D.	Team Leader, Biotech Manufacturing Team
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**Office of Pharmaceutical Science, Office of Biotechnology Products, Division of Monoclonal Antibodies**

Chana Fuchs, Ph.D.	Team Leader
Sang Bong Lee, Ph.D.	Quality Reviewer

**Office of Surveillance and Epidemiology/Division of Risk Management (DRISK)**

Amarilys Vega, Pharm.D.	DRISK reviewer
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**Center for Devices and Radiological Health (CDRH); Office of Device Evaluation**

LCDR Keith Marin, RN, MS, MBA	Combination Product Team Lead I
-------------------------------	---------------------------------

**Office of the Commissioner; Office of Combination Products**

Patricia Love, M.D.; MBA	Deputy Director
Bindi Nikhar, M.D.	Associate Clinical Director

**Eastern Research Group**

So Hyun Kim	Independent Assessor
-------------	----------------------

**Sanofi attendees**

Barry Sickles, PhD	Vice President, Head, Global Regulatory Affairs, North America and Global
Nia Tatsis, PhD	Associate Vice President, Head, Global Regulatory Affairs, PCSK9 and Specialty Care 1 Products
Jana Bodorova, MSc	Director, Global Regulatory Affairs
Jay Edelberg, MD, PhD	Vice President, Head, PCSK9 Development and Launch Unit
Laurence Bessac, MD, MSc	Associate Vice President, Head, Clinical Development, PCSK9 Development and Launch Unit
Corinne Hanotin, MD,	Lead Clinical Research Director, Clinical Development, PCSK9 Development and Launch Unit
Christelle Lorenzato, MSc	Biostatistics
James Collins, P.E., MBA,	Vice President, Devices Development Unit, Medical Devices
Martin Solberg, DRSc	Vice President, Head, Global Regulatory CMC Biologic Products

Catherine Dubuisson-Brengel, PhD	Associate Director, Global Regulatory CMC Biologic Products
John Schalago, MSc, RAC	Associate Vice President, Head of CMC/Devices, Global Regulatory Affairs
Marie-Therese David-Comte, PhD	Director, Biotherapeutics
Stephen Fitzpatrick, PhD,	Senior Director, Global Regulatory CMC Biologic Products, Sanofi

**Regeneron attendees**

Ned Braunstein, MD	Vice President, Regulatory Affairs
Mary Alice Raudenbush, MSc,	Senior Director, Regulatory Affairs
Bill Sasiela, PhD	Vice President, Program Direction, Cardiovascular & Metabolism Therapeutics
Robert Porody, MD	Vice President, Clinical Sciences, Cardiovascular & Metabolism Therapeutics
Jennifer McNay, PhD,	Senior Director, Process Sciences

**1.0 Background**

Sanofi Aventis and Regeneron Pharmaceuticals are developing alirocumab to treat hypercholesterolemia. Alirocumab is a humanized monoclonal antibody which binds human proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 normally functions to down-regulate LDL-receptor activity (via increased degradation of LDL receptors). Alirocumab binds PCSK9, disrupting its interaction with the extracellular domain of the LDL-receptor. This allows increased LDL-receptor presence on the surface of hepatocytes in the liver, increasing LDL clearance, and lowering total and LDL-cholesterol levels detected in the blood.

An end-of-phase 2 meeting was held on February 21, 2012 to discuss the phase 3 development program. The purpose of this meeting is to discuss submission of a biologics license application (BLA) for alirocumab (preassigned # 125559), including the requirements for a complete application. The company will seek the approval of 2 doses of alirocumab, 75mg and 150 mg, and of 2 presentations for these doses: prefilled syringes (PFS) and prefilled pens (PFP).

Of note, on July 29, 2014, Regeneron purchased a rare pediatric disease (RPD) priority review voucher (PRV) from BioMarin. It was ultimately transferred to Regeneron's partner, Sanofi Aventis, and Sanofi plans to use it to obtain a priority review for BLA 125559 (alirocumab). The Agency has been notified of the transfer from BioMarin and Sanofi's intent to use the voucher.

Alirocumab is a new molecular entity (NME) and will be reviewed under "The Program."

The expected outcome of this meeting is for the sponsor and FDA to reach agreement on the requirements for a complete BLA submission.

## 2.0 Discussion

### 2.1. Regulatory and Administrative Questions

#### **Question 1**

Table 7 contains a list of proposed studies to be included in the BLA to support the requirements under 21 CFR 54 (financial disclosure). *Does the Agency agree with the list of proposed studies?*

#### **FDA Pre-Meeting Response**

Your proposal appears acceptable. We recommend that you review “Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators” found at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf>.

#### **Question 2**

Table 8 contains a list of ‘reviewer guides’ intended to ease the navigation and review of the application. *Does the Agency agree that the Sponsor’s planned reviewer guides are sufficient?*

#### **FDA Pre-Meeting Response**

We agree with the four reviewer guides that you have presented. In addition, reviewers’ guides should accompany tabulation and analysis datasets so that there is no ambiguity with regard to how variables were defined or derived.

In addition, please provide a reviewer’s guide for the device constituent part and the combination product as a whole. The guide would provide a high-level overview (with reference links) of the submission’s content and list where the information is located in the eCTD. For example, it would identify where drug, device, and combination product manufacturing information is located. In addition, in the guide narrative, you should identify which documents address compliance with the applicable requirements specified in 21 CFR Part 4 for the combination product, using either the streamlined or conventional approach.

#### **Question 3**

It is the Sponsor’s position that alirocumab represents a first-in-class therapeutic with demonstrated safety and efficacy in patients suffering from hypercholesterolemia (familial and non-familial) who are unable to achieve sufficient lowering of their LDL-C with currently available lipid lowering therapies (including statins). As such it treats a serious condition (elevated LDL-C in patients with increased CV risk) and, if approved, would provide a significant improvement in effectiveness. Therefore, the Sponsor intends to request Priority Review at the time of submission of the BLA. *Does the Agency have a position on Priority Review for the BLA? Can you please share your thoughts on this topic?*

#### **FDA Pre-Meeting Response**

We are aware of your intent to use your priority review voucher (PRV) for this application, which would allow for a priority review. If you choose not to use this PRV for this application, then a determination for priority review designation will be made following submission of the BLA.

#### **Question 4**

The proposed electronic Table of Contents (eTOC) of the BLA for Modules 1, 2, 4 and 5 is provided in [Section 4.3](#) (Appendix 3). *Does the Agency agree with the Sponsor's proposed dossier content, structure, format and eTOC above?*

#### **FDA Pre-Meeting Response**

- a. In Module 2, the section 2.3 (Quality Overall Summary) should not include any information that is not also included in section 3.2 of Module 3.
- b. In section 5.3.1.4 of Module 5, immunogenicity assay validations for detection of anti-alirocumab antibodies and neutralizing anti-alirocumab antibodies should also include the protocols for these assays.
- c. Module 5 should include the clinical human factors study reports. These may be provided in Module 5.3.5.2. See response to question 7 for information on leaf node titles.

#### **Sponsor's Pre-Meeting Response regarding point (c):**

The sponsor has previously submitted for review and comment to the IND the Summative Human Factors Study protocols. The Summative HF Studies were performed as a simulated use study, i.e. injection in to a pad to validate the device and device labeling. Per FDA guidance, the protocol included user task analysis.

Given that the HF Studies were performed under simulated use conditions only, the sponsor does not consider the HF study a clinical study. Therefore, as described in the Pre-BLA meeting package, the sponsor intends to provide Human Factors Validation protocols and study reports in Module 3 Section 3.2.P.2.4.

Sponsor's follow-up question: Does the FDA agree with this proposal?

#### **Meeting Discussion**

**FDA clarified that the human factors (HF) study conducted by the sponsor did qualify as a clinical study. However, absent published guidance, for purposes of this submission, data may be submitted in an alternative location (other than Module 5) as long as its location is clearly identified in the reviewers' guides in Module 1.**

## **2.2. Chemistry, Manufacturing and Controls Questions**

#### **Question 5**

Does the Agency agree that the proposed stability strategy for the 75 mg/mL PFP supports acceptance of the BLA for review?

#### **FDA Pre-Meeting Response**

Yes. The proposed stability strategy supports filing of the BLA for review.

In a briefing package submitted 02/02/2014 (SN0232), table 31 identifies that breakloose and gliding forces on PFS will be measured at  <sup>(b) (4)</sup> stability timepoints, and table 34 identifies that no testing of breakloose and gliding forces were planned for the PFP. As the

(b) (4)

You should revise the stability protocols to include glideforce assessment in the timepoints that will be available during the BLA review timeline for lots currently on stability based on the (b) (4)

The meeting package specified that (b) (4) are required to be used in the production of PFP DPs within (b) (4). No further information was provided in the meeting package on the relationship between the inherent (b) (4) before production of PFPs. This would have to be addressed in the BLA in support of your proposed stability strategy.

You identified additional stability data that will be available during the BLA review timeline. Under a priority review process, more stability data are required in the original BLA submission in order to review DP stability data in a timely manner based on the shortened review cycle. Based on the estimated November 2014 submission, if a priority review is granted, the nine-months stability data for the 75 mg/mL (b) (4) data would not be available in time for assessment within the BLA review timeline. The nine and twelve months stability data for the PFS (with plunger rod) and the six months stability data for the 75 mg/mL (b) (4) PFP DP appear to be available within a timeline for review. During the review cycle, FDA may assess whether these data points may be needed to address any uncertainties on product stability. Under PDUFA V, data should not be submitted more than 30 days after the submission of the original application unless it is requested by the Agency. During the review period, the Agency may request submission of a "simple stability update." "Simple stability updates" are defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the "simple stability update" will use the same tabular presentation as in the original submission, as well as the same mathematical or statistical analysis methods (if any), and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA.

Sponsor's pre-meeting follow-up response and a follow-up question:

- We agree to revise the stability protocols to include the (b) (4) assessment in the future stability time points.
- With regard to submission of stability data during a BLA priority review, we could provide a "simple stability update" with (b) (4) stability data on the 75 mg PFP the third week in April 2015 barring any need for retests. Would that be adequate?

**Meeting Discussion**

**FDA noted that because alirocumab was a new molecular entity (NME) and because of the priority review voucher (PRV) use, the BLA would be reviewed on an eight-month clock under "the Program." According to the 21<sup>st</sup> Century Program timelines, primary reviews would be due by the end of month five. If the BLA is submitted in mid-November as planned, reviews would be due by mid-April 2015. Submission of stability data the 3<sup>rd</sup> week in April would create a very tight review timeframe.**

The sponsor indicated that they would be updating the specifications for the PFP. They were considering a (b) (4) and did not believe this would invalidate any of the data collected thus far. FDA commented that the concept appeared reasonable, noting that acceptability of proposed specifications would be addressed after review of the data in the BLA.

FDA asked if machinability would be affected and the sponsor stated it would not.

FDA requested that information provided in the BLA include data that supports Sanofi's requirements regarding the production of 75 mg PFPs (b) (4).

### Question 6

In the EOP2 questions to the Agency the Sponsor asked if the Agency agreed that the safety and efficacy data [from Phase 3] will be sufficient to support the approval of both the auto-injector and pre-filled syringe in both strengths and that no additional clinical studies are required. Following the EOP2 meeting, the Division confirmed to the Sponsor that "the proposed Phase 3 program appeared to provide adequate Phase 3 clinical data to support the safety and efficacy of the pre-filled syringe and auto-injector device."

The Sponsor intends to seek registration of and launch with the PFS and the PFP as different presentations for the alirocumab drug product. Per the Agency's guidance on bundling multiple drug product presentations in a single application (22 June 2007), it is the Sponsor's understanding that both presentations (2 dosage strengths per presentation) may be bundled in a single application. However, it is also understood that FDA does not require Applicants to bundle multiple presentations, and the Applicant may choose to submit separate BLAs. The Sponsor's preference is to bundle these in a single application

- a. *Can the Agency please confirm that this would be acceptable. Even if acceptable, does the Agency anticipate problems or have concerns with this approach?*
- b. *In the situation where the PFS and PFP applications are unbundled and if Priority Review is granted, would the Agency assign Priority Review to both applications or only to one?*

### FDA Pre-Meeting Response

Yes, this is acceptable. Different configurations (e.g, pre-filled syringes, pre-filled pen) of one finished pharmaceutical product intended to be for the same route of administration for the same indication(s) may be bundled in a single application.

When an original application is split, priority review may or may not be granted for both split original applications, depending on the reason for the split.

Sponsor pre-meeting response:

(b) (4)

**Meeting Discussion**

(b) (4)

(b) (4)

(b) (4)

**Question 7**

*Does the Agency agree with the proposed contents and organization of the Module 3.2 Body of Data for the submission?*

**FDA Pre-Meeting Response**

We have the following comments based on the proposed contents and organization presented in the meeting package:

1. Sections 3.2.S and 3.2.P should provide a tabular listing of all lots manufactured as well as the genealogy of each lot showing batch/lot number, date of manufacture, manufacturing site, manufacturing process, disposition (including the clinical protocols in which each lot was used as well as any other uses for these lots such as stability studies, toxicology studies, formulation studies, lots to be marketed, etc.), QC status (for example, whether the batch was released, pending, quarantined, rejected). For DP lots, identify the lot(s) of DS from which they originate. (b) (4)
2. Sections 3.2.S.2.1 and 3.2.P.3.1 (manufacturers) should include the specific activities executed at each manufacturing and testing site, including listing the individual tests run at each site.
3. In sections 3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.3 and 3.2.P.3.4, provide detailed descriptions of each step in the manufacturing process including certain equipment information (b) (4), and the control strategy that will be utilized.
4. Section 3.2.S.2.3 should include protocols to monitor ongoing stability of the (b) (4)

5. You note that cross-referred related documents are also attached in some sections, for example sections 3.2.S.2.3 (control of materials – cell line development), 3.2.S.2.6 (manufacturing process development), etc. Note that the BLA should attempt to be as comprehensive as possible and only rely on cross-referencing another IND, BLA, or DMF in a very limited manner.
6. For validation or qualification studies and reports in sections 3.2.S.4.3 and 3.2.P.5.3, include product-specific validation parameters that are part of the compendial assay qualification and any assay transfer qualification reports for assays validated at another site.
7. Section 3.2.S.5 should include requalification protocol for reference standards.
8. For the Regional section (Table 49), differences between executed batch records and master batch records for bulk PFSs, PFSs and PFPs should be provided in English in the Introduction to batch records subsection of 3.2.R Regional information section.
9. Detailed information about what will be required to support release, stability, and validation have been relayed to you in meeting minutes from the Type C CMC only briefing package (03/05/2014); therefore, we are not commenting on the details, e.g. whether the data identified are sufficient to support stability. The BLA should also ensure that your terminologies, e.g. what is meant by “complementary testing,” is clearly defined, for example, how “complementary testing” relates to the comprehensive control strategy and to the regulatory and GMP requirements associated with these tests.
10. For methods using EP compendial procedures that are non-harmonized with USP, information identifying that the EP method is equivalent or better for the intended purpose than the USP method should be included
11. We disagree with the use of 3.2.R for location of what is identified as the “21 CFR Part 820 Quality System Regulation.” The following recommendations apply to the location of the manufacturing information of the device constituent part, the drug constituent part, and the drug-device combination product in the marketing application when submitted in the eCTD format.
  - a. All information pertaining to the manufacturing, assembling, or documentation of the finished combination product to demonstrate compliance with regulatory requirement applicable to 21 CFR Part 4 should be located in Section 3.2.P.3.
  - b. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembling, or testing processes taking place at each site with regards to the device constituent part, the drug constituent part, and the combination product as a whole.
  - c. For FDA to determine compliance to 21 CFR Part 4 manufacturing requirements, certain information should be submitted in the marketing application for Agency review. For example,
    - If you use the streamlined process based on a drug GMP combination product operating system, you should submit materials related to the additional QS regulation requirements identified in 21 CFR 4.4(b)(1). While the Agency has not issued guidance on the documents to provide for review of a combination product, considerations for the type of documents to submit for review related to these

requirements can be found in “*Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff*,” accessible at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>.

12. Location of device constituent part information using the eCTD format and use of the system
  - a. Please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say “Container Closure System.”
13. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
14. When including and referencing device information, we recommend the following:
  - a. You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.
  - b. In 3.2.P.7 you could include a leaf titled something similar to the following, “Table of Contents for Drug-Device Autoinjector.” This leaf/document could provide reference links to the other files in module 3.2.P.7. Obtaining concurrence from the Review Division on the proposed outline is recommended.
  - c. The leaf titles should be clear, concise and indicative of the document's content.
15. Module 1.4.4 (cross reference to other applications) is a location where you can provide references to other applications and you can include copies of an application’s table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 Letter of authorization, 1.4.2 Statement of right of reference, 1.4.3 List of authorized persons to incorporate by reference). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.

Sponsor pre-meeting Response: For all points except 11, we agree. Please see our comments and a follow-up question on Point #11 below.

The sponsor wishes to clarify that the document to be provided in 3.2.R is only intended as a reference and guide regarding compliance to combination products GMPs/QSR requirements. According to the Agency’s requirements, the sponsor confirms that:

- Information on manufacturing and assembly of the combination product will be located in 3.2.P.3,
- Design control data will be included in section 3.2.P.2.4 or in the device Master File, as applicable.

Sponsor’s follow-up question: Is this acceptable to the Agency?

## Meeting Discussion

**FDA stated that device manufacturing information should be located with other manufacturing data. Reviewer guides and any sub-table of contents for location of device manufacturing can be placed with other guides in Module 1.**

### 2.3. Nonclinical Questions

#### Question 8

The Agency sent an advice and information request letter (b) (4) of anti-PCSK9 therapeutics on June 7, 2011. The letter contained a recommendation to include, in the investigator brochure (IB) and informed consent (ICF), a potential risk for increased susceptibility to hepatitis C virus (HCV) infection. The letter referenced, as the basis for this recommendation, the results of a published study in which PCSK9, engineered to be expressed artificially on the cell membrane, reduced CD81 expression and modulated the ability of HCV to infect the transfected cells. The Sponsor complied with the Agency's recommendation.

Following the amendment of both the IB and ICF, the Sponsor submitted to the Agency results from study number REGN727-MX-12103-SR-01V1, titled "Role of anti-PCSK9 on CD81 levels and HCV entry into hepatocytes." The study demonstrated that there is no functional relationship between the presence and amount of secreted, soluble PCSK9 and total or surface CD81 levels. Antibody (i.e., alirocumab) blockade of PCSK9 had no impact on CD81. Furthermore, the addition of soluble PCSK9 or treatment with alirocumab had no effect on the HCV entry process (HCV pseudoparticles were used). The study report was submitted to the IND on 18 July 2013 (SN0175) along with the following question:

(b) (4)

The Division responded via email on 25 October 2013 that they did not agree with the Sponsor's position (b) (4)

The Sponsor has since conducted a comprehensive literature review and additional experiments that further support our position that administration of alirocumab is unlikely to increase a patient's susceptibility to HCV infection. The updated report is located in [Section 4.4](#) (Appendix 4) of this document, as part of a summary paper.

Importantly, all experiments described in the report used the physiologically relevant, extracellular, secreted form of PCSK9 in concentrations spanning the entire range of concentrations measured in human sera and one concentration that is approximately 20-fold higher than the mean concentration in humans. (b) (4)

(b) (4) the totality of the preclinical data to date do not support including this as a concern in product labeling.

*Does the Agency agree?*

### FDA Pre-Meeting Response

(b) (4)

#### **Question 9**

At the End-of-Phase 2 (EOP2) meeting (21 February 2012), the Division agreed that the Sponsor's current nonclinical program appeared appropriate to support Phase 3 clinical trials per ICH M3(R2) "Nonclinical Safety Studies for the Conduct of Human Trials and Marketing Authorization for Pharmaceuticals" and ICH S6 "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (official EOP2 meeting minutes). Since then, the Sponsor has carried out additional preclinical studies to further characterize the nonclinical pharmacology/safety profile of alirocumab. Additionally, a carcinogenicity assessment was submitted to the IND on 18 July 2013 (SN0172) for which the Agency responded on 25 October 2013 that "no additional evaluation of carcinogenic potential is warranted based on available data". The Sponsor considers there to be no outstanding or unresolved topics in the alirocumab nonclinical development program, that the requirements for registration have been met, and that the planned content of the nonclinical sections of the BLA is acceptable. *Does the Agency agree?*

#### **FDA Pre-Meeting Response**

The sponsor's nonclinical program appears appropriate to support filing of the application.

## **2.4. Clinical Questions**

#### **Question 10**

The patient safety database and exposure data that will be present in the BLA will meet the requirements agreed to at the EOP2 meeting – data from approximately 3390 patients treated with alirocumab at or above the planned marketed doses, including approximately 1890 patients treated for 12 months or longer and 400 patients from the long-term safety and efficacy study number LTS11717 (ODYSSEY LONG TERM) treated for 18 months.

In addition to the safety database and exposure data agreed to at the EOP2 meeting above, the Sponsor is planning to include in the 4-month safety update data from the on-going clinical studies. *Does the Agency agree with the proposed approach to the 4-month safety update?*

#### **FDA Pre-Meeting Response**

For item #1:

- Please confirm that you will be sending us unblinded data for the 3 studies with database lock between August 31 and December 31, 2014.

#### **Sponsor pre-meeting response:**

yes, we will provide unblinded tables. The list of tables is provided in the briefing document (Page 48).

- Please clarify if you intend to supply updated tables from the original submission, new tables for the safety update period only, or both. It would be helpful to have updated tables from the original submission (clearly specifying which original table you are updating) as well as to have the breakdowns from the safety period only to help track events.

Sponsor pre-meeting response: We had not planned to provide the breakdown, but given that you indicate this would be helpful, we will provide both the updated tables from the original submission and new tables for the safety update period only.

Pre-meeting Follow up question: Can the Agency confirm that the ISS tables (see the description in the briefing book page 48) that we propose to update in the 4-month safety update are acceptable?

### **Meeting Discussion**

**Your proposal is acceptable.**

**The company confirmed that for ongoing blinded studies, blinded SAEs would be submitted as a single list and not distinguished as “group A” or “group B.”**

- Please confirm that you will not be looking at, or submitting, analyses of unblinded CV-related SAE data from your CVOT, protocol EFC11570 (ODYSSEY Outcomes).

Sponsor pre-meeting response: We confirm that we will not be unblinding the CVOT at this time.

For item #3:

- For ongoing open-label studies, please provide the patient narratives as well as the listings of SAEs and deaths and counts (by SOC and PT) of SAEs.

Sponsor pre-meeting response: We will provide.

### **Question 11**

Could the Agency please provide their thoughts regarding the need for a REMS for the class of anti-PCSK9 compounds?

#### **FDA Pre-Meeting Response**

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

### **Question 12**

As indicated in the cover letter for the statistical analysis plan for the Integrated Summary of Safety/Summary of Clinical Safety (ISS/SCS) and the Integrated Summary of

Efficacy/Summary of Clinical Efficacy (ISE/SCE) (submitted to the IND on 10 April 2014; SN0250), for the ISS, the

Sponsor is planning to provide the comprehensive document, including a narrative text, tables, graphs and listings as well as the datasets in Module 5.3.5.3. A summary of the narrative text from the ISS and key tables will be provided in the SCS in Module 2.7.4.

For the ISE, the Sponsor anticipates that the narrative text and key tables will be within the size/page limit for SCE. Therefore, the Sponsor plans to provide the narrative text and key tables in Module 2.7.3. The ISE in Module 5.3.5.3 will not contain any text, instead it will have a reference to Module 2.7.3. The complete tables, graphs, listings and datasets will be provided in Module 5.3.5.3. *Does the Agency agree with this approach?*

#### FDA Pre-Meeting Response

Your proposed approach for the ISE and ISS appears appropriate as long as there are hyperlinks within the text that links to referenced tables regardless of whether they are in Module 2 or Module 5.

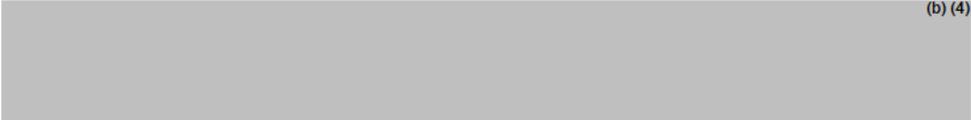
In the ISS, please provide injection-procedure-related AEs, such as local injection site events, for the combination product provided as PFS vs the autoinjector. We also request that you provide reporting of device-related events (e.g., device breakage, needle separation, wet injection, failure to inject, etc.) and provide this information for the two different delivery systems.

Sponsor pre-meeting response: We will provide.

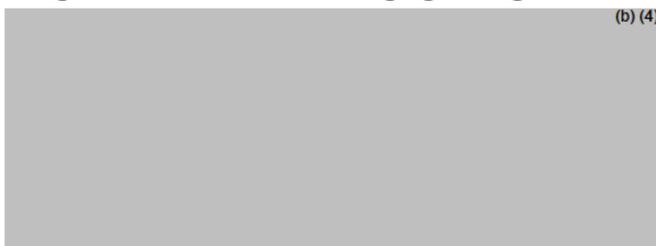
#### Question 13

The initial alirocumab Pediatric Study Plan (PSP) was submitted to the IND on 23 December 2013 (SN0215). The Agency provided comments on 16 April 2014 and the Sponsor submitted the Revised PSP1 on 20 June 2014. On 23 July 2014 the Agency requested a revision of the deferral request statement prior to issuing a letter indicating agreement, which the Sponsor provided via e-mail on 24 July 2014 and formally to the IND on 28 July 2014. The Agency issued an agreement letter on 25 July 2014.

The Sponsor is requesting a full waiver for:

-  (b) (4)

Regarding treatment of patients with heterozygous familial hypercholesterolemia, the Sponsor is requesting a waiver in the following age categories:

 (b) (4)

Does the Agency agree that the studies described in the PSP satisfy the requirements of the Pediatric Research and Equity Act?

FDA Pre-Meeting Response

Conducting the studies as described in the Agreed iPSP according to the Division's recommendations should satisfy PREA. The complete pediatric protocols must be reviewed and agreed upon prior to trial initiation.

**Question 14**

In the Agency's Written Response to the Sponsor (dated 09 May 2014), the following was stated (pg.3), ".....If you decide to submit [the BLA for alirocumab] prior to reaching the 25% of endpoints threshold, however, you should include the number (%) of *first secondary endpoint* events that have been accrued, ....."

We believe that the Agency meant to write "of primary endpoint events" as the OUTCOMES study protocol has no first secondary endpoint events being measured. OUTCOMES is based upon (and powered for) a single primary endpoint – the occurrence of major cardiovascular events (composite endpoint of CHD, death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization).

Could the Agency please confirm or clarify the above?

FDA Pre-Meeting Response

Yes, your clarification is correct. Thus, if you decide to submit the BLA for alirocumab prior to reaching the 25% of endpoints threshold, you should include the number (%) of primary endpoint events that have been accrued, the number (%) that have been adjudicated and the results of adjudication (i.e., the number accepted as endpoints vs. rejected), and the number (%) of subjects that have been randomized at the time of BLA submission.

**2.5. Additional FDA Comments**

**Clinical/Statistics/Clinical Pharmacology**

1. Clarify whether the alirocumab formulation used in Phase 3 clinical trials is identical to the proposed to-be-marketed formulation.

Sponsor pre-meeting response: yes

2. You have designed your program using the 75mg dose initially and only titrating to the 150mg dose if needed for efficacy reasons. For these trials, there are control data to assess the efficacy and safety of the dosing regimen, but not the individual 75mg and 150mg doses. Please comment on how you plan to present, analyze and discuss your data for the individual doses.

Sponsor pre-meeting response:

The alirocumab program was designed such that the starting dose could be either 75 mg or 150 mg Q2W. Eight (8) studies investigated starting patients with the 75 mg Q2W (1560 patients) with potential uptitration to 150 mg Q2W at week 12, and 2 studies 150 mg Q2W as the only

dose (1622 patients), respectively. We plan the following analyses to understand the effects of the individual doses:

Efficacy:

- In the ISE, a comparison of 12-week data from patients treated with either 150 mg Q2W (from LONG TERM and HIGH FH individual studies) or 75 mg Q2W (from individual studies with uptitration);
- In each CSR, exploratory analysis comparing 75 mg to 150 mg Q2W after week 12 for the studies with uptitration.

Safety:

- In the ISS, a comparison of patients treated with either 150 mg Q2W (from pooled LONG TERM and HIGH FH studies) or 75/150 mg Q2W (from pooled studies with uptitration);
- In each CSR and in the ISS, the following will be provided:
  - Safety data at the 75 mg Q2W dose up to week 12 for the studies with uptitration will be also provided;
  - Exploratory analysis comparing 75 mg to 150 mg Q2W in the alirocumab arm after week 12 for the studies with uptitration.

### **Meeting Discussion**

**The sponsor explained that they would submit data supporting both doses as the “starting” dose. Approximately 1600 patients were treated with the 150 mg dose from beginning to end of study. About 1500 patients were uptitrated, from 75 mg to 150 mg, if they were not at goal by week 12. If they were at goal, they remained on the lower dose.**

**The sponsor clarified that the ISE would contain 12-week data for 75 and 150 mg use. The CSR would contain exploratory analysis after week 12. The ISS would contain a comparison of data from patients treated with 150 mg or 75 mg uptitrated to 150 mg. The CSR would contain safety data for the 75 mg dose.**

**FDA noted that the presentation of clinical safety information was acceptable for review. Efficacy data based on trials employing titration designs are not as clean as parallel-group trials, and this would need to be considered during the review. FDA encouraged the sponsor to consider these issues in their interpretation and description of their results.**

3. You have designed your program using the 75mg dose initially and only titrating to the 150mg dose if needed for efficacy reasons. For these trials, there are no control data to assess the efficacy and safety of the 150mg dose, specifically. Please comment on how you plan to present, analyze, and discuss your data for the 150mg dose.

Sponsor pre-meeting response:

There will be 2 sources of the 150 mg Q2W data:



ezetimibe-controlled studies into a global pool EXCEPT for the analysis of ADA, injection-site reactions, and adjudicated CV events; by limiting the analysis to these endpoints, we can use meta-analytic approaches to control for treatment-by-study interactions.

### **Meeting Discussion**

#### **FDA finds this approach acceptable.**

6. For tables displaying liver enzyme abnormalities, please include a row for potential “Hy’s Law” cases (ALT or AST >3x upper limit of normal AND TBL > 2xULN)

Sponsor’s pre-meeting response: There were only 3 cases of patients of ALT >3x upper limit of normal AND TBL > 2xULN in the Phase 3 trials. One patient was treated with alirocumab, but was diagnosed with Hepatitis A infection. The other 2 patients were treated with placebo. Considering the number of these cases, we propose to provide this information in text of the Section 4.2.4 Liver Function Tests of the ISS.

### **Meeting Discussion**

#### **FDA finds this proposal acceptable.**

7. Ensure that you include narratives for deaths, serious adverse events, and adverse events leading to drug discontinuation for every trial. Hyperlinks should be used to allow navigation between eCRFs and corresponding narratives. In addition, provide a table of contents for narratives for each trial, with active hyperlinks, organizing the listing by deaths, SAEs, and AEs leading to discontinuation, with subcategorization by treatment group.

Sponsor’s pre-meeting response: we agree to provide.

8. Exposure data should be presented as the mean and median duration of time on study medication for the placebo or control group and the alirocumab group (for each dose) for the 12-week studies and the long-term studies.

Sponsor’s pre-meeting response: In the ISS we will provide mean and median duration of time on study medication for the placebo or control group and the alirocumab group (for 75 and 150 mg Q2W doses).

9. At BLA submission, provide the minutes of all DSMB and steering committee meetings.

Sponsor’s pre-meeting response: we will provide

10. Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report.

Sponsor’s pre-meeting response:

As pre-specified in the SAPs, we have used SMQs/Company MedDRA Queries (CMQs) for the analysis of adverse events of special interest (AESI), i.e. injection site reactions, general allergic events, neurological events (including neurocognitive events), ophthalmological events, and for the ALTERNATIVE study only, skeletal muscle related events. In addition, SMQs/CMQs were used for hepatic disorders and diabetes.

**Meeting Discussion**

**FDA requested that the sponsor provide their rationale for which MedDRA terms were included in the CMQs and why a CMQ was used rather than an SMQ.. Also, the sponsor should explain if the selection of the MedDRA terms was prespecified.**

11. Provide time to event analysis that includes time to onset and resolution and overall duration for selected events (common AEs/SAEs/AEs that led to study drug discontinuation) that are relevant for your investigational agent. An example table is provided below.

Sponsor’s pre-meeting response: we will provide for selected events in the ISS.

<b>Preferred Term or selected AE (such as liver test abnormalities, liver-related abnormalities, CK abnormalities, muscle-related abnormalities, injection site reactions, memory impairment etc)</b>	<b>Placebo (N=) n (%)</b>	<b>Total NB (N=) n (%)</b>
<b>Name of selected AE</b>		
Median time to onset (days or weeks)		
Median duration (days or weeks)		
Subjects with event resulting in discontinuation from study medication		
Subjects with event that resolved on or prior to discontinuation from study medication		
Subjects with event that resolved after discontinuation from study medication		
Subjects with event that persisted after discontinuation from study medication		
Study Disposition subsequent to discontinuation from study medication		
Completed		
Withdrew		
Adverse event		
Lost to follow up		
Other		
Withdrawal of consent		

12. Include a chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

Sponsor’s pre-meeting response: we will provide.

13. For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” “other,” or similar reasons, the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In

addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

Sponsor's pre-meeting response:

We reviewed these terms prior to the database locks to minimize these types of discrepancies. The verbatim reasons will be provided in the listings.

14. In your long-term studies please evaluate if lowering LDL-C with alirocumab led to changes in vitamin E levels. In your submission, you should include results for total vitamin E (without normalizing to plasma lipid), including appropriate reference ranges.

Sponsor's pre-meeting response: we will provide this for the LONG TERM study.

15. Based on your proposed indication, please specify your definitions for primary hypercholesterolemia and mixed dyslipidemia when you submit the BLA. You will need to ensure that a reasonable number of subjects with each of these definitions are enrolled in trials intended to support each claim. Ensure that you submit data specifically supporting the use of your drug in each of these populations, including descriptive data for the populations themselves (i.e., demographics, baseline characteristics, etc.).

Sponsor's pre-meeting response: we will provide in the BLA

16. As part of your BLA, please include a justification for each lipid parameter that you intend to list in your indications. For each, you should justify why you believe that drug-induced changes in the parameter are clinically meaningful.

Sponsor's pre-meeting response: we will provide in the BLA

17. Please provide key safety analyses by eGFR tertiles. Although it is difficult to make a specific request at this time given that we do not know the distribution of eGFR in your trials, consider using eGFR cutpoints that are commonly used in clinical practice (e.g., <30, 30-60 [or 30-45 and 45-60],  $\geq 60$  mL/min/1.73m<sup>2</sup>).

Sponsor's pre-meeting response: we will provide in the BLA

18. Laboratory values from narratives should be included in your submitted datasets. If a reviewer wanted to independently tabulate peak ALT or creatinine values, for example, this should be possible from using the laboratory dataset alone (e.g., LB.xpt) as opposed to some values only appearing in a narrative describing results obtained during a hospitalization.

Sponsor's pre-meeting response:

All central lab data are included in the datasets. Investigators were instructed to include available local labs in the CRFs and as such are included in the datasets. In addition, during database reconciliation and medical review clinically relevant abnormal local lab values that were not in the clinical database were noted and queried, so that they could be included in the

clinical database. Based on this process the clinical database of laboratory values provided in the BLA will be adequate for Agency review.

### **Meeting Discussion**

**The sponsor restated their pre-meeting response.**

19. We would like you to submit additional data in your Adjudication Listing and the related datasets. We recognize that these data are exploratory for your lipid-lowering phase 2/3 trials, but our comments should be applied to your ongoing cardiovascular outcome trial as well. Your CEC charter states that two CEC adjudicators will independently review each complete endpoint event. If the adjudicators agree, then the adjudication of the potential endpoint event is considered complete. If they disagree, the adjudicators will discuss the potential endpoint event at a moderated CEC meeting (Phase II review comprised of at least 3 CEC physician members) until they come to consensus. Please submit the following information in addition to the event description as reported by the investigator:
- a. Date of adjudication by adjudicator #1 along with the event description that the adjudicator reports (which may or may not be the same as what the investigator reported, especially if the adjudicator assigns a subcategory to an event, such as cause of death)
  - b. Same information as above for adjudicator #2
  - c. Final event categorization along with date of final adjudication
  - d. Listing of who made the final adjudication decision (i.e., Phase I review; Phase II review consensus)
  - e. How the potential endpoint event was identified and referred for adjudication (i.e., Investigator, CEC, sponsor)

Sponsor's pre-meeting response: We propose to provide this additional information within the 30-day window post BLA submission. Does the Agency agree?

### **Meeting Discussion**

**The sponsor asked if they could provide the additional data related to the adjudication process within 30 days of the original BLA submission. FDA commented that this was acceptable.**

20. Please confirm that information on lipid values as well as any reference to patient lipid levels (eg, "high/low LDL", "lipid panel normal/abnormal", etc.) has been and will be redacted from the adjudication packages as this could unblind adjudicators to study treatment.

Sponsor's pre-meeting response: The lipid values were never provided in the adjudication packages, in order to prevent potential unblinding of the adjudicators.

21. The clinical information contained in the NDA/BLA 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

([www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf)). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

- a. Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
- b. Exposure-Response Relationships – important exposure-response assessments.
- c. Less common adverse events (between 0.1% and 1%).
- d. Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
- e. Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.

Sponsor's pre-meeting response: we will provide a - e

- f. Marked outliers and dropouts for laboratory abnormalities. Also provide the criteria used to identify marked outliers.

Sponsor's pre-meeting response:

Patients discontinuing for laboratory abnormalities would have an associated AE captured as the reason for discontinuation. Outliers are analyzed using the PCSA criteria as specified in the SAP.

- g. If there is a signal for abnormal laboratory or vital sign changes, please provide an analysis of persistence of the change (for example, percentage of individuals with 2 consecutive values > x or change in these parameters over time in the individuals that experienced the elevations).

Sponsor's pre-meeting response:

We have not identified any signals that would require this. We had pre-specified this type of analysis only for low LDL-C.

- h. Analysis of vital signs focused on measures of central tendencies.

Sponsor's pre-meeting response: we will provide

- i. Analysis of vital signs focused on outliers or shifts from normal to abnormal.

Sponsor's pre-meeting response:

Analysis of vital signs focused on outliers based on pre-defined PCSAs. We have not identified any signals in our data related to perturbations in vital signs.

- j. Marked outliers for vital signs and dropouts for vital sign abnormalities.

Sponsor's pre-meeting response: see response to comment (i) above.

- k. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

Sponsor’s pre-meeting response:

Vital signs and laboratory value analyses based on change from baseline to worst value will be included. In addition, listings will be provided separately for patients with laboratory or vital sign PCSAs. Tabulations as per this request will be provided combining hyperglycemia/diabetes and also hepatic disorders/liver function test abnormalities.

- l. Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- m. Standard analyses and explorations of ECG data.
- n. Overdose experience.
- o. Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.

Sponsor’s pre-meeting response: we will provide l - o

- p. Explorations for:
  - i. Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.

Sponsor’s pre-meeting response:

We can provide this type of analysis of early treatment discontinuation, with the exception of analysis by study site.

- ii. Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.

Sponsor’s pre-meeting response:

We do not have “average dose” in our analyses. However, please see our response to your comment (iii) below, which we think is more applicable to alirocumab.

- iii. Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.

Sponsor’s pre-meeting response: we will provide

- iv. Drug-demographic interactions

- v. Drug-disease interactions
- vi. Drug-drug interactions
- vii. Dosing considerations for important drug-drug interactions.
- viii. Special dosing considerations for patients with renal insufficiency and patients with hepatic insufficiency.

Sponsor's pre-meeting response: we will provide iv - viii

**CDRH Human Factors Study Advice:**

We understand that you are planning to use two device configurations (prefilled syringe and autoinjector) for the combination product. However, the meeting package does not include a systematic evaluation of use-related risks, a determination of the necessity of human factors validation and, if necessary, how you would undertake the human factors validation. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users.

Please note that a comprehensive risk analysis should include a comprehensive evaluation of all the steps involved in using your product (e.g., based on a task analysis or known problems), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the device).

Based on this use-related risk analysis, you will need to determine whether you need to perform human factors validation study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use. The risk analysis can be used to inform the design of a human factors validation study protocol for your product.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

To ensure your approach and methodology are acceptable, please submit your risk analysis and study protocol (if applicable) for review prior to study implementation for Agency review and

comment. Please note that we will need 60 days to review and provide comments on your study risk analysis and protocol under the IND.

### **CDRH Device Testing Advice**

1. Please provide the following information so that CDRH may determine if the Alirocumab PFS is safe for its intended use in the future marketing application:
  - a. As you have indicated the needle is staked, please provide clarification on whether your testing you have conducted is in conformance to the ISO standard for staked needles (ISO 9626) for the pre-filled syringe and for ISO 11608-2 for the pre-filled pen.
  - b. As there appears to be a needle stick protection device, please provide performance data demonstrating the reliability of the safety mechanism as recommended in the FDA Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features:  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>
  - c. Please provide clarification on whether the dose accuracy testing you have conducted is according to ISO 11608-1 Needle-based injection systems for medical use — Requirements and test methods— Part 1: Needle-based injection.
  - d. Please ensure your testing addresses the following considerations brought up in the below guidance:  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>

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#### **Sponsor's pre-meeting response:**

The alirocumab configurations include a prefilled syringe and a prefilled pen. The prefilled syringe is not offered with a needle-stick protection device.

The prefilled syringe has been designed and tested according to the following:

- ISO 9626 “Stainless steel needle tubing for the manufacture of medical devices”
- Dose Accuracy - USP 35 <1> “Injections/General requirements”. The specification used is: volume  $\geq$ 1ml
- ISO 11040-4 Prefilled syringes -- Part 4: Glass barrels for injectable

The Prefilled Pen with a needle shield has been designed and tested according to the following:

- ISO 11608-1 Needle-based injection systems for medical use. Part 1: Needle-based injection
- ISO 11608-5 Needle-based injection systems for medical use. Part 5: Automated functions

Consistent with the Scope of ISO 11608-2, the sponsor does not consider it applicable for Prefilled Pen.

Sponsor's follow-up question:

Does the FDA agree with the sponsor's strategy for PFP and PFS performance testing?

### **Meeting Discussion**

The sponsor explained that the prefilled syringe was a well-established platform and was tested under ISO11040 and not ISO11608. The prefilled pen (PFP) was tested using ISO11608.

FDA commented that the pen shield cover would require needle stick testing. (b) (4)

FDA explained that the problem is that patients may think that it will prevent inadvertent needle sticks due to the fact that the activation of the shield will result in the covering of the needle. Bench testing would be helpful, but a simulated use study would be needed. The testing should include 500 devices and does not need to be done with the drug. Guidance on the needlestick prevention feature testing can be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071663.htm>.

FDA noted that home administration of injections does not require a shield but since the device includes one, it could cause confusion for patients. They may make the assumption that they are protected from needle sticks.

FDA commented that the sponsor should assume they need an appropriate study. The sponsor queried if this could be submitted during the BLA review. The Agency requested that the company provide a rationale and timeframe prior to BLA submission and the Agency would respond. The company agreed to provide timing for submission of a clinical needle stick study in a patient population.

The company stated that they were applying ISO9626 to the PFS. FDA agreed that was acceptable.

### **Post-Meeting Comment**

As explained in an email exchange on September 30, 2014, and telephone call on October 1, 2014, we recommend providing the needle stick protocol for review prior to submission of the BLA. However, you may submit the study results during the first 30 days after submission of the original BLA, with or without prior submission/review of the protocol.

### **Office of Scientific Investigations Advice**

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

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

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

Sponsor's pre-meeting response: We will comply with the Agency's recommendations.

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

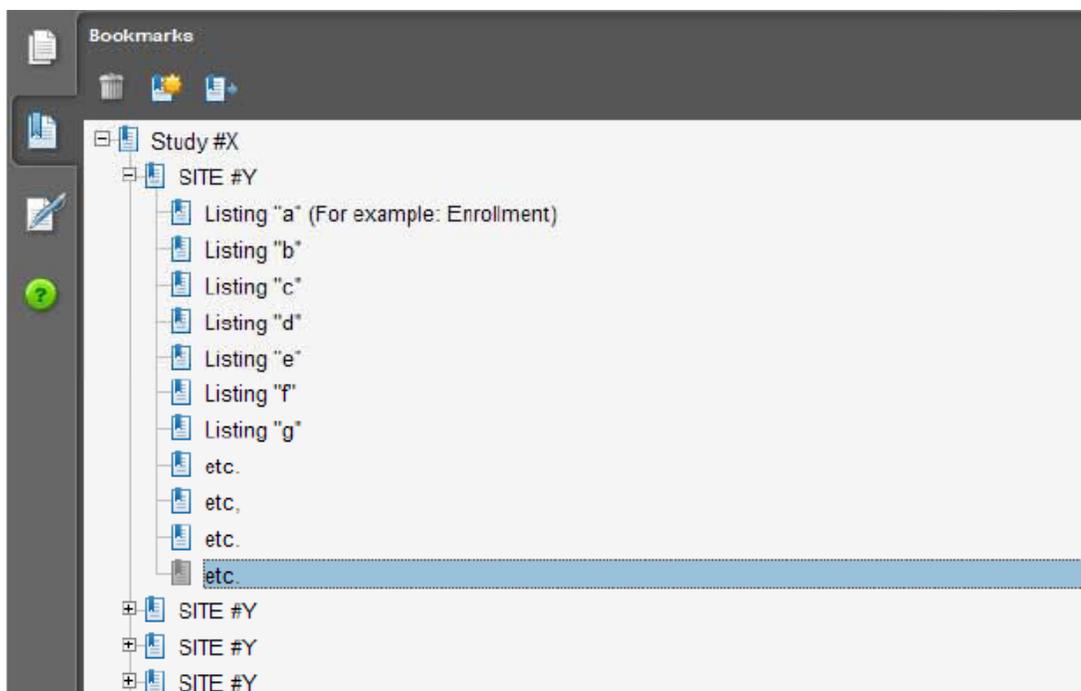
1. Please include the following information in a tabular format in the original NDA/BLA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal Investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA/BLA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued at each site
3. Please include the following information in a tabular format in the NDA/BLA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
  - b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format

previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.

- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial, provide the original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

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

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



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> ) for the structure and format of this data set.

#### Technical Instructions:

#### Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

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

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



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

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

References:

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

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

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

**Post-Meeting Comments**

CDRH expects the firm to provide a summary of its procedures (including copies of main procedures) describing how it will comply with the following Quality System Requirements:

1. Management Control, CFR 820.20
  - a. Confirming who the most responsible is and describing the relationship/responsibility with other contractors involved in the manufacturing of the combination product.
2. Design Control, General, CFR 820.30
  - a. Describing the procedure(s) used to control the design of the combination product (from conceptualization to design validation).
3. Production and Process Controls, 820.70
  - a. Describing the manufacturing process and controls to be used.
4. Purchasing Controls, 820.50
  - a. Describing the supplier qualification process and how the sponsor firm will control suppliers.
  - b. Listing copies of agreements with suppliers requiring notification and approval of changes before implementation
5. Receiving Acceptance Activities, 820.80(b)
  - a. Describing receiving tests planned to be performed on receiving parts to be used in combination product assembly.
6. Final Acceptance Activities, 820.80(d)
  - a. Describing final acceptance tests to be performed to ensure combination products meet set specifications before distribution.
7. Corrective and Preventive Action (CAPA), 820.100
  - a. Describing responsibility for CAPA controls over the combination product and the quality system.

In addition, please review the following guidance document on combination products:  
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm#perspectives>

### 3.0 Additional Important Information

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

- The content of a complete application was discussed.

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

- A preliminary discussion on the need for a REMS was not required since the FDA pre-meeting response to question #11, which explained the FDA position regarding the need for a REMS, was clear to the company. The pre-meeting comment stated that the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application component may be submitted within 30 calendar days after the submission of the original application:
  1. **It was agreed that the sponsor could provide the additional data related to the adjudication process within 30 days of the original BLA submission.**
  2. **It was agreed that the sponsor could provide a stability update with additional stability data within 30 days of the original BLA submission.**
  3. **In a post-meeting email exchange on September 30, 2014, and telephone conversation on October 1, 2014, it was agreed that results from the needle stick study could be submitted within 30 days of the original BLA submission.**

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

**BLA NUMBER: LATE COMPONENT - BIOMETRICS**  
**BLA NUMBER: LATE COMPONENT - CLINICAL**  
**BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY**  
**BLA NUMBER: LATE COMPONENT - NONCLINICAL**  
**BLA NUMBER: LATE COMPONENT - QUALITY**

## **PREA REQUIREMENTS**

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

**MANUFACTURING FACILITIES**

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

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

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

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

Corresponding names and titles of onsite contact:

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

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

**None**

**5.0 ACTION ITEMS**

**None**

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/s/  
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JAMES P SMITH  
10/02/2014



IND 105574

**SPECIAL PROTOCOL - AGREEMENT**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for SAR236553 for injection.

We acknowledge your request dated and received on May 24, 2012, for a special protocol assessment (SPA) of clinical protocol EFC11570, titled *A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of SAR236553/REGN727 on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced Coronary Syndrome*.

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as “**Special Protocol Assessment - Amendment**”. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

As stated on page 9 in the “Guidance for Industry: Special Protocol Assessment,” a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

We also have the following responses (**in bold**) to your questions.

1. Does the Agency agree that Study EFC11570, provided its objectives are met, will support approval of SAR236553 (b) (4)

**FDA Response: Study EFC11570, provided its objectives are met,** (b) (4)

- a. Does the Agency agree with the proposed patient population to be enrolled in the EFC11570 study?

**FDA Response: Yes, we agree.**

- b. Does the Agency agree with the proposed up-titration and down-titration scheme to be applied in the EFC11570 study?

**FDA Response: Yes, the up-titration and down-titration scheme appears reasonable.**

- c. Does the Agency agree with the choice of the primary endpoint and the secondary endpoints as described in the protocol and the supporting study documents?

**FDA Response: Yes, we agree.**

- d. Does the Agency agree with the definition of the primary endpoint and the secondary endpoints as described in the protocol and the supporting study documents?

**FDA Response: Yes, we agree.**

- e. Does the Agency agree that the statistical methods proposed for the study EFC11570 are appropriate? In particular:

- i. Does the Agency agree with the statistical analyses of the primary endpoint and secondary endpoints to form a basis for the approval of SAR236553 in this indication?

**FDA Response: Yes, we agree,**

- ii. Does the Agency agree with the proposed futility and efficacy interim analyses?

**FDA Response: We recommend that the trial go to completion to obtain sufficient long-term safety information. If the Data and Safety Monitoring Board (DSMB) and Sanofi feel it is imperative to stop the trial early for efficacy, we have the following comments:**

- **We agree that the 1<sup>st</sup> Interim Analysis should only be done as a futility assessment because stopping the trial after the 1<sup>st</sup> Interim Analysis will not provide adequate safety data.**
- **Stopping the trial after the 2nd Interim Analysis requires consistency of the effect on the primary outcome (p<0.0001) as well as highly significant results on other secondary endpoint outcome measures plus, at a minimum, directionally consistent effect on all-cause mortality. We note that you have stated in your SPA that early stopping of the study for overwhelming efficacy at the second Interim Analysis, will require overwhelming efficacy (p<0.0001) and (b) (4) for secondary efficacy endpoints, including all cause mortality. (b) (4)**

- f. Does the Agency agree that the proposed number and percentage of North American (US and Canadian) patients in Study EFC11570 is adequate?

**FDA Response: We would prefer that the North American percentage be closer to 30% but we are reassured with the limited number of more subjective major adverse cardiac event (MACE) components in the primary endpoint and with your intention to provide subgroup analyses of the primary efficacy endpoint in US vs. non-US countries.**

2. Does the Agency agree with the proposed list of pre-specified efficacy events that we ask to be waived from the expedited safety reporting (see [Section 10.4.3] of the protocol)?

Does the Agency grant the waiver from the expedited safety reporting requirements for the events listed in [Section 10.4.3] of the protocol?

**FDA Response: Yes, we do.**

You are 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). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this new clinical protocol. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to IND 105574 clinical protocol submitted on DATE, your clinical protocol number, if available, and that it contains the FDA Form 3674 that was to accompany that submission.

If you have already submitted the certification for this submission, please disregard the above. If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

*{See appended electronic signature page}*

Eric Colman, M.D.  
Deputy Director  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ERIC C COLMAN  
07/13/2012



IND 105574

**MEETING MINUTES**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova M.Sc.  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive  
Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SAR236553.

We also refer to the meeting between representatives of your firm and the FDA on May 9, 2012. The purpose of the meeting was an EOP2 CMC only meeting.

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

If you have any questions, call Joel Welch, Regulatory Project Manager at (301) 796-2017.

Sincerely,

*{See appended electronic signature page}*

Chana Fuchs, Ph.D.  
CMC Team Leader  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** End of Phase II, CMC Only  
**Meeting Date and Time:** May 9, 2012; 10:30 AM to 11:30 AM (EST)  
**Meeting Location:** NIH Campus Bld 29B, Conf. Room A/B  
**Application Number:** IND 105574  
**Product Name:** SAR236553/REGN727  
**Indication:** hypercholesterolemia  
**Sponsor Name:** Sanofi-Aventis  
**Meeting Chair:** Chana Fuchs  
**Meeting Recorder:** Joel Welch

**Office of Pharmaceutical Science**  
**Office of Biotechnology Products**  
**Division of Monoclonal Antibodies**

Sang Bong Lee, Ph.D. Quality Reviewer  
Chana Fuchs, Ph.D. CMC Team Leader  
Patrick Swann, Ph.D. Deputy Division Director  
Joel Welch, Ph.D. Regulatory Health Project Manager

**Office of Compliance**  
**Biotechnology Manufacturing Assessment Branch**

Candace Gomez-Broughton, Ph.D. Microbiology Reviewer  
Bo Chi, Ph.D. Microbiology Reviewer  
Patricia Hughes, Ph.D. Team Leader

**Sanofi-Aventis**

Rima Nassar, Ph.D. Sr. Director, Global Regulatory Affairs  
Nathan Tzodikov, Ph. D. Associate Director, Global Regulatory Affairs  
Helge Neidhardt, Ph. D. Senior Expert, R&D Biologics  
Andreas Staerk Department Head Biotherapeutics, Industrial Affairs  
Jean-Francois Hau Manager, Drug Product Clinical Manufacturing, Industrial Affairs  
Jana Bodorova Associate Director, Global Regulatory Affairs  
Laurence Goldenberg Project Director, Industrial Affairs

**Regeneron**

James P. Fandl, Ph.D. VP, Protein Expression Sciences  
Joel Martin, Ph.D. Director Molecular Biology, Bioassay & Protein Development Research  
(b) (4) Senior Director (b) (4) Manufacturing Operations  
Jennifer McNay, Ph.D. Senior Director Process Sciences

Kris Ghosh, Ph.D.  
Michele Lastro, Ph.D.  
Susan Barbaritz

Director CMC Regulatory Affairs  
Mgr CMC Regulatory and Process Sciences  
Assoc Mgr CMC Project Management

## 1.0 BACKGROUND

Sanofi-Aventis is developing SAR236553 for the treatment of hypercholesterolemia. On February 17, 2012, Sanofi-Aventis requested Type C CMC-only meeting with the FDA. The FDA granted that meeting on March 7, 2012. A clinical EOP2 meeting took place on February 21, 2012 and covered the clinical and non-clinical aspects of SAR236553.

SAR236533 is being developed as a lipid lowering treatment for patients with primary hyperlipidemia and mixed dyslipidemia. SAR236553 is a monoclonal antibody (mAb) with the proposed mechanism of action of binding human PCSK9 and blocking its interaction with the huLDLR, thereby decreasing the rate of huLDLR turnover and enhancing LDL-C clearance.

Manufacturing of SAR236553 has undergone a number of process changes throughout the clinical development program. (b) (4)

(b) (4)  
For the pivotal phase 3 studies, SAR236553 drug product in liquid formulation will be supplied in a prefilled syringe as well as (b) (4) syringe (b) (4) autoinjector device. For the proposed phase 3 studies, SAR236553 will be supplied at concentration of 75 and 150 mg/mL for subcutaneous injection to be administered once every 2 weeks.

## 2. DISCUSSION

### 2.1. CMC only Questions

#### **Sponsor Submitted Questions and FDA Response:**

**Question 1: Comparability tests and studies for change in cell line, manufacturing process and scale:**

**Does the Agency agree that based on the results of the analytical, nonclinical PK and human PK/PD comparability studies, the clinical materials produced using processes (b) (4) are comparable and that additional studies are not required to bridge drug substance used in Phase 1 and Phase 2 with material that will be used in Phase 3 studies and for commercialization?**

*FDA Preliminary Response:*

*Overall, minor differences in the levels of the [REDACTED] (b) (4)*

*However, the analytical data appear to be sufficiently comparable in conjunction with the non-clinical PK for use of the product in phase 3 clinical trial. Barring any further changes to manufacturing or new information that would raise a concern, further non-clinical characterization will not be required.*

*We also note that you have conducted a PK/PD bridging study between products manufactured using processes [REDACTED] (b) (4). You indicated that the pivotal phase 3 trials will be conducted with the final to-be-marketed product manufactured using process [REDACTED] (b) (4). Based on this, no additional PK/PD comparability studies are required at this point provided analytical and nonclinical comparability is established. Acceptability of the results of the PK/PD study however, is a review issue.*

*We note that CHO cell host cell proteins (CHOP) are assessed using the [REDACTED] (b) (4), and that an amendment to your IND stated that [REDACTED] (b) (4)*

*The anti-HCP antiserum needs to be qualified for its ability to detect potential HCP impurities in your cell lines. The BLA should include data demonstrating that the CHOP assay can detect the majority of proteins present in your CHO cell extract. [REDACTED] (b) (4)*

*This assessment should include 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis (or another similarly sensitive assay) using the antiserum employed in the assay. Please provide these data which can be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum. It is the agency's experience that analysis of HCP coverage by a [REDACTED] (b) (4) is not sufficiently sensitive for this purpose.*

Additional Discussion During Meeting:

There was no further discussion during the meeting.

**Question 2: Cell Line Genetic Stability:**

**Does the agency agree that the proposed cell line characterization testing [REDACTED] (b) (4)**

**[REDACTED] (b) (4) is adequate to demonstrate genetic stability of the sponsor's cell line and support the manufacture and use in production of subsequent Working Cell Banks? Does the agency agree that the procedure for [REDACTED] (b) (4), such that in the future, additional WCBs can be implemented, based on an established procedure, and that the Agency can be notified in an Annual Report?**

*FDA Preliminary Response:*

*Based on the high level information provided in the meeting package, and the stated efficiency of* (b) (4)

*Regarding additional WCB implementation, introduction of new WCBs should be done in a timely manner with the information on the WCB and resulting antibody product submitted as an amendment to the IND. The mechanism for reporting of any changes to a WCB after approval of a BLA will be dependent on the approval status of protocols for implementation of new WCBs and can be part of the BLA review. Please note that lots from new WCB should be placed on stability.*

**Additional information provided by Sponsor prior to the meeting:**

(b) (4)

We confirm that we will place the first lot from each new WCB on stability.  
Does the Agency concur with this approach?

**Additional Discussion During Meeting:**

*The Agency stated that this strategy was acceptable as long as the conditions for manufacturing of a new WCB do not significantly deviate from those currently employed and are consistent with the current control strategy. An example given* (b) (4)

(b) (4)

*FDA clarified that for any post-approval changes to the WCB a protocol for qualification of new WCBs can be submitted and approved within the BLA.*

**Question 3: Bio-assay Testing Procedure Suitability:**

**Does the Agency agree that the HepG2 cell based bioassay satisfies the Agency's requirements for a relevant and appropriate procedure to assess the biological activity of SAR236553 for release testing?**

*FDA Preliminary Response: The HepG2 cell based bioassay may be appropriate as a potency assay for SAR236553 release testing, though it is not clear whether or how the differences in SAR236553 binding to normal PCSK9 as compared to the PCSK9 gain of function mutant (b) (4) (reported IC<sub>50</sub> values of (b) (4), respectively) and (b) (4) PCSK9 mutant impacts the relevance of this bioassay. The BLA should include data regarding this point in support of use of this assay format as a lot release assay.*

*Please note that based on the protocol in the appendix, validation data should be provided to support the variability allowed by the assay. For example; robustness studies should address (b) (4)*

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(b) (4)



### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

### **4.0 ACTION ITEMS**

There were no outstanding action items.

### **5.0 ATTACHMENTS AND HANDOUTS**

The Sponsor provided a written document prior to the meeting to guide the discussion. That handout is presented as an attachment.

IND105574  
EOP2 (CMC) – Scheduled on 9 May 2012  
Sponsor pre-meeting responses (8 May 2012)

## IND 105574

### SAR236553 (REGN727) End of Phase 2 (CMC) Meeting Scheduled 9 May 2012 Sponsor Pre-Meeting Responses

We would like to thank the Agency for their feedback. Our comments to the Agency's draft responses are included below. We would like to focus our discussion tomorrow on Questions 2 and 6, and would welcome further feedback on Questions 5, 4 and 3 (in order of priority). We have no further comments on Question 1.

#### **Priority Discussion Topics: (Q2 and Q6)**

#### **Question 2: Cell Line Genetic Stability**

##### **Sponsor clarifications:**

We would like to clarify the information regarding (b) (4) is intended for all current and future WCBs (results to be provided in IND amendments); whereas the tests (b) (4) are intended to be performed once on a single WCB to confirm the cell line stability and will be provided in the BLA.

We confirm that we will place the first lot from each new WCB on stability.

*Sponsor follow-up question: Does the Agency concur with this approach?*

#### **Question 6: Excipient concentration in Drug Substance and Formulated Drug Substance**

##### **Sponsor clarification:**

The histidine monitoring data available to date indicate that the (b) (4) manufacturing process achieves consistent histidine levels. Please note that the histidine level is expected to be higher for the 75 mg/mL formulation compared to the 150 mg/mL formulation due to the (b) (4). We routinely measure pH for both 150 and 75 mg/mL formulations. The available batch release and stability data (both real time and accelerated) indicate that pH remains constant at observed histidine concentrations. Proven Acceptable Range (PAR) studies determining (b) (4) range of histidine concentrations in relation to other parameters as noted by the Agency will be conducted and included in the BLA.

IND105574  
EOP2 (CMC) – Scheduled on 9 May 2012  
Sponsor pre-meeting responses (8 May 2012)

(b) (4)

*Sponsor follow-up question: Does the Agency agree that the proposed approach to histidine control and batch release is acceptable?*

**Additional Discussion Topics (Q5, Q4, and Q3)**

**Question 5: Manufacturing Process Validation Strategy**

**Sponsor clarifications:**

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IND105574  
EOP2 (CMC) – Scheduled on 9 May 2012  
Sponsor pre-meeting responses (8 May 2012)

- i. At the time of briefing package finalization, the design validation studies of the auto-injector were not complete. These design validation studies are now complete and will be submitted in an IND amendment. These studies show that the auto-injector assembly (b) (4). The assembly process controls will be submitted in the BLA. Sterility testing is a component of specifications of DP in the auto-injector.
- ii. Container closure integrity testing and the worst case scenario of impact conditions will be incorporated in the auto-injector process validation, which will be provided in the BLA.

We acknowledge the Agency's general comments for the DS and DP manufacturing strategy at time of BLA submission.

**Question 4: Introduction of** (b) (4)

**Sponsor clarification:**

(b) (4)

**Question 3: Bio-assay Testing Procedure Suitability**

**Sponsor clarification:**

The equilibrium dissociation constants for the interaction between SAR236553 and human PCSK9 or GOF PCSK9 (b) (4) are similar (KD of ~1.8 nM and (b) (4) nM, respectively at 37° C and pH 7.2). The increased affinity of GOF PCSK9 (b) (4) for LDLR (b) (4) nM compared to PCSK9 (169 nM) decreases the theoretical bottom of the assay and allows for more sensitive detection of PCSK9 activity. Data supporting the use of GOF PCSK9 (b) (4) in this assay will be included in the BLA.

**No further comments on Question 1: Comparability tests and studies for change in cell line, manufacturing process and scale**

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/s/  
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CHANA FUCHS  
06/28/2012



IND 105574

**MEETING MINUTES**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SAR236553.

We also refer to the meeting between representatives of your firm and the FDA on February 21, 2012. The purpose of the meeting was to discuss the clinical data obtained through Phase 2 and to discuss the planned Phase 3 clinical program and nonclinical program to support the registration of SAR236553 in the proposed indications.

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

If you have any questions, call me at (301) 796-1940.

Sincerely,

*{See appended electronic signature page}*

Raymond Chiang, MPT, MS, MS  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** February 21, 2012; 2:00-3:00PM EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1417  
Silver Spring, Maryland 20903

**Application Number:** 105574  
**Product Name:** SAR236553  
**Proposed Indication:** In combination with or without a statin as adjunct therapy to diet for the reduction of elevated low density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), non-high density lipoprotein cholesterol (non-HDL-C), total cholesterol (total-C), triglycerides, and lipoprotein(a) [Lp(a)], and to increase HDL-C and apolipoprotein A1 (Apo A1) in patients with primary (heterozygous familial and non-familial) hyperlipidemia and mixed dyslipidemia.

**Sponsor/Applicant Name:** Sanofi-Aventis

**Meeting Chair:** Eric Colman, M.D.  
**Meeting Recorder:** Raymond Chiang

**FDA ATTENDEES**

**Office of Drug Evaluation II**

Eric Colman, M.D.	Deputy Director, Division of Metabolism and Endocrinology Products (DMEP)
Raymond Chiang, MPT, MS, MS	Regulatory Project Manager, DMEP
Eileen Craig, M.D.	Clinical Reviewer, DMEP

**Office of Clinical Pharmacology**

Immo Zadezensky, Ph.D.	Clinical Pharmacology Reviewer
Jayabharathi Vaidyanathan,	Clinical Pharmacology Team Leader
Jingyu Yu	Pharmacometrics Reviewer

**Office of Biometrics**

J. Todd Sahlroot, Ph.D.  
Japobrata Choudhury

Deputy Director, Division of Biometrics II (DBII)  
Biostatistics Reviewer

**Center for Devices and Radiological Health**

Jaqueline Ryan  
Quynh Nhu Nguyen

Combination Products Team Leader  
CDRH reviewer

**Office of Surveillance and Epidemiology**

Carlos Mena Grillasca  
Reasol Agustin, Pharm.D.

OSE team leader (DMEPA)  
OSE Safety Evaluator (DMEPA)

**SPONSOR ATTENDEES**

**Sanofi**

Alan Kerr, BSc (hons)

Vice President, Head of Diabetes R&D Regulatory  
Affairs, Global Regulatory Affairs

Jana Bodorova, MSc  
Galina Hesse, MSc,

Associate Director, Global Regulatory Affairs  
Head of Projects Department, Diabetes Division  
Research & Development

Anusch Peyman, PhD

Project Director - SAR236553 Program, Diabetes  
Division

Laurence Bessac, MD

Associate Vice President, Clinical Development,  
Diabetes Division

Corinne Hanotin, MD  
Aurelie Brunet, PharmD

Clinical Development, Diabetes Division  
Drug Disposition Expert, Disposition Safety and  
Animal Research (DSAR)

Jacques Rey, PhD

Director, Clinical Investigations, Clinical and  
Exploratory Pharmacology

Christelle Lorenzato, MSc  
Ingo Stammberger, DVM, PhD,

Biostatistics  
Preclinical Safety Expert, Disposition, Safety and  
Animal Research (DSAR)

Serpil Heger  
Helge Neidhardt, PhD

Global Device Leader, Medical Devices  
Senior Expert, R&D Biologics

**Regeneron Pharmaceuticals, Inc**

Ned Braunstein, MD  
Mary Alice Raudenbusch,  
Bill Sasiela, PhD

Executive Director and Head, Regulatory Affairs,  
Senior Director, Regulatory Affairs  
Vice President, Program Direction, Cardiovascular  
& Metabolism Therapeutics

Robert Porody, MD

Head, Cardiovascular & Metabolism Therapeutics

## 1.0 BACKGROUND

SAR236533 is being developed as a lipid lowering treatment for patients with primary (heterozygous familial and non-familial) hyperlipidemia and mixed dyslipidemia (also designated as Frederickson Type IIa and IIb dyslipidemia). SAR236533 is also referred to as REGN727. SAR236553 is a monoclonal antibody (mAb) with the proposed mechanism of action of binding human PCSK9, preventing it from binding to the LDLR, leading to increased LDLR numbers, enhanced LDL-C clearance and, thus, lower levels of plasma LDL-C.

SAR236553 drug product is supplied in ready-to-use liquid formulations. The liquid formulation for SAR236553 will be supplied ready-to-use at concentration of 75 and 150 mg/mL for subcutaneous (SC) injection in the proposed Phase 3 studies. For the long-term safety study SAR236553 drug product in liquid formulation is supplied in prefilled syringes. For the pivotal Phase 3 studies, SAR236553 drug product in liquid formulation will be supplied as a drug-device combination product consisting of the liquid drug product (b) (4) prefilled syringe (b) (4) autoinjector. SAR236553 is to be administered subcutaneously once every 2 weeks.

SAR236553 is currently in the Phase 2 stage of the clinical development. Among the Phase 2 studies only the DF11566 study has been completed, the two other studies (DF11565 and R727-CL-1003) are still ongoing. A long-term safety study (LTS11717) is planned to start in the near future.

The purpose of the requested meeting was to present the clinical data obtained with SAR236553 through Phase 2 and to discuss the planned Phase 3 clinical program and the nonclinical program to support the registration of SAR236553 in the proposed indications.

## 2.0 DISCUSSION

Your questions are repeated below, followed by FDA's response in **bold** print and discussion in *italics*. The sponsor's pre-meeting responses appear in *underlined italics*. The sponsor's post-meeting comments appear in ***bold, underlined italics*** and FDA's responses regarding the sponsor's post-meeting comments appear in ***bold italics***.

### NonClinical

1. The sponsor has conducted several subchronic and chronic toxicology studies in rats and monkeys of up to 26 weeks in duration (followed by up to 16 weeks of recovery). The no observed adverse effect dose level (NOAEL) was established at 50 mg/kg/week (SC) in the 13-week and the 26-week rat studies and at 75 mg/kg/week in the 13-week (IV and in the 26-week (SC) monkey toxicity studies, the highest dose levels examined in both species. In addition, the sponsor has conducted a 5-week and a 13-week toxicology study of SAR236553 in combination with atorvastatin in cynomolgus monkeys (each with an 8-week recovery period). There have been no significant additive or synergistic toxicologic effects of SAR236553 when administered in combination with atorvastatin for up to 13 consecutive weeks. Moreover, the sponsor plans to conduct a second 13-week

combination toxicology study of SAR236553 in combination with atorvastatin in cynomolgus monkeys to evaluate, in parallel with the proposed Phase 3 studies, the additional endpoints requested by the Agency in the letter of July 7, 2011.

Does the Agency agree that the subchronic and chronic toxicology studies in rats and monkeys with SAR236533, together with the reproductive and developmental toxicity program described below in Question 2, and in the absence of any other unexpected findings, are sufficient to support the BLA submission and evaluation?

**FDA Preliminary Response: Your current nonclinical program appears appropriate to support Phase 3 clinical trials per ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Based on an Advice letter sent to you on 7 July 2011 outlining additional information needed to assess immune and related carcinogenicity concerns, a three month combination toxicology study with immune and bile acid end-points was recommended. We acknowledge your 11 October 2011 response that outlined plans to conduct this second 13-week toxicology study in monkeys with SAR236553 in combination with atorvastatin to evaluate immune and bile acid endpoints. The thorough carcinogenicity assessment is needed for review by the expanded Executive Carcinogenicity Assessment Committee (ECAC) as this is a biologic intended for chronic use and minimally there are theoretical concerns for tumorigenicity in combination with statins as outlined in the advice letter mentioned above. We recommend you complete this assessment as soon as possible to avoid potential regulatory delay if it is determined that carcinogenicity studies will be required following review by the expanded ECAC for biologic products. Any unexpected findings may necessitate further toxicology testing.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

2. The sponsor has evaluated reproductive and developmental toxicity of SAR236553 in an embryo-fetal toxicity study in rats and during a pre- and post-natal embryo-fetal development study in monkeys. In addition, the sponsor has performed comprehensive fertility assessments (conducted as part of the 26-week chronic toxicity study in monkeys). The study in rats demonstrated maternal toxicity (mortality, clinical signs, and pale liver) at the 75 mg/kg/dose (maternal NOEL=15 mg/kg/dose) and no effects on fetal growth or development at any dose (embryofetal NOEL= 75 mg/kg/dose; highest dose in study). The study in monkeys demonstrated non-adverse reductions in LDL-C, total-C and triglyceride levels in maternal animals, and no drug-related changes in infants (maternal and embryofetal NOEL=75 mg/kg/dose). In the reproductive function assessment in mature monkeys (conducted as part of the 26-week chronic toxicity study in monkeys), no adverse effects on fertility and toxicity endpoints were evident.

Does the Agency agree that the embryofetal toxicology studies in rats and monkeys combined with the comprehensive fertility assessments are sufficient to support the evaluation of embryofetal toxicity in the envisioned BLA submission?

**FDA Preliminary Response: The currently available reproductive toxicology program appears appropriate to support Phase 3. The program may support marketing, pending data from your to-be-completed ePPND monkey study and if no additional safety concerns arise prior to submission of the marketing application.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

### Clinical

3. Based on the results of the Phase 2 trials, the sponsor plans to evaluate 2 dosing regimens of SAR236553 in the proposed Phase 3 program: 75 mg and 150 mg to be administered subcutaneously every 2 weeks.

Does the Agency agree with the proposed Phase 3 dosing regimens?

**FDA Preliminary Response: These two dosing regimens appear to be reasonable for your proposed Phase 3 program.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

4. The initial BLA will include results from the SAR236553 clinical development program to support use of SAR236553 in patients with primary (heterozygous familial and non familial) hyperlipidemia and mixed dyslipidemia in combination with diet and statins (with or without other lipid modifying therapy), or in patients for whom statins are considered inappropriate or not tolerated, to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-HDL-C, apolipoprotein B (Apo B), Lp(a) and triglycerides (TG), and to increase HDL-C and Apo A1.

In addition, the sponsor proposes to conduct Phase 3 clinical studies to obtain data to support the specific claims of superiority versus ezetimibe and versus statin up-titration on these lipid parameters in the Clinical Studies section of the labeling.

Does the Agency agree that the design of the proposed Phase 3 program supports the proposed LDL-C lowering indications and the additional claims?

Specifically, does the Agency agree with the:

- a) General study designs
- b) Patient populations
- c) Ezetimibe superiority efficacy claim
- d) Superiority to statin up-titration

**FDA Preliminary Response:** The decision to approve SAR236553 for the proposed indications will be based on the direction and magnitude of drug-induced changes in not only LDL-C, but other lipoprotein lipid parameters and markers of cardiometabolic risk (e.g., hsCRP, blood pressure), as well as evidence for off-target toxicities. If the data that you propose to include in your BLA submission raise concern about SAR236553's <sup>(b) (4)</sup> safety, results from a completed cardiovascular outcomes trial (CVOT) may be required prior to approval. The results of IMPROVE-IT may also influence the decision on whether the CVOT needs to be completed prior to approval.

You state that a CVOT (EFC11570) that evaluates the first occurrence of CHD death, NFMI, ischemic stroke, and unstable angina requiring hospitalization of SAR236553 compared to placebo when added to statin-treated (atorvastatin 80 mg) subjects with residual hyperlipidemia will be initiated during Phase 3 and will be ongoing at the time of the BLA submission. We agree with this approach; however, a minimum of 50% of the major adverse cardiac events from the CVOT must be accrued prior to application submission.

*a) General study designs*

We have the following concerns with the protocol for Study R727-CL-1119

- Statins are generally contraindicated in women who are pregnant or may become pregnant, nursing mothers, and patients who have active liver disease, which may include unexplained persistent elevations in hepatic transaminases. Define the population you refer to as “statin inappropriate” and compare that to your definition of “statin intolerant”
- Provide literature references that support your definition of statin intolerance
- Provide your definition and the references that support your definition of skeletal muscle-related symptoms
- Re-challenge the subjects in a blinded manner with the statin and dose that led to previous withdrawal or intolerance
- Recommend assessing the rate of withdrawal of SAR236553 vs. ezetimibe for skeletal muscle-related symptoms
- There is a concern that the sample size (n=50 for the ezetimibe arm and the SAR236553 arm) is insufficient to assess withdrawal rates and other safety differences between the 2 treatment arms
- Consideration should be given for adding an arm that includes a statin less likely to cause skeletal muscle-related symptoms such as lower doses of pravastatin or fluvastatin

*b) Patient populations*

You state that the study populations will consist of patients with non-familial and heterozygous familial hypercholesterolemia with a) LDL-C >70 mg/dL and history

of MI or ischemic stroke or b) LDL-C > 100 mg/dL without history of MI or ischemic stroke. All patients will be on a maximum tolerated dose of statin [simvastatin (we discourage initiation of 80 mg simvastatin because of concerns about myotoxicity), atorvastatin and rosuvastatin] with the exception of 4 studies: 2 studies (monotherapy, statin intolerance) where patients will not be on any statin and 2 studies where SAR236553 will be added-on to submaximal doses of atorvastatin or rosuvastatin. In placebo-controlled studies, patients are expected to be receiving intensive background therapy, including a maximum tolerated dose of statin with or without other lipid-modifying agents.

In general, we agree that this is an appropriate patient population. Please provide information on how people with nonfamilial hypercholesterolemia or mixed dyslipidemia will be identified and defined. Please refer to our comments regarding specific protocols.

*c) Ezetimibe superiority efficacy claim*

*d) Superiority to statin up-titration*

Protocols EFC11569, EFC11716, R727-CL-1110, and R727-CL-1118 explore LDL-C lowering of SAR236553 vs. ezetimibe or vs. statin up-titration. While this would be a review issue, statistically significant and clinically meaningful improvements in lipid parameters may be allowed to be described in the clinical trials section of the label. However, we would not consider adding these data to the labeling until the CVOT was completed and provided a very robust assessment of the long-term safety and efficacy profiles of SAR236553.

Sponsor's Response emailed on February 20, 2012:

Topic 1

1a) Can the FDA comment on their request for the accrual of 50% CVOT primary endpoints at the time of the initial submission and the basis for this requirement?

We would like to clarify that we plan to start this study in Q4 2012. At the time of our proposed BLA submission in Q4 2014, the CVOT will be approximately 50% enrolled. This study will have a DSMB reviewing the unblinded safety data on a regular basis.

The following table shows the expected percent of events and patients enrolled over time, based on the assumptions used for the sample size calculation:

Date	Expected % events	N patients enrolled
Q4 2014 (planned date of initial BLA submission)	10% to 15%	~9 000 pts (50% enrolment)
Mid-2015	~25%	12 000 pts

		(2/3 of enrolment)
End-2015	~35%-40%	16 000 pts
Mid-2016	50%	18 000 pts
Q2 2018 (Study end date)	100%	18 000 pts

Note: total events = 1613

1b) Can the FDA elaborate on the impact of the IMPROVE-IT trial on whether the CVOT needs to be completed prior to approval?

Topics 2 and 3

2) FDA comments on protocol R727-CL-1119:

Sponsor response (to discuss d-f):

- (a) We recognize that “statin inappropriate” and “statin intolerant” have different connotations and propose to focus on statin intolerant patients only.
- (b) We will provide the literature sources supporting our definition of statin intolerance after the meeting. Of note, our definition was developed in consultation with an external expert panel.
- (c) We will provide skeletal muscle related symptoms definitions and references after the meeting.
- (d) A re-challenge with statin was considered and discussed within Regeneron/Sanofi, with our Phase 3 program steering committee and with the external expert panel on statin intolerance. At the end of the process we concluded not to include this element for the following reasons:
- We are concerned that Ethics Committees would not accept a re-challenge, knowingly inducing adverse events in patients.
  - We are concerned that including this element could discourage patients with more severe statin intolerance from participating in the trial and bias the patient population in the trial.
  - We are proposing to use clinical sites for this trial that are knowledgeable and skilled in understanding the aspects of statin intolerance and able to

identify appropriate patients for this trial. This includes a number of the participants from the statin intolerance external expert panel.

- (e) Assessment of skeletal muscle related withdrawal rates between SAR236553 and ezetimibe. We will assess the rate of withdrawal due to skeletal muscle related symptoms with SAR236553 and ezetimibe in our overall program, which includes 5 studies that use ezetimibe as a comparator.
- (f) Sample size. Study R727-CL-1119 is designed and powered to show LDL-C efficacy of SAR236553 versus ezetimibe in patients with statin intolerance. For withdrawal rates and other safety differences, please see point 5 above.
- (g) Addition of a pravastatin or fluvastatin arm. Introduction of pravastatin or fluvastatin would increase the complexity of this study and we do not see them adding to our understanding of the benefit of SAR236553 in statin intolerant patients. These statins are also known to cause some degree of muscle toxicity and this trial may already include patients that have failed treatment with these statins.

3) Patient populations:

- a. FDA request regarding identification and definition of patients with nonfamilial hypercholesterolemia or mixed dyslipidemia:

Sponsor response:

Nonfamilial hypercholesterolemia refers to patients with primary hypercholesterolemia that are not defined to have familial hypercholesterolemia. These are the patients with the more common/traditional hypercholesterolemia that is also referred to as being polygenic in origin. This is a subset of the older Frederickson Type II classification that excludes those with familial hypercholesterolemia.

Mixed dyslipidemia would be any patient with both elevation in LDL-C, as defined in our protocols, and additional TG elevations; previously termed Frederickson Type IIb. We would use a cut-off of TGs >150 mg/dL based on the following points:

- TGs >150 mg/dL are part of the ATP III definition of metabolic syndrome
- TGs 150-199 mg/dL are considered borderline high by ATP III
- Many patients in the REGN727/SAR236553 program will be coming into the trial on statins and therefore those with TGs > 150 mg/dL most likely had TGs > 200 mg/dL on an untreated basis.

Sponsor follow-up question:

Do you agree with the above definitions?

- b. Sponsor's follow-up question:

You stated that we are studying an appropriate patient population for the indications we are seeking. As we informed you, we might adjust the inclusion criteria for some studies

based on new ATP guidelines for patients who qualify for lipid lowering therapy to get their LDL-C below 70 or 100 mg. We would like to confirm that this would be acceptable.

Sponsor's follow-up question:

You stated that we are studying an appropriate patient population for the indications we are seeking. As we informed you, we might adjust the inclusion criteria for some studies based on new ATP guidelines for patients who qualify for lipid lowering therapy to get their LDL-C below 70 or 100 mg. We would like to confirm that this would be acceptable.

*Discussion at meeting: Regarding question 1a emailed to FDA on February 20, 2012, FDA stated that several developments have formed the basis for their request for the accrual of 50% CVOT primary endpoints at the time of the initial submission.*

*FDA stated that the goal of lipid lowering therapy is cardiovascular disease risk reduction. SAR236553 is a new molecular entity that provides a novel mechanism for potentially profound LDL-C lowering. This Division's experience with drugs that induce favorable changes in lipid parameters, such as increasing HDL-C and decreasing LDL-C with torcetrapib in the ILLUMINATE trial, increasing HDL-C with niacin in the AIM-HIGH trial and decreasing triglycerides and increasing HDL-C with fenofibrate as demonstrated in the ACCORD-Lipid trial, is that these changes do not always translate into the expected CV benefit when tested in controlled clinical trials.*

*Furthermore, FDA stated that their experience with Vytorin (approved 2004) and Zetia (approved 2002) and the prolonged length of time, over 10 years, from product approval to the results of the CV outcome trial IMPROVE-IT, compel them to shorten that time period from approval based on a valid, yet still a surrogate, biomarker and the gold-standard of CV outcome.*

*FDA appreciated the additional information provided in the table. However, FDA needed more internal discussion before we can provide definitive answers regarding the 50% event accrual versus a different threshold requirement.*

*Regarding question 1b emailed to FDA on February 20, 2012, FDA stated that if the IMPROVE-IT trial shows no CV benefit with additional LDL lowering with ezetimibe as compared to simvastatin monotherapy, that result would make us re-consider the approval of novel non-statin LDL lowering agents without pre-approval CV outcomes data. FDA added that if Sanofi's BLA was first-in-class, the Advisory Committee would be asked whether or not SAR236553 should be approved before the CVOT has been completed. Sanofi/Regeneron was encouraged to reach out to the Division to understand any change in their position regarding LDL lowering after completion of the IMPROVE-IT trial results.*

*Regeneron/Sanofi stated that a re-challenge with statin was considered and discussed within Regeneron/Sanofi, with their Phase 3 program steering committee and with the external expert panel on statin intolerance. At the end of the process they concluded not to include this element for the following reasons:*

- We are concerned that Ethics Committees would not accept a re-challenge, knowingly inducing adverse events in patients.*
- We are concerned that including this element could discourage patients with more severe statin intolerance from participating in the trial and bias the patient population in the trial.*
- We are proposing to use clinical sites for this trial that are knowledgeable and skilled in understanding the aspects of statin intolerance and able to identify appropriate patients for this trial. This includes a number of the participants from the statin intolerance external expert panel.*

*FDA appreciated their thoughts on the re-challenge statin arm. FDA stated that they will need more internal discussion before they can provide comments on Sanofi/Regeneron's conclusion not to include a re-challenge statin arm in the trial. However, FDA was concerned that other trials of "statin-intolerant" patients have had difficulty confirming statin intolerance when assessed in a double-blind trial. FDA believed a statin re-challenge arm, obviously undertaken in those subjects who have not experienced a severe myopathy reaction such as rhabdomyolysis, will provide a more robust assessment of patients who are truly "statin intolerant".*

*FDA stated that an important aspect of the sponsor's proposed trial in the statin intolerant patient population would be to provide information on withdrawal rates for SAR236553/REGN727 and ezetimibe. FDA said that analyses pooling withdrawal and adverse event rates from all trials were acceptable, but they also want to see data from this specific trial and patient population. The FDA also mentioned that the analysis of withdrawal rate is more important than the comparison of symptoms, because what is really important is whether or not patients stay on the drug.*

*Regarding the assessment of skeletal muscle related withdrawal rates between SAR236553 and ezetimibe, Sanofi/Regeneron will assess the rate of withdrawal due to skeletal muscle related symptoms with SAR236553 and ezetimibe in our overall program, which includes 5 studies that use ezetimibe as a comparator. FDA stated that they would also want to see the rate of withdrawal of SAR236553 vs. ezetimibe for skeletal muscle-related symptoms for R727-CL-1119 presented separately. FDA stated that it is important to assess how many patients remain on SAR236553 vs. ezetimibe throughout a trial done in "statin-intolerant" subjects.*

*Regarding FDA's request regarding identification and definition of patients with nonfamilial hypercholesterolemia or mixed dyslipidemia, Sanofi/Regeneron reiterated the following response:*

*Nonfamilial hypercholesterolemia refers to patients with primary hypercholesterolemia that are not defined to have familial hypercholesterolemia. These are the patients with the more common/traditional hypercholesterolemia that is also referred to as being polygenic in origin. This is a subset of the older Frederickson Type II classification that excludes those with familial hypercholesterolemia.*

*Mixed dyslipidemia would be any patient with both elevation in LDL-C, as defined in our protocols, and additional TG elevations; previously termed Frederickson Type IIb. We would use a cut-off of TGs  $\geq 150$  mg/dL based on the following points:*

- *TGs  $\geq 150$  mg/dL are part of the ATP III definition of metabolic syndrome*
- *TGs 150-199 mg/dL are considered borderline high by ATP III*
- *Many patients in the REGN727/SAR236553 program will be coming into the trial on statins and therefore those with TGs  $> 150$  mg/dL most likely had TGs  $> 200$  mg/dL on an untreated basis.*

*Sanofi/Regeneron asked whether FDA agrees with the above definitions. FDA had no objections to these definitions.*

*FDA thanked Sanofi/Regeneron for sending in the information on the references that support your definitions. FDA stated no objections to your definition but, to date, the Division has not decided on the definitive definition for statin intolerance.*

*FDA confirmed that they would not add the LDL-C lowering of SAR236553 vs. ezetimibe or vs. statin up-titration to the label until the CVOT was reviewed and represented in the label. FDA did not believe that a trial of LDL-lowering of several weeks duration is adequate to claim superiority when compared to an agent that has proven cardiac risk reduction.*

***Sponsor's Post-Meeting Response emailed on February 29, 2012:  
Sanofi/Regeneron provided information on the literature references that support the sponsor's definition of statin intolerance and the definition and the references that support the sponsor's definition of skeletal muscle-related symptoms.  
Sanofi/Regeneron also provided their definition and references that support their definition of skeletal muscle symptoms. See attachment.***

***Final FDA Post-Meeting Comment:***

***Upon further internal discussion, DMEP has agreed to reduce the required minimum percentage of major adverse cardiac events from the CVOT that must be accrued prior to application submission from 50% to 25%.***

***DMEP continues to recommend strongly that the trial done in "statin-intolerant" subjects (Study R727-CL-1119) should include a statin re-challenge arm that evaluates***

*subjects in a blinded manner with the statin and dose that led to previous withdrawal or intolerance. The statin re-challenge arm should be undertaken in those subjects who have not experienced a severe myopathy reaction such as rhabdomyolysis and will provide a more robust assessment of patients who are truly “statin intolerant”.*

*Regarding the definition for statin intolerance and your interest in pursuing an indication in this population, we recommend that you develop, in consultation with the Study Endpoints and Labeling Development (SEALD) team, an instrument to assess and measure statin-associated myalgia.*

5. Does the Agency agree with the proposed plan for the assessment of LDL-C, regarding the use of calculated and measured LDL-C?

**FDA Preliminary Response: Your proposed plan for the assessment of LDL-C, regarding the use of calculated and measured LDL-C, appears reasonable.**

*Discussion at meeting: The sponsor accepted FDA’s response, no discussion occurred.*

6. As indicated under Question 4 above, the initial BLA will comprise efficacy studies with the mean percent change in LDL-C from baseline as the primary endpoint. While it is well recognized that levels of and changes in LDL-C are a valid surrogate for atherosclerotic cardiovascular event risk, the sponsor understands that it would be valuable to demonstrate a beneficial effect on cardiovascular events. Therefore, the sponsor plans to initiate a large cardiovascular (CV) outcome study prior to the initial BLA submission, which will be evaluating the ability of SAR236533 to reduce CV events in patients with recent Acute Coronary Syndrome. This study will be ongoing at the time of the initial submission supporting the lipid lowering indications and the results will be submitted post-registration as per the Agency’s pre-IND advice.

The CV outcome study will be a randomized, double-blind, placebo-controlled study in patients who recently experienced an acute coronary syndrome. It is estimated that approximately 18,000 patients will be enrolled with a minimum follow-up of approximately 24 months for all patients. The proposed primary endpoint in this study will be the effect of SAR236553 compared to placebo (on top of best standard of care therapy including background treatment with atorvastatin 80 mg for hyperlipidemia) on the occurrence of the following composite endpoints: coronary heart disease (CHD) death, non-fatal myocardial infarction, non-fatal and fatal ischaemic stroke, and hospitalization for unstable angina with stringent criteria for the definition of this latter endpoint.

We plan to submit the complete protocol to FDA soon after this EOP2 meeting for a formal Special Protocol Assessment.

- a. Does the Agency agree that the outlined CV outcome Phase 3 study would support the labeling of SAR236553 as a treatment to reduce cardiovascular

events in patients with recent Acute Coronary Syndrome to be submitted after the approval of the initial BLA?

**FDA Preliminary Response: As discussed in Question 4, 50% of primary endpoints must be accrued prior to BLA submission.**

*Discussion at meeting: See Discussion from Question 4.*

- b. Will the FDA accept the protocol for the outlined CV outcome Phase 3 study for Special Protocol Assessment?

**FDA Preliminary Response: It is acceptable to submit the protocol for the outlined CVOT for Special Protocol Assessment.**

*Discussion at meeting: See Discussion from Question 4.*

**We have some additional comments:**

- **Provide all definitions for your inclusion criteria and endpoints in the protocol. These definitions should be based on the May 31, 2011, or most recent, FDA/CDISC *Standardized Definitions for End Point Events in Cardiovascular Trials*. For the definition of myocardial infarction, the most recent Thygesen Universal Definition should be used.**
- **Will ALL adverse events be collected or will the adverse event collection be limited to serious adverse events, withdrawals due to adverse events, and adverse events of particular interest?**
- **Will all adverse events be coded using the Medical Dictionary for Regulatory Activities (MedDRA)?**
- **Provide an estimate of the number of sites and subjects that will be from the US. What percentage will this represent of the total study population?**
- **In order to maintain the blind if the dose is adjusted, is the volume of the injection for the 75mg dose similar to the 150 mg dose?**
- **Provide your rationale for why the Treatment Emergent Adverse Event period extends for 70 days (10 weeks) after the last dose of double-blind treatment.**

Sponsor's Response emailed on February 20, 2012: Regarding feedback on the design of the CVOT, thank you for your feedback, we will address the majority of your comments in our SPA request. Please see our responses to two of your comments below:

- We plan to collect ALL adverse events.
- Volume of 75 mg, 150 mg and placebo autoinjectors are the same.

*Discussion at meeting: Sanofi reiterated that they will collect all adverse events.*

7. At the time of the initial submission, the sponsor expects to have a safety database of a total of approximately 3390 patients treated with SAR236553 at or above the two planned marketed doses, including approximately 1890 patients treated for 12 months or longer and 400 patients (from study LTS11717) treated for 18 months.

Does the Agency agree that the proposed clinical program provides an adequate patient exposure in terms of number of patients treated and treatment duration for registration of SAR236553 for the targeted indications?

**FDA Preliminary Response: Please refer to our response to question 4 where we discuss our request for 50% of the primary endpoints from the CVOT to have accrued prior to the BLA submission.**

Sponsor's Response emailed on February 20, 2012: Can you confirm that the proposed safety database (patient numbers and durations of exposure) to support the LDL-C lowering indications is acceptable, notwithstanding your request on for 50% of the primary endpoints from the CVOT to have accrued prior to the BLA submission (see sponsor's comments to FDA response on Question 4)?

*Discussion at meeting: FDA clarified that at the time of the initial submission, Sanofi/Regeneron expects to have a safety database of a total of approximately 3390 patients treated with SAR236553 at or above the two planned marketed doses, including approximately 1890 patients treated for 12 months or longer and 400 patients (from study LTS11717) treated for 18 months. FDA stated that this safety database is acceptable.*

8. The Phase 3 long term safety study will be conducted using a pre-filled syringe containing 150 mg dosage. The Phase 3 efficacy program will be conducted using either pre-filled syringes (PFS) or auto-injectors in two different doses, 75 and 150 mg, as described below. The same pre-filled syringe will be used in the auto-injector (respective for each dose). The sponsor plans to market the product for commercial use using both the auto-injectors and pre-filled syringes.

Does the Agency agree that regardless of which device is used in the Phase 3 program, that the safety and efficacy data obtained will be sufficient to support the

approval of both the auto-injector and the pre-filled syringe in both dosage strengths and that no additional clinical studies are required?

**FDA Response:**

**If you plan to market the product for commercial use using both the auto-injectors and pre-filled syringes, then we strongly recommend that you provide adequate Phase 3 clinical data that supports the safety and efficacy of each device.**

**CDRH will need to review performance data in the DMF and 510(K) respectively for the (b) (4) glass barrel 1ml syringe that is the primary drug container closure and (b) (4) disposable auto-injector that will be used in the pivotal Phase 3 studies to assure that they are safe and effective for their intended users.**

**Consolidated CDRH/DMEPA Comments:**

**Auto Injector Design and Human Factors Considerations**

1. **Be advised that post marketing reports from the FDA Adverse Event Reporting System (AERS) database for (b) (4) auto-injectors include the following:**

**Wrong dose medication errors (n=28):**

**Twenty-eight cases reported to AERS were categorized as wrong dose errors that included seventeen overdoses and eleven under doses.**

**Twenty four cases reported problems with the autoinjector or pain during injection that led to multiple injections or underdosing. In most of the wrong dose cases, no specific adverse events were reported other than those that included injection site irritation.**

**Fingersticks during administration (n=26):**

**Twenty-six cases reported fingersticks. Twenty five cases cited the fingerstick occurred due to technique errors (holding the pen upside down) during administration. The remaining case reported the needle hit the patient's back finger during discarding of the device.**

**(NOTE: We recommend that you consider using different and contrasting colors for the needle end vs. the button end of the auto injector. Also, you might consider adding a warning indicating from which end of the pen the needle come out of (e.g. "Needle end →"))**

**Dose omissions (n=11):**

**Eleven cases reported dose omissions. Eight cases cited difficulties or malfunctions of the (b) (4) Autoinjector.**

**Accidental exposure (n=5):**

**Five cases reported accidental exposure by a child accessing the pen or exposure into face or eyes during administration. Three cases reported that**

**accidental exposure occurred because the autoinjector malfunctioned or due to administration technique.**

**We recommend that you include these failure modes into consideration in your design and risk assessment during your Human Factors/Usability studies.**

- 2. The meeting package indicated that a summative usability validation study will be preformed performed with the device, and that a test plan will be developed using the 2011 FDA Guidance on Human Factors. It is not clear from this information how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of the highest priority task pertinent to their device. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Please provide a comprehensive use-related risks and a Human Factors/usability validation study protocol for review. Please ensure that your protocol provides a clear description of the following items:**

- a. Devices and Labeling Used and Training**

**FDA noted that there are two device configurations that can be used with the proposed drug product: autoinjector and prefilled syringes. Please describe the overall interaction between the users and the two configurations. In addition, to establish the scope and facilitate understanding of the testing you perform, please provide a graphical depiction of the user interface for your device. For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.**

**We also noted that you intend to market the auto injector in two different strengths. Post-marketing experience with pen devices has shown that pen label differentiation alone is a low leverage approach to differentiate between similar devices of different strengths. We strongly recommend that you consider color differentiation between the two strengths auto injector devices (i.e. different body color). Your human factors/usability studies should include testing to demonstrate that the devices are adequately differentiated.**

**A key component of human factors/usability validation testing is that users who are representative of actual users be used for the testing. Based on your analysis of your intended users and the use of your device, you should decide whether or not training is required for use with your product. If training is required, please determine the extent and type of training needed and indicated for users prior to using your device. After the training need is established and the training materials prepared, you should train the user participants for you human factors/usability validation testing in the same manner that actual users will be trained. You should provide at least some lag time**

**between training and the testing. When you design your human factors/usability validation protocol, please include this analysis and ensure that representative (i.e., realistic) training is given to all test participants. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.**

**In the Human Factors/usability validation study, participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.**

**b. User Tasks and Use-Related Risks Analysis**

**FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.**

**Please provide a use-related risk analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.**

**In addition, for human factors/usability validation testing, the Agency needs to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related failures that could have an undesirable clinical impact. Please provide a rationale for the completeness of the user tasks you include in your Human Factors/Usability validation testing.**

**c. Use Environment and Conditions**

**You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.**

**Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated and should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.**

**Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.**

**d. Study Participants**

**You should include as many representative users in your human factors/usability validation as your analysis indicates are necessary to achieve a reasonable validation. Please note that the Agency’s expectations for the number of study participants to be used in Human Factors/Usability Validation are a minimum 15 per user group. Please plan to submit results of a study that includes minimum of 15 participants per group of distinct users consistent with your indicated population of users, and also describe sufficient demographic information to indicate how these participants are representative of the intended population of users. If users fall into distinct groups that are expected to interact differently with the device (different user tasks) or carry different risk profiles (e.g. level of disabilities/impairments) then the testing should include representative samples from each of these groups, divided roughly evenly but where the total could be no less than 25.**

**Regardless of the number of groups you test, please provide a rationale that these groups are representative of the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.**

**For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.**

**e. Realism of simulated use**

**The testing environment and realism of the simulated use was not described in sufficient detail to determine if it is reasonable for a validation study of device use, however a “focus group” approach is not likely to represent actual use conditions. Please determine the conditions under which the testing will be undertaken and include realistic and challenging scenarios of use that, in aggregate, include all critical user tasks which you have identified.**

**f. Data Collection and Analysis**

**Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA**

**expects you to collect both empirical and qualitative data in a design validation study.**

**Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.**

**Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.**

**Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.**

**g. Report**

**The Agency expects to review a report of the human factors/usability evaluation and validation testing. The report should begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify**

**design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.**

**We strongly recommend that you submit your draft protocol for review prior to initiating your study in advance for us to review in order to ensure that your methods and the resulting data will be acceptable. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.**

**Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.**

**Additional Comments:**

- 1. Collect reports and provide a summary and line listing of all medication errors from the Phase 3 Clinical Trials, serious and non-serious, including those related to the devices (pre-filled syringes and auto-injectors). All drug product units which patients believe are malfunctioning, should be returned to the sponsor for laboratory evaluation and testing.**

*Sponsor's Response emailed on February 20, 2012: Thank you for the advice regarding the device development, we plan to address the device specific topics at a later interaction with the CDRH and the Division.* (b) (4)

*You are recommending that we provide adequate Phase 3 clinical data that support safety and efficacy of each device.*

*Sponsor follow-up question:*

*Do you agree that the use of the devices in the Phase 3 studies including the long-term safety study (LTS11717) as described in our briefing book fulfill this requirement?*

*Discussion at meeting: FDA stated that if Sanofi/Regeneron plans to market the product for commercial use using the auto-injectors, then FDA strongly recommends that they provide adequate Phase 3 clinical data that supports the safety and efficacy of this device. FDA requested that Sanofi/Regeneron provide number of subjects and duration of exposure with autoinjector device. Sanofi/Regeneron agreed.*

*Sponsor's Post-Meeting Response emailed on February 29, 2012:*

*The sponsor provided information on the number of subjects and duration of exposure with the autoinjector device. See attachment.*

***FDA Final Post-Meeting Comment: The proposed Phase 3 program appears to provide adequate Phase 3 clinical data that supports the safety and efficacy of the pre-filled syringe and the auto-injector device.***

9. The pharmacokinetics of SAR236553 was assessed through full pharmacokinetic profile from Phase 1 studies, and through sparse serum samples collected in clinical efficacy/safety studies. These concentrations were analyzed using noncompartmental analysis or using a descriptive approach. Additionally, a population pharmacokinetic analysis will be conducted from samples collected in Phase 1 and Phase 2 studies and to be collected in selected Phase 3 studies. The mean percentage change in LDL-C will be used as a marker for describing the pharmacodynamic effect in the population PK/PD analysis. The sponsor plans to perform population PK and population PK/PD modeling as follows:
- Population PK modeling: modeling of the clinical Phase 1 studies will be initiated using two models: Michaelis Menten and the Target Mediated Drug Disposition (TMDD). This will be followed by a decision on which model will be used in subsequent PK and PK/PD modeling in Phase 2 and 3 studies. Several general and specific covariates will be evaluated.
  - Population PK/PD modeling: will be performed in a two-step approach. First step, PK will be fitted and second step drug/total or free PCSK9 concentrations will be calculated at all times necessary to be integrated in the turnover rate model.

Does the Agency consider this pharmacometric assessment acceptable to support registration?

**FDA Preliminary Response: Yes, your population PK/PD approach is reasonable. We encourage you to evaluate the injection device as a covariate in the population PK analysis with Phase 3 data. Any conclusions based on the model to support labeling or dosing decisions will be a review issue.**

**We encourage you to refer to the following pharmacometric data and models submission guidelines:**

- **All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
- **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural**

**model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).**

- **A model development decision tree and/or table which gives an overview of modeling steps.**
- **For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line, and the population prediction line.**
- **In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

- 10.** The intended route of administration for SAR236553 is subcutaneous. The sponsor intends to allow flexibility in the choice of the injection site (abdomen, thigh or upper arm) in all Phase 3 studies including the CV outcome study and the long term safety study. The safety, tolerability and efficacy will therefore be assessed in the context of the drug having been administered via these different sites. In addition, in the long-term safety study (LTS11717) and the monotherapy study EFC11716, the impact of the three different injection sites on the pharmacokinetics of SAR236553 will be investigated within the covariate analysis of the population PK.

Does the Agency agree that the Sponsor's planned program is sufficient to support labeling to give the patient the option to inject subcutaneously SAR236553 either in the abdomen, the thigh or the upper arm?

**FDA Preliminary Response: Your planned population PK approach to evaluate the impact of the injection site on the pharmacokinetics of SAR236553 is reasonable. However, whether the population PK analysis will be sufficient to support labeling will be a review issue. Additional studies may be required if the number of subjects for each injection site is not sufficient.**

*Sponsor's Response emailed on February 20, 2012: We would like to ensure that it was clear from our proposal that each patient can choose a different injection site for each administration, thus an individual patient can use multiple injection sites during the study. We will document this in patient diaries and if needed, we will consider evaluating the impact of the injection sites in a specific study.*

*Discussion at meeting: FDA cautioned that sufficient patients for each injection site with pharmacokinetic measurements are needed for evaluation of injection site as a covariate in the proposed population PK analysis. Sanofi/Regeneron agreed that in case an evaluation in the population PK analysis is unfeasible, a separate study evaluating the influence of injection site on PK may be warranted.*

11.

- a. Does the Agency agree that the nonclinical and clinical program is appropriate to assess the drug-drug interaction potential of SAR236553 and to support registration?

**FDA Preliminary Response: This appears to be an acceptable approach.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

- b. Does the Agency agree with the Sponsor's proposal to not evaluate pharmacokinetics of statin and its metabolites in Phase 3?

**FDA Preliminary Response: This appears to be acceptable.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

12. The sponsor considers the disposition of SAR236553 in patients with renal impairment and elderly subjects to be comparable to the targeted hypercholesterolemic population. Therefore, the sponsor proposes not to perform clinical pharmacology studies in subjects with renal impairment or in elderly subjects. Instead, the sponsor intends to analyze age and renal function as part of the population PK/PD analyses. However, for the population of subjects with mild and moderate hepatic impairment the sponsor plans to perform a separate clinical pharmacology study (POP12671) taking into an account that PCSK9 as target is located in the liver and is partly involved in the clearance of SAR236553, and that no information on PCSK9 levels in subjects with hepatic impairment is available.

(b) (4)

Does the Agency agree that separate pharmacology studies in elderly subjects or subjects with renal impairment are not required to be conducted for the BLA submission of SAR236553?

**FDA Preliminary Response: Your approach of evaluating the effect of renal impairment and age in the population PK analysis seems reasonable. However, additional pharmacology studies may be required if the number of**

**patients with renal impairment (mild and moderate) or patients greater than 65 years is not sufficient to draw meaningful conclusions about the impact of these covariates on PK of SAR236553.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

13. The anti-drug antibody (ADA) assay is a bridging immunoassay which potentially involves three steps in the evaluation of a clinical sample: screening, confirmation, and titer. The ADA assay is validated (Validation report number REGN727-AV-10014-SA-01V1) and submitted to the IND. ADA assessment in patients to be enrolled in the long-term safety (LTS) study and in the Phase 3 studies will include the determination of ADA status (positive/negative) at selected time points. The titer determination will be conducted for samples positive in the confirmation assay. Samples from the LTS study and Phase 3 pivotal trials that are positive in the ADA confirmation assay described above will be further evaluated for their potential neutralizing activity.

Neutralizing activity in ADA positive patients from Phase 1 and Phase 2 studies were evaluated by examining LDL-C levels. Therefore, possible correlation of circulating ADA and titers with LDL-C endpoints as well as with clinical adverse events will be evaluated in the LTS and Phase 3 studies. In addition, a non-quantitative, competitive ligand binding assay to monitor neutralizing antibodies (NAb) in the ADA positive samples in the LTS study and Phase 3 studies is currently being validated.

Does the Agency agree with the anti-drug antibody/immunogenicity testing approach proposed for the Phase 3 clinical studies and registration?

**FDA Preliminary Response:**

**You note that in the long-term safety study (LTS11717) and further pivotal studies, possible clinical effects of circulating anti-drug antibodies (ADA) will be evaluated by correlating antibody status and titers with LDL-C levels as well as with clinical adverse events. In the long-term safety study (LTS11717) assessment of ADA response will be performed at Baseline, Week 4, Week 12, Week 24, Month 12, Month 15 and Month 18, and at the follow-up visit (10 weeks after the last SAR236553 dose). In addition, potential additional late follow-up samples will be collected 6 months minimum after the last dose of SAR236553 from patients that are ADA positive (titers > 240) until such time that they are no longer positive for ADA. For all of your Phase 3 trials, we recommend following up patients who develop ADA until their titers return to baseline.**

(b) (4)



**antibodies return to baseline and evaluated for their potential neutralizing activity.**

**We also have the following comments based on your validation report REGN727-AV-10014-SA-01V1 included in the annual report received on January 10, 2011:**

- a. **We note that system suitability for the mid and high positive controls are set at 25% for sample analysis, though the validation data results were well below this number. Although there may be reasons supporting this relatively high rate, please consider whether this is appropriate for your assay. Published literature (Geng, et al., Journal of Pharmaceutical and Biomedical Analysis 39 (2005) 364–375; Shankar, et al., Journal of Pharmaceutical and Biomedical Analysis 48 (2008) 1267–1281 and DeSilva, et al. Pharmaceutical Research 20 (2003)1885-1900) suggest that the level should be at or below 20%, and the data from your validation studies would support this.**
- b. **Your validation study identifies no hook effect up to 100ng/mL, but there is no information on whether a hook effect is seen at higher concentrations. Please identify how limiting the study of hook effects to under100ng/mL will assure that study samples with antibody concentrations above this level would be detected as such. Include data or any controls implemented to mitigate this concern in your immunogenicity study report that will be submitted to the BLA.**

*Sponsor's Response emailed on February 20, 2012: Per the current LTS protocol, there is one additional follow-up visit at 6-12 months after the last dose for ADA positive patients (titers above 240). We will amend the protocol to follow these patients until they return to below the titer of 240.*

*We will also add these post study visits to the Phase 3 studies.*

*Discussion at meeting: FDA stated that Sanofi's February 20, 2012, response was acceptable.*

14. The sponsor refers to the "Remove Partial Clinical Hold" letter sent by the Agency on March 3, 2010 in which the Agency strongly recommended that troponin levels be assessed at appropriate time points in future clinical studies. The Agency stated that if preclinical and clinical assessments of troponin levels indicate that there is no evidence of cardiac myocyte degeneration with SAR236553 (REGN727), this monitoring can be eliminated.

The sponsor conducted a review of all available Phase 1 studies (R727-CL-0902, R727-CL-0904 and R727-CL-1001) and Phase 2 studies (R727-CL-1003, DFI11565, and DFI11566) and cardiotoxicity data from preclinical studies. No changes in troponin I levels and no other significant cardiac safety concerns with

SAR236553 were observed that would require further assessment of troponin I in the Phase 3 program.

Does the Agency agree with the Sponsor's proposal not to conduct troponin I assessment in Phase 3 studies?

**FDA Preliminary Response: Yes**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

15. Based on the results of the preclinical toxicology studies and Phase 1 and 2 clinical trials, no QT signal attributable to SAR236533 has been detected. The ECG assessment planned in the LTS11717 study will further evaluate QT and other ECG parameters. Thus, at this time, a thorough QT study is not considered necessary and therefore is not included in the development plan.

Based on the data provided, does the Agency agree that a thorough QT in healthy subjects is not required to be conducted at this time?

**FDA Preliminary Response: Yes, we agree.**

**Additional comments:**

**You should perform a categorical analysis and submit it to the BLA. The analysis should include the number and percentage of individuals with:**

- **Absolute QT/QTc values > 450 ms, >480 ms, and >500 ms; as well as the number and percentage of individuals with change from baseline >30 ms and >60 ms.**
- **PR changes from baseline  $\geq$ 50% if absolute baseline value was < 200 ms and  $\geq$ 25% if absolute baseline value was >200 ms.**
- **QRS changes from baseline  $\geq$ 50% if absolute baseline value was <100 ms and  $\geq$ 25% if absolute baseline value was >100 ms.**
- **Number and percentage of individuals with abnormal ECG findings.**
- **Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

16.

 (b) (4)  
A waiver for children below the age of  (b) (4) will be requested.

Does the Agency agree with the sponsor's request to defer pediatric studies?

**FDA Preliminary Response:**

(b) (4)

**. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Please provide your request and rationale for any waiver or deferral at the time of the BLA submission. If you plan to ask for a deferral of the pediatric trial for a certain age group, please provide, at the time of the BLA submission, a brief description of the proposed trial, focusing on collection of adequate information on dose, safety and efficacy, as well as the protocol submission date, the study completion date, and the final report submission date.**

*Discussion at meeting: The sponsor accepted FDA's response, no discussion occurred.*

### **3.0 DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

### **4.0 ATTACHMENTS and HANDOUTS**

Document sent by Sanofi on February 29, 2012.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAYMOND S CHIANG  
03/09/2012

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



BLA 125559

**LATE-CYCLE MEETING MINUTES**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Senior Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Praluent (alirocumab) injection, 75 and 150 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on May 28, 2015.

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

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



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

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** May 28, 2015 at 10:00 AM  
**Meeting Location:** White Oak Campus, Silver Spring, MD  
**Application Number:** BLA 125559  
**Product Name:** Praluent (alirocumab) injection  
**Applicant Name:** Sanofi-Aventis  
**Meeting Chair:** James P. Smith, M.D., M.S.  
**Meeting Recorder:** Patricia Madara, M.S.

**FDA ATTENDEES**

**Office of Drug Evaluation II (ODE II)**

Mary H. Parks, M.D. Deputy Director  
Sara Stradley, M.S. Administrative Director of Regulatory Affairs

**ODE II; Division of Metabolism and Endocrinology Products**

Jean-Marc Guettier, M.D. Director  
James P. Smith, M.D., M.S. Deputy Director  
Julie Golden, M.D. Medical Officer  
Mary Roberts, M.D. Medical Officer  
Julie Van der Waag, MPH Chief, Project Management Staff  
Patricia Madara, M.S. Regulatory Project Manager

**Office of Clinical Pharmacology; Division of Clinical Pharmacology II**

Jaya Vaidyanathan, Ph.D. Clinical Pharmacology Team Leader  
Sang Chung, Ph.D. Clinical Pharmacology Reviewer

**OPO / Office of Process and Facilities; Division of Inspectional Assessment**

Michael Shanks Biologist

**OPO / Office of Process and Facilities, Division of Microbiology Assessment (DMA):**

Patricia Hughes, Ph.D. Team Leader, Biotech Manufacturing Team  
Colleen Thomas, Ph.D. Microbiologist

**OPO / Office of Biotechnology Products, Division of Biotechnology Review and Research III**

Amy Rosenberg, M.D. Director  
Susan Kirshner, Ph.D. Review Chief  
Howard Anderson, Ph.D. Team Leader



## **Applicant Attendees**

### **Sanofi attendees:**

<b>Nia Tatsis, Ph.D.</b>	Associate Vice President, Head, Global Regulatory Affairs, PCSK9 and Specialty Care 1 Products
<b>Jana Bodorova, M.Sc., Jay Edelberg, M.D., Ph.D.,</b>	Senior Director, Global Regulatory Affairs Vice President, Head, PCSK9 Development and Launch Unit
<b>Corinne Hanotin, M.D.,</b>	Lead Clinical Research Director, Clinical Development, PCSK9 Development and Launch Unit
<b>Leslie Dondoy-Nouvel, M.D.,</b>	Head of Safety Surveillance Risk Management Strategic Development, Global Pharmacovigilance and Epidemiology
<b>Guillaume Lecorps, M,Sc, James Collins, P.E., MBA,</b>	Biostatistics Vice President, Devices Development Unit, Medical Devices
<b>Stephen Fitzpatrick, Ph.D.,</b>	Senior Director, Global Regulatory CMC Biologic Products
<b>Catherine Dubuisson-Brengel Ph.D</b>	Associate Director, Global Regulatory CMC Biologic Products
<b>Nicolas Fontaine, Pharm D,</b>	CMC project leader, Integrated CMC New Products Program

### **Regeneron Attendees:**

<b>Ned Braunstein, M.D.</b>	Senior Vice President, Regulatory Affairs
<b>Mary Alice Raudenbush, MSc, Brian Walter, PhD, Robert Pordey, MD,</b>	Senior Director, Regulatory Affairs Executive Director, Regulatory Affairs Vice President Clinical Sciences, Cardiovascular & Metabolism Therapeutics
<b>A. Thomas DiCioccio, Ph.D., Kathryn Miller, MSc, Jennifer McNay, PhD, Kris Ghosh, PhD,</b>	Exec. Director, Pharmacometrics Director, Biostatistic Senior Director, Process Science Senior Director, CMC Regulatory Affairs

## **1.0 Background**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review.

Proposed indication(s): as adjunct to diet, for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce LDL-C, Total-C, non-HDL-C, Apo B, TG, and Lp(a), and to increase HDL-C and Apo A-1, either in combination with a statin, with or without

other lipid-modifying therapy (LMT), or as monotherapy, or add-on to other non-statin LMT, including in patients who cannot tolerate statins.

PDUFA goal date: July 24, 2015

FDA issued a Background Package in preparation for this meeting on May 20, 2015.

## 2.0 Discussion

### 1. Introductory Comments

***Discussion:*** FDA noted that the discussion today remains preliminary, as not all primary reviews have been finalized.

### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

#### A. Clinical

Following review of the data contained within the original BLA submission as well as the information submitted in response to the Division's information requests throughout the review cycle, the clinical review team may take into consideration the following when developing our benefit/risk assessment of alirocumab. Please note this is not a comprehensive listing of what may ultimately be considered in the benefit/risk evaluation and is subject to change following discussion with our advisors at the June 9<sup>th</sup> EMDAC meeting. Furthermore, we are providing this list simply to be transparent with regard to efficacy/safety issues that we have discussed during the review; we do not believe that it would be helpful for you to provide additional data at this time.

- i. LDL-C as a surrogate: As we have stated previously, it will be a review issue whether alirocumab could be approved based on effects on lipid parameters such as LDL-C before cardiovascular (CV) outcomes data are available and, if so, for what population(s). Uncertainty is greater with regard to net clinical benefit when the benefit of a drug is assessed solely by its effects on a biomarker, regardless of whether or not the biomarker is considered a valid surrogate endpoint for a given patient population.
- ii. Glycemic control: A higher proportion of alirocumab-treated patients experienced an unfavorable shift in glycemic control defined by adverse events and laboratory data compared to placebo or ezetimibe-treated patients.
- iii. Allergic reactions: Serious and non-serious allergic reactions occurred with higher incidence with alirocumab treatment and included serious events of leukocytoclastic vasculitis and hypersensitivity requiring discontinuation of treatment and in some cases steroid therapy.
- iv. Neurologic: Rare events of neuropathic conditions (variant of Guillain-Barre syndrome-Miller Fisher, transverse myelitis, multiple sclerosis, and optic neuritis) occurred in 4 alirocumab-treated patients in a clinical development program of 3340 alirocumab exposed patients with average treatment duration of 58 weeks.

- v. Elevations in liver enzymes: A higher incidence of patients treated with alirocumab reported abnormalities in liver enzymes. While some had alternative etiologies, there were examples of positive rechallenge with alirocumab reinitiation.
- vi. Safety of very low LDL-C values: The safety database does not permit a robust evaluation of adverse events that may emerge with longer exposure to very low LDL-C levels.
- vii. Immunogenicity: A number of patients appear to have experienced loss-of-efficacy coincident with neutralizing antibodies.

We recommend you consider how you might further investigate these concerns in ongoing or new clinical trials. In addition, we advise you to consider how you might inform patients and mitigate these potential risks through labeling.

**Discussion:**

***FDA noted that the items listed would be among those discussed at the Advisory Committee (AC) meeting. Also, the Agency noted that, as we have stated numerous times through development, we plan to discuss the alirocumab-induced reduction in LDL-cholesterol as a surrogate for cardiovascular risk reduction.***

***The applicant stated that upon review of FDA's background package for the AC meeting, they were pleased to see that FDA's interpretation of the data appeared very similar to their own. The applicant noted that they have a pharmacovigilance plan that includes monitoring for adverse events of special interest. They asked if FDA had any thoughts about issues of special interest. FDA stated that these were still being considered and the AC discussion could have an impact on our path forward.***

B. Product Quality Microbiology

i.



**Discussion:**

***FDA noted there will be a post-marketing commitment in the approval letter. The applicant can submit a protocol for review, if they wish.***

3. Minor Review Issues

A. Product Quality Microbiology

- i. [REDACTED] (b) (4)  
[REDACTED] The study performed by [REDACTED] (b) (4)  
[REDACTED] showed that the method is capable of detecting [REDACTED] (b) (4)

B. Devices

- i. At this time, we have not identified any outstanding issues related to the device constituent parts of the combination product.

**Discussion:**

*Regeneron and Sanofi noted that all four presentations of the product were being manufactured for launch and inquired about the FDA proposed shelf life. FDA explained that real-time data is required for determining the commercial product expiration date. Therefore, they would be recommending 18 months. The applicant can submit additional stability results when they become available as per the stability protocol and extend the expiration date. The stability results should be submitted in the annual report.*

*The applicant explained that there were some specific issues related to the pen and syringe labels. [REDACTED] (b) (4)*

*[REDACTED] They noted that real-time stability data of the pens and syringes centered around data obtained for the 150 mg dose.*

*FDA noted that two changes had been made to the 75 mg dose pen: [REDACTED] (b) (4)*

*[REDACTED] With regard to the mechanics of the pen, we agree that data from the 150 mg dose can be used to determine shelf life.*

*FDA reiterated that the BLA contains stability results to support an 18-month expiration date at this time. The Applicant agreed with FDA's comments regarding the suitability controls for container closure integrity testing of syringes and pens.*

C. Information Requests

- i. Clinical
- a. Clinical information request sent 8 May 2015, regarding findings during OSI inspection.

**Discussion:**

*FDA requested clarification related to a "tool" that had been used to estimate pre-statin-treatment LDL-C to confirm the diagnosis of heFH in the clinical trials. In particular, the Agency referred to the response dated May 22, 2015, to an information request that stated in part, "The tool was not implemented to screen for heFH in a general population with hypercholesterolemia, but rather to evaluate whether patients were likely to fit the criteria for certain/definite heFH based on clinical criteria." FDA asked for clarification on this point. The Applicant stated the tool was not used in their general screening process, but rather to confirm the inclusion criteria for heFH, since the majority of heFH patients had a known diagnosis.*

***FDA also asked for clarification regarding inclusion of coronary artery calcium scoring as a non-invasive test for evidence of CHD to determine inclusion in the OPTIONS I and OPTIONS II trials. FDA noted that this test was not mentioned in any protocol or clinical study report, and was only identified during the sponsor inspection. The applicant stated that, originally, this test was not used to determine eligibility. However, it may have been used in a very small number of cases. They will get back to the FDA with more information.***

***[Post-meeting comment: The sponsor provided additional information in a submission dated June 1, 2015, which stated in part: "On review of the patients enrolled in these 3 trials, PIs for only 3 patients requested calcium scores be considered (1 in OPTIONS I and 2 in ALTERNATIVE) as part of the entry criterion for "clinically significant CHD diagnosed by invasive or non-invasive test.." However, all 3 of the patients would have qualified for study entry without the calcium score, based on their calculated SCORE (> 1% for the ALTERNATIVE patients and > 5% for the OPTIONS I patient). Accordingly, no patients in the program were enrolled based solely on calcium scoring as an entry criterion."]***

- b. Clinical Information Request sent 11 May 2015, regarding follow-up of patient safety issues
  - c. Clinical information request sent 11 May 2015, requesting follow-up information of patient who developed neutralizing antibodies associated with LDL-C worsening
  - d. Clinical information request sent 18 May 2015, requesting submission of a Pharmacovigilance Plan, if one is available.
- ii. Statistics
    - a. Statistical information request sent May 18, 2015, requesting results from analyses of the key secondary efficacy endpoints using a pattern mixture model.
  - iii. Product Quality Microbiology
    - a. Responses to previous information requests are under review and additional information requests will be sent. Drug Master File reviews are not yet complete.

**Discussion:**

***The applicant asked if they could expect new information requests (IR), particularly with regard to CMC specifications. FDA responded that there was none now but microbiology would issue an IR in the near future. FDA also indicated at the time of the meeting there were no CMC specifications IRs, but the CMC review was still on going.***

4. Additional Applicant Data

**Discussion: none**

5. Information Requests: ***see previous discussions***

6. Upcoming Advisory Committee Meeting

**Date of AC meeting:** June 9, 2015

**Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: approximately May 20, 2015**

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

We anticipate that AC members will be asked to discuss and vote on the overall risk-benefit of alirocumab for the proposed indication, as framed by the following considerations:

- Alirocumab-induced lowering of LDL-C as a surrogate for an effect on clinical outcomes in various patient populations
- Safety of alirocumab
- Overall benefit/risk assessment

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

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

**Discussion:**

*FDA noted that the Applicant will have 90 minutes to present data and additional time for clarifying questions. The clinical reviewers would present for FDA, however, other disciplines will be present, if questions arise. FDA had spoken with the applicant earlier to confirm the company would be presenting the details of their clinical development program, such as trial design. The Applicant stated they had decided to present only the information in the ISS in order to prevent confusion. They will be submitting an addendum to the briefing document to make this change.*

7. Postmarketing Requirements/Postmarketing Commitments

A. Product Quality Microbiology

- i.  (b) (4)
- ii. Qualification of the bioburden and sterility test methods was performed with only two lots of drug product, with the exception of qualification of the sterility test method for the recovery of *A. brasiliensis*. As a post-marketing commitment, provide bioburden and sterility test qualification data from one additional batch of 150 mg/ml drug product that was not manufactured from drug substance batches 8065000001 or 8065000002. The study may be done with bulk drug product. The data should be provided in the first annual report.

- B. The possibility of additional PMRs or PMCs remain under internal discussion. Some may be informed by the discussion at the AC meeting.

**Discussion:**

*FDA reiterated that it was premature to discuss additional PMRs, as the AC meeting would likely inform these discussions. FDA noted, however, that they did not plan to discuss potential PMRs at the AC. The applicant noted that their clinical program included 5300 patient years in the safety database. They felt residual issues could be handled by pharmacovigilance.*

8. Major Labeling Issues

It is premature to discuss labeling at this time. At minimum, we anticipate substantive revision to Indications & Usage, Warnings & Precautions, Adverse Reactions, and Clinical Studies.

**Discussion:**

*FDA noted that labeling would be informed by the discussion of the advisory committee members. It may be determined that the benefit / risk is acceptable for some populations but not for others. We will have labeling discussions after the AC.*

*The applicant noted that they had submitted revised labeling on May 8, which amended the Dosing and Administration section to reflect a recommended starting dose of 75 mg, with an increase to the 150 mg dose for those patients needing additional LDL-C lowering. This change was made to address concerns about the safety of very low LDL-C over long periods of time. The intent was to avoid LDL-C values less than 25 mg/dL for most patients. Some populations, such as those with HeFH, may need to start with the 150 mg dose.*

*The applicant asked if FDA could expand on their thinking with regard to (b) (4) (b) (4) FDA responded that (b) (4) since safety data were still under review.*

9. Review Plans

- A. Review of responses to outstanding information requests
- B. Obtain feedback from Advisory Committee panel
- C. Completion of consults and tertiary reviews
- D. Completion of facilities inspections: final compliance decisions regarding drug product and drug substance facilities are pending
- E. Labeling discussions (as needed)

**Discussion:**

*FDA stated they would be reviewing responses to information requests as they are received. They noted that the outcome of facilities inspections can always present an issue. Regarding the completed inspections, the Agency was waiting for finalization of secondary reviews, but no issues had been identified at this point.*

10. Wrap-up and Action Items –

***This application has not yet been fully reviewed by the signatory authority, division director, or office director; therefore, this meeting did not address the final regulatory decision for the application.***

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/s/  
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JAMES P SMITH  
07/07/2015



BLA 125559

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 28, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

James P. Smith, M.D., M.S.  
Deputy Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** May 28, 2015 at 10:00 AM  
**Meeting Location:** White Oak Campus, Silver Spring, MD / building 22  
**Application Number:** BLA 125559  
**Product Name:** Praluent (alirocumab)  
**Indication:** Treatment of hypercholesterolemia  
**Sponsor/Applicant Name:** Sanofi-Aventis U.S. Inc.

### INTRODUCTION

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

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

## **BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE**

### **1. Discipline Review Letters**

No Discipline Review letters have been issued to date.

### **2. Substantive Review Issues**

The following substantive review issues have been identified to date:

#### **A. Clinical**

Following review of the data contained within the original BLA submission as well as the information submitted in response to the Division's information requests throughout the review cycle, the clinical review team may take into consideration the following when developing our benefit/risk assessment of alirocumab. Please note this is not a comprehensive listing of what may ultimately be considered in the benefit/risk evaluation and is subject to change following discussion with our advisors at the June 9<sup>th</sup> EMDAC meeting. Furthermore, we are providing this list simply to be transparent with regard to efficacy/safety issues that we have discussed during the review; we do not believe that it would be helpful for you to provide additional data at this time.

- i. **LDL-C as a surrogate:** As we have stated previously, it will be a review issue whether alirocumab could be approved based on effects on lipid parameters such as LDL-C before cardiovascular (CV) outcomes data are available and, if so, for what population(s). Uncertainty is greater with regard to net clinical benefit when the benefit of a drug is assessed solely by its effects on a biomarker, regardless of whether or not the biomarker is considered a valid surrogate endpoint for a given patient population.
- ii. **Glycemic control:** A higher proportion of alirocumab-treated patients experienced an unfavorable shift in glycemic control defined by adverse events and laboratory data compared to placebo or ezetimibe-treated patients.
- iii. **Allergic reactions:** Serious and non-serious allergic reactions occurred with higher incidence with alirocumab treatment and included serious events of leukocytoclastic vasculitis and hypersensitivity requiring discontinuation of treatment and in some cases steroid therapy.
- iv. **Neurologic:** Rare events of neuropathic conditions (variant of Guillain-Barre syndrome-Miller Fisher, transverse myelitis, multiple sclerosis, and optic neuritis) occurred in 4 alirocumab-treated patients in a clinical development program of 3340 alirocumab exposed patients with average treatment duration of 58 weeks.
- v. **Elevations in liver enzymes:** A higher incidence of patients treated with alirocumab reported abnormalities in liver enzymes. While some had alternative etiologies, there were examples of positive rechallenge with alirocumab reinitiation.

- vi. Safety of very low LDL-C values: The safety database does not permit a robust evaluation of adverse events that may emerge with longer exposure to very low LDL-C levels.
- vii. Immunogenicity: A number of patients appear to have experienced loss-of-efficacy coincident with neutralizing antibodies.

We recommend you consider how you might further investigate these concerns in ongoing or new clinical trials. In addition, we advise you to consider how you might inform patients and mitigate these potential risks through labeling.

B. Product Quality Microbiology

i.



**ADVISORY COMMITTEE MEETING**

**Date of AC meeting:** June 9, 2015

**Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management:** approximately May 20, 2015

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

We anticipate that AC members will be asked to discuss and vote on the overall risk-benefit of alirocumab for the proposed indication, as framed by the following considerations:

- Alirocumab-induced lowering of LDL-C as a surrogate for an effect on clinical outcomes in various patient populations
- Safety of alirocumab
- Overall benefit/risk assessment

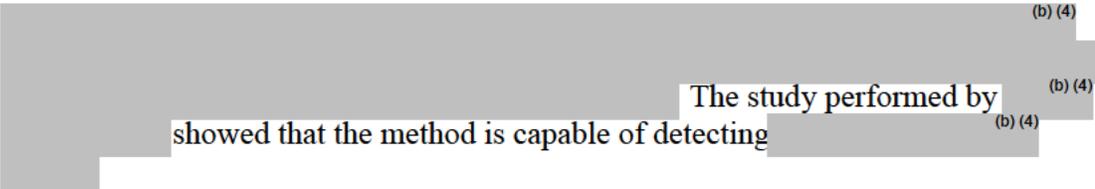
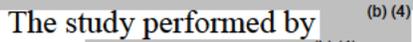
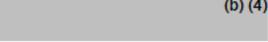
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## REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

## LCM AGENDA

1. Introductory Comments – Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – Each issue will be introduced by FDA and followed by a discussion.
  - A. Clinical
  - B. Product Quality Microbiology
3. Discussion of Minor Review Issues –
  - A. Product Quality Microbiology
    - i.  (b) (4)  
The study performed by  (b) (4) showed that the method is capable of detecting  (b) (4)
  - B. Devices
    - i. At this time, we have not identified any outstanding issues related to the device constituent parts of the combination product.
  - C. Information Requests
    - i. Clinical
      - a. Clinical information request sent 8 May 2015, regarding findings during OSI inspection
      - b. Clinical Information Request sent 11 May 2015, regarding follow-up of patient safety issues
      - c. Clinical information request sent 11 May 2015, requesting follow-up information of patient who developed neutralizing antibodies associated with LDL-C worsening
      - d. Clinical information request sent 18 May 2015, requesting submission of a Pharmacovigilance Plan, if one is available.
    - ii. Statistics
      - a. Statistical information request sent May 18, 2015, requesting results from analyses of the key secondary efficacy endpoints using a pattern mixture model.

- iii. Product Quality Microbiology
  - a. Responses to previous information requests are under review and additional information requests will be sent. Drug Master File reviews are not yet complete.
- 4. Discussion of Upcoming Advisory Committee Meeting
- 5. Postmarketing Requirements/Postmarketing Commitments
  - A. Product Quality Microbiology
    - i.  (b) (4)
    - ii. Qualification of the bioburden and sterility test methods was performed with only two lots of drug product, with the exception of qualification of the sterility test method for the recovery of *A. brasiliensis*. As a post-marketing commitment, provide bioburden and sterility test qualification data from one additional batch of 150 mg/ml drug product that was not manufactured from drug substance batches 8065000001 or 8065000002. The study may be done with bulk drug product. The data should be provided in the first annual report.
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  - E. Labeling discussions (as needed)
- 8. Wrap-up and Action Items –

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/s/  
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JAMES P SMITH  
05/20/2015