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RESEARCH**

APPLICATION NUMBER:

125559Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125559
Product Name: Praluent (alirocumab) injection

PMR #1 Description: Conduct a dose-finding study (Phase 2) and an efficacy and safety study (Phase 3) evaluating alicumab in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less than 18 years. If children younger than age 10 are included, the eligibility criteria should ensure that other available interventions to lower LDL-C have been insufficient. Phase 2 will be a randomized, open-label, 8 week, ascending repeated dose-finding study of alicumab with an optional open-label extension study in patients 10 years to less than 18 years of age with HeFH on stable lipid modifying therapy with LDL-C \geq 130 mg/dL. Phase 3 will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C \geq 130 mg/dL. Patients treated in Phase 2, the dose-finding study, will be offered enrollment in Phase 3, the efficacy and safety study.

PMR Schedule Milestones:	Final Protocol Submission (Phase 2):	<u>January 2016</u>
	Final Protocol Submission (Phase 3):	<u>December 2017</u>
	Study Completion (Phase 2):	<u>December 2018</u>
	Study Completion (Phase 3):	<u>April 2022</u>
	Final Report Submission (Phase 2 and 3):	<u>September 2022</u>

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Praluent is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to establish the pharmacokinetics of Praluent in the pediatric population ages 10 to < 18 to determine appropriate dosing, and to establish the safety and efficacy of Praluent in that same population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Phase 2 will be a randomized, open-label, 8-week, ascending repeated dose-finding study of alirocumab with an optional open-label extension study in patients 10 to <18 years with HeFH on stable lipid modifying therapy with LDL-C \geq 130 mg/dL. Phase 3 will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study followed by an 18-month open-label extension in patients 10 to <18 years with HeFH on stable lipid-modifying therapy with LDL-C \geq 130 mg/dL.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125559
Product Name: Praluent (alirocumab) injection

PMR #2 Description: Conduct a prospective observational study of pregnant women exposed to Praluent to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to Praluent and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The study should have validated/adjudicated outcomes, a comparator group, be powered to detect the outcomes of interest, and include the justification for the proposed detectable differences in incidence rates.

PMR Schedule Milestones:	Final Protocol Submission:	<u>July 2016</u>
	Interim Report Submissions:	July 2017
		July 2018
		July 2019
		July 2020
		July 2021
		July 2022
		July 2023
		July 2024
		July 2025
		July 2026
	July 2027	
	July 2028	
July 2029		
	Study Completion:	<u>June 2030</u>
	Final Report Submission:	<u>December 2030</u>

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A long-term study of women exposed to Praluent during pregnancy is needed; this is only feasible in the post-approval setting.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In cynomolgus monkeys, suppression of the humoral immune response to keyhole limpet hemocyanin (KLH) antigen was observed in infant monkeys at 4 to 6 months of age when alirocumab was dosed during organogenesis to parturition at 15 mg/kg/week and 75 mg/kg/week by the subcutaneous route, corresponding to 13- and 81-fold the human exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC. The lowest dose tested in the monkey resulted in humoral immune suppression; therefore it is unknown if this effect would be observed at clinical exposure. No study designed to challenge the immune system of infant monkeys was conducted. No additional embryo-fetal, prenatal or postnatal effects were observed in infant monkeys, and no maternal effects were observed, when alirocumab was dosed at up to 75 mg/kg/week by the subcutaneous route, corresponding to maternal exposure of 81-fold the exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC.

Given the nonclinical findings described above, there is concern for the possibility of adverse events in infants such as poor vaccine response and increased infections.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective observational study of pregnant women exposed to Praluent to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to Praluent and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The study should have validated/adjudicated outcomes, a comparator group, be powered to detect the outcomes of interest, and include the justification for the proposed detectable differences in incidence rates.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125559
Product Name: Praluent (alirocumab) injection

PMR #3 Description: Conduct a large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity, and adverse events potentially related to demyelination with alirocumab treatment will be evaluated.

PMR Schedule Milestones:	Final Analysis Plan Submission:	<u>January 2016</u>
	Trial Completion:	<u>March 2018</u>
	Final Report Submission:	<u>August 2018</u>

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

To assess the potential safety issues of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity, and adverse events potentially related to demyelination, a large long-term trial is needed. This is only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to evaluate signals of new-onset diabetes mellitus, injection site reactions, hypersensitivity, and immunogenicity.

There was a slightly greater proportion of PRAULENT treated patients that met the criteria for worsening glycemic control by adverse event or laboratory value in the pooled phase 3 placebo-controlled trials. In this exploratory analysis, 5.7% and 3.8% of patients in the PRALUENT and placebo groups, respectively, shifted from impaired glucose control at baseline to diabetes as defined by laboratory values and/or adverse event reports. However, a similar proportion of patients taking PRALUENT (20.6%) and placebo (18.6%) shifted from impaired glucose control to the normal glycemic category. For the majority of patients treated with PRALUENT, glucose control remained stable. It is unknown if these observed shifts in glycemic control categories represent a true risk for new onset diabetes with PRALUENT treatment.

Local injection site reactions including erythema/redness, itching, swelling, and pain/tenderness were reported more frequently in patients treated with PRALUENT (7.3%) versus placebo (5.2%).

Allergic reactions were reported more frequently in patients treated with PRALUENT (8.6%) versus placebo (7.8%). The proportion of patients who discontinued treatment due to allergic reactions was higher among those treated with PRALUENT (0.6%) versus placebo (0.2%). Serious allergic reactions, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported in patients using PRALUENT in controlled clinical trials.

In a pool of ten placebo- and active-controlled trials, 4.8% of patients treated with PRALUENT had anti-drug antibodies (ADA) newly detected after initiating treatment as compared with 0.6% of patients treated with control. Patients who developed ADA had a higher incidence of injection site reactions compared with patients who did not develop ADA (10.2% vs. 5.9%). A total of 1.2% of patients treated with PRALUENT developed neutralizing antibodies (NAb) on at least one occasion as compared with no patients treated with placebo, with 0.3% of patients both testing positive for NAb and exhibiting transient or prolonged loss of efficacy. The long-term consequences of continuing PRALUENT treatment in the presence of persistent NAb are unknown.

In the placebo-controlled trials, there were 4 (0.2%) serious cases potentially related to demyelination among patients treated with PRALUENT and none among those treated with placebo. These cases included events that would be expected to have very low incidence in the general population: Miller-Fisher syndrome (a variant of Guillain-Barre syndrome), transverse myelitis, optic neuritis, and demyelination (suspicious for multiple sclerosis).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A large, randomized, controlled, long-term trial. (b) (4)
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125559
Product Name: Praluent (alirocumab) injection

PMR #4 Description: Conduct a randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with alicocumab treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.

PMR Schedule Milestones:	Final Protocol Submission:	<u>February 2016</u>
	Trial Completion:	<u>August 2020</u>
	Final Report Submission:	<u>December 2020</u>

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The concern described below is theoretical, and may not be relevant to PCSK9 inhibitors as (1) the molecule is generally not expected to cross the blood-brain barrier, and (2) evidence suggests that the brain generates its own cholesterol. Neurocognitive events were similar between Praluent (0.8%) and placebo (0.7%).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to evaluate the theoretical concern for neurocognitive effects. There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use (class labeling), which led to the concern regarding potential neurocognitive effects associated with low LDL cholesterol.

The preferred terms of confusional state and memory impairment occurred at a higher incidence in the alicocumab group (0.2% for both preferred terms) than in the placebo group (<0.1% for both preferred terms).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In the 8 patients from the phase 3 program, the presence of higher titer (>1:240) or neutralizing antibodies (NAB) correlated with changes in LDL-C, free PCSK9 and alirocumab levels, though the latter was often inconsistent. At this time, there are no data to guide how a clinician should respond if efficacy wanes as a result of immunogenicity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This purpose of this PMC is to develop an algorithm for decision-making in the face of loss of efficacy due to antibody response. This should include an examination of the binding of alirocumab-specific neutralizing antibodies to the LDL receptor in patients in whom the presence of anti-drug antibodies are associated with LDL-C levels > 1.5-fold baseline in the absence of other confounding factors (e.g., non-adherence or intentional changes in concomitant LDL-C-lowering medications).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

The sponsor provided microbial retention data (b) (4). The results met the acceptance criteria. However, the sponsor had to perform a modified test (product exposure followed by bacterial challenge) in order to meet the acceptance criterion for challenge organism viability over the duration of the study. Other aspects of the study design were not ideal, such as (b) (4) and the batch size simulated during the bacterial challenge stage (b) (4).

The sponsor later agreed (b) (4) in response to a request from the Agency. A (b) (4) would be feasible for this time limit. The goal of the study is to confirm that (b) (4) is acceptable under worst-case processing conditions.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

5. To be completed by

The sponsor will repeat the microbial retention study as a (b) (4) test. The study will simulate worst-case processing conditions and (b) (4).

Completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

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

PMR/PMC Development Coordinator:

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

_____ (signature line for BLAs only)

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

Because the drug product is a relatively complex large molecule drug, method qualification data from three different lots is required for method qualification.

The goal of the study is to complete method qualification by obtaining data from one additional lot of drug product.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

5. To be completed by

The sponsor will provide bioburden and sterility test method qualification data from one additional lot of 150 mg/mL drug product that was not manufactured from drug substance batches 8065000001 or 8065000002.

pleted by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

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

NDA/BLA # BLA 125559
Product Name: Praluent (alirocumab)

PMC #8 Description:

(b) (4)
[Redacted]
[Redacted] . Revise the container closure integrity test method to include a system suitability control with [Redacted] (b) (4) .

PMC Schedule Milestones:	Study Completion:	<u>05/31/2016</u>
	Final Report Submission:	<u>09/30/2016</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 21 CFR 314.101 OR WILL BE PUBLICALLY REPORTABLE**

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

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

[Redacted] (b) (4)
The PMC is for improvement of one of the assay controls.

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

[Redacted content with (b) (4) in the top right corner]

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

The sponsor will revise the [Redacted content with (b) (4) in the top right corner] additional method validation may not be required.

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

PMR/PMC Development Coordinator:

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

_____ (signature line for BLAs only)

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

(b) (4)

The goal is to establish procedures for (b) (4). The hold time limits for endotoxin testing will be based on data from endotoxin hold time studies (refer to PMC 10).

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

5. To be completed

The sponsor will implement (b) (4). The hold time limits will be based on data from endotoxin testing hold time studies (refer to PMC 10).

ed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

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

PMR/PMC Development Coordinator:

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

_____ (signature line for BLAs only)

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

The drug product manufacturing site uses the [REDACTED] (b) (4). Because differences in endotoxin recovery over time have occasionally been observed when using [REDACTED] (b) (4).

The goal of the study is to establish endotoxin testing [REDACTED] (b) (4).

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

The sponsor will perform an endotoxin [REDACTED] (b) (4). The study will be designed to support the proposed endotoxin testing [REDACTED] (b) (4).

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

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

The ^{(b) (4)} bioburden limit for ^{(b) (4)}

The goal of the study is to determine whether lower in-process bioburden limits are supported by process capability.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

5. To be com

The sponsor will revise the ^{(b) (4)} bioburden limit for ^{(b) (4)} after data from additional drug product batches has been analyzed.

pleted by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

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

PMR/PMC Development Coordinator:

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

_____ (signature line for BLAs only)

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

/s/

JENNIFER R PIPPINS
07/24/2015



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Memorandum to the File

Date: July 16, 2015

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Acting Division Director,
Division of Pediatric and Maternal Health

To: The Division of Metabolism and Endocrinology Products (DMEP)

Drug: Praluent (alirocumab)

BLA: 125559

Subject: Consult request about a postmarketing study (PMR or PMC) for potential adverse events in infants including humoral immune suppression with use of Praluent in pregnancy

Applicant Sanofi-Aventis U.S. LLC

Consult Questions: DMEP is asking DPMH the following questions as a follow up to a meeting on July 10, 2015 for (b) (4)

- 1) Is there a study that DPMH can envision, that would be both feasible and ethical, and which could address the specific safety issue of suppressed humoral immunity?

- 2) If the answer to (1) is no, then does DPMH (in consultation with DMEP clinical) recommend asking for a PMC study with the goal of collecting additional information regarding use of Praluent in pregnancy?
- 3) If the answer to (2) is yes, then does DPMH (in consultation with DEPI) consider an observational study in pregnancy (e.g., what (b)(4) is already proposing is a reasonable design for such a PMC study)?
- 4) The signal identified from the nonclinical data is a suppression of humoral immunity. Nonclinical noted that in order to further elucidate this issue, the only truly useful metric would be response to vaccination. What are your thoughts on this?
- 5) PV is subject to a number of limitations (e.g., retrospective, voluntary, limited amount of data, no comparator, cannot determine incidence). DPV noted that they think it is unlikely that the data provided by a pregnancy PV program will be able to address the safety issue of humoral immunity suppression. What are your thoughts on this?
- 6) Does your recommendation for (b)(4) still stand?
- 7) What are your views on (b)(4) proposed observational study in pregnancy?

Materials Reviewed:

- Consult request for Praluent (BLA 125559)
- Review of the consult request and response for (b)(4)

INTRODUCTION

On November 24, 2014, Sanofi-Aventis US LLC submitted BLA 125559 for Praluent (alirocumab), subcutaneous injection, to be used for as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

BACKGROUND

Product Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secretory serine protease that homeostatically regulates the amount of plasma LDL-C by interacting with the LDL receptor (LDL-R). After binding to LDL-R and internalization, PCSK9 directs the LDL-R to lysosomal degradation, thus inhibiting LDL-R recycling to the hepatocyte surface. This action inhibits catabolism of plasma LDL-C¹. LDL-R is the primary receptor that clears circulating LDL, therefore, the decrease in LDL-R levels by PCSK9 results in higher blood levels of LDL-C.

Praluent is a human monoclonal antibody (IgG1 isotype). It belongs to the group of PCSK9 inhibitor antibodies. Praluent binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to LDL-R on the liver cell surface, thus preventing PCSK9-mediated LDL-R degradation and permits LDL-R to recycle back to the liver cell surface. Increasing liver LDL-R levels result in associated reductions in serum LDL-C. By inhibiting the binding of PCSK9 to LDL-R, alirocumab increases the number of LDL-Rs available to clear LDL, thereby, lowering LDL-C levels.

¹ Santos RD and Watts GF. Familial hypercholesterolemia: PCSK9 inhibitors are coming. *The Lancet*, 2015;385(9965):331-340

Alirocumab is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension culture. Alirocumab has an approximate molecular weight of 146 kDa.

Regulatory Issues

(b) (4)
The purpose of the meeting was to discuss the concern that Pharmacology/Toxicology reviewers raised about the nonclinical safety data, specifically the humoral immune suppression. The reviewer identified a signal of a serious risk related to the use of alirocumab. Humoral immune suppression (IgG) was demonstrated in the offspring of pregnant cynomolgus monkeys administered alirocumab. (b) (4)

Such a study is a requirement as the guidance to the industry for pharmacology toxicology studies provides for the study.

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute. DPMH has determined that the signal of humoral immune suppression, demonstrated in the offspring of pregnant cynomolgus monkeys administered alirocumab, identifies a potential safety concern for neonates and infants when a pregnant woman is administered Praluent (b) (4). Further assessment of this potential safety concern is necessary to monitor for adverse neonatal and infant outcomes (i.e., recurrent infections with encapsulated bacteria, life-threatening enterovirus infections, failure to respond to appropriate antibiotic therapy). In addition, due to the lack of adequate safety information on the use of Praluent (b) (4) in pregnant women, assessment of pregnancy outcomes and embryo-fetal growth and development are recommended. DPMH has proposed a trial should be conducted to evaluate adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant outcomes related to humoral immune suppression. The study may be conducted as a pregnancy pharmacovigilance program.

The reader is referred to the approval letter for the final negotiated post-marketing requirement.

DMEP QUESTIONS AND DPMH RESPONSES

- 1) Is there a study that DPMH can envision, that would be both feasible and ethical, and which could address the specific safety issue of suppressed humoral immunity?

DPMH response: Yes, we recommend a pregnancy pharmacovigilance study. This study will not evaluate specifically the humoral immune suppression signal but rather will evaluate potential adverse events in infants that may warrant further investigation in the future (e.g., increased infections, poor response to vaccination which would lead to specific infections, etc.).

- 2) If the answer to (1) is no, then does DPMH (in consultation with DMEP clinical) recommend asking for a PMC study with the goal of collecting additional information regarding use of Praluent in pregnancy?

DPMH response: We consider a PMR would be a reasonable approach. Further discussions about the specific study and what program should be implemented may be decided after the approval of the drug. We recommend a broadly worded PMR prior to approval. Such a PMR will allow us more time to reevaluate the options and select the best strategy.

- 3) If the answer to (2) is yes, then does DPMH (in consultation with DEPI) consider an observational study in pregnancy [REDACTED] (b) (4) Is this a reasonable design for such a PMC study?

DPMH response: See our response to question #2

- 4) The signal identified from the nonclinical data is a suppression of humoral immunity. Nonclinical noted that in order to further elucidate this issue, the only truly useful metric would be response to vaccination. What are your thoughts on this?

DPMH response: We recognize that more discussion is needed to arrive at the most appropriate metric to evaluate humoral suppression. However, some clinical information may be gained from a pregnancy pharmacovigilance program with follow up of infant outcomes. Our proposed PMR language is more general due to these considerations, and would allow the sponsor to consider an appropriately designed program. The study design issues will be determined later with input from the sponsor and other consultants as needed.

- 5) PV is subject to a number of limitations (e.g., retrospective, voluntary, limited amount of data, no comparator, cannot determine incidence). DPV noted that they think it is unlikely that the data provided by a pregnancy PV program will be able to address the safety issue of humoral immunity suppression. What are your thoughts on this?

DPMH response: Even though a pregnancy pharmacovigilance program may have some limitations, a pregnancy pharmacovigilance program may also capture prospective cases. The design may be modified [REDACTED] (b) (4)

6)

7)



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

/s/

CHRISTOS MASTROYANNIS
07/21/2015

TAMARA N JOHNSON
07/21/2015

LYNNE P YAO
07/23/2015

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 17 July 2015

FROM: John R. Senior, M.D., Associate Director for Science (Hepatology), Office of Pharmacovigilance and Epidemiology (OPE)

TO: James Smith, M.D. Deputy Director and acting Medical Team Leader,
Division of Metabolic and Endocrine Products (DMEP)
Jean-Marc Guettier, Director, DMEP
Mary Roberts, M.D., Medical Safety Reviewer (DMEP)
Julie Golden, M.D., Medical Efficacy Reviewer (DMEP)
Patricia Madara, Regulatory Project Manager (DMEP)

CC: Mark Avigan, M.D., Associate Director, OPE
Solomon Iyasu, M.D., Director, OPE
Robert Ball, M.D., Deputy Director, OSE
Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Request dated 19 June 2015 for urgent review of possible Hy's Law case, as soon as possible, received at OSE/OPE 19 June 2015:1803

Documents reviewed:

- 1) Consultation request from Drs. Mary Roberts and James Smith of DMEP concerning a 48-year-old South African woman under long-term treatment for hypercholesterolemia with alirocumab (Praluent^R, Sanofi/Regeneron) who developed fatigue, malaise, and conjunctival jaundice on 2 March 2015, followed by sharp rises in serum alanine aminotransferase and total bilirubin on [REDACTED]^{(b) (6)}, hospitalization, and close follow-up
 - 2) Copy of MedWatch report dated 11 June 2015 submitted by sponsor 18 June, with tabulated test results and narrative comments
 - 3) Urgent Information Request for BLA 125559, dated 20 June 2015 (sent 0036 am)
 - 4) Request for urgent meeting Tuesday 23 June @ 0930-1000 in 22:4201
 - 5) Response to Agency Requests, Items 1 and 2, forwarded by J. Smith on 22 June @1539
 - 6) Response to Agency Requests, Item 3, received 6 July
 - 7) Clinical Review of BLA 125559, 7 July 2015, by Julie Golden and Mary Roberts
 - 8) Serial safety reports to IND 105574, 16 March to 18 June, for case 2015SA028033
 - 9) Minutes of late-cycle meeting 28 May 2015
 - 10) Updated Investigator's Brochure, Edition 08 dated 11 May 2015, received 16 June 2015
 - 11) Amendment to BLA 125559 by Sanofi 29 June
 - 12) Pertinent medical literature citations
-

The consultation request for urgent response sent late afternoon on Friday 19 June appeared to have been triggered by DMEP becoming aware of a case of serious hepatotoxicity for which no clear explanation of cause had been found in a patient in South Africa who developed symptoms of malaise, nausea, and jaundice on 2 March 2015, was found to have very elevated serum ALT and AST the next day, and was hospitalized on (b) (6). As stated in the consultation request, a possible DILI event was described in a safety report just received under the IND (105574) but not included in the BLA (125559). In addition, an urgent request was sent to the sponsor just after midnight on 20 June, requesting immediate responses to three questions:

- 1) specifically about the patient 710-408-007, whether testing had been done for hepatitis E or immunogenity testing, and asking for all gastroenterology/hepatology consultation reports;
- 2) details for patient 11570-348-010-008 who had been reported to have had unexpected serious adverse liver test abnormalities;
- 3) query the entire clinical trial database for subjects showing serum ALT > 3xULN & TBL >2xULN, or ALT >5xULN & interruption of treatment, especially cases not submitted with the original BLA, those with the 4-month safety update, or submitted only to the IND 105574, with narratives and serial test values, and possible causes.

The sponsor replied quickly by email on 22 June 2015 to the first two questions, saying that the patient in South Africa had shown IgM antibodies to hepatitis E on 12 and 17 June, and that she was no longer being considered as having drug-induced hepatitis related to the alirocumab. Dr. Smith notified us immediately of this information on 6/22 @ 3:59 pm.

Even before learning from Sanofi about the hepatitis E findings, Dr. Avigan and I separately had reviewed the MedWatch report submitted with the consultation on 19 June and concluded that the cause of the acute liver abnormalities of case 710-208-007 was very unlikely to have been the experimental drug and was very likely to have been acute viral hepatitis, probably hepatitis E. We spoke together on the morning of 22 June, and Dr Avigan sent an email at 1:40 saying:

“Both John and I agree that given the characteristics of the case’s time of onset (9 months into treatment initiation and on day 4 of the treatment cycle), rapid resolution etc, acute viral hepatitis seems to be at the very top of the differential. Alirocumab, a s/c injected monoclonal has a relatively long half-life and thus systemic exposure to this agent would have continued beyond the spontaneous resolution phase of the hepatitis. When I looked at the report on the weekend I was going to ask for Hepatitis E viral RNA and/or IgM serology to r/o acute hepatitis E (Aggarwal R, 2013)) and Hep C RNA (which can appear during the very early phase of acute hepatitis C before serological conversion).”

Prior to our talking together, I had summarized data from the MedWatch report included with the consultation request of 19 June. A few minutes later (1:53) I sent them as an Excel document:

BLA 125559 alirocumab (PRALUENT, Sanofi)
IND 105574 PCSK9 inhibitor

for heterozygous familial hypercholesterolemia

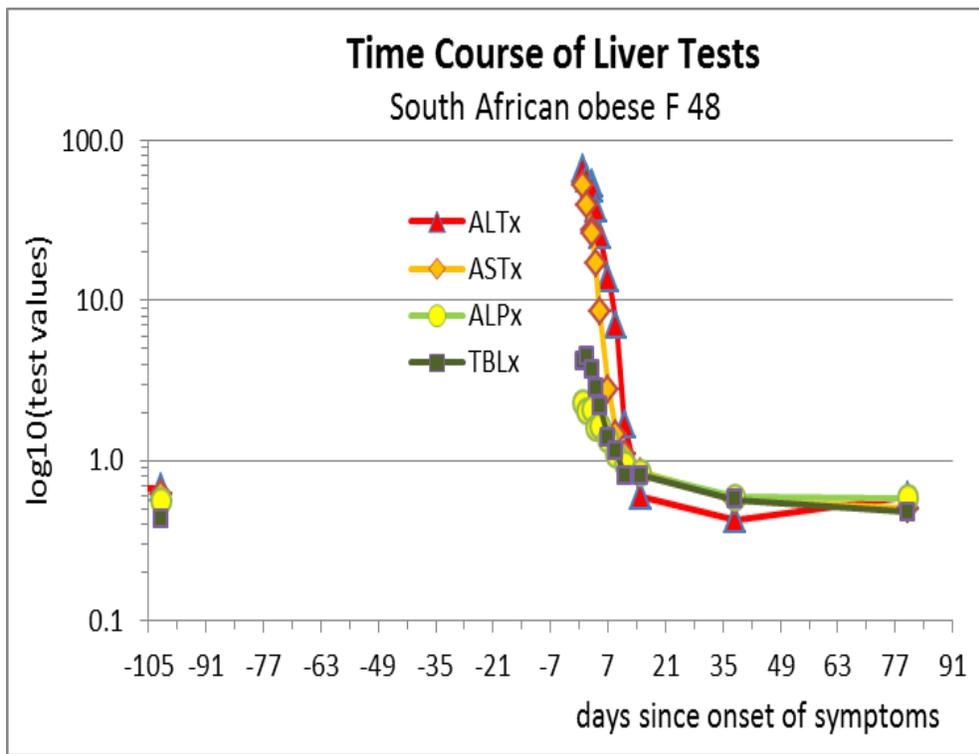
case report rec'd 11 June 2015

on 75 mg sc q. 2 weeks 6/5/2014---2/26/2015; oral 40 mg/day simvastatin 40 ezetimibe 10/d since 9/1/12

Obese F48 #710-408-007 at site 710-313 in open-label extension study LTS13463 after EFC12492

BMI 41.8 130/74 diabetic history of hypertension, CV disease, depression, spastic colon, back pain, cystitis, hysterectomy, Achilles tendon thickening, myopia

Other meds: COZAAR, SPIRACTIN, DISPRIN, since 1/15/2014; and FYBOGEL since 2009



"Day"	ALTx	ASTx	ALPx	TBLx
-102	0.7	0.6	0.6	0.4
0	onset:	malaise	nausea	jaundice
1	66.2	52.9	2.3	4.1
2	57.5	38.9	2.1	4.5
3	54.0	27.8		
3	49.9	26.3	2.1	3.7
4	37.6	17.0	1.6	2.9
5	25.6	8.6	1.7	2.2
7	13.9	2.8	1.4	1.4
9	7.1	1.5	1.1	1.1
11	1.7	1.1	0.9	0.8
15	0.6	0.8	0.8	0.8
38	0.4	0.6	0.6	0.6
80	0.6	0.5	0.6	0.5
112	reported	Hepatitis	E	IgM

Although the day of onset of reported symptoms, 2 March 2015, is arbitrarily taken as Day 0 in the graphic depiction, it would seem very probable that the serum enzymes had begun to rise some days before the symptoms were noticed. The time course of abnormal liver tests was short, resolving spontaneously in less than a month, and with the appearance of acute IgM antibodies against hepatitis E. It will be of interest to confirm that the patient eventually will develop IgG antibodies indicating permanent immunity. The values in the graph are in multiples of the testing laboratory's upper limit of the normal reference range, depicted in an \log_{10} scale

With the concurrence of Dr. Avigan and me, and the report of hepatitis E acute-phase antibodies, we all agreed that an emergency meeting on 23 June was not needed, and it was cancelled. Dr. Avigan sent an additional comment on 22 June at 5:19 pm about confirming IgG antibodies to be done in September (Krain et al. 2014; Mayo Clinical laboratories 86212). In lieu of a meeting on 6/23, I sent a comment @9:26 am and a few more current references (Perez-Gracia 2014; Ahmed 2015; Sridhar 2015). We agreed to await the further responses from the sponsor, particularly for answering question 3, and further followup of the patient. An amendment to BLA 125559 was submitted by Sanofi 29 June to allow time for responding in detail to question 3 (Item 3) of the 20 June request from DMEP.

In the meantime, Dr. Avigan went on vacation leave to Italy 29 June-17 July and I to update New York 6-10 July. On return, I found that new entries into DARRTS included the 6 July sponsor's preliminary response to Item 3 of the 20 June request from DMEP for review of the clinical trial database for other possible cases of hepatotoxicity. It listed another 23 cases, 20 from study 011570, 2 from ongoing study 001308 and 1 from open-label study 1003. The sponsor had also submitted on 29 June an amendment to BLA 124449 in response to the DMEP request. Also entered into DARRTS on 7 July was the clinical review by Drs. Julie Golden (efficacy) and Mary Roerts (safety) that had been prepared for the advisory committee meeting of 9 June 2015, but had a cut-off date of 31 August 2014 and did not include the case of interest that triggered this consultation request and flurry of urgent activity 19-22 June.

The very comprehensive (321 pages) combined efficacy-safety clinical review by Drs Golden - Roberts was prepared for presentation at the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting on 9 June 2015. It included analyses of 10 multicenter phase 3 clinical trials that randomized 5296 patients, 9 of which enrolled patients with heterozygous familial hypercholesterolemia (HeFH); 5 trials were placebo-controlled, 5 active agent-controlled, at biweekly subcutaneous injection of 75 or 150 mg alirocumab. Very consistent and substantial reduction in serum low-density lipoprotein cholesterol (LDL-C) was found in all trials, with prompt and sustained effect. Whether this clear surrogate effect will translate into true benefit remains unproved, and in put from EMDAC will be sought. Very careful safety analyses of 3340 patients from 4 small phase 2 trials and 10 larger phase 3 studies, was carried out, with results showing 17 (0.9%) deaths in the control group and 20 (0.6%) in the alirocumab group. There was no significant difference seen in all treatment-emergent serious adverse events: 14.3% in the placebo-treated and 13.7% in alirocumab-treated patients, but when hepatic-related events were considered, there were somewhat more (2.5%) in alirocumab-treated patients than in placebo-treated patients (1.8%). Most of the abnormalities detected were of serum enzyme elevations but there were 3 cases with both $ALT > 3 \times ULN$ and $TBL > 2 \times ULN$ but for whom other causes were found (hepatitis A, cholecystitis, cholangitis).

Finding the case of apparent drug-induced serious hepatotoxicity in the index case for this consultation resulted from careful review of the many safety reports submitted to the IND 105574 that were not submitted to BLA 125559. The index case, 710-408-007, the 48 year-old South African woman, had first been reported to the IND on 16 March as initial (3/12) and follow-up #1 (3/15) MedWatch reports shortly after onset of the patient's symptoms on 2 March and finding very high aminotransferase values on 3 March, as case 2015SA028033 in LTS13463. These were buried among scores of other MedWatch reports submitted dutifully to the IND, and were followed by serial reports of the incremental progress of findings during the patient's recovery as:

Follow-Up # 2	MedWatch report dated 3/23	Submitted to IND 3/24
Follow-Up # 3	MedWatch report dated 3/25	Submitted to IND 4/1
Follow-Up # 4	MedWatch report dated 3/27	Submitted to IND 4/1
Follow-Up # 5	MedWatch report dated 4/1	Submitted to IND 4/1
Follow-Up # 6	MedWatch report dated 4/3	Submitted to IND 4/14
Follow-Up # 7	MedWatch report dated 6/3	Submitted to IND 6/11
Follow-Up # 8	MedWatch report dated 6/11	Submitted to IND 6/18

The last of the MedWatch reports was included in the consultation request and was used for data to construct the Excel file and graphic shown above.

The sponsor's *preliminary* response to Item 3 of the DMEP urgent request of just after midnight 20 June was received on 29 June, inserted in Module 1.11.2, and entered into the DARRTS BLA 1225559 on 6 July as Sequence No. 0057. It included two documents: 1) information on topics requested by DMEP on 20 June 2015, with information on 6 patients; and 2) Appendix A – narratives and laboratory data for 23 patients. The request had asked specifically for information on any patient in the entire study database, including on-going and still-blinded studies who developed ALT>3xULN & TBL>2xULN or ALT>5xULN & serious event or leading to discontinuation of treatment addressed in the first document, which included 3 patients with (ALT>3xULN & TBL>2xULN) from on-going open label studies and 3 more from on-going, still-blinded studies. Detailed narratives with baseline and follow-up liver test results were requested for all cases not submitted with the original BLA, or links to narratives if already submitted. The sponsor recognized that not all the information requested could be provided immediately, that some information from contract research organizations was not yet available, and that data cleaning from on-going studies was in process. That said, the sponsor stated that this comprehensive search corresponding to a database of 16,537 patients did not identify any particular signal linking disturbed liver function with alirocumab exposure.

SERUM (ALT>3xULN & TBL>2xULN) or (ALT>5xULN & serious event or leading to discontinuation of treatment)

ON-GOING OPEN-LABEL EXTENSION STUDIES – 3 patients from 1550 (0.3%) considered were identified:

Patient **012492-710-408-007**, the 48 year-old South African woman described as the index case - -- probable acute viral hepatitis E;

Patient **011717-528-001-022 SUR** (4-month safety update), who showed elevated serum aminotransferases when started on alirocumab on 5/23/2014, peaking 20 days later at ALT 32.9xULN, AST 21.2xULN, ALP 1.3xULN and TBL 2.1xULN, normalizing within 6 weeks despite continued treatment with alirocumab and diagnosed as caused by acute hepatitis E.

Patient **1003-840-309-002** in CL-1032 study, a woman 53 who showed persistent low grade aminotransferase elevations in the 1–2xULN range with normal ALP and TBL, started on alirocumab 9/11/2012 with no worsening of aminotransferases until a transient peak of ALT 7.3xULN and AST 7.8xULN was noted on 5/21/2014 some 20.6 months later, with resolution despite continuing alirocumab. A liver mass was suspected by ultrasound but no diagnosis was made.

ON-GOING DOUBLE-BLIND PHASE 3 STUDIES – 3 patients of 14,987 (0.02%) considered were identified:

Patient **011570-804-001-022** in the OUTCOMES study, a 74 year-old woman with normal liver tests at screening and initiation of treatment on 6/18/2014, who developed modest aminotransferase elevations on 10/21, ALT 4.5xULN, AST 2.9xULN with ALP 2.0xULN and TBL 1.9xULN. The aminotransferases subsided within two weeks, but the TBL peaked at 2.1 xULN and the ALP subsided more slowly. She has no symptoms, only minimal work-up and no hepatology consultation, but was classified as having had cholestasis. Her treatment was stopped, and it was not reported if it had been restarted.

Patient **011570-826-030-021** in the OUTCOMES study, a man 67 with history of at least weekly alcohol use, and coronary syndrome. He was started on treatment on 8/27/2014, at which time his liver tests were in the normal range. On 12/29 he presented with jaundice, and the next day has ALT 12.5xULN, AST 13.1xULN, TBL 3.1xULN. The abnormalities subsided within 10 days and no cause was found. Although he was considered to have drug-induced liver injury, he had been receiving placebo.

Patient **011570-826-207-018** in the CHOICE I study, a man 64 who started treatment 3/7/2014 with normal liver test results but developed symptomatic acute hepatitis C on 11/10, with ALT 14.1xULN, AST 14.3xULN, rising 6 days later to ALT 24.4xULN, AST 20.8xULN but persistently normal ALP and TBL. The aminotransferases slowly fell but rose again to ALT 7.9xULN, AST 8.3xULN on 4/7/2015, suggesting possible transition from acute to chronic hepatitis C. He was found to have been receiving alirocumab, but it was not considered to have been the cause of the liver injury.

A larger number of patients was found for whom narratives were provided in Appendix A of the preliminary response to Item # of the DMEP request of 20 June:

1 NARRATIVE ONGOING DOUBLE-BLIND STUDIES

1.1 CL-1038 (CHOICE I)

NARRATIVE PATIENT 001-308-826-207-018 - described above

NARRATIVE PATIENT 001-308-840-104-070, a man 68 with no history of liver disorders, who showed normal test values at start of treatment 12/20/2013, but showed mild elevation of ALT to 2.2xULN on 6/6/2014 without other abnormalities. The elevation subsided but recurred to ALT 5.3xULN, AST 2.3xULN on 8/29, rising to ALT 8.9xULN, AST 3.3xULN on 9/8, then subsiding again to normal on 10/8, but again rising to ALT 7.4xULN, AST 2.9xULN on 10/22. The last values on 1/16/2015 showed that he had again normalized. No explanation was found for these mild, asymptomatic, and non-dysfunctional findings (.TBL was persistently normal, as was the ALP). He was found to have been on alirocumab.

1.2 STUDY EFC11570 (OUTCOMES)

NARRATIVE PATIENT 011570-144-008-013, a man 48 was found to have normal screening values for liver test a month before he was started on treatment but had slight bilirubin elevation to 1.7xULN with no other liver test abnormalities.

NARRATIVE PATIENT 011570-710-004-003, a woman 62 with history of diabetes and hypothyroidism, showed an isolated high ALT 2.0xULN at screening 4 weeks before starting injections on 22 June 2013. Four weeks later her ALT was 5.4xULN, AST 1.4xULN, ALP 3.4xULN but TBL normal, without symptoms. Injections were discontinued, atorvastatin 40 mg/day was continued. At day 120 (19 October 2013) her ALT was still 1.3xULN, AST 1,1xULN, ALP 3.3xULN and TBL normal. No cause was found and she had no further testing done.

NARRATIVE PATIENT 011570-710-018-145, a woman 61 with history of coronary syndrome and hepatomegaly, showed normal liver tests at screening a month before starting injections on 28 July 2014. On the day injections were started ALT was found to be 10.8xULN. AST 8.3xULN but ALP and TBL were normal. Tests for viral markers A, B, C, E, CMV were negative but HSV 1 and 2 showed IgG antibodies. Rosuvastatin was decreased from 20 to 10 mg/day and the intraperitoneal injections were interrupted. Two weeks later all liver tests were normal and injections were restarted, with no subsequent rise in liver test values out to Day 116 (11/20/2014).

NARRATIVE PATIENT 011570-724-025-072, a man 52 with history of coronary syndrome, had had normal liver test at screening 4 weeks before the first injection on 15 April 2014, when mild aminotransferase elevations were noted: ALT 3.8xULN, AST 2.4xULN. They continued to rise on Day 22 three weeks later: ALT 11.6, AST 7.9xULN but ALP and TBL normal. Atorvastatin was reduced from 40 to 20 mg/day, the elevated enzyme activities declined within 4 months, despite continued injections. The abnormalities were attributed to the statin.

NARRATIVE PATIENT 011570-752-012-019, a man 48 with history of coronary syndrome, had normal liver test at screening 6 weeks before and at onset of treatment on 21 May 2014. On 18 September, 4 months later his ALT rose to 4.5xULN, AST 4.7xULN, ALP 1.5xULN and TBL 1.1xULN. Four days later the serum enzymes peaked at ALT 5.1xULN, AST 5.1xULN, ALP 1.6xULN, TBL 1.1xULN. The intraperitoneal injections were continued but the atorvastatin dose was reduced from 80 to 40 mg/day. The ALT normalized within 2 months and remained so at 4 and 9 months after onset of the test abnormalities, which were attributed to the statin.

NARRATIVE PATIENT 011570-840-097-014, a man 54 with history of coronary syndrome, had ALT at the upper limit of normal at screening a month before and at initiation of injections on (b) (6). His ALT was slightly increased to 1.9xULN 28 days later and on Day 61 (b) (6) he had sudden lower abdominal pain, fever, nausea, vomiting, constipation, and weakness, and was hospitalized. Serum lipase was elevated and MRI showed pancreatic phlegmon and dilated biliary ducts. He recovered from the acute pancreatitis, and the liver tests 2/3/2014 and thereafter were found to be normal. He had been receiving alirocumab.

NARRATIVE PATIENT 011570-032-003-017, a woman 68 with normal liver tests at screening a month before the first injection of study drug on 10 July 2014, showed slight ALT elevation 1.1xULN that day, but 25 days later complained of abdominal pain and dyspnea. Her ALT had risen sharply to 18.0xULN, AST 6.5xULN, ALP 3.6xULN but TBL normal at 0.24xULN. Three days later the enzyme activities were ALT 10.9xULN, AST 7.9xULN, ALP 3.1xULN and TBL still normal. She improved rapidly by 10 days but still showed slight ALT increases at 42 and 119 days after starting treatment. She was found to have been taking alirocumab, which was assumed to have caused the problems.

NARRATIVE PATIENT 011570-032-019-038, a man 60 with history of coronary syndrome had pruritus and vomiting before the first treatment injection on 14 November 2014, and was found to have moderate elevations of ALT 5.3xULN, AST 5.1xULN, ALP 1.8xULN, TBL 1.9xULN. His liver tests had been normal screening a month before. Despite this, the injection was given once and a week later his ALT was 6.6xULN, AST 4.2xULN, ALP 1.9xULN, TBL 1.3xULN. After another week, his ALT was 3.4xULN, AST 1.9xULN, ALP 1.5xULN, TBL 1.5xULN, and at 38 days after the single injection ALT 2.6xULN, AST 2.4xULN, ALP 1.2xULN, TBL normal. All test values were in the normal range within 2 months and thereafter at 4 months. Hepatitis IgM antibody was detected, and hepatitis E considered the cause of the problem.

NARRATIVE PATIENT 011570-032-030-001, a man 72 with hepatic steatosis and alcohol use showed normal liver test values at screening a month before starting injections on 31 October 2013 but slight aminotransferase elevations that day: ALT 1.8xULN, AST 1.2xULN. On Day 33 his serum enzyme activities were sharply up to ALT 15.8, AST 9.8, ALP 1.1, with normal bilirubin. He complained of reduced appetite and abdominal pain and tests on Day 36 showed ALT 18.9xULN, AST 11.4xULN, but normal ALP and TBL. Echography showed hepatic steatosis, and his 40 mg/day atorvastatin was stopped. The enzymes decreased and atorvastatin was later restarted at 20 mg/day, but recurrent ALT rise after 18 months recurred.

NARRATIVE PATIENT **011570-056-007-013**, a man 44 with history of coronary syndrome, past smoking, and spondylising ankylosis showed slight serum aminotransferase elevations at screening (ALT 2.0xULN, AST 1,1xULN) four weeks before starting injections on 2/5/2014. The elevated aminotransferases subsided but rose again on Day 118 to ALT5.7xULN, AST2.8xULN with normal ALP and TBL. The injections were found to be placebo, and the test abnormalities were attributed to statin exposure.

NARRATIVE PATIENT **011570-356-060-002**, a woman 65 with history of coronary syndrome, hypertension, and diabetes showed normal liver test at screening 4 weeks before start of injections on 2 July 2014, when mild enzyme elevations were noted: ALT 1.7xULN, AST 1.6xULN, ALP 2,1xULN. However, on Day 31(1 August) her ALT was 19,5xULN, AST 20.3xULN ALP 3.9xULN, TBL 1.05xULN. Injections and atorvastatin were stopped, and serology showed IgM for hepatitis E, negative for A and C. She was found to have small stones in the gallbladder and common duct. She made full recovery within 2 months. She had been receiving alirocumab.

NARRATIVE PATIENT **011570-428-004-010**, a man 64 with history of coronary syndrome, hypertension, and diabetes was suspected of having hepatitis C but that was not confirmed and his liver tests were normal at screening 8 weeks before starting injections on 13 May 2104. On that day his ALT was 1.8xULN, AST 1.5xULN with normal ALP and TBL. Repeat testing on Day 36 showed ALT 5.7xULN, AST2.0xULN. His hepatitis C RNA was positive, but injections were continued. He recovered, and all liver tests were normal a year later.

NARRATIVE PATIENT **011570-752-001-013**, a woman 78 with history of coronary syndrome, hypertension, and diabetes showed normal liver tests at screening 4 weeks before starting injections on 11 February 2014, when liver tests were again normal. On Day 298 (12/5) his ALT was 11.2xULN and AST 21.2xULN with near-normal ALP and TBL. He had been complaining of weakness, nose bleeds, dark urine, pale stools, nausea, and vomiting. He also showed greatly elevated plasma myoglobin and creatine phosphokinase activities, slightly elevated serum creatinine, attributed to drug-induced myopathy (atorvastatin). The atorvastatin was stopped and she recovered within 3 weeks.

NARRATIVE PATIENT **011570-826-030-021** - described above

NARRATIVE PATIENT **011570-840-229-020**, a woman 63 with history of coronary syndrome, smoking habit, depression, gastroesophageal reflux disease, and allergies showed normal liver tests at screening 2 weeks before starting injections (alirocumab) on 20 January 2015. She developed a urinary tract infection with fever, cloudy urine, costovertebral pain, nausea, and culture positive for E. coli. She was treated with ceftriazone and levofloxacin. Her ALT rose to 8.8xULN and AST to 19.1xULN on 5 June (Day 137), after which she recovered.

NARRATIVE PATIENT **011570-840-258-005**, a man 75 with history of gastroesophageal reflux disease, hepatitis C showed normal liver tests at screening a month before starting injections on (b) (6). Four months later, on Day 120 (b) (6) his serum enzymes rose to ALT 3.3xULN, AST 1.2xULN, ALP 1.5xULN with normal bilirubin, and had nausea, vomiting, abdominal pain, and weakness. The injections were interrupted temporarily and he recovered. Acute hepatitis A, B, C and CMV were ruled out, and possible small gallbladder polyps were seen. Six months later, asymptomatic ALT of 4.5xULN was noted and atorvastatin was stopped, but two weeks later acute abdominal pain occurred and he was hospitalized, where mild pancreatitis was diagnosed. Biliary sludge and non-functioning gallbladder were found and cholecystectomy was done two weeks later.

NARRATIVE PATIENT **011570-804-001-022** - described above

NARRATIVE PATIENT **011570-208-001-022**, a man 53 with history of alcohol use, smoking habit, and cardiovascular disease showed normal liver tests at screening prior to start of injections on 25 July 2014. At 4 months, his ALT was 6.9xULN, AST 3.9xULN, ALP 1.1xULN and bilirubin normal. He admitted to increased alcohol intake, and injections were stopped but atorvastatin was continued. Unblinding showed he had been receiving alirocumab, and the case was still being investigated in January 2015.

NARRATIVE PATIENT **011570-752-007-010**, a woman 76 with history of gallstones, depression, alcohol use had normal liver tests at screening before starting injections on 20 May 2014, but on 19 June (Day 31) ALT was 4.5xULN, AST 2.3xULN, ALP 2.3xULN and bilirubin normal. Small gallstones were seen by ultrasound. Injections were stopped and atorvastatin interrupted but ALT peaked at 7.7xULN, AST 3.7xULN, ALP 3.7xULN, then subsided. Recurrent ALT increase on Day 120 led to permanent stopping of the atorvastatin.

NARRATIVE PATIENT **011570-804-010-058**, a woman 66 with history of asthma, atrial fibrillation, hypertension, and diabetes showed only slight ALP elevation to 1.2xULN at screening 6 weeks before starting injections on 1 March 2015, on which day ALT was 2.9xULN, AST 1.2xULN, ALP 1.4xULN with normal bilirubin. Hepatitis C antibodies turned positive and hepatitis C RNA was 54200 on Day 8. The injections were stopped after only the first dose. The ALT peaked at 7.4xULN, AST 2.1xULN, ALP 1.5xULN, and she was recovering at last testing on 14 April 2015 (Day 35).

2 NARRATIVE ONGOING OPEN LABEL STUDIES

2.1 STUDY CL-1032

NARRATIVE PATIENT **1003-840-309-002** - described above

Comments

It became evident, following the flurry of events and actions 6/19-6/23, that the index case was probably not induced by the study drug but by acute hepatitis E. Several additional references beyond those already sent are listed below and full copies will be sent on request if any of the readers of this document wish them. The sponsor has submitted an amendment to the BLA 125559, and will be working to round out missing information concerning the cases of interest they listed in their response to Item 3 of the DMEP request of 20 June. Confident diagnoses of cause cannot yet be made for several of them, and alternative explanations have already been found for some.

We shall stay tuned for further information or commentary from readers of this consultation response. Thank you for asking our opinion about this interesting case and novel compound.

John R. Senior, M.D.

cc: J. Smith, DMEP
M. Roberts, DMEP
J. Golden, DMEP
J-M. Guettier, DMEP
P. Madara, DMEP
S. Iyasu, OPE
R. Ball, OSE
G. DalPan, OSE
M. Avigan, OPE

References

Aggarwal R, Jameel S. Hepatitis E. *Hepatology* 2011 Dec; 54(6): 2218-26. PMID 21932388

Aggarwal R. Diagnosis of hepatitis E. *Nat Rev Gastroenterol Hepatol*. 2013 Jan; 10(1):24-33. PMID 23026902

Cook N, van der Poel WH. Survival and elimination of hepatitis E virus. *Food Environ Virol*. 2015 May 20; Epub ahead of print. PMID 25989918

Ganova-Raeva L, Punkova L, Campos DS, Dimitrova Z, Skums P, Vu NH, Dat DT, Dalton HR, Khudyakov Y. Cryptic hepatitis B and E in patients with acute hepatitis of unknown etiology. *J Infect Dis*. 2015 Jun 8; Epub ahead of print. PMID 26155829

Kenney SP, Meng XJ. Therapeutic targets for the treatment of hepatitis E virus infection. *Expert Opin Ther Targets*. 2015 Jun 13; Epub ahead of print. PMID 26073772

Kmush BL, Labrique AB, Dalton HR, Ahmed ZB, Ticehurst J, Heaney CD, Nelson JE, Zaman K. Two generations of „gold standards“: the impact in hepatitis E virus testing innovation on population seroprevalence. *Am J Trop Med Hyg*. 2015 Jul 6; Epub ahead of print. PMID 26149865

Krain LJ, Nelson KE, Labrique AB. Host immune status and response to hepatitis E virus infection. *Clin Microbiol Rev*. 2014 Jan; 27():139-65 PMID 24396140

Kwo PY, Schlauder CG, Carpenter HA, Murphy PJ, Rosenblatt JE, Dawson GJ, Mast EE, Krawczynski K, Balan V. Acute hepatitis E by a new isolate acquired in the United States. *Mayo Clin Proc*. 1997 Dec; 72(12):1133-6. PMID 9413292

Perez-Gracia MT, Suay B, Mateos-Lindermann ML. Hepatitis E: an emerging disease. *Infect Genet Evol*. 2014 Mar; 22:40-59 PMID 24434240

Sayed IM, Vercauter AS, Abdelwahab SF, Vercauteren K, Meuleman P. Is HEV an emerging problem in industrialized countries? *Hepatology* 2015 Jul 14; Epub ahead of print. PMID 26175182

Sridhar S, Lau SK, Woo PC. Hepatitis E: a disease of reemerging importance. *J Formos Med Assoc*. 2015 Mar 12; Epub ahead of print. PMID 25773541

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/s/

JOHN R SENIOR

07/20/2015

Thanks to Pat Madara for assistance in linking this response to her request of 6/19/2015.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 16, 2015

To: Jean-Marc Guettier, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Ankur Kalola, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): alirocumab (SAR236553/REGN727)

Dosage Form and Route: Solution for Subcutaneous Injection

Application Type/Number: BLA 125559

Applicant: Sanofi-aventis

1 INTRODUCTION

On November 24, 2014, Sanofi-aventis submitted, for the Agency's review, an original Biologics License Application (BLA) for alirocumab (SAR236553/REGN727) inhalation powder for the once-daily treatment of asthma in patients aged 12 years of age and older. The proposed tradename of PRALUENT was approved on December 17, 2014. The Applicant proposes that PRALUENT be 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 (ApoB), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by DMEP on August 21, 2014, and November 28, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for PRALUENT (alirocumab) solution for subcutaneous injection.

2 MATERIAL REVIEWED

- Draft PRALUENT (alirocumab) solution for subcutaneous injection PPI and IFUs received on November 24, 2014, and received by DMPP on July 11, 2015.
- Draft PRALUENT (alirocumab) solution for subcutaneous injection PPI and IFUs received on November 24, 2014, and received by OPDP on July 11, 2015.
- Draft PRALUENT (alirocumab) solution for subcutaneous injection Prescribing Information (PI) received on June 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on July 11, 2015.
- Draft PRALUENT (alirocumab) solution for subcutaneous injection Prescribing Information (PI) received on June 30, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on July 11, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFUs the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFUs documents using the Arial font, size 10.

In our review of the PPI and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFUs is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFUs.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
07/16/2015

ANKUR S KALOLA
07/16/2015

MELISSA I HULETT
07/16/2015

LASHAWN M GRIFFITHS
07/16/2015

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

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

Memorandum

Date: July 16, 2015

To: Patricia Madara, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request
BLA 125559 PRALUENT™ (alirocumab) injection, for subcutaneous use

On December 12, 2014, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for Praluent. In addition, on January 19, 2015, OPDP received a consult request from DMEP to review the proposed Carton and Container labeling for Praluent. OPDP's comments on the proposed draft PI and Carton and Container labeling are based on the version available in SharePoint on July 14, 2015 and the version sent via email by Patricia Madara on June 18, 2015, respectively.

OPDP's comments on the PI are provided directly on the marked version below. We have no comments on the Carton and Container labeling at this time.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPI and IFU under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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

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

/s/

ANKUR S KALOLA
07/16/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center – WO66-0609
Silver Spring, MD 20993-0002

InterCenter Consult Memorandum
ICC1400714/B/LA125559

Date: June 17, 2015
To: Patricia Madara
Senior Regulatory Health Project Manager
WO22, RM 3360
OMPT/CDER/OND/ODEII/DMEP
From: Janice Polacek, RN, BSN, CRNI
Nurse Consultant
WO66 RM 2533
CDRH/ODE/DAGRID/GHDB
Subject: BLA125559/ICC1400714
Alirocumab for injection
Praluent

Final summary of CDRH device review issues

Within the CDRH memo dated April 30, 2015 the reviewer had requested that two post approval commitments be reached with the sponsor:

- (1) Commitment to update the BLA with ongoing stability information for the PFP at each future sampling time point
(2) Commitment from the MAF holder to update MAF (b) (4) with ongoing stability information at each future sampling time point

After discussion with the CMC reviewers, the request for post approval commitments is withdrawn. These issues will be addressed and incorporated in the typical post approval regulatory commitments required by CDER.

Table with 2 columns: Signing Authority, Signature. Rows include Reviewer (Janice L. Polacek), Team Lead (Ryan J. McGowan), and Branch Chief (Richard C. Chapman).

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

/s/

PATRICIA J MADARA

07/15/2015

Signing for CDRH reviewers: Janice Polacek and Ryan McGowan.



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: July 15, 2015

Reviewer: Jibril Abdus-Samad, PharmD, Labeling Reviewer
Office of Biotechnology Products Jibril Abdus-
samad -S

Through: Richard Ledwidge, PhD, Quality Reviewer
Division of Biotechnology Review and Research III

Application: BLA 125559/0

Product: Praluent™ (alirocumab)

Applicant: Sanofi-Aventis U.S. LLC

Submission Dates: November 24, 2014; April 29, May 8; June 10; and
July 2, and 9, 2015

Digitally signed by Jibril Abdus samad S
DN: c. US, o U S Government ou HHS ou FDA
ou People
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cn Jibril Abdus samad S
Date: 2015 07 15 15:22:21 04'00

Digitally signed by Richard Ledwidge S
DN: c. US, o U S Government ou HHS
ou FDA ou People
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cn Richard Ledwidge S
Date: 2015 07 15 15:26:54 04'00

Executive Summary

The container labels, blister labeling, and carton labeling for Praluent™ (alirocumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [May 1, 2015 to July 31, 2015]. Labeling deficiencies were identified, mitigated, and resolved. The container labels and blister labeling submitted on July 2, 2015 are acceptable. The carton labeling submitted on July 9, 2015 are acceptable.

Background and Summary Description

The Applicant, Sanofi-Aventis U.S. LLC, submitted BLA 125559 Praluent™ (alirocumab) on November 24, 2014. Table 1 lists the proposed product characteristics of Praluent™ (alirocumab).

Table 1: Proposed Characteristics of Praluent™ (alirocumab).

Trade Name	Praluent™
Proper Name	alirocumab
Indication	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 or as monotherapy including in patients who cannot tolerate statins
Dose	75 mg or 150 mg subcutaneously once every 2 weeks
Route of Administration	Subcutaneous injection (thigh, abdomen, or upper arm)
Dosage Form	Injection
Strength and Container-closure	75 mg/mL or 150 mg/mL in single-use prefilled syringes 75 mg/mL or 150 mg/mL in single-use pens
Storage and Handling	Store in a refrigerator at 36° to 46° F (2°C to 8°C). Do not freeze. Do not expose to extreme heat. Store in the outer carton in order to protect from light

Materials Reviewed:

- Prefilled Syringe (PFS) Container Label
- PFS Blister Tray Labeling
- Pen Container Label
- PFS Carton Labeling
- Pen Carton Labeling

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

PFS Container Label

Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum:

1. name (expressed either as the proper or common name); *conforms*.
2. lot number or other lot identification; *conforms*.
3. name of the manufacturer; *conforms*. **However OBP recommends adding US License Number.**

OBP Request: 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"

Applicant Response: due to the small size of the syringe label and in order to maintain the full manufacturer name (sanofi-aventis U.S. LLC), the Sponsor is unable to include the US License number; however, again, since it is a partial label as per 21 CFR 610.60(c), the Sponsor notes that including this element is not required. *Acceptable*.

4. for multiple dose containers, the recommended individual dose; *not applicable*.
5. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

Pen Container Label and PFS Blister Tray Labeling

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

- (1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *conforms*.
- (2) The name, address, and license number of manufacturer; *conforms*.

(3) The lot number or other lot identification; *conforms*.

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers; *not applicable*.

(6) The statement: "Rx only" for prescription biologicals; *conforms*.

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *conforms*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *not applicable for Pen*. For PFS label see *Partial Label* above.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *conforms*.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*. However, OBP concurs with DMEPA's recommendation to revise the product codes.

OBP and DMEPA request: Revise the product code of the NDC numbers (e.g., 5901, 5902, 5903, and 5904) as the assignment of sequential numbers is not an effective differentiating feature.

Applicant's response July 8, 2015: The NDC number assignment scheme utilized for Praluent is consistent with past Sanofi practices for marketed products with multiple dosage strengths and is utilized by other pharmaceutical manufacturers.

Sanofi proposes, in order to address the Agency's concern and to align with the Draft guidance, to increase the prominence of the middle digits of the NDC number on the carton (by increasing the font size and including in bold type), while maintaining the currently assigned numbers. The size of the NDC numbers on the container and blister labels would remain the same.

We would also like to point out that, consistent with recommendations in this Draft guidance, additional measures like clear display of the product strength and color differentiation have been taken to ensure that the product strength stands out on the container label and carton labeling. *Acceptable*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence]; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*. **does not conform**.

OBP Request: Bold the statements "For subcutaneous injection only. Single-dose. De-bold the Rx only statement and 'Pre-filled Syringe' or 'Pre-filled Pen'. *Applicant revised as requested*.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *conforms*.

I. 21 CFR 201.50 Statement of identity; *conforms (inactive ingredients appear on carton labeling)*.

J. 21 CFR 201.51 Declaration of net quantity of contents; **does not conform**.

OBP Request: Revise the strength statement on the upper right corner to from (b) (4) or (b) (4) to "75 mg/mL" or 150 mg/mL", per USP General Chapters: <1> Injections. 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".
Applicant revised as requested.

K. 21 CFR 201.55 Statement of dosage; *conforms (on carton labeling)*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms (ingredients are listed on full carton)*.

II. Carton

A. 21 CFR 610.61 Package Label

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *conforms*.
- b) The name, addresses, and license number of manufacturer; **does not conform**.

OBP Request: Revise the manufacturer information to comply with 21 CFR 600.3, 21 CFR 610.61, 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
Regeneron Pharmaceuticals
[Fill in address]

Applicant Response: The Sponsor would like to clarify that "A SANOFI COMPANY" should follow the company name, since it is part of the company name presentation. As a result, the US License Number has been placed after "A SANOFI COMPANY". *Acceptable*.

- c) The lot number or other lot identification; *conforms*.
- d) The expiration date; *conforms*.
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.
- f) The number of containers, if more than one; *conforms*.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; **does not conform**.

OBP Request: Revise the strength statement on the upper right corner to from "(b) (4)" or "(b) (4)" to "75 mg/mL" or 150 mg/mL", per USP General Chapters: <1> Injections. 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". *Applicant revised as requested.*

h) The recommended storage temperature; *conforms*.

i) The words "(b) (4)" or the equivalent, as well as other instructions, when indicated by the character of the product; **does not conform**. **Do not shake warning is missing**.

OBP Request: Revise the statement "(b) (4)" to read "Do not freeze. Do not shake." *Applicant revised as requested.*

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *conforms*.

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

- o) The adjuvant, if present; *not applicable*.
- p) The source of the product when a factor in safe administration; *not applicable*.
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.
- s) The statement "Rx only" for prescription biologicals; *conforms*.
 - Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Not applicable*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Praluent™ is a monoclonal antibody for in vivo use.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:

"Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. **Does not conform.**

OBP Request: Revise the manufacturer information to comply with 21 CFR 600.3, 21 CFR 610.61, 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
Regeneron Pharmaceuticals
[Fill in address]

Applicant Response: The Sponsor would like to clarify that "A SANOFI COMPANY" should follow the company name, since it is part of the company name presentation. As a result, the US License Number has been placed after "A SANOFI COMPANY". *Acceptable.*

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter; **does not conform.**

OBP Request: Relocate the QR code on 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. *Applicant revised as requested.*

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*. However, OBP concurs with DMEPA's' recommendation to revise the product codes.

OBP and DMEPA request: Revise the product code of the NDC numbers (e.g., 5901, 5902, 5903, and 5904) as the assignment of sequential numbers is not an effective differentiating feature.

Applicant's response: The NDC number assignment scheme utilized for Praluent is consistent with past Sanofi practices for marketed products with multiple dosage strengths and is utilized by other pharmaceutical manufacturers.

Sanofi proposes, in order to address the Agency's concern and to align with the Draft guidance, to increase the prominence of the middle digits of the NDC number on the carton (by increasing the font size and including in bold type), while maintaining the currently assigned numbers. The size of the NDC numbers on the container and blister labels would remain the same.

We would also like to point out that, consistent with recommendations in this Draft guidance, additional measures like clear display of the product strength and color differentiation have been taken to ensure that the product strength stands out on the container label and carton labeling. *Acceptable*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; **does not conform**.

OBP Requests:

Bold the statements "For subcutaneous injection only. Single-dose. De-bold the Rx only statement and 'Pre-filled Syringe' or 'Pre-filled Pen'. *Applicant revised as requested.*

Add the dosage form, Injection, to appear directly under the proper name, alirocumab. For example:

Praluent™
alirocumab
Injection
Applicant revised as requested.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; **does not conform**.

OBP Request: Relocate the QR code away on a side panel away from the required bar code in a size that does not compete with, distract from the presentations of other required or recommended information on the label. *Applicant revised as requested.*

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; does not conform.

OBP Request: Revise the strength statement on the upper right corner to from "(b) (4)" or "(b) (4)" to "75 mg/mL" or 150 mg/mL", per USP General Chapters: <1> Injections. 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". *Applicant revised as requested.*

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; conforms.
However, the inactive ingredients should be revised to comply with USP General Chapters: <1091> Labeling of Inactive Ingredients.

OBP Request: Revise the inactive ingredients to comply with USP General Chapters: <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: [REDACTED] (b) (4)

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.

Applicant revised as requested.

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant revised the labels and labeling as requested.

A. General Comments

1. Revise any reference of [REDACTED] (b) (4) to "single dose" throughout all the labels and labeling to ensure that the entire dose is delivered and the injectable device is not reused. "Single-Dose" is the appropriate term per USP General Chapters: <659> Packaging and Storage Requirements.

B. PFS Container Label

1. We consider the PFS Container Label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.
2. 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.

3. Revise the strength in the upper right hand corner from (b) (4) or (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".
4. Bold the statements "For subcutaneous injection only. Single-dose." to draw attention to how the medication should be safely handled and used.
5. 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).

Discussion of Proposals from the Applicant

Pens Container Label Revisions

On May 8, 2015, the Applicant submitted revised pen container labels. The purpose of the revision of the labels to be affixed to the prefilled pens (PFP) is to correct the alignment of the proposed label on the PFP so that the product name and dose are aligned on the label and that these two elements further align with the window on the pen.

Despite the critical information such as the proprietary name, proper name, and strength appear in the middle portion of the label, this alignment is appropriate considering the how the label is placed on the pen. The Applicant's proposal is acceptable.

PFS Container Label Revisions

On May 8, 2015, the Applicant submitted revised PFS container labels. The purpose of the revision of the labels to be affixed to the PFS is to move the barcode by 90° to allow for barcode scanning when attached to the PFS.

The container label is placed on the PFS such that the text is perpendicular to the length of the pen which forces readers to turn the pen while reading the text. OBP and DMEPA recommended the label to be placed in fashion such that the text is parallel with the length of PFS and the barcode can be scanned. The Applicant revised as requested.

(b) (4)



Conclusions

The container labels, blister labeling, and carton labeling for Praluent™ (alirocumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, USP 38/NF 33 [May 1, 2015 – July 31, 2015]. Labeling deficiencies were identified, mitigated, and resolved. The container labels and blister labeling submitted on July 2, 2015 are acceptable. The carton labeling submitted on July 9, 2015 are acceptable.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 8, 2015

TO: Julie Golden, M.D., Medical Officer
James P. Smith, M.D., M.S., Deputy Director
Patricia Madara, Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125559

APPLICANT: Sanofi-Aventis U.S. LLC

DRUG: Alirocumab (SAR236553/REGN727)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia

CONSULTATION REQUEST DATE: December 31, 2014

CLINICAL INSPECTION SUMMARY GOAL DATE: May 30, 2015 (revised)

DIVISION ACTION GOAL DATE: July 24, 2015

PDUFA DATE: July 24, 2015

I. BACKGROUND

Sanofi-Aventis U.S. LLC, a Sanofi Company, is seeking approval of alirocumab (SAR236553/REGN727) solution for subcutaneous injection with the proposed trade name Praluent. Alirocumab is a fully human monoclonal antibody that binds proprotein convertase subtilisin kexin type 9 (PCSK9) for the reduction of low-density lipoprotein cholesterol (LDL-C). The application proposes that alirocumab be 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 (ApoB), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1). Inspections were requested for the following clinical studies:

- **EFC11569** A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Versus Ezetimibe in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy [ODYSSEY Combo II]
- **EFC12492** A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy [ODYSSEY FH I]
- **LTS11717** Long-Term Safety and Tolerability of REGN727/SAR236553 in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy: A Randomized, Double-Blind, Placebo-Controlled Study [ODYSSEY LONG TERM]
- **R727-CL-1119** A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients with Primary Hypercholesterolemia Who are Intolerant to Statins

All of the studies were ongoing at the time of submission and the study cut-off dates (for purposes of the first step analysis) were:

- For Study EFC12492, the cut-off date definition for the first step analysis is the last patient last Week 52 visit (April 16, 2014)
- For Study LTS11717, the cut-off date definition for the first step analysis is that approximately 600 randomized patients had completed 18 months of the double-blind treatment period (May 7, 2014)
- For R727-CL-1119, the cut-off date definition for the first step analysis is the date all patients finished the double-blind treatment period and all open label extension (OLE) data collected until this date (May 16, 2014)
- For Study EFC11569, the cut-off date definition for the first step analysis is the last patient last Week 52 visit (May 30, 2014)

For Study **EFC12492**, there are 89 active centers in 14 countries involved in the study. There were 597 subjects screened and 486 subjects randomized; 424 randomized patients had treatment ongoing at the time of the first-step analysis cut-off date. The first subject enrolled July 13, 2012 and the last subject visit was April 16, 2014 (data cut-off). There were seven protocol amendments (two global: February 8, 2013 and February 26, 2014 and five local amendments: August 13, 2012, September 25, 2012, October 2, 2012, October 12, 2012, and December 5, 2013).

The target population in this study was patients with heterozygous familial hypercholesterolemia (heFH) who were not at their LDL-C goal. The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population using all LDL-C values regardless of adherence to treatment.

For Study **LTS11717**, there are 320 active centers in 27 countries involved with the study. There were 5142 subjects screened and 2341 subjects randomized; 607 randomized patients had completed the Week 78 visit at the time of the first-step analysis cut-off date. The first subject enrolled January 6, 2012 and the last subject visit was May 7, 2014 (data cut-off). There were six protocol amendments.

Subjects who were enrolled had high CV risk with hypercholesterolemia not adequately controlled with a statin at a maximally tolerated daily dose with or without other lipid modifying therapy (LMT). The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population using all LDL-C values regardless of adherence to treatment.

For Study **R727-CL-1119**, there are 67 active centers in eight countries involved with the study. There were 519 subjects screened; 361 subjects that entered the single blind phase and 314 subjects randomized; 281 subjects have entered the open label extension phase. The first subject enrolled September 28, 2012 and the date of the last patient's Week 24 visit was May 16, 2014 (data cut-off). There were four protocol amendments.

Only patients willing to be rechallenged with atorvastatin 20 mg were included in the study. Statin-intolerant patients with primary hypercholesterolemia and moderate, high, or very high

cardiovascular (CV) risk were enrolled. See protocol for inclusion/exclusion criteria. The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to week 24 in the intent-to-treat (ITT) population using all LDL-C values regardless of adherence to treatment.

For Study **EFC11569**, there are 126 active centers in 10 countries involved with the study. There were 1112 subjects screened and 720 subjects randomized; 612 randomized patients had treatment ongoing at the time of the first-step analysis cut-off date. The first subject enrolled August 9, 2012 and the last subject visit was May 30, 2014 (data cut-off). There were six protocol amendments (September 5, 2012 for South Korea only; September 25, 2012 for France only; October 12, 2012 for Denmark only; February 7, 2013 for all sites; March 7, 2013 for Germany only; and February 26, 2014 for all sites).

The target population in this study was patients at high cardiovascular (CV) risk not at goal with their maximally tolerated statin therapy at stable dose for at least four weeks prior to the screening visit (Week -3). The control arm selected for this study was ezetimibe 10 mg PO daily. The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population using all LDL-C values regardless of adherence to treatment.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of BLA 125559 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Pending Classification
D. Eric Bolster Site 840073 Site 840915 Site 840992	LTS11717 18 subjects R727-CL-1119 11 subjects EFC11569 6 subjects	01/29 – 02/12/2015	No Action Indicated (NAI)
Richard Shultzaberger Site 840955	EFC11569 11 subjects	03/30 – 04/15/2015	No Action Indicated (NAI)
Henry Ginsberg Site 840408	EFC12492 14 subjects	01/16 – 01/23/2015	Voluntary Action Indicated (VAI)

Michael Koren Site 840980	R727-CL-1119 5 subjects	01/28 – 02/02/2015	Voluntary Action Indicated (VAI)
Patrick Moriarty Site 840970	R727-CL-1119 17 subjects	01/07 – 01/12/2015	No Action Indicated (NAI)
Gil Vardi Site 840113	LTS11717 24 subjects	01/27 – 02/04/2015	No Action Indicated (NAI)
Karl Zuzarte Site 840966	EFC11569 15 subjects	03/19 – 03/26/2015	Voluntary Action Indicated (VAI)
Hofit Cohen Site 376934	R727-CL-1119 14 subjects	05/14 – 05/15/2015	No Action Indicated (NAI)
Nyda Fourie Site 710405	EFC12492 14 subjects	04/28 – 04/30/2015	No Action Indicated (NAI)
Tasneem Vally Site 710008	LTS11717 100 subjects	04/13 – 04/24/2015	No Action Indicated (NAI)
Veronika Horvathova Site 826010	LTS11717 91 subjects	04/27 – 05/01/2015	Voluntary Action Indicated (VAI)
Akos Kalina Site 348903	EFC11569 21 subjects	05/19 – 05/22/2015	No Action Indicated (NAI)
Robert Dufour Site 124401	EFC12492 10 subjects	04/20 – 04/24/2015	No Action Indicated (NAI)
Lawrence Leiter Site 124407	EFC12492 7 subjects	04/20 – 04/24/2015	No Action Indicated (NAI)
(b) (4)			
Sanofi-Aventis U.S. LLC	EFC11569 EFC12492 LTS11717 R727-CL-1119	03/16 – 03/27/2015	No Action Indicated (NAI)

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. D. Eric Bolster, M.D.

Palmetto Clinical Research
201 Oakbrook Lane, Suite 255
Summerville, SC 29485

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All records for studies LTS11717 and R727-CL-1119 were reviewed. For Study EFC11569, the six randomized subjects' records were reviewed.
- b. General observations/commentary:** For Study **LTS11717**, there were 31 subjects screened and 18 subjects randomized. The first subject was consented May 10, 2012. The IRB of record was (b) (4). During the course of the inspection, it was discovered that there were numerous instances where subjects had been consented using outdated versions of the consent form. The site had not received the updated informed consent documents in a timely manner. There had been conversion of the IRB's paper documents to electronic format during the course of the study and, therefore, there was a lag in receipt of approved consent forms. This was specifically applicable to ICF version 4.0. There was no under-reporting of adverse events. The screening and baseline LDL-C values and all subsequent blood draws were verified.

For Study **R727-CL-1119**, there were 16 subjects screened and 11 subjects randomized. The first subject was consented July 10, 2013. The IRB of record was (b) (4). There were no issues with consent. There was no under-reporting of adverse events; the primary efficacy endpoint was not verifiable as the study was still on-going. Review of source documentation for all enrolled subjects confirmed that blood samples were collected appropriately on the dates reported for randomization and follow-up. The dates of the samples matched the dates reported in the data listings for the study endpoints.

For Study **EFC11569**, there were 10 subjects screened and six (6) subjects randomized. The first subject was consented April 4, 2013. The IRB of record was (b) (4). Subject 001 at Visit 12 had the adverse event of dizziness not entered initially on the case report form but then the information was entered during the inspection. This was the only adverse event omission observed. There were no issues with consenting. There was no under-reporting of adverse events other than the isolated AE noted previously; the primary efficacy endpoint was not verifiable as the study was still on-going. Review of source documentation for all enrolled subjects confirmed that blood samples

were collected appropriately on the dates reported for randomization and follow-up. The dates of the samples matched the dates reported in the data listings for the study endpoints.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Richard Shultzberger
1800 N. Greene St., Suite B
Greenville, NC 27834

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 23 screened subjects' informed consents were reviewed. All 11 randomized subjects' records were reviewed.
- b. **General observations/commentary:** There were 23 subjects screened and 11 subjects enrolled into the study. There were five early terminations. There were two subjects still active in the study at the time of the inspection.

There was no evidence of under reporting of adverse events. Review of source documentation for all enrolled subjects confirmed that blood samples were collected appropriately on the dates reported for randomization and follow-up. The dates of the samples matched the dates reported in the data listings for the study endpoints. The site was blinded to all subsequent results as they still have two active subjects. Other data such as concomitant medications, protocol deviations, laboratory values, drug accountability and adverse events were verified up to the data cutoff and were reviewed for the remainder of the study. There was one discrepancy on the drug accountability log. Management stated that procedures would be implemented to document all study IP including unused IP.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. **Henry N. Ginsberg, M.D.**

Columbia University Medical Center
622 West 168th Street, 10th Floor
New York, NY 10032*

* All post-inspectional correspondence should be addressed to: Henry N. Ginsberg, MD, Columbia University Medical Center, 630 West 168th Street, PH-10-305- Irving Institute, New York, N.Y. 10032.

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 14 subject records were reviewed.
- b. **General observations/commentary:** There were 14 subjects screened and 14 subjects enrolled into the study. The first subject was consented December 10, 2010. The last subject completed the double-blind treatment period on October 9, 2014. The IRB of record was (b) (4). The site does not utilize electronic medical records; all records are paper. The clinical research coordinators (CRC) transcribed the data from the paper source into the electronic data capture (EDC) Inform that was provided by the CRO.

The site has remained blinded to the primary and secondary efficacy endpoints. Baseline efficacy information, from the sponsor's line listings, was verified against source documents for all 14 subjects covered during this inspection.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan.
 - Serum pregnancy tests were required at Screening for all subjects of childbearing potential. Subject 840-408-004, a 44 year old female, did not undergo serum pregnancy testing. *The laboratory report indicated that the subject was not of childbearing potential. The doctor's note indicated that an error was made; this subject never had a hysterectomy*

and was still menstruating. Of note, a urine pregnancy test had been obtained.

- A lipid sample was not collected from Subject 840-408-012 during their Week 78 visit.
 - Subject 840-408-004's Visit 8 urine sample was discarded and not sent to the laboratory. *Record shows that this was discarded in error.*
 - Subject 840-408-011's Visit 12 source record shows that their blood pressure was measured in the supine position only and not in the sitting position as required by the protocol.
2. For protocol number EFC12492, the following adverse events were documented in the site's source records but were not recorded in the subject's electronic case report form and were not listed in the sponsor's data line listings:
- Subject 840-408-012: Urine white blood cell (WBC), 11/ HPF, which occurred on August 14, 2013. *Dr. Ginsberg disagreed with this observation as it did not fit the protocol defined adverse event reporting criteria. Subject was asymptomatic and follow-up urine testing was negative.*
 - Subject 840-408-012: Gamma-glutamyl transferase (GGT), 75 IU/L (range 0-51 IU/L), which occurred on August 14, 2013. *Dr. Ginsberg disagreed with this observation as it did not fit the protocol defined adverse event reporting criteria. The GGT remained elevated. The subject was instructed to avoid all alcohol.*
3. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
- The Eligibility Inclusion and Exclusion criteria for all 14 enrolled subjects were reviewed by an Investigator after randomization had occurred. *Eligibility was reviewed but not documented in a timely manner. The corrective action for this repeated discrepancy was to re-train research staff to sign and date all documents at the time of review.*
 - The 12-lead Electrocardiograms (ECG's) taken during four of the enrolled subjects' screening visits (840-408-002, 840-408-011, 840-408-013, and 840-408-014) were reviewed by an Investigator after randomization had occurred. *The corrective action for this repeated discrepancy was to re-train research staff to sign and date all documents at the time of review.*

OSI Reviewer Comment: Dr. Ginsberg responded to the inspectional observations in a letter dated February 10, 2015. Corrective actions have been put into place and are acceptable.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data

from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. Michael J. Koren, M.D.

Jacksonville Center for Clinical Research
4085 University Boulevard South, Suite 1
Jacksonville, FL 32216-4362

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All subject records were reviewed.
- b. General observations/commentary:** There were 10 subjects screened and five (5) subjects enrolled into the study. The first subject signed the informed consent form on December 18, 2012. The IRB of record is [REDACTED] (b) (4) [REDACTED]. Study data was collected on source documents and then entered by a study coordinator or research assistant into the electronic data case report forms.

The baseline LDL-C was reviewed and verified for all five subjects. The calculation made from the data points was also verified. However, the actual Week 24 LDL-C could not be verified as the results are still blinded to the site. All cholesterol results after randomization are also blinded. As of the time of inspection, the site remained blinded as to the treatment of subjects. There was no under-reporting of adverse events.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Subject #840-980-007 met exclusionary criteria #42, which excludes subjects having a screening creatine phosphokinase (CPK) lab result >2 x the upper limit of normal (ULN). This subject's screening CPK value was 428 (reference range is 18-169 U/L). The CPK was repeated for subject enrollment. *Exclusionary criteria #42 identifies some labs that are allowed to be repeated one time (triglycerides, alanine aminotransferase, thyroid stimulating hormone), but the creatine phosphokinase is not a lab test that is allowed by the protocol to be repeated. The second laboratory result shows the CPK value as 114 U/L.*
2. The subject case history file for Subject #840-980-005 includes discrepant documentation regarding the subject's concomitant medications. Screening source worksheets completed by a study coordinator document the subject

stopped taking a prohibited statin medication on April 22, 2013, prior to screening. Additional screening source records include a physical examination conducted by a sub-investigator that documents this same prohibited statin medication as a current medication on April 26, 2013 with no end date. *The protocol refers to prohibited concomitant medications in section 5.7.2. Statin medications are prohibited from the initial screening visit until the follow up visit. The site stated that the sub-investigator made a mistake with her dictation.*

OSI Reviewer Comment: Dr. Koren submitted a response to the inspection observations in a letter dated February 18, 2015. He disagreed with the observations with continued misinterpretation of the protocol and good clinical practice.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. Patrick M. Moriarty, M.D.

9301 Rainbow Blvd
Kansas City, KS 66160

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, randomization, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 22 subject records were reviewed.
- b. **General observations/commentary:** There were 22 subjects screened and 17 subjects enrolled into the study. The first subject was screened on January 18, 2013. There have been no discontinuations and the study is still on-going at the site. The IRB of record is (b) (4).

All records were legible and organized. All subjects met inclusion/exclusion criteria. There was no under-reporting of adverse events.

There were several discussion items at the close-out:

1. Subjects 015, 016, and 017 were screened using site created worksheets that lacked the last three exclusion criteria. Therefore, Inclusion/Exclusion was not totally reviewed by the staff during screening. The FDA investigator reviewed laboratory test results and all three subjects met inclusion/exclusion criteria. The three items missing were as follows:

- a.* Exclusion: Known hypersensitivity to monoclonal antibody therapies
- b.* Exclusion: Pregnant or breast feeding woman
- c.* Exclusion: Woman of childbearing potential with no effective contraceptive birth control and/or unwilling/unable to be tested for pregnancy.

Two of the three subjects were women and were determined to be post-menopausal. A Note-to File was added to the documentation to address this discrepancy.

2. Training of subjects on the National Cholesterol Education Program [NCEP] Adult Treatment Panel [ATP] III therapeutic lifestyle changes [TLC] diet or equivalent was not documented in the source records. The study coordinator said that all subjects were patients in the practice and had been trained when they became a new patient. A Note-to-File was added to the records to discuss the normal practice of the firm to discuss the TLC diet with all patients in the practice.
3. One adverse event for Subject 004 had no determination of relatedness. This was reviewed by Dr. Moriarty, was corrected and updated during the inspection.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

6. Gil M. Vardi, M.D.

11155 Dunn Road, Suite 304E
St Louis, MO 63136-6111

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, case report forms, randomization, subject diaries, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, CRO correspondences, site SOPs, and adverse event reports. All 45 subject records were reviewed.
- b. General observations/commentary:** There were 45 subjects screened and 24 subjects enrolled into the study. The first subject signed the informed consent

July 5, 2012. The last subject follow-up visit was conducted October 15, 2014. (b) (4) was the IRB of record.

There were three early terminations per the source records and eCRFs: subjects 840113008 (withdrew consent), 840113019 (death, unrelated to study drug) and 840113041 (lost to follow-up). The information provided to the FDA by the sponsor indicates these subjects were discontinued. Subjects 840113007 and 840113020 were also listed as discontinued from the study but both did fully complete all study visits per the source and eCRF records. *(It was later determined that these two subjects did not continue into the open-label extension study).*

There was no under-reporting of adverse events. Review of source documentation for all enrolled subjects confirmed that blood samples were collected appropriately on the dates reported for randomization and follow-up. The dates of the samples matched the dates reported in the data listings for the study endpoints.

There were several discussion items at the close-out meeting:

1. Correspondence between the IRB and the site were not available to the FDA investigator in a timely manner. The communications were not filed in the IRB correspondence binder and it took six days to receive the documents for review.
2. The laboratory reports were not always dated when signed by the investigator or co-investigator.
3. The regulatory binder was disorganized and difficult to review.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

7. Karl M. Zuzarte, M.D.

1565 North Main Street, Suite 301
Fall River, MA 02720

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports.

Twenty-one subject records were reviewed.

- b. General observations/commentary:** There were 21 subjects screened and 15 subjects enrolled into the study. The IRB responsible for reviewing the study was (b) (4). There was no under-reporting of adverse events. Review of source documentation for all enrolled subjects confirmed that blood samples were collected appropriately on the dates reported for randomization and follow-up. The dates of the samples matched the dates reported in the data listings for the study endpoints.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Three subjects met exclusion criteria and were randomized into the study, one subject was randomized prior to the randomization physical examination, and the stratification criterion for two subjects was entered incorrectly during randomization.
 - Subjects 840966005 and 840966006 met exclusion criteria # 9 “Use of fibrates in the past 6 weeks prior to screening visit (Week -2)” and were randomized into the study on November 15, 2012.
 - Subject 840966018 met exclusion criteria # 8 “Use of cholesterol absorption inhibitor (i.e., ezetimibe), omega-3 fatty acid (at doses ≥ 1000 mg daily), nicotinic acid, bile acid-binding sequestrant, or red yeast rice products within the past 4 weeks prior to screening visit (Week -2) or between screening and randomization visits” and was randomized in the study on April 11, 2013.
 - Subject 840966005 was randomized in the study on November 15, 2012 and the physical examination required for randomization was performed on November 16, 2012. *The medical assistant mistakenly thought the subject had an appointment that day for the physical exam.*
 - Stratification criteria “Prior History of Myocardial Infarction or Ischemic Stroke” for Subject 840966006 was entered as “Yes” during randomization when the subject did not have prior history of either myocardial infarction or ischemic stroke. *The study coordinator made an error in IXRS when entering data for this subject and it was corrected and acknowledged by IXRS. Although it was corrected, IXRS had no mechanism to re-stratify the subject through the CRO’s IXRS system.*
 - Stratification criteria “High Intensity Statin” for Subject 840966019 was entered as “No” during randomization when the subject was on a daily dose of 80 mg atorvastatin. *The study coordinator made an error in IXRS when entering data for this subject and it was corrected and acknowledged by IXRS. Although it was corrected, IXRS had no mechanism to re-stratify the subject through the CRO’s system.*

OSI Reviewer Comment: Dr. Zuzarte responded to the inspectional observations in a letter dated April 6, 2015 and the response is acceptable. Corrective actions were put into place. The Principal Investigator, or other delegated physician, will review Inclusion/Exclusion and all subjects' Medical History thoroughly to ensure the subject meets the requirements of the protocol. The Principal Investigator, or other delegated physician, will confirm and document in the subject's source documents proper inclusion/exclusion medical assessment prior to any subject being randomized. Under no circumstances will a subject be randomized without all study related procedures being completed at the time of randomization. If the Principal Investigator, or other delegated physician, is not available to conduct the required study-related procedures, the visit will be either not scheduled or will be rescheduled. The Study Coordinator fully understood stratification in IXRS and it was a manual error. An additional step was put in place for QC prior to the IXRS data entry by the Principal Investigator. Site staff was retrained by the Principal Investigator on April 6, 2015 to prevent a future reoccurrence.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

8. Hofit Cohen, DrMed

Tel-Hashomer
Ramat-Gan, 52621
Israel

- a. What was inspected:** This was an abbreviated inspection due to the scheduling of the Principal Investigator. The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, inclusion/exclusion criteria, enrollment logs, drug accountability, and adverse event reports. One subject record underwent 100% review.
- b. General observations/commentary:** There were 15 subjects screened and 14 subjects enrolled into the study. There were four early terminations. Ten subjects are currently in the open label phase. All subject records were checked for informed consent and inclusion/ exclusion criteria. One subject record that underwent 100% full review had no issues noted. At the conclusion of the inspection, discussion items included the secure storage of the test article, documentation of start times for BP resting period, and appropriate strike through of errors. Dr. Cohen promised to have the drug storage cabinet fitted with a lock within one week.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form

FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. As noted earlier, this was an abbreviated inspection.

9. Nyda Fourie

Quantum Building
1 Third Avenue
Middle Block, Ground Floor, Westdene
Bloemfontein, 9301
South Africa

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, delegation of duties, monitoring logs, inclusion/exclusion criteria, enrollment logs, drug accountability, randomization, concomitant medication records, and adverse event reports. Seven subject records underwent full review.
- b. **General observations/commentary:** There were 16 subjects screened and 14 subjects enrolled into the study. The first subject (001) was screened on November 1, 2012 but was a screen failure. Subject 02 was also screened on November 1, 2012 and was subsequently randomized into the study on November 16, 2012. The total number of subjects completing the double blind study treatment visits (Week 78) and entering into the open label extension study was 10.

Records were well maintained and organized. There was no under-reporting of adverse events. The laboratory data needed to confirm primary and secondary endpoints was not available at the firm which remains blinded. The audit did confirm the cholesterol levels at screening for seven subjects to ensure they met inclusion criteria.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

10. Tasneem Vally

Watermeyer Clinical Research Centre
182 Watermeyer Street Meyerspark
Pretoria, 184
South Africa

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Thirty-eight (38) enrolled subject records were reviewed. Six screen failure records were reviewed.
- b. General observations/commentary:** There were 202 subjects screened and 100 subjects enrolled into the study. There were 86 subjects that have completed the study.

It was documented that the site requested hospital records repeatedly for study subjects but did not always receive the records. Out of 28 hospitalizations for all 100 enrolled study subjects, the site received inpatient and outpatient procedure records for 12 study subjects' hospitalizations. The site did not receive hospital records for 16 of the hospitalizations. For these study subjects, it is unknown whether or not the study subjects received excluded medications during their hospitalization or whether any AEs or SAEs occurred during hospitalizations or outpatient procedures.

The site now has a full-time employee devoted to requesting study subject's inpatient and outpatient procedure records. The Principal Investigator stated that their hospital record recovery rate has improved since adding the full-time employee to their staff.

There was no evidence of under-reporting of adverse events. The site is still blinded, so the only LDL-C laboratory values at the site were the screening and baseline values. Both screening and baseline values were verified for all 38 enrolled subjects.

There were randomization irregularities. These irregularities included 20 stratification errors, which were reported in the application. During the inspection, nine of the 20 study subjects with stratification errors were reviewed (Subjects 008, 018, 026, 034, 055, 072, 097, 098, and 154). Documentation of the stratification errors appeared to be adequate. Most of the stratification errors were due to confusing CRFs where a myocardial infarction (MI) and coronary artery bypass graft surgery (CABG) were in the same category and the only option was to check "yes" or "no" for both when the subject would have had one but not the other in the history. For one study subject, 710-008-097, the subject had a documented MI but was stratified as "No Prior History of MI or Stroke" in error.

The site had protocol deviations for “failure to report SAEs within protocol specified timeline.” During the inspection, it was discovered that the firm had reported the SAEs within the protocol specified timeline to the Sponsor through the eCRFs. The firm failed, however, to FAX the SAE to (b) (4) as instructed during the site initiation training. However, after subsequent training, the site did not repeat these deviations. All protocol deviations were consistent with the FDA data listings.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

11. Veronika Horvathova

Venture Building 1 Kelvin Campus
West of Scotland Science Park, Maryhill Road
Glasgow, G20 0SP
Great Britain

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. There were 31 subject records reviewed.
- b. **General observations/commentary:** There were 351 subjects screened (with 43 rescreened) and 91 subjects enrolled into the study. There were 38 subjects terminated.

There was no under-reporting of adverse events. The screening and baseline lipid levels and all blood draws were verified.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Five subjects (121, 281, 287, 298 and 303) of the 31 reviewed subjects were randomized to the study before completion of the exclusionary criteria determination. The firm contacted the IVRS system and randomized the subjects as eligible before completing the collection and verification of the blood pressure on the day of randomization as required per protocol. Three

(287, 298, 303) of the five subjects met the exclusionary criteria of high blood pressure (>180/110 mmHg).

2. Three subjects of the 31 reviewed had diary entry discrepancies for drug accountability. The subjects were required to inject themselves with study drug approximately every two weeks.
 - a. Subject 291 had two separate diary entries for Weeks 12, 14, and 16. The injection times did not correlate for Weeks 14 and 16.
 - b. Subject 281 had two separate diary entries for Weeks 26, 28, and 36. The injection time did not correlate for Week 28.
 - c. Subject 153 had a diary entry completed for Week 20. However, there was a note at the bottom stating that subject did not receive this dose.

OSI Reviewer Comment: There has been no response to the 483 findings. As explained during the inspection, the site said that they were calling the subjects between office visits to verify if the subjects were taking their injections and recording dates and times as the subject told them on the phone. An employee (who is no longer with the site) would record such information in the source. If the subject didn't bring back the diary, this staff person was filling out a separate diary entry for the subject, but no initials, date or explanation was recorded with the second diary record or in the source.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

12. Akos Kalina

Robert Karoly korut. 44
Budapest, 1134
Hungary

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Eight subject records were fully reviewed.
- b. **General observations/commentary:** There were 33 subjects screened and 21 subjects enrolled into the study. The study is still on-going at the site.

Study records were complete and information was well documented. There was no under-reporting of adverse events. Protocol deviations were properly reported. There were no issues with data discrepancies, drug accountability, and all subjects signed the approved informed consent prior to beginning screening activities. The FDA investigator was able to verify baseline LDL measurements and that blood samples were collected at Week 24 as per the protocol to measure the primary efficacy endpoint.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

13. Robert Dufour

110 Pine Avenue West
Montreal, Quebec H2W 1R7
Canada

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 10 subject records were reviewed.
- b. **General observations/commentary:** There were 10 subjects screened and 10 subjects enrolled into the study. The inspection found the subjects completed their Week 78 visit and were consented to participate in the open-label extension study (LTS13463).

There was no under-reporting of adverse events. Review of source documentation for all enrolled subjects confirmed that blood samples were collected appropriately on the dates reported for randomization and follow-up. The dates of the samples matched the dates reported in the data listings for the study endpoints. No data discrepancies were noted. No deviations were identified regarding ethics committee submissions and approvals, consenting of subjects, inclusion/exclusion criteria, or test article disposition and accountability.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

14. Lawrence Leiter

St. Michael's Hospital
61 Queen Street East
6th Floor, Suite 6121
Toronto M5C 2T2
Ontario, Canada

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, subject diaries and adverse event reports. All eight subject records were reviewed.
- b. General observations/commentary:** There were eight subjects screened and seven subjects enrolled into the study. One subject has been withdrawn.

There were no major deficiencies identified regarding IRB submissions and approvals, consenting of subjects, inclusion/exclusion criteria, test article disposition and accountability. The site has not had any up-titration issues related to laboratory data transfer during the study. One subject was randomized incorrectly based on history of MI (noted in deviation listings).

There was no under-reporting of adverse events and the unblinded (but not the blinded) study data was verifiable.

At the conclusion of the inspection, there were two discussion items:

1. The investigator and sub-investigators were not signing off dipstick UAs performed in the clinic; however, the central lab UAs were all signed-off appropriately
2. The SAEs for Subject 004 were reported to the ethics committee approximately two and a half months after the episodes; the SAEs were reported in a timely manner to the Sponsor.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

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16. Sanofi-Aventis U.S. LLC

55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

- a. What was inspected:** The inspection focused on organizational structure and personnel, staff responsibilities, contracts, SOPs, monitor selection, monitor plans, monitoring of sites, quality assurance, training, CVs, site selection, site termination, safety reporting, data management, protocol and clinical study writing, medical monitoring, ethics committee correspondences, oversight committees, protocol waivers, drug dispensing and accountability, translation of documents, record retention, study trial oversight and all study documents pertaining to Studies EFC11569, EFC12492, LTS11717, and R727-CL-1119. The inspection also focused on the randomization, stratification and titration

errors reported in the application.

- b. General observations/commentary:** There were several presentations given by Sanofi and Regeneron staff throughout the inspection. Files were well organized and readily available. Staff from different departments was available to discuss issues noted and answer questions. Staff was knowledgeable and cooperative. There were also several teleconferences with the vendor [REDACTED] (b) (4).

Transfer of obligations for studies EFC11569, EFC12492, LTS11717, and R727-CL-1119 are as follows:

- EFC11569: Sanofi – monitoring; [REDACTED] (b) (4) – trial management and data management
- EFC12492: [REDACTED] (b) (4) – monitoring, trial management and data management
- LTS11717: [REDACTED] (b) (4) – monitoring, trial management, data management
- R727-CL-1119: [REDACTED] (b) (4) – monitoring, trial management and data management

In general, the selection and training of sites and the monitoring of the sites was adequate. There were no issues noted with the selection and oversight of the Data Monitoring Committee or the Clinical Event Committee. Contracts and SOPs were in order. Safety monitoring and reporting was adequate. Full drug accountability could not be done as the studies were still on-going and the documents had not been submitted to the trial master files.

There were several topics of interest that were evaluated:

1. The randomization errors noted and reported to the FDA October 22, 2014 under IND 105574 were confirmed. The errors in treatment assignments were in [REDACTED] (b) (4)



(b) (4) The errors were not seen in any of the inspected studies. A full investigation was done by the Sponsor and appropriate corrective actions have been made at the Sponsor site and at the vendor (b) (4). There are also additional CAPAs that were generated from the audit of the IRT system that are appropriate.

OSI Reviewer Assessment: (b) (4)
(b) (4) under IND 105574, the above finding does not impact subject safety and data reliability of the studies in support of BLA 125559. The Sponsor has made appropriate corrective actions and implemented CAPAs based on the audit of the IRT system that are appropriate. The above findings were not observed in the studies presented to support BLA 125559.

2. There were titration errors reported in the application by the Sponsor. These were investigated and discussed in depth with Sanofi staff, Regeneron staff, and with the vendor (b) (4). In Study EFC11716 (Mono), patients were up-titrated if they failed to achieve an LDL-C <70 mg/dL. The protocol specified <100 mg/dL. This was the only protocol that used 100 mg/dL instead of 70 mg/dL so (b) (4) kept those specifications in their system. The lab transfer specification contained a notes section that was added at the request of the central laboratory (b) (4). (b) (4) reviewed the portion of the specification relevant to the IXRS functions and approved the specifications but did not perform a review of the (b) (4) notes to ensure accuracy. Of note, there were no safety issues reported. Moving forward, the Sponsor plans to review and approve specifications between vendors to ensure that it represents what is expected for the protocol. (b) (4) updated the User Requirements Management SOP to include instruction not to include extraneous notes which are not relevant to (b) (4) system requirements.

OSI Reviewer Assessment: Although Study EFC11716 was not requested by the review team to be inspected, the titration error reported in the application by the Sponsor was investigated and it was determined to be study specific. As noted, the Sponsor failed to up-titrate at Week 12 according to the investigational plan and reported the findings to FDA. As noted in the application, a sensitivity analysis examined the potential impact of the error where an LDL-C threshold of ≥ 70 mg/dL (instead of 100 mg/dL) was applied in 13 patients. The observation does not appear to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

For Studies EFC12492, EFC11569, and R727-CL-1112 there were laboratory vendor errors with the transfer of data to (b) (4) that resulted in errors that were reported in the application. These vendor errors resulted in a few titration errors. For example, the Week 8 LDL-C results were received

too late by the IVRS for some patients whose LDL-C values would have resulted in up-titration to 150 mg Q2W (in such cases, Week 4 values were to be used by the IVRS). As previously reported by the Sponsor, those subjects affected were nine (9) of 486 subjects in Study EFC12492, one (1) of 720 subjects in Study EFC11569, and four (4) of 249 subjects in Study R727-CL-1112.

OSI Reviewer Comment: These vendor titration errors were isolated and do not impact the overall data reliability of the reported studies.

In the future, the Sponsor plans to review and approve specifications between vendors to ensure that it represents what is expected for the protocol.

3. There were several stratification errors reported in the CSRs. Stratification factors are defined in each study protocol. Site staff had to input the correct information into the IVRS system. Once the site put in the wrong information and the subject was randomized, it could not be changed. This accounts for most of the stratification errors that were noted in the application. There was documented training and repeat training of the sites. There were also statements of reminders and updates in the newsletters to the sites. The monitoring had been transferred to (b) (4), which did the training.

There were also region stratification errors. An excel file manually completed by (b) (4) and used by (b) (4) was incorrect with regional mapping.

Despite these stratification errors, treatment allocation between treatment groups was balanced for each stratum. To investigate the potential impact a sensitivity analysis was performed by the Sponsor using the actual strata in the Mixed-Effect Model Repeated Measure (MMRM) model for all phase 3 studies. Results of these sensitivity analyses are located in each clinical study report (CSR).

OSI Reviewer Assessment: Most of the stratification errors were present in Study LTS11717. In spite of documented repeat training, site staff inputted errors, which, due to the nature of randomization tools, could not be changed once made. All errors have been reported in the appropriate CSRs. As noted, despite these stratification errors, treatment allocation between treatment groups was balanced for each stratum. The stratification error rate was also increased somewhat erroneously due to the Sponsor's activities noted below. These stratification errors will need to be assessed by the review team for impact of the reported stratification errors on safety and efficacy.

4. Regarding Study LTS11717, inclusion criterion required CHD/CHD risk

equivalent **and/or** heterozygous familial hypercholesterolemia (heFH) diagnosis. Sites were not required to identify subjects with heFH if the subject met the required CHD/CHD risk equivalent. Once the Open Label Extension Study became available to patients with heFH diagnosis only, this triggered the Sponsor to ask sites to calculate the clinical score and further investigate possible diagnosis of heFH by newly performing genotyping and obtaining additional information on family history, which was not already known to the site or present in the CRFs.

The Sponsor study team reviewed data on heFH in January-February 2014. For patients with a score of eight (8) or more, review using EDC data was performed. Patients with a medical history of tendon xanthomas or arcus cornealis with age < 45 years were reviewed to see if they achieved clinical score >8. The Sponsor study team reviewed with sites to confirm heFH diagnosis and correct CRF, if needed. There were 108 patients re-evaluated by sites. For those 108 subjects re-evaluated as potentially having heFH, genotyping was performed on no subject (167 had genotyping done prior to randomization/post randomization during the study). There were 51 of the 108 subjects subsequently diagnosed with heFH by clinical criteria out of 1924 who had not had the initial diagnosis. These were counted as additional stratification errors by the Sponsor and represented the majority of the stratification errors for this study.

5. After submission of the application, it was discovered March 3, 2015 that there was an incorrect Patient Number for an HCV patient in the ISS. Patient No. 011717-840-001-007 is incorrect and should instead be Patient No. 011717-840-117-008. Although this was an isolated finding, it was investigated during the inspection. The root cause was human error. The wrong patient number was provided to Medical Writing. Medical Writing conducted a check of links for patients with narratives and in this case the link went to the narrative for the wrong patient and that patient was HCV positive – this led to a QC error. The correct patient had no event triggering a narrative; therefore, there was no opportunity to compare narratives. The correct patient had a “positive Ab” HCV test and “missing” RNA test at baseline and was classified as “positive” in the original ISS. Subsequently, the RNA test became available and was “negative” and the correct patient is later classified as HCV negative in the 4-month Safety Update Report.

OSI Reviewer Comments: The above isolated finding does not impact data reliability, nor did it compromise the safety of the subject in the study.

6. During discussion of data collection, it was discovered that a lipid calculator was used and the Clinical Director explained its use. Diagnosis of heterozygous familial hypercholesterolemia (heFH) must be made in Study LTS11717 either by genotyping or by clinical criteria. In order to determine the category of diagnosis with the clinical criteria, a pre-treatment LDL-C

may be needed. The pre-treatment LDL-C should be obtained by a review of the patient's medical records. In the event that medical records cannot be obtained, then sites were told that it is acceptable to estimate the pre-treatment LDL-C by use of a lipid calculator. This instrument is an excel spread sheet that was e-mailed to all the sites. This calculator had been received by an academic investigator. There were no publications or validation documents available during the inspection. There was no mention of this procedure in the protocol or clinical study report (CSR). The pre-treatment calculation was not captured in the EDC and is only in the source record; therefore, it was not recorded in the CSR. [Of note, this is not the calculation of LDL particles using the Friedewald equation $L \approx C-H-kT$].

As all patients were already on background statin therapy and/or other lipid modifying therapy at the time of screening and because most patients had a long-standing diagnosis of heFH, some patients with heFH may not have had an off-treatment LDL-C in their historical medical records. The Sponsor felt it was unethical to stop lipid modifying therapy in subjects with high CV risk.

Further information was submitted by the Sponsor post-inspection on the background and use of this lipid tool. 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. Per the Sponsor, the use of this tool has been accepted and incorporated in the Dutch FH guidelines to determine off-treatment LDL-C in order to confirm the clinical diagnosis of heFH.

OSI Reviewer Comment: The additional information and publications provided by the Sponsor shed more light on the use of this lipid tool. It is currently not known by the Sponsor how many subjects who did not have genotyping (55.4%) also did not have sufficient medical records to review an off-treatment LCL-C. Further information is being submitted to the review team and will need to be assessed as to the appropriateness of its use.

7. While reviewing records, it was noticed that some sites were ordering local lipid panels. Per Section 6.1 of Protocol LTS11717 *“The laboratory measurement of lipid parameters will be performed by a central lab during the study. Local lab testing for lipid parameters is generally prohibited after randomization of the patient and up to Week 90 of the open label period, except for the safety of the patient as per investigator’s judgment. The specific results of the central lab testing for lipid parameters will not be communicated to the sites during the double blind period of the study...”*

Avoidance of local laboratory testing for lipid parameters was emphasized

in protocol training materials for monitoring teams and for sites. During Investigator meetings, this information was also reinforced. Reminders were sent to the monitoring team and sites in newsletters and email news bulletins.

A list of all local laboratory results was requested and received during the inspection. In reviewing the CSRs for the studies, no discussion of these local lipid panels being ordered was found. There was no listing of any such event in the protocol deviation list in the CSR for Study LTS11717. As the protocol was worded as noted above with the use of the investigator's judgment, no definite protocol violation could be cited. However, it was felt that such information should be gathered and reported to the review team.

Post-inspection, the Sponsor has undertaken a systematic approach for detecting cases of potential unblinding based on lipid testing done through local laboratories during the study and reported to the site and/or patient. As a result, the number of patients in the LONG TERM study with lipid testing done through local laboratories and reported to the site and/or patient is 81 patients. Sponsor has conducted additional sensitivity analyses on the primary efficacy endpoint by excluding the patients with potential unblinding based on lipid testing done through local laboratories at any time during the study and reported to the site and/or patient regardless of whether the unblinded LDL-C value was obtained before or after the primary efficacy endpoint, and regardless of whether the patient had discontinued investigational medicinal product or not. The Sponsor's conclusion is that it had no meaningful impact on the primary efficacy results. This has been submitted to the review team for further evaluation.

Systematic checks are in place now in all current studies to detect any lipid value recorded in the local laboratory eCRF page. The monitoring team is being re-trained to ensure these issues are recorded as deviations to be escalated to the Sponsor. Then, the Sponsor will review these deviations carefully and regularly assess repeated occurrences at any given site and analyze general trends.

OSI Review Comment: Although there is no evidence that any site investigator actually determined the treatment of any subject based on results of a local lipid profile (and, therefore, became unblinded), it was felt that further information regarding these activities be provided to the review team.

8. While reviewing records, it was discovered that in March 2013, medical directors from Regeneron and Sanofi agreed to allow use of coronary artery calcium scoring for non-invasive test evidence of CHD when investigators are considering patients for inclusion in the Regeneron studies. Because wording in the protocol has "Clinically significant CHD diagnosed by

invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)”, the Sponsor study team did not feel a protocol amendment was needed nor a discussion in the newsletter. In reviewing the CSR for Study R727-CL-1119, there is no mention of this additional inclusion scoring. An informational request was sent to the Sponsor post-inspection. Per the Sponsor, three (3) patients had calcium scores considered during the enrollment period, but none had to rely solely on the calcium score to meet entry criteria. Its use apparently was rare in the alirocumab program. The additional information was submitted to the review team.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was not issued. Although there were several errors reported in the application for various studies concerning randomization, stratification, and titration they were isolated and not systemic. Corrective and preventive actions have already taken place at both the Sponsor and vendors. (b) (4)



- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although several procedural errors have occurred in several studies within the alirocumab program, the inspection established that all appear to have been reported to the FDA, they were sporadic and not systemic across the studies, and corrections of the data have been submitted to the application. The audit did not indicate serious deviations/findings that would significantly impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this BLA consisted of seven domestic and seven foreign clinical sites representing 16 sites (four for each protocol), as well as the Sponsor and CRO.

Observations noted above for Drs. Bolster, Ginsberg, Koren, Leiter, Moriarty, Vardi, Zuzarte, the CRO and the Sponsor are based on the preliminary review of the Establishment Inspection Reports. Observations noted above for Drs. Cohen, Dufour, Fourie, Kalina, Shultzaberger, and Vally are based on communications from the FDA field investigators. Observations noted above for Dr. Horvathova are based on communications from the FDA field investigator and review of the Form FDA-483. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

Four clinical sites inspected, Drs. Ginsberg, Horvathova, Koren, and Zuzarte, were each issued a Form FDA-483, citing inspectional observations and preliminary classifications for each of

these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for all four sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites is acceptable for use in support of the indication for this application.

Drs. Bolster, Cohen, Dufour, Fourie, Kalina, Leiter, Moriarty, Shultzaberger, Vally, Vardi, the CRO and the Sponsor were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites, the CRO and the Sponsor are considered reliable based on the available information. Although several procedural errors have occurred in several studies within the alirocumab program, the inspection established that all appear to have been reported to the FDA, they were sporadic and not systemic across the studies, the reverse randomization occurred in a non-pivotal study, and corrections of the data have been submitted to the application. As noted above, there were protocol design issues discovered during the Sponsor inspection that may have an impact on the review of the application. These protocol design issues have been communicated to the review division. The review division has requested additional information (IR) from the sponsor to assess whether these issues impact assessment of efficacy. Responses to the IRs are currently being evaluated.

In general, based on the inspections of the fourteen clinical sites, the CRO and the Sponsor, the inspectional findings support validity of data as reported by the Sponsor under this BLA.

{See appended electronic signature page}

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/s/

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: May 22, 2015
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: BLA 125559
Product Name and Strength: Praluent (alirocumab) Injection, 75 mg/mL, 150 mg/mL
Product Type: Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Sanofi
Submission Date: November 24, 2014
OSE RCM #: 2014-2423, 2014-2445
DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the results of the Human Factors Study (HFS), container label, carton labeling, Prescribing Information labeling, Instructions for Use labeling, and Reference Guide labeling for Praluent (alirocumab) 75 mg/mL and 150 mg/mL prefilled syringe and prefilled pen, BLA 125559, submitted on November 24, 2014. The Division of Metabolism and Endocrinology requested that DMEPA review the HFS study results, and proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 Human Factors Study

Praluent Prefilled Syringe (PFS)

Based upon the results of the Human Factors Study, the prefilled syringe appears to be safe and effective when used by patients and healthcare professionals who receive training and/or have training materials (Instructions for Use) available for review.

With regard to the methodology of the Human Factors Study for PFS, DMEPA notes a flaw in that prior to administering the testing scenario, the moderator gave participants time to read through the Instructions for Use (IFU) at their own pace, which represents training (i.e., self-training) if the moderator prompted participants to read the IFU. If the Applicant's intention was to include participant arm with no training, this participant arm should not be prompted to review the IFU. However, in the actual use environment, we expect that this patient population will typically receive training from their health care providers prior to use because it is likely that this patient population is injection-naïve since there are currently no marketed injectable therapies for this indication (non-familial and heterozygous familial primary

hypercholesterolemia and mixed dyslipidemia). Thus, we find the methodology regarding training acceptable.

Additionally, there was a deviation in protocol as most of the first 44 patient participants did not find the IFU when they opened the packaging ((b) (4)). The design of the packaging was modified during the study to fold the IFU around the blister pack to make it easier for the user to find and tested with the last 16 participants. Per the Sponsor, an additional modification to the package design will be made for the final product, in which the final carton will have perforation only on the end that the user should open. Thus, we find the protocol deviation acceptable.

With regard to the results of the device handling session¹ of the Human Factors Study, 149 failures² occurred during the study as follows:

- 32 difficulties: 30 patient participants, 2 nurse participants
- 117 use errors: 102 patient participants, 15 nurse participants

Failures occurred within the following tasks of the study:

1. Store the product in a refrigerator
2. Store the product out of reach of children
3. Open packaging and remove device
4. Open packaging and find the IFU
5. Select the correct device (correct concentration)
6. Select the correct box (correct concentration and correct drug)
7. Check expiry date; check barrel including drug condition
8. Warm up at room temperature for 30 to 40 minutes
9. Remove the cap
10. Do not remove the air bubbles
11. Clean injection site
12. Press on plunger
13. Inject full dose
14. Do not recap syringe
15. Dispose of device and cap according to local regulatory requirements
16. Perform follow-up treatment

The following errors are not associated with the device-user interface of the product, but rather with other aspects of product use and are not unique to this injectable device. However, additional recommendations to address some of these errors through improvements in labels, labeling, and packaging will provided in Section 4:

¹ Per Sponsor response to Information Request dated February 14, 2015, during the supervised injections performed by participants in the training session, all participants completed the simulated self-injection into the skin pad successfully; there were no use errors or close calls on the simulated injections.

² Total failures include errors associated with the revised packaging, not the original packaging.

- **Failures to store product in refrigerator, store product out of reach of children, and to check expiry date and syringe barrel, including drug condition (Errors 1, 2, and 7):**
We recommend that the Sponsor increase the prominence and readability of this information in the proposed IFU and mitigate this type of error.
- **Difficulty opening packaging and removing device and failures to find the Instructions for Use (IFU) (Errors 3 and 4):**
Difficulty in opening the packaging may result in delay of treatment but do not affect the results of the study in terms of the safe and effective use of the prefilled syringe. Per the Sponsor, the final packaging will have perforation only on the end the user should open in order to make the IFU more visible. We also recommend placing the IFU on the top of the blister pack to increase visibility when opening the packaging.
- **Failures to select correct concentration and correct box (drug and concentration) (Errors 5 and 6):**
Selection of the wrong drug and concentration occurred with one patient participant. However, this task is more appropriate to assess among health care providers (i.e., pharmacists and nurses). Therefore, the error may be considered a study artifact.
- **Failure to warm up at room temperature for 30-40 minutes (Error 8):**
Failure to wait 30 to 40 minutes for the drug to reach room temperature occurred among 12 participants (patients and nurses) for various reasons related to perception of the product rather than labeling of the product (See Appendix D for details regarding participants responses as to why they did not wait 30 to 40 minutes to warm up Praluent). We attribute this error to perceptual failures, participants' previous experience, and forgetfulness. This type of error may result in uncomfortable injections and underdosing as end users may have difficulty delivering the complete injection due to the product's viscosity. Thus, we recommend that the Sponsor increase the prominence of this information in the proposed IFU and explain the importance of waiting the recommended amount of time before delivering the injection, in order to mitigate this type of error.
- **Failure to clean injection site (Error 11):**
Failure to clean the injection site occurred among 25 participants (7 trained patients, 16 untrained patients, and 2 nurses). Since participants were injecting into an injection pad, rather than a patient, they may have not felt it necessary to clean the injection site and therefore, this error is considered a study artifact. The proposed IFU states in "Step A: Getting ready for an injection", to "Clean skin in the injection area with an alcohol wipe". However, recommendations will be made to reorganize the information in Step A.4 to increase readability.
- **Failure to dispose of device and cap according to local regulatory requirements (Error 15):**
Such errors can lead to the possible transmission of blood-borne diseases. However, these use errors have also been reported with the use of similar, currently marketed, prefilled syringes.
- **Failure to perform follow-up treatment (Error 16):**
Failure to perform follow-up treatment occurred in 32 participants. Of these errors, 25 participants responded correctly after guidance from the moderator to look at the Patient Package Insert. Although patients will be informed about their dosage regimen by their

prescriber and the pharmacy label placed on the product, we defer to Division of Medical Policy Programs (DMPP)/Patient Labeling Team regarding recommendations to address such errors in the Patient Package Insert.

Failures also occurred in the following tasks of the study, which were associated with the device-user interface of the product.

Failure when removing the cap:

Errors associated with the failure to remove the syringe cap occurred with two patient participants. One patient participant bent the needle slightly when removing the cap. Another trained patient participant held the syringe by the plunger when trying to remove the cap, and pulled the plunger out, losing some of the medication. On a second attempt, the nurse held the syringe by the barrel, but lost some medication as she pulled the cap off because the plunger moved down and pressed against the table. The plunger and needle cap of the 150 mg/mL concentration prefilled syringe that was used in the Human Factors validation study are both gray in color, which may have led to confusion. However, we may attribute this error to learning effect associated with the initial use of the prefilled syringe. The proposed IFU displays the parts of the syringe, labeling the prefilled syringe plunger (“green plunger” or “gray plunger”) and needle cap. Additionally, the proposed IFU states in the section titled “Step B: (b) (4)” to “hold the syringe in the middle of the syringe body with the needle pointing away from you” and to “keep your hand away from the plunger”. Despite such instructions, we recommend that the Sponsor consider labeling the plunger and needle cap in Step B.1.

Failure to not remove the air bubbles:

One untrained patient participant and one nurse participant attempted to remove the air bubbles in the prefilled syringe. The patient lost a small amount of medication when trying to get rid of an air bubble and the nurse removed air bubbles without losing any medication. No root cause analysis was provided for this error. Removal of air bubbles may lead to chronic underdosing if medication leaks out and it occurs consistently during multiple injections. However, none of these errors affect the results of the study in terms of the safe and effective use of the prefilled syringe. In the section titled “Step B: (b) (4)”, the proposed IFU states “Do not (b) (4) any air bubbles in the syringe before the injection”. Therefore, no additional modifications to the Instructions for Use are needed to mitigate this type of error.

Failure to press on the plunger:

Failure to press on the plunger occurred with two trained and one untrained patient participants. One trained patient participant inserted the needle and was unable to push the plunger down. The participant removed the needle from the site and reported that the needle looked bent. The participant attempted to administer the injection with a second syringe. Another trained patient experienced resistance when trying to start the injection, and medication leaked onto the surface of the injection pad. According to the Sponsor, it appeared that the injection pad was full during the injection and prevented the medication from being injected and also caused the medication to leak out during the process. The participant was able to deliver a full dose of medication, despite using a full injection pad. We consider this error a study artifact. One untrained patient had difficulty pushing down on the plunger, removed the syringe from the pad, pressed the plunger and lost some medication, reinserted

the needle into a different spot of the injection pad, and delivered the remaining amount of medication. Upon second attempt, all three patient participants successfully pressed on the plunger.

Failure to press on the plunger can lead to missed or partial dosing, which is considered acceptable given the low severity of the anticipated clinical effect. However, chronic underdosing may occur if the error occurs consistently during multiple injections, which would result in decreased efficacy of the product, given the infrequent administration of Praluent. In the currently proposed IFU, Step B4 states “Inject all of the solution by slowly and steadily pushing down the plunger”. Due to the errors seen in pushing the plunger rod all the way down, we recommend that the Sponsor emphasize that due to the viscosity of the product, end users may experience resistance when pushing down on the plunger rod but they must continue to push down until the syringe is empty and the complete dose is delivered.

Failure to inject full dose:

Failure to inject the full dose occurred in three patient participants (2 untrained and 1 trained). One trained patient removed the needle too soon, not realizing that there was still medication in the syringe, because the injection pad was moving around while pinching it, which is considered an artifact of the study since this would not occur in actual use. The patient injected approximately 90% of the dose. One untrained patient unintentionally pulled the syringe out of the pad and spilled some of the medication, but injected 90% of the dose. Another untrained patient administered a small amount of the medication and then removed the syringe from the pad after injecting approximately 25% of the dose based on previous experience of administering her diabetes medication. When asked to perform a second injection, all three participants successfully completed the injection without error, which demonstrated that users learned how to use the syringe correctly. Failure to inject the complete dose would lead to underdosing, which is considered acceptable given the low severity of the anticipated clinical effect. However, chronic underdosing may occur if the error occurs consistently during multiple injections, which would result in decreased efficacy of the product, given the infrequent administration of Praluent. In the currently proposed IFU, Step B5 states “Before you remove the needle check the syringe is empty”. Due to the errors seen with administering the complete dose, we recommend that the Sponsor emphasize that injection time may be longer than most medications administered subcutaneously, but they must continue to push down until the syringe is empty and the complete dose is delivered.

Failure of recapping syringe:

Fourteen patients recapped the syringe without a needle stick injury. Such errors can lead to needle stick injuries and possible transmission of blood-borne diseases. However, these use errors have also been reported with the use of similar, currently marketed, prefilled injection pen devices. Step B6 of the IFU instructs users to “not put the gray needle cap back on”. Therefore, no additional modifications to the Instructions for Use are needed to mitigate this type of error. However, we defer to DMPP regarding recommendations to address such errors.

Recommendations to improve the IFU in terms of the readability and prominence of important information may mitigate the errors seen in this study. The failures encountered in this study

have also been reported with the use of similar, currently marketed, prefilled syringes and therefore, we do not believe that the risks present a safety concern.

Praluent Prefilled Pen/Autoinjector

Based upon the results of the Human Factors Study, the prefilled pen/autoinjector appears to be safe and effective when used by patients and healthcare professionals who receive training and/or have training materials (Instructions for Use) available for review.

With regard to the methodology of the study, there were deviations from the protocol. In the main Human Factors validation study, most of the patient participants (40/65) opened the package on the end rather than on the side as intended, which resulted in participants not finding the Quick Reference Guide located on the underside of the top of the carton. The artwork on the outside of the carton was modified to make the opening edge more noticeable. The new package artwork was used in the supplemental Human Factors validation study. Additionally, in the main validation study, participants were not asked questions regarding storing the product out of the reach of children and performing follow-up treatment. Therefore, these tasks were added to the protocol and included in the supplemental validation study. Because the Patient Package Insert included information regarding the frequency of follow-up treatment, the PPI was also added to the protocol and included in the supplemental validation study. Because the protocol deviations do not affect the results of the study in terms of the safe and effective use of the prefilled pen/autoinjector, we find the protocol deviations acceptable.

With regard to the results of the device handling session³ of the Human Factors Study, 138 failures occurred during the main study as follows:

- 43 difficulties⁴: 22 patient participants, 3 nurse participants
- 95 use errors: 86 patient participants, 9 nurse participants

Fifty-two (52) failures occurred during the supplemental study:

- 6 difficulties (5 patient participants and 1 nurse participant)
- 46 use errors among patient participants.

Failures occurred within the following tasks of the study:

1. Store the product in a refrigerator
2. Store the product out of reach of children
3. Open package in the intended way
4. Select the correct device (correct concentration)
5. Check expiry date
6. Check window, including drug condition

³ Per Sponsor response to Information Request dated February 14, 2015, during the supervised injections performed by participants in the training session, all participants completed the simulated self-injection into the skin pad successfully; there were no use errors or close calls on the simulated injections.

⁴ Total includes 18 unspecified participants who had difficulty in Task 3.4 Release the button

7. Warm up at room temperature for 30 to 40 minutes
8. Remove the cap
9. Choose correct injection site
10. Clean injection site
11. Press device on the site for injection (unlock button)
12. Press button for injection
13. Release the button
14. Wait until the injection is complete
15. Remove device from skin
16. Dispose of device and cap according to local regulatory requirements
17. Perform follow-up treatment

The following errors are not associated with the device-user interface of the product, but rather with other aspects of product use and are not unique to this injectable device. However, additional recommendations to address some of these errors through improvements in labels, labeling, and packaging will be provided in Section 4:

- **Failures to store product in refrigerator, store product out of reach of children, and to check expiry date and window, including drug condition (Errors 1, 2, 5, and 6):**
We recommend that the Sponsor increase the prominence and readability of this information in the proposed IFU and mitigate this type of error. Therefore, the Sponsor noted that the size of the font used for the expiration date will be enlarged, which should mitigate the error.
- **Failure to open the package in the intended way (Error 3):**
Failure to open the package in the intended way would not affect the results of the study in terms of the safe and effective use of the prefilled pen as end users would simply not see the Quick Reference Guide if opened on the wrong end. The carton labeling states “Open Here” and includes arrows to indicate how to open the package. Therefore, no additional modifications to the packaging are needed.
- **Failures to select correct device (concentration) (Error 4):**
Two trained patients initially selected the incorrect concentration, but then self-corrected their errors. One nurse selected the 75 mg/mL concentration and did not recognize the error until Task 3 (Injection delivered by user). The different concentrations of the device are adequately distinguished by color of the packaging. We can attribute such errors to a learning effect as the participants either self-corrected or noted their mistake prior to the administration of the injection.
- **Failure to warm up at room temperature for 30-40 minutes (Error 7):**
Failure to wait 30 to 40 minutes for the drug to reach room temperature occurred among 9 patient participants, in which 7 patients experienced difficulty (1 trained, 6 untrained) and 2 untrained patients experienced use errors for various reasons related to perception of the product rather than labeling of the product (See Appendix D for details regarding participants responses as to why they did not wait 30 to 40 minutes to warm up Praluent). We may attribute this error to cognitive failure/forgetfulness and participants’ previous

experience. This type of error may result in uncomfortable injections and underdosing as end users may have difficulty delivering the complete injection due to the product's viscosity. Thus, we recommend that the Sponsor increase the prominence of this information in the proposed IFU and explain the importance of waiting the recommended amount of time before delivering the injection, in order to mitigate this type of error.

- **Failure to clean injection site (Error 10):**

Failure to clean the injection site occurred among 21 participants (6 trained patients, 14 untrained patients, and 1 nurse). Since participants were injecting into an injection pad, rather than a patient, they may have not felt it necessary to clean the injection site and therefore, this error is considered a study artifact. The proposed IFU states in Step A.4 to "Clean skin in the injection area with an alcohol wipe". However, recommendations will be made to reorganize the information in Step A.4 to increase readability.

- **Failure to dispose of device and cap according to local regulatory requirements (Error 16):**

Such errors can lead to the possible transmission of blood-borne diseases. However, these use errors have also been reported with the use of similar, currently marketed, prefilled syringes.

- **Failure to perform follow-up treatment (Error 17):**

Failure to perform follow-up treatment occurred in 30 participants. Of these errors, 25 participants responded correctly after guidance from the moderator to look at the Patient Package Insert. Although patients will be informed about their dosage regimen by their prescriber and the pharmacy label placed on the product, we defer to Division of Medical Policy Programs (DMPP)/Patient Labeling Team regarding recommendations to address such errors in the Patient Package Insert.

Failures also occurred in the following tasks of the study, which were associated with the device-user interface of the product.

Failure when removing the cap:

Errors associated with the failure to remove the syringe cap occurred with two patient participants. One trained patient participant did not remove the cap initially, but then self-corrected. One untrained patient did not remove the cap and was not aware of this as they repeatedly attempted to administer the injection with the cap on, not realizing that they did not deliver the injection. We may attribute this error to learning effect associated with the initial use of the prefilled pen. The proposed IFU displays the parts of the pen, labeling the blue cap. Additionally, the proposed IFU states in Step B.1 to "pull off the blue cap" and includes an image of the cap being pulled off with an arrow. Despite such instructions, we recommend that the Sponsor consider labeling the cap in Step B.1.

Failure to choose the correct injection site:

Errors associated with selecting the wrong injection site occurred with one untrained patient who did not read the Instructions for Use and reported that no information was provided regarding the injection site. The patient participant mentioned that they would inject into the forearm. The proposed Instructions for Use indicates the injection site in Step A.4 and provides an image highlighting the appropriate areas. Therefore, no additional modifications to the proposed IFU are needed to mitigate this type of error.

Failure to press device on the site for injection (unlock button):

Errors associated with pressing the device on the injection site for injection occurred with 9 patient participants, of which there were 6 difficulties and 3 use errors. One trained patient and 5 untrained patients were not able to activate the device due to failure to follow correct activation sequence, but self-corrected. We can attribute such errors to the learning effect associated with the device. Two untrained patients did not press the device firmly on the site, and pressed the injection button before fully retracting the needle cover to activate the pen. The patients realized that they did not administer the injection and stated they would call the help line before attempting another injection. Their second attempt with assistance from the moderator was successful. We can also attribute such errors to the learning effect associated with the device. One untrained patient tried to use the device like an insulin pen based on their previous experiences, in which they attempted to dial a dose and search for a location to attach the needle. After being advised to read the Instructions for Use, the patient was successful. Users need to press the device on the injection site in order to activate the autoinjector as the needle cover needs to be fully depressed in order to release the actuator button, depress it, and initiate the injection. Failure to fully depress the needle cover would result delay of treatment. With regard to the proposed Instructions for Use, Step B.3 states to “Press and firmly hold the pen against your body until the yellow safety cover is no longer visible. The pen will not work if the yellow safety cover is not depressed fully.” Although some of these errors can be learnable, due to the errors associated with these steps in the study and potential resulting delay of treatment, we recommend that the Sponsor increase the prominence of this information in the proposed Instructions for Use and emphasize the force required to activate the autoinjector due to the product’s viscosity to mitigate these types of errors.

Failures to press button for injection and release the button:

One nurse tried to activate the device without pressing the actuator button, but noticed and self-corrected. We can attribute this error to the learning effect associated with the device. Errors associated with releasing the actuator button occurred among 18 participants. No root cause analysis was provided for this error. According to the Sponsor, failure to release the actuator button prevents the user from getting the audible end-of-dose feedback (“click”) and therefore has no effect on the injection. These use errors have also been reported with the use of similar, currently marketed, prefilled injection pen devices. Step B.4 of the proposed Instructions for Use notes to “Push and immediately release the green button with your thumb” and includes an associated image. Despite the lack of clinical significance associated with failure to release the button, we recommend that the Sponsor provide a clearer image in the proposed IFU to separate the two steps and mitigate these types of errors.

Failure to wait until the injection is complete:

Errors associated with the failure to wait until the injection is complete occurred in 7 participants (4 difficulties, 3 use errors). Three untrained patients and 1 nurse did not look at the window while the injection was in progress, although one of these patients counted to 20. These participants delivered complete injections. Two patients and 1 nurse removed the device too early. One of the patients had an injection time of 6 seconds and removed the pen immediately after the start of the injection; no dose was delivered. Another patient had an injection time of 9 seconds and removed the pen after 7 seconds; approximately 7/9 of the

3.2 Praluent Labels and Labeling

In addition to the Human Factors Study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted that the container labels, carton labeling, Prescribing Information labeling, and Instructions for Use Praluent can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information.

In summary, DMEPA expects that patients, caregivers, and health care professionals will be able to use the Praluent prefilled syringe and autoinjector safely and effectively when training is provided and/or training materials (i.e., Instructions for Use) are available for review.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors studies for the Praluent prefilled syringe and autoinjector demonstrated that end users (patients, caregivers, and health care professionals) are able to use the product safely and effectively when used with the availability of formal training and/or training materials (i.e., Instructions for Use). Although some errors have occurred with both pre-filled syringes and pre-filled pen/autoinjector, these errors would not result in serious harm. Additionally, many errors are not related to the user interface and can be addressed through labels and labeling rather than modifications to the device.

Additionally, the proposed labels and labeling can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this BLA:

- A. We recommend changing any reference to (b) (4) prefilled syringe or prefilled pen in the Prescribing Information labeling to “single dose” to ensure that the entire dose is delivered and the injectable device is not reused.
- B. Full Prescribing Information
 1. Section 2 Dosage and Administration
 - i. Include the following statement at the beginning of Section 2.1 (b) (4) Dosing Information to ensure that end users refer to the Instructions for Use for information regarding the administration of Praluent:
See the Praluent (alirocumab) “Instructions for Use” insert for detailed information on injection site selection and dose administration
 - ii. To ensure that all end users, including caregivers, receive training prior to use of Praluent, we recommend revising the statement (b) (4)

to as follows:

(b) (4)

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

2. Section 3 Dosage Forms and Strengths

- i. To reduce redundancy and improve readability, we recommend revising

(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

- i. 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.*”

4.2 RECOMMENDATIONS FOR (b) (4)

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

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. Praluent Prefilled Syringe

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.⁵ 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	
<ul style="list-style-type: none"> • 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). 	<ul style="list-style-type: none"> • 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:	
<ul style="list-style-type: none"> • 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 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 (b) (4)”, 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.

⁵ 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.

- 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.”

C. Praluent Prefilled Pen

- 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.⁶ 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>Important Information</p> <ul style="list-style-type: none"> • The device is a single dose disposable pen. It contains 150 mg of Praluent (alirocumab) in 1 mL. • The Praluent pen contains medicine prescribed by your (b) (4). • This pen can only be used for one single injection, and must be discarded after use. <p>Storage of Praluent:</p> <ul style="list-style-type: none"> • Store unused pens in the refrigerator (b) (4) 36° F to 46° F (2° C to 8° C). • (b) (4). • Keep the Praluent pen out of the reach of children. • (b) (4). 		<ul style="list-style-type: none"> • 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. • ...Include other important information located in this section here.
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⁶ 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 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.

Container Label and Carton Labeling:

- A. 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.
- B. **Prefilled Syringe Label**

1. Rotate the placement of the syringe label on the syringe by 90 degrees (label is parallel to the syringe) so the information is readable without having to turn or rotate the syringe.⁷
2. Revise the strength in the upper right hand corner from [REDACTED] ^{(b) (4)} to “75 mg/mL” or “150 mg/mL”, respectively, in accordance with USP General Chapter <1>.
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.⁸
4. Bold the statements “For subcutaneous use injection. Single-dose.” to draw attention to how the medication should be safely handled and used.

C. Prefilled Syringe Tray Labeling

1. See Recommendations B.2 – B.4.

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 [REDACTED] ^{(b) (4)} to “75 mg/mL” or “150 mg/mL”, respectively, in accordance with USP General Chapter <1>.
3. Include the finished dosage form on the line below the proper name.⁹ For example:

Praluent
alirocumab
injection

E. Prefilled Pen Label

1. Revise the strength in the upper right hand corner from [REDACTED] ^{(b) (4)} to “75 mg/mL” or “150 mg/mL”, respectively, in accordance with USP General Chapter <1>.

⁷ 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.”

⁸ 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.”

⁹ 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.”

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 established name on the Principal Display Panel.¹⁰
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.2 and B.3.
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>.
3. Include the finished dosage form on the line below the proper name.¹¹ For example:
Praluent
alirocumab
injection

¹⁰ 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."

¹¹ 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."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Praluent that Amgen submitted on November 24, 2014.

Table 2. Relevant Product Information for Praluent	
Initial Approval Date	N/A
Active Ingredient	alirocumab
Indication	<ul style="list-style-type: none"> 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). Indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT). Indicated as monotherapy, or as add-on to other non-statin LMT, including in patients who cannot tolerate statins.
Route of Administration	subcutaneous injection
Dosage Form	solution for injection
Strength	75 mg/mL, 150 mg/mL
Dose and Frequency	<p>75 mg or 150 mg administered subcutaneously once every 2 weeks.</p> <p>(b) (4)</p> <p>The dose can be adjusted based on treatment response. Lipid levels may be analyzed after 4 weeks when maximum LDL-C reduction is usually achieved.</p>
How Supplied	<ul style="list-style-type: none"> Praluent 75 mg/mL and 150 mg/mL single-use prefilled glass syringe is available in cartons containing 1, 2 (b) (4) prefilled syringes Praluent 75 mg/mL and 150 mg/mL single-use prefilled pen is available in cartons containing 1, 2 (b) (4) prefilled pens
Storage	Store in a refrigerator at 36° to 46° F (2°C to 8°C). Do not freeze. Do not expose to extreme heat. Store in the outer carton in order to protect from light.
Container Closure	Praluent Prefilled Syringe:

	<ul style="list-style-type: none">• composed of a 1 mL clear glass syringe barrel equipped with a 27G (b) (4) stainless steel staked needle, protected by a soft rubber needle shield, and a (b) (4) rubber plunger stopper. <p>Praluent Prefilled Pen/Autoinjector:</p> <ul style="list-style-type: none">• provided fully assembled with the prefilled syringe containing alirocumab solution for injection.• disposable, (b) (4) device, which is spring-powered and designed to administer the entire contents of the prefilled syringe during one injection.
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APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on February 20, 2015 using the term, 'alirocumab', to identify reviews previously performed by DMEPA. We also searched DARRTS for meeting preliminary comments.

C.2 Results

Our search identified the Sponsor's response to DMEPA Human Factors Protocol Comments¹², and we confirmed that our previous recommendations were implemented in the Human Factors Study Protocols.

¹² Response to Agency Request: Information on topics requested on 19 February and 13 March 2014 (regarding submissions of December 12, 2013 and December 19, 2013) – Alirocumab (IND 105574) (dated 3 April 2014).

APPENDIX D. HUMAN FACTORS STUDY

Praluent Prefilled Syringe (PFS)

D.1 Study Design

The Human Factors Study Results and IFU for Praluent prefilled syringe submitted on November 24, 2014 were evaluated. Below is a brief overview of the study objectives, description of the study participants, study design, data collection, and data analysis.

Study Objectives:

- **Differentiation Session:** Confirm that representative users can successfully differentiate the pre-filled syringe and its packaging from other Sanofi pre-filled syringes and other comparator syringes that are likely to be present in the same real world use environment.
- **Handling Session:** Confirm that representative users can handle the device safely and effectively in a realistic normal-use scenario (i.e., successfully deliver the intended dose, making no safety-critical errors).

Study Participants:

Table 3 provides information on the study participants and demographics.

User Groups	Subgroups	Syringe Experienced		Injection Naïve		TOTAL
		Trained	Untrained	Trained	Untrained	
Patients	Adult patients with hypercholesterolemia (>240 mg/dL)	15	17	15	13	60
Health Care Professionals (HCPs)	Nurses	0	16	N/A	N/A	16
	Prescribers	0	16	N/A	N/A	16
	Pharmacists	0	17	N/A	N/A	17

16 participants had Type 2 diabetes mellitus; 7 participants with color vision deficiencies were included in the study. Additionally, some participants had disease-related tactile/manual impairments caused, for instance, by neuropathy. Some participants also reported having hearing impairments.

Table 4 provides information on the types of study sessions.

User Groups	Study Sessions		
	Differentiation	Handling	Readability
Patients (n=60)	X	X	X
Nurses (n=16)	X	X	X
Prescribers (n=16)	X		
Pharmacists (n=17)	X		

Training and Testing Sessions:

Thirty-one (31) patient participants received training 5 to 7 days before the validation study session. Of the 31 participants, 30 were recommended to participate in the training session and 1 was disqualified based in the patient's inability to comprehend the training and perform an injection successfully. 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. The study facilitator provided help and feedback as needed to train the participant to use the device safely and correctly. The study facilitator took notes on each participant's performance of performing the injection, which consisted of removing the syringe cap, holding the device in correct orientation, inserting the needle into the injection pad, pushing the plunger down, checking that the syringe was empty and removing the syringe from the injection site. These same sub-tasks were assessed in the test session of the human factors validation study. During the supervised injections performed by the participants during the training sessions, all participants completed the simulated self-injections into the skin pads successfully; there were no use errors or close calls on the simulated injections.

All participants were given a general introduction regarding safety aspects and the indication for use of the syringe. Participants were given time to read the IFU at their own pace. The IFU was available during the study session but no other assistance was given. None of the untrained participants were provided training on how to use the device.

Materials used in the study were fully representative of the commercial product and included:

- Alirocumab prefilled syringe, 150 mg/mL, including package, Instructions for Use, and Patient Package Insert
- Comparator prefilled syringes, devices and their packaging (alirocumab 75 mg/mL [light green plunger], Lovenox 40 mg/0.4 mL [yellow plunger], Lovenox 100 mg/mL [black plunger], Lovenox 150 mg/mL (blue plunger), Pegasys (b) (4) 180 cg/0.5 mL [red plunger], BD Safety-Lok Insulin Syringe with Permanently Attached Needle 1 mL)

Other materials provided included an injection pad, alcohol swabs (or similar), sharps container for disposal of used syringe, and a waste basket. The study environment was designed to be consistent with home use and included a cupboard where the devices and packaging for the differentiability session were stored, and a refrigerator for the unused alirocumab prefilled syringes in its packaging.

The test was divided into three sessions:

- Package and device differentiation: Prescribers were asked to select the correct device in the blister pack from a group of seven prefilled syringes in the blister pack. Pharmacists were asked to select the correct box from a group of seven packages of prefilled syringes. Nurses and patients were asked first to select the correct box from a group of seven packages of pre-filled syringes, and then to select the correct device in the blister pack from a group of seven pre-filled syringes
- Handling: Prior to performing an injection, the nurse and patient participants were asked to open the alirocumab packaging and remove one of the two prefilled syringes from the box and from the blister pack. The participants were then asked to perform a single injection with the prefilled syringe into the injection pad, which was placed at an

injection site chosen by the participant. If the participants failed in the injection attempt, they were asked to perform another injection with the second syringe. The participants were informed that the moderator would not provide any help or direct assistance to complete the task.

- IFU Readability: Nurses and patients were asked to read the IFU and rate its usability.

User tasks were assessed through direct observation and targeted questioning (Table 5).

Table 5. User Tasks Evaluated				
Task	Patients	Nurses	Pharmacists	Prescriber
1. Pre-filled syringe stored by user				
1.1 Pharmacist stores product	-	-	x	-
1.2 Pharmacist hands over product (package) to the patient	-	-	x	-
Prescriber hands over product (device) to the patient	-	-	-	x
1.3 Patient to store product in a refrigerator	x	-	-	-
2. Injection prepared by user				
2.1 Open packaging and remove device	x	x	-	-
2.2 Select correct device	x	x	-	-
2.3 Check expiry date	x	x	-	-
2.4 Check barrel including drug condition	x	x	-	-
2.5 Warm up at room temperature for 30 to 40 minutes	x	x	-	-
2.6 Remove the cap	x	x	-	-
2.7 Choose correct injection site	x	x	-	-
3. Injection delivered by user				
3.1 Pinch skin and insert needle fully at perpendicular or 45° angle	x	x	-	-
3.2 Press plunger and inject full dose	x	x	-	-
3.4 Remove needle from skin	x	x	-	-
4. Pre-filled syringe disposed by user				
4.1 Dispose device and cap	x	x	-	-
5. Further treatment				
5.1 Perform follow-up treatment	x	x	-	-

Data Collection and Analysis

During each session, the moderator observed participants' actions and behaviors on each step and recorded task success, use errors, and other indicators of behavior that could result in unsafe or incorrect use of the device. After performing each task, the participants were interviewed to provide a subjective narrative on their experience using the device and to share any feedback or concerns they had regarding the device. The measures can be grouped into three classes:

- Performance Measures: related to the tasks and sub-tasks of use were recorded before, during, and after each task, and answers to the knowledge probe questions asked.
- Behavioral Measures: included verbal comments made by participants (if any) and any expressions of difficulty made by the participants while performing the tasks. Also, behaviors that were clearly associated with use errors or difficulties were observed and documented.
- Subjective Measures: included participants stating whether or not they had any difficulty performing any of the tasks or sub-tasks, or related to any task or knowledge probe administered in the study.

In the early HF validation study, most of the first 44 participants did not find the IFU when they opened the packaging because the IFU (b) (4). As a result of this finding, the design of the packaging was modified during the study (the IFU was folded around the blister pack to make it easier for the user to find) and tested with the last 16 participants.

D.2 Results

During the supervised injections performed by the participants in the training sessions, all participants completed the simulated self-injections into the skin pad successfully; there were no use errors or close calls on the simulated injections.

Results of the human factors validation study testing sessions are presented in Tables 6 and 7.

Table 6. Use Errors and Operational Difficulties by Distinct User Groups					
Task (Task ID)	Pharmacists (n=17)		Prescribers (n=16)		Total
	Difficulty	Use Error	Difficulty	Use Error	
Pharmacist stores product (1.1)	0	0	N/A	N/A	0
Pharmacist hands over product (packaging) to the patient (1.2)	0	0	N/A	N/A	0
Prescriber hands over product (device) to the patient (1.2)	N/A	N/A	0	1	1
Perform follow-up treatment	N/A	N/A	0	2	2
Total	0	0	0	3	3
Task (Task ID)	Patients (n=60)		Nurses (n=16)		Total
	Difficulty	Use Error	Difficulty	Use Error	
Store the product in a refrigerator (1.3)	0	9 (1 trained, 8 untrained)	0	4	13
Store the product out of reach of children	2 (2 untrained)	0	1	0	3
Open packaging and remove device (2.1)	2 (1 trained, 1 untrained)	0	0	0	2
Open packaging and find the IFU	0	*Original packaging: 44 Revised packaging: 1	0	Original packaging: 7	Original: 51 Revised: 1
Select correct device (correct drug)	0	0	0	0	0
Select the correct device (correct concentration)	1 (1 untrained)	0	0	0	1
Select correct box (correct concentration and correct drug)	0	1 (1 untrained)	N/A	N/A	1
Check expiry date (2.3) Check barrel, including drug condition (2.4)	0	19	0	7	26
Warm up at room temperature for 30 to 40 minutes (2.5)	2 (2 trained)	8	0	2	12
Remove the cap (2.6)	1	1 (1 trained)	0	0	2

Do not remove the air bubbles	0	1 (1 untrained)	1	0	2
Choose correct injection site (2.7)	0	0	0	0	0
Clean injection site	0	23 (7 trained, 16 untrained)	0	2	25
Pinch skin and insert needle fully at perpendicular or 45° angle (3.1)	0	0	0	0	0
Press on plunger (3.2)	2 (2 trained)	1 (1 untrained)	0	0	3
Inject full dose	1 (1 trained)	2 (2 untrained)	0	0	3
Remove needle from skin (3.3)	0	0	0	0	0
Do not recap the syringe (4.1)	14	0	0	0	14
Dispose of device and cap according to local regulatory requirements (5.1)	2 (2 untrained)	9 (1 trained, 8 untrained)	0	0	11
Perform follow-up treatment	3 (1 trained, 2 untrained)	27**	N/A	N/A	30
TOTAL	30	102***	2	15	149***

*The packaging was revised and tested with the last 16 participants (these 16 participants opened the original packaging and the revised packaging): All 60 patient participants used the original packaging (use errors: 44/60); 16 of the 60 patient participants used the revised packaging (use errors 1/16).

**Most participants who gave an incorrect response or did not know were prompted by the study moderator to refer to the Patient Package Insert (PPI). When told where to find the information, all participants succeeded in finding it.

***Totals based upon revised packaging

Detailed Results:

Table 7. Essential and Safety Critical Steps with Results

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
1.1	Pharmacist stores product	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Pass: 16/16	-	-
1.2	Pharmacist hands over product (packaging) to the patient	Overdose leading to increase in LDL-C reduction and potentially increased transaminases Underdose leading to lack of efficacy Potential side effects and/or toxic effects of incorrect drug	Marginal Negligible Very serious	Pass: 16/16	-	-
	Prescriber hands over product (device) to the patient	Overdose leading to increase in LDL-C reduction and potentially increased transaminases Underdose leading to lack of efficacy Potential side effects and/or toxic effects of incorrect drug	Marginal Negligible Very serious	Pass: 16/17 Use error: 1/17	One prescriber (PR03) selected a comparator syringe (Lovenox) in the blister pack that was the same dosage as the alicromab pre-filled syringe. When selecting the syringe, the participant said she focused on the concentration of the drug only and not the drug name. When she was asked what she would check for before using the device, she noticed that she had picked up the Lovenox syringe.	This finding could be considered a test artifact because in a clinical setting, it is unlikely that both drugs would be stored in the same clinical environment or delivered by the same clinician. Importantly, to prevent medication errors, most clinical facilities have multiple layers of confirmation, such as review by other clinicians, that the drug about to be delivered is correct
No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
1.3	Patient to store the product in a refrigerator	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Pass: 51/60 Use error: 9/60	One trained patient (PA14) and 4 untrained patients (PA41, PA46, PA52, PA59) indicated that they would store the syringe in a medicine cabinet in the bathroom. When asked to look back at the IFU, all 5 patients recognized that the syringe should be stored in the refrigerator. 2 untrained patients (PA47, PA51) said they would store the syringe in a cool, dry place. The moderator asked both participants to clarify what they meant by cool, dry place. PA47 said she would likely store it in the bathroom, and PA51 said he would store it in temperatures between 60° and 70°F. Neither participant was asked to look back at the IFU. 2 untrained patients (PA39, PA54) said they would store it on a shelf away from children. When prompted to look back at the IFU, both patients recognized that the syringe should be stored in the refrigerator.	In the differentiation session, the devices and packages were stored in a cupboard and presented to the participants that way. This could have influenced the participants' responses. This result is considered to be a test artifact.
	Nurse to store the product in a refrigerator	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Pass: 12/16 Use error: 4/16	4 nurses (NU04, NU10, NU15, N16) said they would store the syringe at room temperature before injecting. The moderator asked these participants to look back at the IFU to see if it contained any information about storage requirement. Upon reviewing the IFU, 3 of the 4 nurses (NU04, NU10, NU15) recognized that the syringe should be stored in the refrigerator. NU16 was instructed to look back at the IFU, but was unable to locate the information about storing the syringe in the refrigerator.	In the differentiation session, the devices and packages were stored in a cupboard and presented to the participants that way. This could have influenced the participants' responses. This result is considered to be a test artifact.

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
	Patient to store the product out of reach of children	Sharps injury with sterile needle (slight injury without the need to see a doctor)	Marginal	Pass: 58/60	-	-
		Inhalation of small parts which can lead to suffocation	Very serious	Difficulty: 2/60	2 patient untrained patients (PA41, PA42) indicated that he would store the device in the refrigerator, but that he would not do anything differently if children were present. PA41 and PA42 were contacted after the study to clarify their responses. PA41 said he would store it the refrigerator, but that he would try to keep out of reach of children while it was in the fridge or place it in some type of container with a lock on it. PA42 said she would store it in the refrigerator and keep it as far out of reach as possible.	-
	Nurse to store the product out of reach of children	Sharps injury with sterile needle (slight injury without the need to see a doctor)	Marginal	Pass: 15/16	-	-
		Inhalation of small parts which can lead to suffocation	Very serious	Difficulty: 1/16	One nurse (NU01) said that she would not store the device differently. She said that it still needed to be refrigerated. NU01 was contacted after the study and asked to clarify her response. She stated that she would still keep syringes in the fridge, but that she would cover them to make them less visible or put it in some type of container that children would not be able to get into.	-
2.1	Patient: Open packaging and remove device	Underdose leading to lack of efficacy	Negligible	Pass: 58/60 Difficulty: 2/60	- One trained patient (PA01) had some difficulties opening the blister pack. One untrained patient (PA60) roughly removed the syringe from the blister pack, causing the needle to bend slightly. With the cap still on, she straightened the needle and then continued with the injection.	- -
No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
	<i>Early part of study with original packaging:</i> Patient: Open packaging and find the IFU	Patient does not receive information regarding proper storage and disposal.	Very serious	Pass: 16/60 Use error: 44/60	- 44 patients did not find the IFU when opening the package.	- The IFU (b) (4) This packaging was subsequently modified. See the following rows "last part of study with revised packaging".
	<i>Last part of study with revised packaging:</i> Patient: Open packaging and find the IFU	Patient does not receive information regarding proper storage and disposal.	Very serious	Pass: 15/16 ^a Use error: 1/16	One patient (PA50) opened the box on the end opposite the end on which the IFU was wrapped around the blister pack. She removed the blister packs from the box, but never looked in the box to see if it contained any additional contents.	In the study, a box with perforation on both ends was used. However, the final box will have perforation only on the end that the user should open (because the IFU is there), so the user will get the IFU every time he/she opens the box.
	Nurse: Open packaging and remove device	Underdose leading to lack of efficacy	Negligible	Pass: 16/16	-	-
	<i>Early part of study with original packaging:</i> Nurse: Open packaging and find the IFU	Nurse does not receive information regarding proper storage and disposal.	Very serious	Pass: 9/16 Use error: 7/16	- 7 nurses did not find the IFU when opening the package.	- The IFU (b) (4) This was subsequently modified. See the results of the patients of task 2.1 for the "last part of study with revised packaging".
2.2	Patient: Select correct device (correct drug)	Potential side effects and/or toxic effects of incorrect drug	Very serious	Pass: 60/60	-	-
	Patient: Select correct device (correct concentration)	Overdose leading to increase in LDL-C reduction and potentially increased transaminases	Marginal	Pass: 59/60	-	-

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
		Underdose leading to lack of efficacy	Negligible	Difficulty: 1/60	One untrained patient (PA32) initially selected the 75 mg/mL concentration instead of the 150 mg/mL concentration but corrected himself.	-
	Patient: Select correct box (correct concentration and correct drug)	Underdose leading to lack of efficacy	Negligible	Pass: 59/60	-	-
		Overdose leading to increase in LDL-C reduction and potentially increased transaminases	Marginal	Use error: 1/60	One patient (PA47) selected two packages, the correct package and a comparator syringe package (Lovenox 150 mg/mL); she said she thought that the Lovenox box was a larger box of the same (Voypaz) medication.	This participant selected the correct syringe from among the group of syringes on the shelf, so she was able to recognize the correct syringe and to distinguish it from the other syringes.
		Potential side effects and/or toxic effects of incorrect drug	Very serious			
	Nurse: Select correct device (correct drug)	Potential side effects and/or toxic effects of incorrect drug	Very serious	Pass: 16/16	-	-
	Nurse: Select correct device (correct concentration)	Overdose leading to increase in LDL-C reduction and potentially increased transaminases	Marginal	Pass: 16/16	-	-
		Underdose leading to lack of efficacy	Negligible			

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
2.3	Patient:	Ineffective drug	Negligible	Pass: 41/60	-	-
+	Check expiry date	Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible	Use error: 19/60	19 patients did not mention that they would check the expiration date. <ul style="list-style-type: none"> 15 of these patients were prompted by the moderator to refer to the IFU. Then they could answer the question. 4 (PA09, PA13, PA31, PA47) patients were not asked to look back at the IFU. But 2 patients (PA09, PA13) said they would check the appearance of the solution and check to make sure they had the correct drug and one patient (PA13) mentioned he would check that the drug was refrigerated and the packaging was intact and 3 patients (PA09, PA13, PA47) said they would check to make sure they had the correct dose. 	This finding is based solely on observation; the participants were not specifically asked if they would do this in real life. <p>Since in a study like this one, participants might not expect to be handed a drug product that is contaminated or expired and therefore might think there was no reason to check the expiry date of the medication. Their failure to check the drug may be considered to be a <u>test artifact</u>.</p> <p>Finally, the consequence severity of this use error is negligible.</p>
2.4	Check barrel, including drug condition					
	Nurse:	Ineffective drug	Negligible	Pass: 9/16	-	-
	Check expiry date	Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible	Use error: 7/16	5 nurses (NU03, NU06, NU07, NU08, NU12) did not mention that they would check the expiration date. All five nurses said they would check the dose. <p>2 nurses (NU03, NU06) said they would check the appearance of the medication.</p>	This finding is based solely on observation; the participants were not specifically asked if they would do this in real life. <p>Since in a study like this one, participants would not expect to be handed a drug product that is contaminated, their failure to check the drug may be considered to be a <u>test artifact</u>.</p> <p>Finally, the consequence severity of this use error is negligible.</p>
	Check barrel, including drug condition					

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
2.5	Patient: Warm up at room temperature for 30 to 40 min	Underdose leading to lack of efficacy	Negligible	Pass: 50/50 Difficulty: 2/60 Use error: 8/60	- One trained patient (PA23) said to wait 20 minutes before injecting. This participant was not asked to look back at the IFU. One trained patient (PA29) said the medicine should be room temperature before injecting, but did not specify a certain amount of time to wait. This participant was not asked to look back at the IFU. After being asked to look back at the IFU, 7 patients answered correctly. One untrained patient (PA45) said you do not have to wait at all before injecting, but noted that the injection would be more comfortable if the medication was at room temperature. This participant did not use the IFU to answer this question. He based his answer off his experience with his insulin injections. This participant was not asked to look back at the IFU.	- Every patient knew that they had to wait before using the device. This task has no effect on the efficacy of the drug. Allowing the drug to come up to room temperature makes the injection easier and more comfortable. When the drug is cold, the injection time increases and the injection pain increases. If the warm-up period is very short, the drug will be cold and the injection time and force will increase. Consequently, a patient might not be able to press the plunger completely down and would not get the full dose. However, patients would still get the visual feedback concerning the status of the injection. Even if an underdose occurred, the consequences would have a low (negligible) severity.
	Nurse: Warm up to room temperature for 30 to 40 min	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Pass: 14/16 Use error: 2/16	- One nurse (NU02) said she did not know and that she did not remember reading that information in the IFU. This participant was not asked to look back at the IFU. One nurse (NU03) said it should be used immediately or within 30 minutes after being removed from the refrigerator. This participant was not asked to look back at the IFU.	- If the warm-up period is very short, the drug will be cold and the injection time and force will increase. Consequently, a nurse might not be able to press the plunger completely down and would not inject the full dose. However, patients would still get the visual feedback concerning the status of the injection. Even if an underdose occurred, the consequences would have a low (negligible) severity.
2.6	Patient: Remove the cap	Delay of treatment which may constitute an underdose leading to lack of efficacy	Negligible	Pass: 58/60 Difficulty: 1/60 Use error: 1/60	- One patient (PA06) bent the needle slightly when removing the needle cap. One trained patient (PA13) held the syringe by the plunger when trying to remove the cap. Therefore, when she tried to pull the cap off she pulled the plunger out and lost some of the medication. This participant started over with a new syringe. On her second attempt, she corrected her previous mistake and held the syringe by the barrel as she removed the cap. However, she held the syringe with the needle pointing upward and as she pulled the cap off, the plunger moved down and pressed against the table and she lost some medication. This participant continued using the syringe and finished the injection.	- These errors could be considered to be <u>learning</u> effects.
	Nurse: Remove the cap	Delay of treatment which may constitute an underdose leading to lack of efficacy	Negligible	Pass: 16/16	-	-

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
	Patient/nurse: Do not remove air bubbles	Underdose leading to lack of efficacy	Negligible	Pass: 74/76 Difficulty: 1/76 Use error: 1/76	- One nurse (NU01) removed air bubbles without losing medication. One patient (PA51) lost a small amount of medication when trying to get rid of an air bubble.	- - -
2.7	Patient/nurse: Choose correct injection site	No effect on drug efficacy expected, rupturing of very small vessels (ecchymosis) possible	Negligible	Pass: 76/76	-	-
	Patient: Clean injection site	Marginal infection or reaction (eg, skin) towards contamination	Negligible	Pass: 37/60 Use error: 23/60	- 7 trained and 16 untrained patients did not clean the injection site.	- Many participants did not clean the injection site, but this can be considered a <u>test artifact</u> . The participants were injecting into an injection pad, not themselves, so they might not have felt the need to clean the injection site as they would for an actual injection in their home environment.
	Nurse: Clean injection site	Marginal infection or reaction (eg, skin) towards contamination	Negligible	Pass: 14/16 Use error: 2/16	- 2 nurses (NU04, NU12) did not clean the injection site.	- Many participants did not clean the injection site, but this can be considered a <u>test artifact</u> . The participants were injecting into an injection pad, not into a patient, so they might not have felt the need to clean the injection site as they would for an actual injection in their normal clinical environment.
No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
3.1	Patient: Pinch skin and insert needle fully at perpendicular or 45° angle	More painful injection (intramuscular) Underdose leading to lack of efficacy	Negligible Negligible	Pass: 60/60	-	-
	Nurse: Pinch skin and insert needle fully at perpendicular or 45° angle	More painful injection (intramuscular). Underdose leading to lack of efficacy	Negligible Negligible	Pass: 16/16	-	-
3.2	Patient: Press on plunger	Underdose leading to lack of efficacy	Negligible	Pass: 57/60 Difficulty: 2/60 Use error: 1/60	- One trained patient (PA26) inserted the needle and was unable to push the plunger down. This participant then removed the needle from the site and said that the needle looked bent. She then disposed of the syringe, removed the second syringe from the package, and continued giving the injection. One trained patient (PA12) experienced a lot of resistance when trying to start the injection. She re-gripped the syringe three times before getting the plunger to move. Once she got the plunger to move the medication leaked out onto the surface of the injection pad. It appeared that the pad was full during this injection and prevented the medication from being injected and also caused the medication to leak out during the process. But in the end the participant was able to administer a full dose of medication. One untrained patient (PA42) initially was not able to push down the plunger. She removed the syringe from the pad, pointed the needle towards the floor, and then pressed the plunger and lost some of the medication. She then reinserted the needle into a different spot on the pad and administered the remaining amount of medication.	- This difficulty might have been caused by a device malfunction or it might have been a <u>test artifact</u> , e.g. if the injection pad was full. This difficulty was caused by a full injection pad, which is a <u>test artifact</u> . This use error can be described as a <u>learning effect</u> . In the second attempt for all three participants, the task went well.

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
	Nurse: Press on plunger	Underdose leading to lack of efficacy	Negligible	Pass: 16/16	-	-
	Patient: Inject full dose	Underdose leading to lack of efficacy	Negligible	Pass: 57/60 Difficulty: 1/60	One trained patient (PA16) removed the syringe from the pad before it was empty. After removing the syringe, the participant realized there was still medication in the barrel and he reinserted the needle into the pad and injected the remaining medication. The participant said that he removed the needle too soon because the pad moved around while he was pinching it.	Removing the syringe before the injection is complete could be considered a <u>learning effect</u> . Having the injection pad move around during the injection is a <u>test artifact</u> . The participant had no difficulty with his second injection attempt.
				Use error: 2/60	One untrained patient (PA36) unintentionally pulled the syringe out of the pad during the injection and spilled some of the medication. One untrained patient (PA50) administered a small amount of the medication and then removed the syringe from the pad. The patient said that she only administered a little medication because it is how she administers her diabetes medication. She realized that she made an error.	This use error can be described as a <u>learning effect</u> . In the second attempt for both participants, the task went well.
	Nurse: Inject full dose	Underdose leading to lack of efficacy	Negligible	Pass: 16/16	-	-
3.3	Patient: Remove needle from skin	Third-party sharps injury with used needle and possible transmission of a blood-borne disease	Very serious	Pass: 60/60	-	-
	Nurse: Remove needle from skin	Third-party sharps injury with used needle and possible transmission of a blood-borne disease	Very serious	Pass: 16/16	-	-
No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
4.1	Patient: Do not recap the syringe	Sharps injury with sterile needle (slight injury without the need to see a doctor)	Marginal	Pass: 46/60 Difficulty: 3/60	14 patients recapped the syringe without getting a needle-stick injury.	This hazard is present for all syringes and many people do not know that they should not recap needles.
	Nurse: Do not recap the syringe	Third-party sharps injury with used needle and possible transmission of a blood-borne disease	Very serious	Pass: 16/16	-	-
5.1	Patient: Dispose of device and cap according local regulatory requirements treatment	Sharps injury with sterile needle (slight injury without the need to see a doctor) Third-party sharps injury with used needle and possible transmission of a blood-borne disease	Marginal Very serious	Pass: 46/60 Difficulty: 2/60	2 untrained patients set the syringe on the table and did not put the syringe into the sharps bin after the injection. They were asked what they would do with the syringe if they were in their home setting: <ul style="list-style-type: none">• Patient PA35 said he would dispose of it according to local regulations.• Patient PA56 said he would dispose of the syringe into a sharps container.	-
				Use error: 9/60	One trained and 8 untrained patients set the syringe on the table after the injection and did not put the syringe into the sharps bin: <ul style="list-style-type: none">• 2 untrained patients were asked what they would do with the syringe if they were in their home setting:<ul style="list-style-type: none">○ Patient PA48 said he would dispose of the syringe in the trash.○ Patient PA58 said he would remove the needle and then throw it away in the trash.• 7 patients were not asked to look back at the IFU.	This hazard is present for all syringes and many people do not know that they should discard them into a sharps container or other puncture-resistant container.

No	Task/ID	Consequences	Severity	Results	Observations	Root Cause/Comments
	Nurse: Dispose of device and cap according local regulatory requirements	Third-party sharps injury with used needle and possible transmission of a blood-borne disease	Very serious	Pass: 16/16	-	-
	Patient: Perform follow-up treatment	Too-frequent administration would be an overdose, which could lead to increase in LDL-C reduction and potentially increased transaminases	Marginal	Pass: 30/60 Difficulty: 3/60	- One trained patient (PA04) and 2 untrained patients (PA40, PA50) said the drug should be administered as prescribed by their doctor.	The primary way that the patient will be informed about the dosage regimen is to be told by the doctor when the drug is prescribed.
		Too-infrequent administration would be an underdose, which could lead to lack of efficacy	Negligible	Use error: 27/60 ^b	25 patients gave a correct answer, but only with guidance from the moderator to look at the patient package insert. One patient (PA01) was not shown the PPI during the training and said he did not get any information about the frequency of injections, and therefore did not know how often to administer the medication. He was not prompted to look in the PPI. One trained patient (PA10) guessed that the drug should be administered once per week.	The primary way that the patient will be informed about the dosage regimen is to be told by the doctor when the drug is prescribed. When told where to find the information, all participants succeeded in finding it.
	Prescriber: Perform follow-up treatment	Too-frequent administration would be an overdose, which could lead to increase in LDL-C reduction and potentially increased transaminases	Marginal	Pass: 15/17	-	-
		Too-infrequent administration would be an underdose, which could lead to lack of efficacy	Negligible	Use error: 2/17	One prescriber (PR15) said that the drug should be administered once per day. One prescriber (PR16) gave a correct answer, but only with guidance from the moderator to look at the patient package insert.	Prescribers will be informed of, and will learn, the dosing regimen for the drug. They are not likely to depend on the PPI to provide this information.

^a The packaging was revised (Section 5.4) and tested with the last 16 participants (these 16 participants opened the original and the revised packaging).

^b Most participants who gave an incorrect response or did not know were prompted by the study moderator to refer to the patient package insert (PPI).

Sponsor Conclusions:

The human factors validation study for the alirocumab prefilled syringe did not result in any patterns of use errors or task failures on the critical tasks, and was therefore shown to be safe and effective for use by all intended user populations under simulated but realistic use conditions.

Praluent Prefilled Pen/Autoinjector

D.3 Study Design

The Human Factors Study Results and IFU for Praluent prefilled pen/autoinjector submitted on November 24, 2014 were evaluated. Below is a brief overview of the study objectives, description of the study participants, study design, data collection, and data analysis.

Study Objectives:

- Differentiation session: confirm that end-users can successfully differentiate the prefilled pen and its packaging from other Sanofi prefilled pens, including the same pen with another concentration, and other companies' pens/auto-injectors that are likely to be present in the same real-world use environment.
- Handling session: confirm that end-users can handle the device safely and effectively in a realistic normal-use scenario (i.e., successfully deliver the intended dose, making no safety-critical errors)

Study Participants:

Table 8 provides information on the study participants and demographics.

Table 8. Distinct End User Groups in Main and Supplemental Human Factors Validation Study			
Distinct User Groups – Main HF Validation Study (n=113)			
User Groups	Pen Experienced	Injection Naïve	Total
Patients Adult patients with hypercholesterolemia (>240 mg/dL)	15 untrained	18 untrained	33
<ul style="list-style-type: none"> • 31 male, 34 female • 23 also had Type 2 diabetes mellitus • 10 also had color vision deficiencies • 5 also had tactile/manual or hearing impairments 	16 trained	16 trained	32
Total	31	34	65
Nurses Nurse educators, licensed practical nurses, or registered nurses currently administering insulin in an inpatient or outpatient setting	15 untrained	N/A	15
	0 trained	N/A	0
Total	15	0	15
Prescribers Internal medicine physicians, endocrinologists, primary care physicians, and nurse practitioners actively seeing and treating diabetes patients.	N/A	N/A	17
Nurses Retail, specialty, and hospital pharmacists with a ratio of 2:1:1 for the respective job profiles	N/A	N/A	16
Distinct User Groups – Supplemental HF Validation Study (n=76)			
User Groups	Pen Experienced	Injection Naïve	Total
Patients Adult patients with hypercholesterolemia (>240 mg/dL)	16 untrained	14 untrained	30
<ul style="list-style-type: none"> • 16 also had Type 2 diabetes mellitus • 4 also had color vision deficiencies • 10 also had tactile/manual or hearing impairments 	16 trained	14 trained	30
Total	32	28	60
Nurses Primarily registered nurses, plus licensed practical nurses and nurse educator nurses	16 untrained	N/A	16
	0 trained	N/A	0
Total	16	0	16

Table 9 provides information on the types of study sessions.

Table 9. Participants and Study Sessions			
User Groups	Study Sessions – Main HF Validation Study		
	Differentiation	Handling	Readability
Patients (n=65)	X	X	X
Nurses (n=15)	X	X	X
Prescribers (n=17)	X		
Pharmacists (n=16)	X		
User Groups	Tasks* – Supplemental HF Validation Study		
	Task 1.3	Task 2.1**	Task 5.1
Patients (n=60)	X	X	X
Nurses (n=16)	X		

*Task 1.3: storage of the device out of the reach of children; Task 2.1: opening the package; Task 5.1: perform follow-up treatment

**No participant was trained or shown how to open the package, including the trained participants

Training and Testing Sessions:

Thirty-two (32) patient participants received training 5 to 7 days before the validation study session. 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. The study facilitator provided help and feedback as needed to train the participant to use the device safely and correctly. The study facilitator took notes on each participant's performance of performing the injection, which consisted of removing the autoinjector cap, holding the device in correct orientation, pressing the device firmly on the site, starting the injection (i.e., press button), watching the window, and removing the autoinjector from the injection site. These same sub-tasks were assessed in the test session of the human factors validation study. During the supervised injections performed by the participants during the training sessions, all participants completed the simulated self-injections into the skin pads successfully; there were no use errors or close calls on the simulated injections.

All participants were given a general introduction regarding safety aspects and the indication for use of the autoinjector. Participants were given time to read the IFU at their own pace. The IFU was available during the study session but no other assistance was given. None of the untrained participants were provided training on how to use the device; additionally, untrained participants were not instructed or asked to read the IFU.

Materials used in the study were fully representative of the commercial product and included:

- Alirocumab prefilled pen, 150 mg/mL, including Instructions for Use and Patient Package Insert
- Alirocumab prefilled pen packaging, 75 mg/mL and 150 mg/mL
- Comparator prefilled syringes, devices and their packaging (alirocumab prefilled pen 75 mg/mL, Lantus SoloStar, Levemir FlexPen, Humalog KwikPen, Enbrel SureClick Prefilled Pen, Pegasys ProClick Prefilled pen)

Other materials provided included an injection pad, alcohol swabs (or similar), sharps container for disposal of used syringe, and a waste basket. The study environment was designed to be consistent with home use and included a cupboard where the devices and packaging for the differentiability session were stored, and a refrigerator for the unused alirocumab prefilled pens.

The test was divided into three sessions:

- **Package and device differentiation:** Prescribers were asked to select the correct device in the blister pack from a group of seven prefilled pens and autoinjectors. Pharmacists were asked to select the correct box from a group of seven packages of prefilled pens and autoinjectors. Nurses and patients were asked first to select the correct box from a group of seven packages of prefilled pens and autoinjectors, and then to select the correct device from a group of seven prefilled pens and autoinjectors.
- **Device Handling:** Prior to performing an injection, the nurse and patient participants were asked to open the alirocumab packaging and remove one of the two prefilled pens from the box. The participants were then asked to perform a single injection with the prefilled pen into the injection pad, which was placed at an injection site chosen by the participant. Participants were informed that the moderator would not provide any help or direct assistance to complete the task.
- **IFU Assessment/Readability:** Nurses and patients were asked to read the IFU and rate its usability.

User tasks were assessed through direct observation and targeted questioning (Table 10).

Table 10. Tasks of Use of the Prefilled Pen

Task	Patients	Nurses	Pharmacists	Prescriber
1. Pre-filled pen stored by user				
1.1 Pharmacist stores product	-	-	x	-
1.2 Pharmacist hands over product to the patient	-	-	x	-
Prescriber hands over product to the patient	-	-	-	x
1.3 Patient to store product in a refrigerator and childproof	x	x	-	-
2. Injection prepared by user				
2.1 Open packaging and remove device	x	x	-	-
2.2 Select correct device	x	x	-	-
2.3 Check expiry date	x	x	-	-
2.4 Check window including drug condition	x	x	-	-
2.5 Warm up at room temperature for 30 to 40 minutes	x	x	-	-
2.6 Remove the cap	x	x	-	-
2.7 Choose correct injection site	x	x	-	-

Task	Patients	Nurses	Pharmacists	Prescriber
3. Injection delivered by user				
3.1 Hold device in the correct orientation	x	x	-	-
3.2 Press device on the site for injection	x	x	-	-
3.3 Press button to start injection	x	x	-	-
3.4 Release button	x	x	-	-
3.5 Wait until injection is complete	x	x	-	-
3.6 Remove device from skin	x	x	-	-
4. Pre-filled pen disposed by user				
4.1 Dispose device and cap	x	x	-	-
5. Further treatment				
5.1 Perform follow-up treatment	x	x	-	-

Data Collection and Analysis

During each session, the moderator observed participants' actions and behaviors on each step and recorded task success, use errors, and other indicators of behavior that could result in the unsafe or incorrect use of the device. After performing each task, the participants were interviewed to provide a subjective narrative on their experience using the device and to share any feedback/concerns they had regarding the device. The measures can be grouped into the following categories:

- Performance measures: related to the tasks and sub-tasks of use were recorded before, during, and after each task, and answers to the knowledge probe questions asked.
- Behavioral measures: Behavioral measures recorded during this study included verbal comments made by participants (if any) and any expressions of difficulty made by the participants while performing the tasks. Also, behaviors that were clearly associated with use errors or difficulties were observed and documented.
- Subjective measures: included participants stating whether or not they had any difficulty performing any of the tasks or sub-tasks, or related to any task or knowledge probe administered in the study.

Protocol Deviations

In the main HF validation study, most of the patient participants (40/65) opened the packaging on the end rather than on the side, as intended, which resulted in participants not seeing the quick reference guide. In response to this finding, the artwork on the outside of the packaging was changed to make the opening edge more noticeable and was used in the supplemental HF validation study (with 60 participants).

Additionally, participants in the main HF validation study (65 patients and 48 health care providers) were not asked the following questions regarding Task 1.3 Storing the product out of the reach of children and Task 5.1 Performing the follow-up treatment. These tasks were included in the supplemental HF validation study (with 60 patients and 16 nurses).

The Patient Package Insert was also included in the supplemental HF validation study as it included information on frequency of follow-up treatment (i.e., the dosing regimen of alirocumab).

D.4 Results

Table 11. Use Errors, Close Calls, and Operational Difficulties by Distinct User Groups						
Distinct User Groups – Main HF Validation Study (n=113)						
Task (Task ID)	Critical or Non-Critical Task	Pharmacists (n=16)		Prescribers (n=17)		Total
		Difficulty	Use Error	Difficulty	Use Error	
Pharmacist stores product (1.1)	Non-critical	0	0	N/A	N/A	0
Hands product over to the patient (1.2)	Critical	0	0	0	0	0
Total	N/A	0	0	0	0	0
Task (Task ID)	Critical or Non-Critical Task	Patients (n=65)		Nurses (n=15)		Total
		Difficulty	Use Error	Difficulty	Use Error	
Store the product in a refrigerator (1.3)	Non-critical	1 (1 untrained)	4 (4 untrained)	0	0	5
Open the package and remove the device (2.1)	Non-critical	0	0	0	0	0
Open the package in the intended way (2.1)	Non-critical	1 (1 untrained)	40 (23 trained, 17 untrained)	0	6	47
Select correct device (correct drug) (2.2)	Critical	0	0	0	0	0
Select correct device (correct concentration) (2.2)	Non-critical	2 (2 trained)	0	0	1	3
Select correct box (correct drug and correct concentration) (2.2)	Critical	0*	0*	N/A	N/A	0
Check expiry date (2.3)	Non-critical	0	2 (1 trained, 1 untrained)	0	0	2
Check window, including drug condition (2.4)	Non-critical	0	6 (6 untrained)	0	0	6
Warm up at room temperature for 30 to 40 minutes (2.5)	Non-critical	7 (1 trained, 6 untrained)	2 (2 untrained)	0	0	9

Task (Task ID)	Critical or Non-Critical Task	Patients (n=65)		Nurses (n=15)		Total
		Difficulty	Use Error	Difficulty	Use Error	
Remove the cap (2.6)	Non-critical	1 (1 trained)	1 (1 untrained)	0	0	2
Choose correct injection site (2.7)	Non-critical	0	1 (1 untrained)	0	0	1
Clean injection site (2.7)	Non-critical	0	20 (6 trained, 14 untrained)	0	1	21
Hold device in the correct orientation (3.1)	Non-critical	0	0	0	0	0
Press device on the site for injection (unlock button) (3.2)	Non-critical	6 (1 trained, 5 untrained)	3 (3 untrained)	0	0	9
3.3 Press button for injection	Non-critical	0	0	1	0	1
3.4 Release the button	Non-critical	18 participants did not release the button (user group not specified)				18
3.5 Wait until the injection is complete	Non-critical	3 (3 untrained)	2	1	1	7
3.6 Remove device from skin	Non-critical	1 (1 untrained)	0	1	0	2
4.1 Dispose of device and cap according to local regulatory requirements	Non-critical	0	5 (1 trained, 4 untrained)	0	0	5
Total	N/A	22**	86**	3**	9**	138

* Four patients did not complete this task due to a protocol deviation (ie, the inclusion of the package differentiation task for patients) early in the study.

** Total does not include 18 unspecified participants who had difficulty in Task 3.4 Release the button

Distinct User Groups – Supplemental HF Validation Study (n=76)						
Task (Task ID)	Critical or Non-Critical Task	Patients (n=60)		Nurses (n=16)		Total
		Difficulty	Use Error	Difficulty	Use Error	
1.3 Store product out of reach of children	Critical	2 (2 untrained)	0	1	0	3
2.1 Open the package in the intended way (on the front side)	Non-critical	0	19	N/A	N/A	19
5.1 Perform follow-up treatment	Non-critical	3 (1 trained, 2 untrained)	27	N/A	N/A	30
Total	N/A	5	46	1	0	52

Detailed Results

No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
1.2	Pharmacist hands over product (packaging) to the patient TPP:U18, TPP:U19, TPP:U20	Overdose leading to increase in LDL-C reduction and potentially increased transaminases	Marginal	Pass: 16/16		
		Underdose leading to lack of efficacy	Negligible			
		Potential side effects and/or toxic effects of incorrect drug	Very serious			
	Prescriber hands over product (device) to the patient TPP:U18, TPP:U20	Overdose leading to increase in LDL-C reduction and potentially increased transaminases	Marginal	Pass: 17/17		
		Underdose leading to lack of efficacy	Negligible			
		Potential side effects and/or toxic effects of incorrect drug	Very serious			
	Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible				
No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
1.3	Supplemental HF validation study: Patient to store the product out of reach of children TPP:U20	Sharps injury with sterile needle (slight injury without the need to see a doctor)	Marginal	Pass: 58/60		
		Inhalation of small parts which can lead to suffocation	Very serious	Difficulty: 2/60		
					2 untrained patients (PA41, PA42) indicated that they would store the device in the refrigerator, but that they would not do anything differently if children were present. PA41 and PA42 were contacted after the study to clarify their responses. PA41 said he would store it in the refrigerator, but that he would try to keep out of reach of children while it was in the fridge or place it in some type of container with a lock on it. PA42 said she would store it in the refrigerator and keep it as far out of reach as possible.	
	Supplemental HF validation study: Nurse to store the product out of reach of children TPP:U20	Sharps injury with sterile needle (slight injury without the need to see a doctor)	Marginal	Pass: 15/16		
		Inhalation of small parts which can lead to suffocation	Very serious	Difficulty: 1/16		
					One nurse (NU01) said that she would not store the device differently. She said that it still needed to be refrigerated. NU01 was contacted after the study and asked to clarify her response. She stated that she would still keep syringes in the fridge, but that she would cover them to make them less visible or put it in some type of container that children would not be able to get into.	
2.1	Patient: Select correct device (correct drug) TPP:U18, TPP:U20	Potential side effects and/or toxic effects of incorrect drug	Very serious	Pass: 65/65		
No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
2.2	Patient: Select correct box (correct concentration and correct drug) TPP:U18, TPP:U19, TPP:U20	Overdose leading to increase in LDL-C reduction and potentially increased transaminases	Marginal	Pass: 61/61 ^c		
		Underdose leading to lack of efficacy	Negligible			
		Potential side effects and/or toxic effects of incorrect drug	Very serious			
	Nurse: Select correct device (correct drug) TPP:U18, TPP:U20	Potential side effects and/or toxic effects of incorrect drug	Very serious	Pass: 15/15		

^a ID numbers see Table 9.

^b N/A : Not Applicable

^c Four patients did not complete this task due to a protocol deviation (ie, the inclusion of the package differentiation task for patients) early in the study.

No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
1.1	Pharmacist stores product TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Pass: 16/16	-	-
1.3	Patient to store the product in a refrigerator TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Pass: 60/65 Difficulty: 1/65 Use error: 4/65	- One untrained patient (PA58) said that she would store it on her dresser with her other medication; during the knowledge probe questions she realized that she answered incorrectly. 3 untrained patients (PA12, PA21, PA51) mentioned that they would store the device at room temperature. One untrained patient (PA31) said that she would store the pen in her hallway closet, and that according to the instructions, it should be stored at room temperature ^c .	- In the differentiation session, the devices and packages were stored in a cupboard and presented to the participants that way. This could have influenced the participants' responses. This result is considered to be a <u>test artifact</u> .
	Nurse to store the product in a refrigerator TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Pass: 15/15	-	-
2.1	Patient/nurse: Opening the packaging and remove device TPP:U19	Underdose leading to lack of efficacy	Negligible	Pass: 80/80	-	-
No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
	Patient: Opening packaging in the intended way (on the front side) TPP:U19 (b) (4)	No patient-safety-related consequences	N/A	Pass: 24/65 Difficulty: 1/65 Use error: 40/65	- One untrained patient (PA12) opened the box first at the end and then correctly, on the side. 40 patients (23 trained) opened the box on the end rather than on the front side.	- The side on which the box is opened is not associated with any patient safety risk.
	Nurse: Opening packaging in the intended way TPP:U19	No patient safety related consequences	N/A N/A	Pass: 9/15 Use error: 6/16	- 6 nurses opened the box at the end (this is not the intended way).	- The side on which the box is opened is not associated with any patient safety risk.
	Supplemental HF validation study: Patient: Opening packaging in the intended way (on the front side) (new artwork). TPP:U19	No patient safety related consequences	N/A	Pass: 41/60 Use error: 19/60	- 19 participants opened the box at the end (this is not the intended way).	- The side on which the box is opened is not associated with any patient safety risk.
	Patient: Select correct device (correct concentration) TPP:U18, TPP:U20	Overdose leading to increase in LDL-C reduction and potentially increased transaminase Underdose leading to lack of efficacy	Marginal Negligible	Pass: 63/65 Difficulty: 2/65	- Two trained patients (PA01, PA10) initially selected the incorrect concentration but self-corrected their mistake before completing the task.	-

No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
	Nurse: Select correct device (correct concentration) TPP:U18, TPP:U20	Overdose leading to increase in LDL-C reduction and potentially increased transaminases. Underdose leading to lack of efficacy	Marginal Negligible	Pass: 14/15 Use error: 1/15	- One nurse (N12) selected the incorrect concentration (75 mg) and did not realize her mistake until she compared it with the package she was given (150 mg) for task 3, <i>Injection delivered by user.</i>	- This is a medication error. However, the consequences of the error would be low. Additionally, the nurse did show a <u>learning</u> behavior and she would be unlikely to repeat the error.
2.3	Patient: Check expiry date TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies).	Negligible Negligible	Pass: 63/65 Use error: 2/65	- One untrained participant (PA46) was not able to find the expiry date. One trained patient (PA20) mentioned that he would check the expiry date prior to using the pen, but was unable to find the location.	- The size of the font used for the expiry date is too small (4 point) and will be enlarged (7 point).
	Nurse: Check expiry date TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies).	Negligible Negligible	Pass: 15/15	-	-
No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
2.4	Patient: Check window, including drug condition TPP:U16, TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies).	Negligible Negligible	Pass: 59/65 Use error: 6/65	- Six untrained participants (PA29, PA31, PA41, PA58, PA59, PA60) did not check the window.	- This finding is based solely on observation; the participants were not specifically asked if they would do this in real life. Since in a study like this one, participants would not expect to be handed a drug product that is contaminated, their failure to check the drug may be considered to be a <u>test artifact</u> . However, even if failure of this task would lead to harm, the consequence severity is negligible.
	Nurse: Check window including drug condition TPP:U16, TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies). Underdose leading to lack of efficacy.	Negligible Negligible Negligible	Pass: 15/15	-	-
No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
2.5	Patient: Warm up at room temperature for 30 to 40 min TPP:U20	Underdose leading to lack of efficacy.	Negligible	Pass: 56/65 Difficulty: 7/65	- 5 untrained (PA12, PA22, PA39, PA42, PA60) and one trained patients (PA11) knew they should wait until the pen was at room temperature before use and said they would wait between 15 and 30 min. One untrained patient (PA64) said he would wait 10 to 15 min to get the chill off.	- Every patient knew that they had to wait before using the device. This task has no effect on the efficacy of the drug. Allowing the drug to come up to room temperature makes the injection easier and more comfortable. When the drug is cold, the injection time increases and the injection pain increases.
	Nurse: Warm up to room temperature for 30 to 40 min TPP:U20	Ineffective drug Potential for increased risk of immunogenicity (anti-drug antibodies)	Negligible Negligible	Use error: 2/65 Pass: 15/15	One untrained patient (PA59) indicated that the pen should be used immediately because he did not read the IFU. One patient (PA46) mentioned that she would use the pre-filled pen the same way she uses her diabetes pen and only wait 3 to 4 minutes after removing from the refrigerator.	If the warm-up period is very short, the drug will be cold and the injection time will increase. Consequently, a patient might withdraw the device too soon and would not get the full dose. However, patients would still get the visual feedback concerning the status of the injection and if they waited until the window turned yellow (which might take longer), they would still get the full dose. Even if an underdose occurred, the consequences would have a low (negligible) severity. PA46 commented that she normally has an aide to assist her with injections at home.

No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
2.6	Patient removes the cap TPP:U15, TPP:U16, TPP:U20	Delay of treatment which may constitute an underdose leading to lack of efficacy.	Negligible	Pass: 63/65	-	-
				Difficulty: 1/65	One trained patient (PA01) did not initially remove the cap but realized his mistake and self-corrected.	-
				Use error: 1/65	One untrained patient (PA59) ^d did not remove the cap and was not aware of this. He repeatedly tried to inject with the cap on and did not understand that he had not given an injection.	Even if a patient could not remove the cap and did not receive the dose in a timely manner, the consequence severity would be low (negligible).
	Nurse removes the cap TPP:U15, TPP:U16, TPP:U20	Delay of treatment which may constitute an underdose leading to lack of efficacy.	Negligible	Pass: 15/15	-	-
2.7	Patient chooses correct injection site TPP:U20	No effect on drug efficacy expected, rupturing of very small vessels (ecchymosis) possible.	Negligible	Pass: 64/65	-	-
				Use error: 1/65	One untrained patient (PA31) mentioned that she would inject into the forearm (arterial injection). She mentioned that the instructions do not account for patients who feel uncomfortable injecting into the thigh.	This patient did not read the first side of the IFU and said that there is no information in the IFU regarding the injection site. The consequence severity for an injection into a wrong body site is low.
	Nurse chooses correct injection site TPP:U20	No effect on drug efficacy expected, Rupturing of very small vessels (ecchymosis) possible.	Negligible	Pass: 15/15	-	-
No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
	Patient: Clean injection site TPP:U20	Marginal infection or reaction (eg, skin) towards contamination.	Negligible	Pass: 45/65 Use error: 20/65	- 6 trained patients (PA01, PA03, PA06, PA08, PA34, PA43) and 14 untrained patients (PA21, PA22, PA29, PA30, PA31, PA39, PA42, PA48, PA50, PA51, PA53, PA57, PA58, PA59) did not clean the injection site.	Many participants did not clean the injection site, but this can be considered a <u>test artifact</u> . The participants were injecting into an injection pad, not themselves, so they might not have felt the need to clean the injection site as they would for an actual injection in their home environment.
	Nurse: Clean injection site TPP:U20	Marginal infection or reaction (eg, skin) towards contamination.	Negligible	Pass: 14/15 Use error: 1/15	- One nurse (N07) did not clean the injection site.	See above
3.1	Patient: Hold device in the correct orientation TPP:U15, TPP:U16, TPP:U20	Slight injury without the need to see a doctor (eg, small amount of bleeding, bruising, pain).	Marginal	Pass: 65/65	-	-
	Nurse: Hold device in the correct orientation TPP:U15, TPP:U16, TPP:U20	Slight injury without the need to see a doctor (eg, small amount of bleeding, bruising, pain).	Marginal	Pass: 15/15	-	-

No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
3.2	Patient: Press device on the site for injection (unlock button) TPP:U15, TPP:U16, TPP:U20	Underdose leading to lack of efficacy.	Negligible	Pass: 56/65	-	-
				Difficulty: 6/65	5 untrained patients (PA22, PA48, PA57, PA58, PA65) and one trained patients (PA08) were not able to activate the device (because they did not follow the correct activation sequence). All noticed their failure without assistance and corrected themselves.	-
				Use error: 3/65	2 untrained patients (PA29, PA33) did not press the device firmly on the site. Both pressed the injection button before fully retracting the needle cover to activate the pen. Both of these participants ultimately recognized that they did not receive the medication. They both stated that they would call the help line before attempting another injection. With guidance from the moderator, the patients repeated the injection and everything went well.	This use error can be described as a <u>learning</u> effect. In the second attempt for all three participants, the task went well.
					One untrained participant (PA46) tried to use device like an insulin pen. She tried to dial a dose and looked for the place to attach a needle. After being advised to read the IFU, the injection went well.	PA46 reported that she normally has an aide to assist her with injections at home.
	Nurse: Press device on the site for injection (unlock button) TPP:U15, TPP:U16, TPP:U20	Underdose leading to lack of efficacy	Negligible	Pass: 15/15	-	-
3.3	Patient: Press button for injection TPP:U16, TPP:U17, TPP:U20	Underdose leading to lack of efficacy.	Negligible	Pass: 65/65	-	-
No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
	Nurse: Press button for injection TPP:U16, TPP:U17, TPP:U20	Underdose leading to lack of efficacy.	Negligible	Pass: 14/15	-	-
				Difficulty: 1/15	One nurse (NU05) tried to activate the device without pressing the button. She noticed her error and corrected herself.	-
3.4	Release the button TPP:U20	The second click to indicate the end of the injection does not occur.	N/A	Pass: 47/65	-	-
				Difficulty: 18/65	18 participants did not release the button after pressing the button.	Not releasing the button prevents the user from getting the audible end-of-dose feedback, but it has no effect on the injection (see task 3.5, too)
3.5	Patient: Wait until injection is complete TPP:U16, TPP:U17, TPP:U20	Underdose leading to lack of efficacy.	Negligible	Pass: 60/65	-	-
				Difficulty: 3/65	3 untrained patients (PA41, PA58, PA63) did not look at the window. One participant (PA63) counted to 20. All four patients injected the full dose.	-
				Use error: 2/65	One patient (PA49) removed device too early. He noticed mistake. His second attempt went well. One patient (PA59) removed device too early. He noticed mistake. In the second attempt, he made same error again.	The first patient (PA49) noticed the mistake. This use error can be described as a <u>learning</u> effect. The second patient (PA59) would not be an appropriate user of the pre-filled pen. He did not understand how to use the device even when the moderator explained the process to him. He also contradicted himself when asked the same question in different ways.

No	Task/ID ^a	Consequences	Severity ^b	Results	Observations	Root Cause/Comments
	Nurse: Wait until injection is complete TPP:U16, TPP:U17, TPP:U20	Underdose leading to lack of efficacy.	Negligible	Pass: 13/15 Difficulty: 1/15 Use error: 1/15	- One nurse (N05) did not look at the window but injected the full dose. One nurse (N12) removed device too early. She noticed mistake. Her second attempt went well.	- - The nurse noticed the mistake. This use error can be described as a <u>learning</u> effect.
3.6	Patient: Remove device from skin TPP:U15	Underdose leading to lack of efficacy.	Negligible	Pass: 64/65 Difficulty: 1/65	- An untrained patient (PA65) was not gripping the pen tightly enough. When the lockout mechanism activated, the pen slipped from their grasp and a small amount of medication was spilled.	- The pen is designed in a way that if the device is removed at the moment the second click occurs, no underdose is delivered. Additionally, the needle safety feature did activate in the observed case, so no risk of needle stick with a contaminated needle existed.
	Nurse: Remove device from skin. TPP:U15	Underdose leading to lack of efficacy.	Negligible	Pass: 14/15 Difficulty: 1/65	- A nurse (N05) was not gripping the pen tightly enough. When the lockout mechanism activated, the pen slipped from their grasp and a small amount of medication was spilled.	- The pen is designed in a way that if the device is removed at the moment the second click occurs, no underdose is delivered. Additionally, the needle safety feature did activate in the observed case, so no risk of needle stick with a contaminated needle existed.
4.1	Patient: Dispose of device and cap according local regulatory requirements TPP:U15, TPP:U20	Due to device design (needle safety feature), no consequence to patient health from inappropriate disposal.	N/A	Pass: 60/65 Use error: 5/65	- One trained (PA34) and four untrained patients (PA21, PA30, PA33, PA49) did not dispose of the used pen correctly. 3 of them would dispose of the device in the trash, one would put the pen back in the box and one would return the pen to the refrigerator.	- The used device has a locking needle shield (needle cover), which minimizes the chance of accidental needle-stick injuries.
	Nurse: Dispose of device and cap according local regulatory requirements TPP:U15, TPP:U20	Due to device design (needle safety feature), no consequence to patient health based on incorrect disposal.	N/A	Pass: 15/15	-	-
5.1	<i>Supplemental HF validation study:</i> Patient: Perform follow-up treatment TPP:U20	Overdose leading to increase in LDL-C reduction and potentially increased transaminases. Underdose leading to lack of efficacy.	Marginal Negligible	Pass: 30/60 Difficulty: 3/60 Use error: 27/60	- One trained (PA04) and 2 untrained patients (PA40, PA50) said the drug should be administered as prescribed by their doctor. One trained patient (PA01) did not know how often to administer the medication. One trained patient (PA10) guessed that the drug should be administered once per week. 25 patients (trained and untrained) gave a correct answer, but only with guidance from the moderator to look at the patient package insert.	- The primary way that the patient will be informed about the dosage regimen is to be told by the doctor when the drug is prescribed. The primary way that the patient will be informed about the dosage regimen is to be told by the doctor when the drug is prescribed. When told where to find the information, all participants succeeded in finding it.

^a ID numbers see Table 9.

^b N/A : Not applicable

^c Patient PA31 was not trained and did not look at the IFU.

^d This patient would not be an appropriate user of the pre-filled pen. He did not understand how to use the device even when the moderator explained the process to him. He also contradicted himself when asked the same question in different ways.

Sponsor Conclusions:

The HF validation test for the alirocumab pre-filled pen did not result in any patterns of use errors or task failures on the critical tasks and was, therefore, shown to be safe and effective for use by all intended user populations for use in a non-sterile environment.

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

/s/

MISHALE P MISTRY
05/22/2015

YELENA L MASLOV
05/22/2015



Food and Drug Administration
Office for Device Evaluation
White Oak Building 66
10903 New Hampshire Ave
Silver Spring, MD 20993

InterCenter Consult Memorandum
ICC1400714/B/LA125559

Date: April 30, 2015

To: Patricia Madara
Senior Regulatory Health Project Manager
WO22, RM 3360
OMPT/CDER/OND/ODEII/DMEP

From: Janice Polacek, RN, BSN, CRNI
Nurse Consultant
WO66 RM 2533
CDRH/ODE/DAGRID/GHDB

Subject: BLA125559/ICC1400714
Alirocumab for injection
Praluent

I. Recommendations

The CDRH recommends NDA approval of the device constituent part of the Alirocumab prefilled syringe and prefilled pen injector.

The recommendation for approval for the device constituent part of this combination product is being made with the following caveats, CDRH will defer to CDER for shelf life determination and recommendation. If agreeable to the review division, two post-approval recommendations have been made for consideration. Additionally, the CDRH reviewer notes that, at the time of memorandum composition, concerns related to device manufacturing process changes remained outstanding, but that review of those outstanding concerns are deferred to CDER clinical and non-clinical review staff.

See Review conclusion below.

II. Review Conclusion

The CDRH reviewer has examined and evaluated the design information for the bulk pre-filled syringe and the pre-filled syringe in two presentations (75mg/ml and 150mg/ml) under BLA125559. The CDRH reviewer recommends approval of this application in the context covered under this memorandum, the device constituent of the combination product.

The CDRH reviewer was unable to locate stability studies beyond 12 months. The BLA holder is requesting ^(b)₍₄₎ month expiration for the combination product. I would defer to CDER as to the recommendation for shelf life of this product.

The CDRH reviewer has examined and evaluated device design information for two prefilled pen (PFP) presentations (75mg/ml and 150mg/ml) under BLA125559. The consulting reviewer recommends approval of the application in the context of the content covered under this memorandum.

The consulting reviewer requests that two post-approval commitments be reached with the sponsor:

- (1) Commitment to update the BLA with ongoing stability information for the PFP at each future sampling time point
- (2) Commitment from the MAF holder to update MAF (b) (4) with ongoing stability information at each future sampling time point

The CDRH reviewer also notes that, at the time of memorandum composition, concerns related to device manufacturing process changes and potential unintended effects on injection site pain, leakage, container closure integrity, and biologic integrity remained outstanding; however review of those outstanding concerns is deferred to CDER or Office of Combination Products clinical and non-clinical review staff. [This is explained further on page 56-57 of this memorandum].

Labeling Recommendations

- Within the submission, the sponsor claims to have designed the pen (b) (4)

(b) (4)

III. Consult Purpose

The Center for Drug Evaluation and Research (CDER) requested a consult from CDRH/ODE regarding BLA125559 alirocumab. The device constituent of the combination product consists of a prefilled syringe and a prefilled pen (auto-injector) designed to deliver a liquid formulation of Alirocumab at concentrations of dosage 75mg and 150 mg/ml for subcutaneous injection.

The Sanofi group has purchased a rare pediatric disease (RPD) priority review voucher (PRV), this application will be on an 8 month clock.

IV. Review Summary

The CDRH reviewer performed an evaluation of the container closure system for drug Alirocumab in concentrations of 75mg/1ml and 150mg/1ml. This drug is a NME biologic being developed for the treatment adult patients with primary hypercholesterolemia or mixed dyslipidemia. This biologic will be administered as a subcutaneous injection. The sponsor proposes two different injection devices: a prefilled syringe and a disposable auto-injector. This evaluation covered the design and design control information for the subject device constituents.

Consultants for this file:

Ryan McGowan-engineering review of the pen injector
Clarence Murray, PhD-sterility
Honggang Wang, PhD-biocompatibility

The review covered the following review content:

Pre-filled syringe:

- Functionality of Pre-filled syringe
- Sterility of the syringe barrel, needle, and needle shield
- Biocompatibility of the syringe barrel, needle shield and plunger rod
- Biocompatibility of the auto-injector for skin contact of a limited duration
- Sharps injury prevention

Auto-injector:

- Inspection of sponsor's design input activities for the PFP
- Inspection of sponsor's design verification activities for the PFP
- Confirmation of standards conformance, where relied upon for the PFP
- Inspection of test methods and results of bench top testing completed for the PFP
- Inspection of stability testing completed on the PFP device constituent part
- Inspection of master file information supporting the PFP for the BLA submission

The review **did not** cover the following items:

- Review of drug product
- Manufacturing of the drug product
- Review of the primary container closure-drug product interaction toxicology including plunger stopper
- Review of the safety and efficacy of drug product after contacting the device constituent parts or while stored in the device constituent parts, including extractable analysis
- Manufacturing of the device constituent part of the combination product
- Review of the final drug kit packaging
- Device constituent part usability or human factors validation information
- Manufacturing of the device constituent part of the combination product
- Shipping of the final kit package
- Mechanical loss testing for the drug product
- Stability of the drug product after aging

V. Documents Reviewed

CDRH/ODE reviews content related to the design of device constituent parts for combination product submissions. This review is limited to design requirements and verification validation information to support the device constituent part, including essential performance of the device constituent part and reliability of the device constituent part over time and after expected environmental exposure. This review does not cover review of the primary "container closure" (i.e. cartridge), manufacturing or process validation of the device, nor usability.

Pre-filled Syringe

- BLA125559, Serial 0000
- DMF (b)(4)
- MAF
- BLA125559, Response to 2-27-2015 IR Request
- BLA125559, Response to 4-8-2015 IR request

Auto-Injector

- BLA125559, Serial 0000

- BLA12559, Serial 0014; Responses to 2-27-15 IR Response
- BLA12559, Serial 0016; Describing Changes to the Injector Post-clinical Study
- BLA12559; Serial 0024; Containing a "White Paper" on the Combination Product
- Device Master File MAF (b) (4) Original Submission by (b) (4) 3rd party device supplier)

Reviewer Note:

Master files and 510(K) clearances cited and cross-referenced by the sponsor were reviewed only where necessary, defined as the BLA having insufficient evidence to support use of the device sub-component. The sponsor is expected to submit sufficient information to demonstrate function and safety of the device constituent parts in their final finished form within the BLA submission materials.

VI. Device Review

Indications for Use:

PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor indicated 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, non-HDL-C, Apo B, TG, and Lp(a) and to increase HDL-C and Apo-A1 either in combination with a statin or as monotherapy including patients who cannot tolerate statins.

Dosage and Administration:

The recommended dose of PRALUENT is 75 mg/ml or 150mg/ml administered subcutaneously once every 2 weeks. One bi-weekly dose of PRALUENT is contained in each syringe. The device is single dose, disposable and ready to use.

Device Description:

The alirocumab prefilled pen (PFP) and the prefilled syringe (PFS) presentations (b) (4) (b) (4) Both configurations are single dose and are designed to deliver the entire volume contained within each unit; therefore, no difference between the expellable volume from the PFP and the PFS is expected.

The pre-filled syringe and pen injector comprise the final finished delivery system. Each of these systems (b) (4)

(b) (4)

(b) (4)

The container closure for Alirocumab solution for injection will be supplied in 2 drug strengths and 2 device presentations.

Alirocumab 75mg/ml & 150mg/ml Pre-Filled syringe (PFS)

Alirocumab 75mg/ml & 150mg/ml Pre-Filled Pen (PFP) auto-injector



(b) (4)

(b) (4)

The bulk pre-filled syringe (b) (4) is manufactured by (b) (4). They provided a certificate of conformity describing materials used and to what standards they conform.

[The certificate and information is located in 3.2.P.7 Container Closure System, Section 2 Syringes (b) (4).]

- (b) (4) Sterilized
- Endotoxin (b) (4) UE/syringe
- (b) (4)

The BLA also provided a release certificate of analysis from the sterilization subcontractor (b) (4). It includes sterility validation, bioburden analysis, endotoxin analysis, and (b) (4).

- Bioburden Routine analyses
- Microbiological analysis ~ No growth from Bacillus atropheus
- Product sterility analysis ~ No growth
- Bacterial Endotoxin analysis < (b) (4) UI/container
- (b) (4)

Quality control testing is performed on syringes. At least one batch per year will be completely tested in-house as per ISO 2859-1 Sampling procedures for inspection by attributes –Part 1: Sampling plans indexed by acceptable quality level for lot-by-lot inspection.

Results for syringe

Part of component	Type of controls (Defect/Test)	Acceptance criteria	Results
Syringe barrel	Visual control*	Particles, breakages and cracks, stain, scratch, or leakage on the outer surface, deformation, (b) (4) barrel	(b) (4) Complies
	Dimensional control*	Barrel external diameter Flange diameter Flange width Total length	Complies
	Functional control	Leakage between syringe barrel and needle, using a plunger stopper and a plunger rod	Complies
	Physical and chemical control of glass*	Glass hydrolytic resistance (b) (4)	Complies Complies
Needle	Visual control*	Needle missing, broken, inverted, no point, foreign particles on the needle, needle beyond the NS	Complies
(b) (4)			(b) (4)
Syringe	Microbiological control*	Sterility test	Complies
	Chemical control*	Endotoxins test	Complies
		Assay of (b) (4)	Complies
	Assurance of sterility	Presence and compliance of sterilization indicator	Complies

* at least one batch per year.
 CFMP: Committee for Proprietary Medicinal Products
 NS: needle shield

Plunger Stopper

Material Composition of the Plunger Stopper

Plunger stopper	(b) (4) rubber (b) (4)	Grey	(b) (4)
	(b) (4)		
	(b) (4)		

The plunger stopper is supplied by (b) (4). They are (b) (4) closures that are provided sterile (sterilized by (b) (4)). All materials are reported to be latex free.

The BLA sponsor provided a quality certificate for the plunger stoppers.

[Information for the plunger stopper located in 3.2.P.7 Container Closure System, Section 3.]

- (b) (4)
- Endotoxin < (b) (4) ml

Drawing of plunger stopper



Quality control testing is performed on plunger stoppers. At least one batch per year will be completely tested in-house as per ISO 2859-1 Sampling procedures for inspection by attributes – Part 1: Sampling plans indexed by acceptable quality level for lot-by-lot inspection

Results for plunger stopper

Type of controls	Defect/Method	Acceptance criteria	Results
Visual control ²	Appearance Particles Moulding defects resulting in risk of leakage	(b) (4)	Complies
Dimensional control ²	Plunger stopper lips' diameter Plunger stopper lips' cavity diameters Plunger stopper length	(b) (4)	Complies
Functional control ²	Leakage	(b) (4)	Complies
Physical and chemical control of elastomer	Elastomer	(b) (4)	Complies
Microbiological control ²	Sterility test	(b) (4)	Complies
	Endotoxins test	(b) (4)	Complies

² at least one batch per year.

STERILITY OF BULK PRE-FILLED SYRINGE

Sterility of alirocumab is achieved by s

(b) (4)

(b) (4)

Moreover, sterility is tested at the beginning and the end of shelf life under long term storage conditions.

In order to demonstrate the ability of the container closure system to maintain the sterility of the product, container closure integrity tests (CCIT) were performed by microbial ingress, using syringes filled on the commercial line with Tryptic Soy Broth (TSB) immersed into a suspension of *Brevundimonas diminuta* as widely recommended for microbial challenge.

Container closure integrity tests by microbial ingress were conducted on both bulk pre-filled syringes 100% visually inspected (without plunger rod) and on the pre-filled syringes (with plunger rod) packed into blister, using the commercial process, in order to demonstrate that respective operations did not impact the container closure integrity.

Microbial Ingress Testing Results:

Results of microbial ingress CCIT on pre-filled syringes before and after plunger rodding

	Bulk pre-filled syringes	Pre-filled syringes
Number of syringes incubated	50	40
Number of syringes with positive TSB turbidity		(b) (4)
Number of syringes with negative TSB turbidity		
Turbidity of TSB in positive control	Complies	Complies
Turbidity of TSB in negative control	Complies	Complies

[Sterility documentation located in BLA 125559 (0000) 3.2.P.2 & 3.2.P.3.3., (0039) 3.2.P.3.5. and in the DMF (b) (4)]

(b) (4)

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[Information regarding the Pre-filled syringe including plunger rod is 3.2.P.7, Container Closure System PFS, Section 2.]

Material Composition of Plunger Rod

Drug product	Component part	Material / Type	Color	Supplier
Ariocumab 150 mg/mL	Plunger rod	(b) (4)	Grey, (b) (4)	(b) (4)
Alirocumab 75 mg/mL	Plunger rod	(b) (4)	Green, (b) (4)	(b) (4)

PERFORMANCE TESTING PRE-FILLED SYRINGE

[Performance testing information can be found in BLA 125559 3.2.P.2. PFS Container Closure System]

Biocompatibility

Biocompatibility studies were carried out following ISO 10993 “Biological Evaluation of Medical Devices. According to ISO-10993-1, medical devices that are analyzed are categorized by nature of body contact and by duration of this contact.

[Information for biocompatibility is located in 3.2.P.2 Pharmaceutical Development PFS-biocompatibility]

Body Contact:

- Externally communication limited contact < 24 hours: glass barrel and needle
- Surface skin contact limited contact <24 hours: plunger rod, needle shield and auto-injector

In Vitro Cytotoxicity Study (ISO 10993-5:2009) – Direct Contact (Quantitative Test)																																													
Device Tested																																													
Test Article is finished sterilized device	Yes. Glass barrel + needle, Plunger rod	Acceptable																																											
Only the direct and indirect patient contacting portions of the device tested	Yes.	Acceptable																																											
Extraction vehicle	IX	Unacceptable																																											
Extraction ratio	3cm ² /ml																																												
Study Controls																																													
Positive control	DMSO diluted in IxMEM at 6.0-3.0-1.5-0.75%	Acceptable																																											
Negative control	Non-cytotoxic tissue culture coverslips extracted at a ratio of 3m ² /ml of IxMEM	Acceptable																																											
Methods																																													
Test System	L-929 Mouse fibroblasts	Acceptable																																											
Assessment Times	72h at 30°C	Need justification																																											
Assessment Methods	Not clear	Acceptable																																											
Assessment Method																																													
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Recommendation																																													
Acceptable																																													

Maximization Sensitization Study (ISO 10993-10:2010)		
Device Tested		
Test article is finished sterilized device	Yes. Glass barrel + needle, Plunger rod	Acceptable
Only the direct and indirect patient contacting portions of the device tested	Yes	Acceptable
Was the study done under GLP conditions?	Yes	Acceptable
Extraction Conditions		
Test Article Extraction Ratio	0.2g/ml	Acceptable
Extraction Vehicle(s)	Polar solvent: 0.9% SC Non-polar solvent: Cottonseed oil	Acceptable
Time/Temperature	37°C for 72h	Acceptable
Study Controls	Extraction vehicles without test material	Acceptable
Appearance of Extract	Clear, free	Acceptable
Extract Storage Conditions	Room temperature for less than 24 hours	Acceptable
Methods		
Test System	Source: (b) (4) Species: Guinea pigs (<i>Cavia porcellus</i>) Body weight: 285-353 g Number: 30 Sex: male	Acceptable
Induction Phase I	Three pair of intradermal injections given on the backs of test animals: <u>Test animals</u> 1. 0.1 ml of a 1:1 FCA/vehicle mixture 2. 0.1 ml of test extract 3. 0.1 ml of a 1:1 mixture of the 1:1 FCA and test extract <u>Control animals</u> 1. 0.1 ml of a 1:1 FCA/vehicle mixture 2. 0.1 ml of vehicle 3. 0.1 ml of a 1:1 mixture of the 1:1 FCA and test extract	Acceptable
Preparation for Induction II	Day 6 after injection (approximately 24h before Induction II), injection sites clipped and treated with a 10% sodium lauryl sulfate (SLS) in petroleum jelly. Any remaining SLS to be removed prior to Induction II treatment.	Acceptable
Induction Phase II	Day 7 after injection, 2x4 cm filter paper patches saturated (~0.3 ml) with test extract or control vehicle applied to injection area for 48 hours. Patches removed after 48 hours.	Acceptable
Challenge Phase	Fourteen days after removal of Induction patches, the right and left flank areas of each guinea pig is clipped and 2x2 cm patches saturated (~0.3 ml) with test extract or control vehicle are prepared. One flank is treated with patch containing the test extract, while the other flank is treated with the control vehicle. Patches are left	Acceptable

Assessment Times after Challenge Patch removal	in place for 24 hours before removal 24h and 48h	Acceptable
Results		
Study Animals Appear Normal Throughout the Study	Yes	Acceptable
Deaths reported	No	Acceptable
Erythema and Edema Scores in Extract Controls and Treated Animals Different	No	Acceptable
Erythema and Edema Scores in Positive Controls and Treated Animals Different	Yes	Acceptable
Conclusion		
Sensitizing Potential	Non-Sensitizing	Acceptable

ISO Intracutaneous Reactivity Test (ISO 10993-10:2010)		
Device Tested		
Test Article is finished sterilized device	Yes. Glass barrel + needle, Plunger rod	Acceptable
Only the direct & indirect patient contacting portions of the device tested.	Yes	Acceptable
Extraction Conditions		
Test Article Extraction Ratio	3cm ² /ml	Acceptable
Extraction Vehicle(s)	0.9% sodium chloride Cottonseed oil, Nf(CSO)	Acceptable
Time/ Temperature	37°C for 72 hours	Acceptable
Appearance of Extract	Clear	Acceptable
Methods		
Test Animals	Source: (b) (4) Species: NEW Rabbit Body weight: >2.5kg Number: 4 Sex: Male Acclimation Period: 5 days	Acceptable
Treatment Procedures	<ul style="list-style-type: none"> Clip the fur on the backs of the animals, allowing a sufficient distance on both sides of the spine for injection of the extracts. Inject intracutaneously 0.2 ml of the extract obtained with polar or non-polar solvent at five sites on one side of each rabbit. Similarly, inject 0.2 ml of the polar or non-polar solvent control on five sites of the contralateral side of each rabbit. 	Acceptable
Assessment Time	<ul style="list-style-type: none"> 24h after treatment, the patches were removed. The sites were gently wiped with a gauze sponges dampened with deionized water to remove any remaining residue. Animals were observed daily for general health. Dermal observation for erythema and edema were recorded at 1, 24, 48, and 72 hours after patch removal. 	Acceptable

Assessment Methods	<p>The reaction were evaluated according to the following subjective rating scale:</p> <table border="1"> <thead> <tr> <th colspan="2">Erythema</th> <th colspan="2">Edema</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>No erythema</td> <td>0</td> <td>No edema</td> </tr> <tr> <td>1</td> <td>Very slight Erythema (pinkish)</td> <td>1</td> <td>Very slight edema (pinprick)</td> </tr> <tr> <td>2</td> <td>Slight Erythema (red)</td> <td>2</td> <td>Slight edema of area will be defined by definite swelling</td> </tr> <tr> <td>3</td> <td>Moderate Erythema (Red)</td> <td>3</td> <td>Moderate edema (appreciable lump)</td> </tr> <tr> <td>4</td> <td>Severe Erythema (bright red)</td> <td>4</td> <td>Severe edema (area four times size of original)</td> </tr> </tbody> </table>	Erythema		Edema		0	No erythema	0	No edema	1	Very slight Erythema (pinkish)	1	Very slight edema (pinprick)	2	Slight Erythema (red)	2	Slight edema of area will be defined by definite swelling	3	Moderate Erythema (Red)	3	Moderate edema (appreciable lump)	4	Severe Erythema (bright red)	4	Severe edema (area four times size of original)	Acceptable
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<p>All study animals appear normal throughout the study.</p> <p>The intracutaneous injection of the polar test item extract as well as the intracutaneous injection of the polar reagent control caused no signs of irritation.</p> <p>The Primary Irritation Index (PII) of the polar test item extract compared to the polar reagent control was 0.</p> <p>The intracutaneous injection of the nonpolar test item extract as well as the intracutaneous injection of the nonpolar reagent control caused no signs of irritation.</p> <p>The Primary Irritation Index (PII) of the nonpolar test item extract compared to the nonpolar reagent control was 0.</p>		Acceptable																								
Conclusion																										
Irritation Potential	Under the conditions of this study there was no evidence of significant or toxicity from the extracts injected intracutaneous into rabbits.	Acceptable																								

ISO Systemic Toxicity Study (ISO 10993-11:2006)		
Device Tested		
Test Article is finished device	Yes Glass barrel + needle, Plunger rod	Acceptable
Only the direct and indirect patient contacting portions of the device tested.	Yes	Acceptable
Test Article Extraction Ratio	3cm ² /ml	Acceptable
Extraction Vehicle(s)	0.9% SC (SC) 1:20 ethanol in 0.9% saline PEG 400 Cottonseed oil (CSO)	Acceptable
Time/Temperature	37°C for 72h	Acceptable
Appearance of test article	Clear	Acceptable
Method		
Test Animals	Source: (b) (4) (b) (4) Species: mouse (Crl:NIH) Body weight: 18 to 23 grams Number: 20 Sex: female, non-pregnant, nulliparous. Acclimation: 5 day	Acceptable
Injection Dose	<ul style="list-style-type: none"> 50 ml/kg (saline, vegetable oil, and alcohol in saline 1:20 solution) 10g/kg PEG 400 	Acceptable
Injection Route	<ul style="list-style-type: none"> Intravenous route : (saline and alcohol in saline 1:20 solution) Intraperitoneal route: CSO and PEG-400 	Acceptable
Assessment Times	4h, 24h, 48h, 72h	Acceptable
Results		
Deaths reported?	No	Acceptable
General appearance of animals during course of study as compared with controls?	Similar	Acceptable
Conclusion		
Systemic toxicity potential	Under the conditions of this study there was no mortality or evidence of systemic toxicity from the extracts each test articles extract met the test requirements.	Acceptable
Recommendation		
Acceptable		

Reviewer Note:

The BLA holder provided data to demonstrate that the glass syringe, needle and plunger rod are characterized as non-cytotoxic, non-sensitizing, non-irritating, non-irritating and does not have acute cytotoxicity.

Of note, According to USP <87>, a result showing no cytotoxic effect of an elastomeric compound suffices to prove its total biocompatibility. Therefore, no further skin sensitization and irritation tests have been performed on the needle shield.

Design control Plan

A design control for the development of alirocumab pre-filled syringe (combined product) was set-up according to the *FDA Design Control Guidance for Medical Device Manufactures* related to *FDA 21 CFR Part 820.30 and Sub-clause 4.4 of ISO 9001*.

The objective of the Design control plan is to define user needs for a product and its specific usability. The needs are identified; it is imperative that the necessary volume of the product, its concentration and its viscosity must be clearly specified, as well as its expected administration time, if applicable. Once these needs are identified, the development activity details and sent in a Design Control Plan. Responsibilities are defined for each stage of the Design control plan. A design FMEA is completed and the Quality risk analysis is finalized according to risk management plan requirements.

(b) (4)

(b) (4)

(b) (4)

An overview of each requirement of the *Guidance for Industry and FDA Staff Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement Organization for Standardization (ISO) standard 11040-Section* is listed below. The pre-filled syringe was tested to determine its applicability for the alirocumab glass syringe as well as a rationale for its use.

Applicability of Functional Performance of Syringe

Test	Applicable	Rationale
Seal integrity testing (Dye immersion test)	Yes	(b) (4)
Break Force and Glide Force (BL & GL)	Yes	
Separation force (Needle pull out force)	Yes	
Uncrewing torque	No	
Ease of assembly	No	
Resistance to overriding	No	
Stress cracking (Burst test)	Yes	
Validation of graduation markings	No	
Dead space (Dead volume)	Yes	
Coring needle test	No	
Performance testing of an anti-needlestick mechanism	No	
Connectivity to other devices necessary for use	No	
Injection force necessary to depress the plunger and eject the drug contents	Yes	
Tip cap removal force (Needle shield removal force)	Yes	
Piston seal blowback (Leak test and Tightness test)	Yes	

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Functional performance results evaluated for Pre-Filled Syringe with Alirocumab at 75mg/ml & 150mg/ml

Pre-filled syringe performance tests

Test	Objective	Method	Sampling	Acceptance criteria	Results	
					Min	Max
Break loose and glide force						
Break loose force						
Alirocumab 150 mg/mL		This test is performed on final assembled product filled with drug. After removal of the needle shield, syringes are placed sequentially on test bench tool to start the analysis of compression forces at a constant speed. Compression forces are divided on two forces:	500 syringes	≤ (b) (4)	4 (b) (4)	(b) (4)
Alirocumab 75 mg/mL						
Glide force	Measure forces necessary to perform injection of drug at constant speed (240 mm/min).					
Alirocumab 150 mg/mL		The break loose force which corresponds to the maximum force measured to initiate the plunger stopper movement.	500 syringes	≤	5	(b) (4)
Alirocumab 75 mg/mL						
		The glide force which is the maximum force required to move the plunger stopper along the syringe barrel in order to complete the injection.				
Stress cracking (Burst test)	Measure the mechanical resistance of the syringe filled with drug and stoppered by applying a hydrostatic internal pressure.	Destructive burst pressure testing is accomplished by application of increasing hydrostatic pressure 'p' (applied by a bench test machine) inside glass barrel of the syringe up to breakage (glass barrel from pre-filled syringe filled with drug which was subject to full process until packaging).	75 syringes	There are no specifications for this test. Burst pressure test is conducted to assess the syringe burst pressure resistance. According to ISO 7458: 2011-11	≥ (b) (4)	≥ (b) (4)
Delivery volume						
Alirocumab 150 mg/mL	This test must demonstrate the user ability to deliver complete injection (delivered volume) by manual operation.	Weighing method	500 syringes		(b) (4) mL	(b) (4) mL
Alirocumab 75 mg/mL			500 syringes	≥ (b) (4) mL	(b) (4) mL	(b) (4) mL
Tip cap removal force (Needle shield removal force)						
	The needle shield pull out force test measures the force required to remove the soft needle shield from syringe barrel.	Syringes are placed sequentially on test bench tool (flange at the bottom) to start the analysis of traction forces with a constant speed (250 mm/min). The pull out force corresponds to the maximum force necessary to remove the needle shield.				
Alirocumab 150 mg/mL			500 syringes	(b) (4) N	(b) (4) N	(b) (4) N
Alirocumab 75 mg/mL			500 syringes		N	N

Reviewer note:

Performance of the Pre-filled syringe is tested to *Guidance for Industry and FDA Staff Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement Organization for Standardization (ISO) standard 11040-Section.*

All results reported as passing. All prefilled syringes delivered (b) (4) ml alirocumab. The glide force and break-loose force: (b) (4) N. Tip cap removal force was well within the design specifications.

Batch testing done on the Alirocumab pre-filled syringes (final finished product)
Testing data located 3.2.P5.4 analysis PFS

Batch Analysis of 150 mg/mL alirocumab in Pre-filled Syringes Lots – Physical Properties and Identity Tests

Test Method	Appearance of Solution		Color of Solution	pH	Total Protein Content (Assay) (mg/mL)	Expellable Volume (mL)	Identity	
	Physical Form/Visible Particles	Clarity and Degree of Opalescence					PCSK9 Specific ELISA	iCIEF
Acceptance Criteria for Commercial Release	Liquid essentially free from visible particulates	(b) (4)	Colorless to pale yellow ²	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
DP Lot #								
8065100001	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass ^b	
8065100002	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8065100003 ^c	CLEFFVP	(b) (4)	Pale yellow	(b) (4)	(b) (4)	Pass	Pass	
8065100005 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8065100006 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8065100007 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8065100008 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8065100009 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8092400001	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8092400003 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8092400003 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8092400004 ^c	CLEFFVP		Colorless		(b) (4)	Pass	Pass	
8092400008 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8092400009 ^c	CLEFFVP		Pale yellow		(b) (4)	Pass	Pass	
8130000002 (060910) ^d	Clear		Pale yellow		(b) (4)	Pass	Pass	

Batch Analysis of 150 mg/mL alicocumab in Pre-filled Syringes Lots - Process-Related Impurities and Break-Loose Glide Force

Test Method	Endotoxin Content ¹	Sterility (Filled Container)	(b) (4) Break-Loose/Glide Force
Acceptance Criteria for Commercial Release	(b) (4) ≤ 0. (4) U/ing	Meets USP and Ph. Eur. requirements	(b) (4)
DP Lot #	(b) (4)		
8065100001		Pass	
8065100002		Pass	
8065100003 ²		Pass	
8065100005 ²		Pass	
8065100006 ²		Pass	
8065100007 ²		Pass	
8065100008 ²		Pass	
8065100009 ²		Pass	
8092400001		Pass	
8092400002 ²		Pass	
8092400003 ²		Pass	
8092400004 ²		Pass	
8092400008 ²		Pass	
8092400009 ²		Pass	
8130000002 (960940) ²		Pass	

Batch Analysis of 75 mg/mL alicocumab in Pre-filled Syringes Lots - Physical Properties and Identity Tests

Test Method	Appearance of Solution		Color of Solution	pH	Total Protein Content (µg/mL)	Expellable Volume (mL)	Identity	
	Physical Form/Visible Particles	Clarity and Degree of Opalescence					PCSK9 ELISA	iCIEF
Acceptance Criteria for Commercial Release	Liquid essentially free from visible particulates	(b) (4)	Colorless to pale yellow ²					(b) (4)
DP Lot #						(b) (4)		
8092500001 ¹	CLEFFVP		Pale yellow				Pass	Pass
8092500002 ²	CLEFFVP		Pale yellow				Pass	Pass
8092500006 ³	CLEFFVP		Pale yellow				Pass	Pass
8092500007 ²	CLEFFVP		Pale yellow				Pass	Pass
8092600002 ²	CLEFFVP		Pale yellow				Pass	Pass
8130100002 (960966) ²	CLEFFVP		Pale yellow				Pass	Pass

¹ Batch lot tested and released by Sanofi.

CLEFFVP = Clear liquid essentially free from visible particulates; RS = Reference standard, TA = Test article.

Table 6: Batch Analysis of 75 mg/mL alirocumab in Pre-filled Syringes Lots - Process-Related Impurities and Break Loose Glide Force

Test Method	Endotoxin Content ^a	Sterility	Break Loose/ Glide Force
Acceptance Criteria for Commercial Release	≤ (b) (4) EU/mg	Meets USP and Ph. Eur. requirements	(b) (4)
DP Lot #			
0092500001 ^c	(b) (4)	Pass	
0092500002 ^c		Pass	
0092500006 ^c		Pass	
0092500007 ^c		Pass	
0092600002 ^c		Pass	
010100002 (060966) ^d		Pass	

^a Reported value reflects the limit of quantitation for the assay performed.

(b) (4)

^d Batch lot tested and released by Sanofi.
(b) (4)

Reviewer Notes:

The BLA holder submitted data on batch and release testing results for alirocumab drug product using the intended commercial composition for alirocumab 150mg/ml & 75mg/ml.

Data for Bulk pre-filled syringes demonstrated performance of the device within the design specifications. Expelled volume (b) (4) ml and the Break loose and glide force of the syringe (b) (4) N. [Testing data located 3.2.P5.4 (b) (4)]

Data for the pre-filled syringe with alirocumab with plunger rod (final finished product) was submitted by the BLA holder. All results demonstrated that the device performs within the design specifications with an expelled volume (b) (4) ml and Break-loose and Glide force (b) (4) N. [Testing data located in 3.2.P.5.4 Batch analysis PFS]

History of changes implemented to the pre-filled syringes

(b) (4)



Human Factors/Usability summary and Results

Summary and results of the study

Summary of study results

Pre-filled syringe	The alicumab pre-filled syringe was found to be safe and effective to use by all user populations (trained and untrained patients, nurses), as it did not produce any patterns of use errors on the critical tasks.
IFU	The IFU were found to be effective in supporting understanding of the use procedures, both in their structure and content; the key facts could be found by the intended users in reasonable time.
Label	The syringe label was found to be effective in communicating the identity of the drug, the expiration date and the concentration of the drug. The alicumab pre-filled syringe label and the blister pack was found to be differentiable by representative users (patients, nurses, pharmacists, prescribers), including color blind users. The ease of differentiation was found to be very high, even under reduced lighting conditions.
Patient package insert (PPI)	The patient package insert was found to be effective in providing the information regarding the dosage regimen.

Reviewer note:

The Human factors will be deferred to DMEPA.

A Human Factors engineering study was conducted to evaluate the user's ability to administer a dose of medications, without error. Hazards known to induce use errors that pertain to combination products, including syringes are: inappropriate device for the drug product, unit of measurement confusion, inadequate product differentiability within a product line, and unusual or unexpected device operation. To mitigate medication errors the drug product comes as a single dose feature, the medication strength is differentiated by color (plunger rod color), clear barrel to allow a user to inspect the drug prior to injection and to know that entire injection has been administered and easy grip of syringe. All residual risks that remain cannot be further reduced by modifications of the user interface design (including the device label and IFU) and are outweighed by the benefits that may be derived from the device's use.

[Human factors Study located in 3.2P.2]

Shipping Studies

Shipping Validation-Pre-Filled Syringe

Information on Shipping is located in BLA125559 3.2.P.

Transport constraints have been simulated according to ASTM D4169-9 Standard for Performance Testing of Shipping Containers and Systems, including road, air and sea freight worst case conditions on 2 loads configuration as follows at a temperature 2-8 °C.

(b) (4)



Details of transportation Simulation

Details of tests realized during transport simulation

Step	Test	Test details	Specific method	General method	Parameters
1	Conditioning Phase	Climatic chamber storage	N/A	N/A	(b) (4)
2	Handling Test	Forklift Truck	ASTM D8055-96 (2007)	ASTM 4169-09 Method A Schedule A Assurance Level II	(b) (4)
3	Impact Test	Horizontal Inclined plane	ASTM D880-92 (2002)	ASTM 4169-09 Method B Schedule A Assurance Level II	
4	Impact Test	Vertical Fall by Tip over on base	ASTM D6179-07	ASTM 4169-09 Method C Schedule A Assurance Level II	
Repeat Handling and impact tests (Step 2 to step 4)					
5	Vibration Test	Road transport mode	ASTM D4728-08	ASTM 4169-09 Schedule E Assurance Level II	(b) (4)
6	Vibration Test	Air transport mode	ASTM D4728-08	ASTM 4169-09 Schedule E Assurance Level II	
7	Low pressure stress Test (Performed only on case submitted to QC Controls)	High Altitude	ASTM D6653-01	ASTM 4169-09 Schedule I Assurance Level II	
Repeat Vibration tests (Step 5 to step 6)					
Repeat Handling and impact tests (Step 2 to step 4)					

(b) (4)

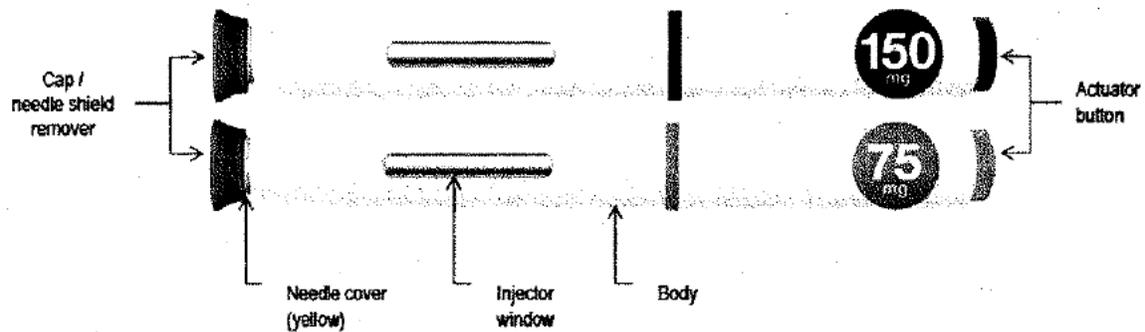
PRE-FILLED PEN PRESENTATION

Device Description

The sponsor developed two PFP presentations for the combination product, one for a 75mg dose, and another for a 150mg dose. The fill volumes for these pens are the same (1mL) | (b) (4)

(b) (4) The PFPs are single use and contain a prefilled syringe (PFS) component. (b) (4)

The injectors are shown in the figure below.



The PFP used is manufactured by

(b) (4)

(b) (4)

(b) (4)

The injector functions through a series of steps as outlined within the patient instructions for use. These steps are briefly repeated below:

- 1) Activation of the Injector: Accomplished through depression of the needle cover and button
(Note: it is not clear if this can occur simultaneously)

Review Update:

Within an Agency information request sent on 2-27-15, the sponsor was asked to provide information on the order of injection. In response, the sponsor stated that the pens require a particular order of steps to activate. First the Needle Cover needs to be depressed fully. Only then the Actuator Button can be depressed and immediately released to initiate the injection. The firm states that this is safety mitigation as it assists in prevention of unintentional activation.

This clarification and response is considered acceptable.

- 2) Penetration: After activation, spring forces the needle into the patient's tissue and depresses the plunger rod, expelling contents
- 3) Injection: The contents continue to fill the subcutaneous space until the plunger is fully seated.
- 4) End of Injection: Once the plunger rod is fully seated, the device will make an audible click and release the needle cover
- 5) Needle Cover Extension: As the device is removed from the skin, the needle shield will cover extend and lock into place.

Device Constituent part-Design Review

The section below details the consultant's review of information submitted to BLA 125553 and associated master file submissions for the injector devices. The submission indicates that a majority of the information supporting the function and safety of the injector is located within a master file created by (b) (4). This master file is referenced as MAF (b) (4).

Essential Performance of the Combination Product

The consultant performed a review of device requirements and specifications. This review, in combination with accepted performance aspects of pen injectors known to CDRH, yielded the following list of items for inspection and evaluation within this memorandum.

- 1. Combination product design inputs
- 2. Combination product verification activities
 - a. Accuracy
 - b. Physical durability
 - c. Biocompatibility
 - d. Stability
 - e. Shipping and storage
- 3. Combination product risk analysis information

4. Information comparing to-be-marketed products to studied products
5. Safety and functionality of studied products

Combination Product Design Inputs

Section 3.2.P.7 of the submission contains a document titled “Solution for injection in pre-filled pen 75 and 150 mg/mL”. This document contains a listing of combination product system-level specifications. Select specifications are reproduced below:

Specification Name	Acceptance Criteria
Shield remover removal force	(b) (4) N
Needle cover pre-injection force	(b) (4) N
Actuator button safety force at 80 N	Maximum displacement (b) (4) mm
Activation force	(b) (4) N
Injection time	(b) (4) seconds
Deliverable volume	(b) (4) mL
Needle cover override force at 80 N	Maximum displacement (b) (4) mm
Injection depth	(b) (4) mm (pass/fail)
Separation force	≥ (b) (4) N (pass/fail)

The above requirements are considered acceptable to serve as system-level combination product requirements. However, in addition to the system level requirements, it was noted that there should also be a number of sub-system requirements for pen injectors. MAF (b) (4) was inspected and was found to contain reference to identical system level requirements as well as to specific requirements for biocompatibility, dimensional tolerances, and drawings. Neither, the BLA nor the MAF appears to establish requirements related to audible or visual feedback. Additionally, acceptability criteria for each specification are not clearly established. For instance, the injection depth and displacement of the needle cover are not justified. This will be requested of the sponsor. The BLA sponsor will be requested to provide additional system level requirements and the MAF holder will be requested to provide detailed engineering requirements documents. The MAF documents to be requested will be:

1. Design Input Requirements (b) (4) color 150 mg/mL, document no. 0226-000-IR-S003 va.1
2. Design Input Requirements (b) (4) color 150 mg/mL, document no. 0226-000-IR-S003 v1.0
3. Design Input Requirements (b) (4) color 75 mg/mL, document no. 0226-002-IR-S003 v0.1
4. Design Input Requirements (b) (4) color 75 mg/mL, document no. 0226-002-IR-S003 v1.0
5. Function Test Matrix for the (b) (4) document no. 0226-000-TM-FOOCI, Rev 03.
6. Final Device Functional Testing Instruction, document no. 0226-000-TI-FOOI, Rev 02.

Review Update: Device design requirements, specifications, and clinical acceptability of design

Within an Agency information request sent on 2-27-15, the sponsor was asked to provide design input information for the injectors. In response, on 3-9-2015, the sponsor provided a table containing a number of essential performance requirements of the injector devices. The listing of requirements and specifications was found to be acceptable as they included all relevant aspects of device performance and safety including: delivered volume accuracy (before and after conditioning), indication of device status, indication of device activation and completion, force to activate, biocompatibility, container closure integrity, needle shield removal force, needle cover activation force, injection depth, needle cover override force, and injection time.

Within an Agency information request sent on 2-27-15, the sponsor was asked to provide clinical acceptability for each specification and requirement selected. In response, on 3-9-2015, the sponsor provided a table containing a listing of device requirements as well as rationale for each requirement in the context of the clinical use of the injector. Select clinical acceptability items are discussed below:

Requirement	Clinical Acceptability Statement
Delivered volume (b) (4) mL	Ensures delivery of 75 mg/150 mg per dose; evaluated in phase 3.
Injection depth (b) (4) mm	Based on Technical Summary - Average Subcutaneous Space Depth in Humans document referenced [QUA-FD-2015-05321] and provided as attachment to this submission, there is a high likelihood that a needle of length 4 mm-8 mm will deliver an injection to the subcutaneous space, when the skin is pinched and the injection is delivered at 90 degrees to the skin.
Injection time (b) (4) seconds	(b) (4)

The rationale supplied for the delivered volume specification is acceptable. The rationale supplied for injection depth is considered acceptable when supported by the reference document and the fact that the needle depth range was not changed from the devices used within the clinical study. Rationale supplied for the (b) (4) second injection time is not considered satisfactory as the sponsor (b) (4). The consulting reviewer notes that all injections operate on this principle, and thus the current device injection time is not rationalized based on this concept. The chief concern with the long injection time is dosing error due to early removal of the injector. This concept is discussed further within the review update below, "Clinical Acceptability of Injection Times"

Review Update: Clinical Acceptability of Injection Times

The sponsor has created a device specification for total time to injection completion once activated. This specification is greater than (b) (4) seconds but less than (b) (4) seconds. It should be noted that this specification can be further translated to "a pen which is manufactured should at no point in its labeled use life produce an injection time of less than (b) (4) seconds or more than (b) (4) seconds". Often with pen injectors, the most common injection times are less than the maximum specified time, however if an injector or lot of injectors were produced with injection times close to the upper end of this specification, they would be considered appropriate for release.

The consulting reviewer believes that a (b) (4) second injection time is representative of a relatively long injection time when compared to other commercially available injectors. In part, this is due to a relatively high viscosity drug product (b) (4) cP) and small needle gauge (27 G).

Engineering performance data which assessed injection times was presented for both injector presentations within

the device master file (MAF (b) (4)) as well as release performance information within the BLA submission. These data showed that injection times were always less than (b) (4) seconds directly after manufacture of the units, with a mean injection time of (b) (4) seconds across each presentation. Note that aging of injectors showed injection times that were out of specification; however this is not relevant to the current discussion of clinical acceptability of design-specified injection times. For more information on injection times after stability, see the section of this memorandum titled *Stability with respect to Aging*.

The consulting reviewer has determined that both device presentations are capable of meeting their design specification for injection time of (b) (4) seconds. The clinical acceptability of this specification is ultimately deferred to CDER/OSE/DMEPA and the clinical reviewers within CDER/DMEP; however the consulting reviewer recommends that the injection time of (b) (4) seconds be considered as acceptable when the following is considered:

- 1) The clinical study used injectors which were representative of the to-be-marketed product, and thus efficacy results seen within the clinical study included the presence of long injection times
- 2) The pen has a reliable means of indicating to the user when the injection is complete (color change and audible feedback)
- 3) Instructions for use for the pen state that the pen should be held against the skin for at least 20 seconds
- 4) DMEPA reports that patient labeling and instructions for use has been satisfactorily validated by means of clinical simulations within human factors studies
- 5) DMEPA and the sponsor report that users who exhibited difficulty completing an injection time for their novel dose were able to successfully complete subsequent doses
- 6) The drug product is not representative of an "emergency use" or "rescue" medication, and therefore long injections leading to partial doses are more tolerable

Combination Product Verification Activities

The sponsor has provided record of verification activities both within the BLA document and within the referenced Master File document. The extent to which these verification activities differ for the system level requirements referenced in the section above is not clear to the reviewer. It is clear that the MAF contains more detail and actual test reports documenting testing activities.

Review Update: NDA Pen Performance Data v. MAF Pen Performance Data

Within an Agency information request sent on 2-27-15, the sponsor was asked to compare the batch analysis verification activities presented within the NDA with the verification activities presented within MAF (b) (4). In response, on 3-9-2015, the sponsor stated that the MAF holder performed (b) (4) activities on the final finished combination product, while the NDA included (b) (4) for formal product qualification. The sponsor states that these processes are complementary; however the consulting reviewer notes that the NDA contains stability information which is not present within the MAF and is the subject of long injection time concerns discussed within other sections of this document. Regardless, to assist the agency in tracing device constituent part verification activities, the NDA sponsor included a separate document within their 3-9-2015 response titled "Auto-injector - Conformity to ISO 11608-1 and 5 - QUA-FD-2013-12446. The consulting reviewer examined this document and found it acceptable from the perspective that it better communicated the methods and outcomes of device verification activities for both the final finished assemblies and the engineering test run.

Review Update: Test Reports Mapping to NDA Summary Pen Design Verification Documentation

Within an Agency information request sent on 2-27-15, the sponsor was asked to provide test reports which support the batch analysis verification activities summarized within the original NDA. In response, on 3-9-2015, the sponsor provided a document titled, "Attachment to Q 4b - subassembly batch release test data used by (b) (4) QUA-FD-2015-05085". This document contained two test reports which were found to be representative and supportive of informational summarized within the original BLA for the 75mg/mL and 150mg/mL pen versions.

Within the BLA, to verify system level requirements, the sponsor provided a number of batch analysis summaries within the "Solution for injection in pre-filled pen 75 and 150 mg/mL" document. These summaries contained analyses for front and rear sub-assemblies of both the 75 and 150mg/mL variations. An example summary table is included below for reference:

Item (Function test)	1	2	3	4	5	6	7	8	9
	Shield Remover Removal Force	Needle Cover Pre-injection Force	Actuator Button Safety Force at 80N	Activation force	Injection Time (in air at standard atmosphere)	Deliverable Volume	Needle cover Override Force at 80N	Injection Depth	Separation Force
Acceptance criteria	(b) (4)								
Sampling Plan	(b) (4)								
Sample Size	(b) (4)								
Mean	(b) (4)								
Maximum	(b) (4)								
Minimum	(b) (4)								
Pass / Fail	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

Rear Subassembly Item (Dimension)	1	2	3
	Dimension C	Dimension D	Dimension E
Acceptance criteria	(b) (4)		
Pass / Fail	Pass	Pass	Pass

Front Subassembly Item (Dimension)	1	2
	Dimension A	Dimension B
Acceptance criteria	(b) (4)	
Pass / Fail	Pass	Pass

The reviewer inspected each of the summary reports and found that they satisfied each of the stated system; however there appeared to be a wide range of verification results. Specifically many of the test results appear to be at the furthest extent of the allowable specifications.

Review Update: Variability in Pen Device Verification Tests

Within an Agency information request sent on 2-27-15, the sponsor was asked to explain and justify the high degree of variability observed within batch analysis activities completed under the NDA. In response, on 3-9-2015, the sponsor provided an explanation and justification. Specifically, the sponsor stated that the two attributes which appeared to show results which suggest the control of product may not be established (b) (4)

(b) (4). This is considered acceptable as the injector is not used for rescue purposes and the verification studies do not show deviation outside of the requirement range. The acceptability of the (b) (4) and is discussed further within section of this memorandum titled *Stability with respect to Aging*.

Additionally, some samples show injection times which are near the maximum allowable time (b) (4). The sample which produced this value was not of the worst case viscosity. It is also not clear if this testing was conducted with the drug product. Additional detail will be requested from the sponsor. Additionally, the sponsor will need to submit full test report information supporting each of the summaries provided.

Review Update: Identity of Pen Devices Used within Verification Testing

Within an Agency information request sent on 2-27-15, the sponsor was asked to state which device configurations were used to produce the summary design verification information found within the NDA and MAF. This was a particularly important consideration given that the 75mg/ml presentation (b) (4)

(b) (4) In response, on 3-9-2015, the sponsor provided clarification that the pens used for the 75mg/ml

Testing of the 75mg/ml (b) (4)

(b) (4) is considered as acceptable as the (b) (4) is considered to be "worst case" from a device performance perspective. Additionally, this accounts for the some samples show injection times which are near the maximum allowable time ((b) (4)).

MAF (b) (4) was inspected for additional evidence of engineering design verification activities. The master file was found to contain assessments of pen attributes mostly in accordance with 11608-1 testing, as summarized in the sections below:

MAF Shield Remover Removal and Needle Cover pre-Injection Force

This verification study examined the force required to remove the needle shield component of the pen and the force required to depress the needle cover.

Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specifications for shield removal force (b) (4) N and needle cover pre injection force ((b) (4)) N.

MAF Actuator Button Safety Force

This verification study was designed to challenge the safety button at the top of the pen which allows the injection cycle to begin. The injection should not begin when a force is applied to this button without the needle cover having been depressed simultaneously.

Results for the (b) (4) 150mg/ml and 75mg/ml versions of the PFP show the injector met the specifications no more than (b) (4) nm of displacement at a force of 80N.

MAF Injection time, Activation Force, Deliverable volume, and Injection Depth

The activation force is the force required to depress the activation button and begin the injection cycle. Results for the 150mg/ml version of the PFP show the injector met the specification that activation force should be no more than (b) (4) N and no less than (b) (4) N.

The deliverable volume is the volume expelled by the injector during the injection cycle. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that deliverable volume (b) (4)

The injection time is the length of time a complete injection requires. Results for the 150mg/ml version of the PFP show the injector met the specification that injection time must be less than (b) (4) seconds.

Injection depth is the distance the end of the needle reaches into the tissue or test fixture during activation. Results for the 150mg/ml version of the PFP show the injector met the specification that injection depth must be more than (b) (4) nm but less than (b) (4) nm.

MAF Needle Cover Override Force and Separation Force

The needle cover override force test challenges the needle cover to a force of 80N. When this force is applied the cover should not move more than (b) (4) mm. Results for the 150mg/ml version of the PFP show the injector met the specification.

The separation force test examines the force required to separate the front and rear assemblies. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that the unit will not separate at forces less than (b) (4) N.

MAF Needle Point Safety

This verification study challenges the distance from the injector front surface to the needle tip after the shield is removed. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that the distance from open pen tip to needle shall not be less than (b) (4) mm.

MAF Separation Force Test from Cap

This verification study examines the force required to remove the needle shield remover from the rest of the injector. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that the cap should not separate at less than (b) (4) N but no more than (b) (4) N.

MAF Device Weight

This verification study examines the weight of the device and assures it is within specification. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification.

MAF Transport/Storage Environment Test

This test examines functionality in terms of injection time and deliverable volume of the injector after being subjected to transportation tests

The deliverable volume is the volume expelled by the injector during the injection cycle. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that deliverable volume must be greater than 1 mL after preconditioning from transport.

The injection time is the length of time a complete injection requires. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that injection time must be less than (b) (4) seconds after preconditioning from transport.

Assessments of deliverable volume were conducted for cool

MAF Storage Test

Dose accuracy and injection time were analyzed with test units that had been subjected to storage in a cold environment and in a hot environment.

The deliverable volume is the volume expelled by the injector during the injection cycle. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that deliverable volume must be (b) (4) after preconditioning in cold and hot environments.

The injection time is the length of time a complete injection requires. Results for the 150mg/ml version of the PFP show the injector met the specification that injection time must be less than (b) (4) seconds after preconditioning in cold and hot environments.

The reviewer could not locate assessments of cool injection times for either the 150mg/ml or 75mg/ml doses. This will be requested from the sponsor.

Review Update: Cool Injection Times:

As part of information request questions issued to the sponsor concerning injection times, an assessment of temperature effects on injection time was requested. In response, on 3-9-2015, the sponsor provided an analysis of injection times in cool environments (2-8°C). This assessment was intended to recreate the effects of activation without waiting for the unit to warm to room temperature. Testing located within the master file documented that the test units were able to achieve their stated injection times when activated in the cooled state. This is considered acceptable.

MAF Free Fall Test

A drop test is performed on the test unit both in a normal temperature and cool state. Visual and functional assessments are completed after each drop.

The deliverable volume is the volume expelled by the injector during the injection cycle. Results for the 150mg/ml and 75mg/ml versions of the PFP show the injector met the specification that deliverable volume must be (b) (4) after dropping in normal and cold environments.

The injection time is the length of time a complete injection requires. Results for the 150mg/ml version of the PFP show the injector met the specification that injection time must be less than (b) (4) seconds after dropping in normal and in cold environments.

MAF Durability Testing

After aging the test units, dose accuracy and injection time are assessed. The durability test preconditioning protocol requires components to be aged by accelerated means, the sub-assemblies to be aged by accelerated means, and then the assembled device to be aged by real time means. The sponsor did not report results of the durability test "since the real time aging are not complete at this time." Additional information on aging of the final finished device will be requested of the MAF holder.

Review Update: Master File and BLA Stability Aging Testing

While the master file is considered to have contained supporting information on the shelf life of the injector under the "durability" test, the final assessment of acceptability after aging is conducted under the BLA stability program. The stability testing presented within the February 20, 2015 stability update contains 18 months of performance information for the injector products. All essential performance attributes are considered verified after aging to a period of 18 months with the exception of (1) injection time, which has a number of failures after aging (please see section of this memorandum titled *Stability with respect to Aging* for evaluation of the acceptability of injection times after aging) and (2) end of injection indicators such as visual and audible feedback features. For end of injection indicators, the MAF is expected to supply an accelerated aging update to the file contain this information.

The MAF sponsor was requested to provide a stability update to the MAF record within deficiencies provided to the CDER regulatory project manager on 2-27-2015. In response, on 4-10-2015, the MAF holder provided a stability update to the MAF. This stability update aged individual device components to an accelerated period of two years. These components were then assembled with the syringe and placed on another aging schedule. The results of testing completed to date (b) (4)

(b) (4) the reviewer considers the MAF testing to be acceptable to allow for an approval recommendation for the injector presentation; however a post-approval request will be requested of the sponsor for stability updates to the submission

MAF Dimensional Attribute Test

The injectors are assessed through visual inspection of attributes as well as a functional assessment of injection. The sponsor constructed a test which assessed the presence of clicks indicating injection started and stopped, the syringe “bottoms out”, the casing of the injector is intact and the cover shield deploys, and that the syringe is not broken. The results of these tests demonstrated that each sample passed the testing.

Stability with respect to Aging

To support functionality of the combination product after aging, the sponsor included the “durability test” as described above, however within the BLA; a separate document was filed relevant to combination product shelf life during the review cycle. This document was received within an updated BLA section (3.P.8.3) on February 20, 2015. This document contained several failures of the 75 mg/ml and 150 mg/ml pen to meet injection time and dose accuracy specifications, as detected during the stability assessment. The sponsor chose to focus on the 75mg/ml products as they showed a higher failure rate. In an effort to correct for these failures, (b) (4) 75mg/ml product, (b) (4) Lots with this modification have continued to show failures, and so the sponsor engaged in a series of evaluations (b) (4)

(b) (4)

(b) (4)

(b) (4)

- Acceptability of the product specification of injection time less than ^(b)₍₄₎ seconds with 95% confidence

Review Update: Injection Time Suitability

See *Review Update: Clinical Acceptability of Injection Times* section of this memorandum.

(b) (4)



Stability with respect to Shipping

To support safety and functionality of the pen device after shipping and transportation studies, the BLA sponsor conducted a shipping and transportation assessment. This assessment follow methods outlined within DIN EN 60068-2-6, DIN EN 60068-2-64 AND DIN EN 60068-2-27, and included the following categories of tests: (b) (4)

Each pen was then assessed for verification to visual and functional requirements and were found to pass. This information is considered acceptable.

Combination Product Risk Analysis Information

Within review of the original BLA submission, the consulting reviewer was not able to locate a risk analysis/risk management plan or associated documentation for the pre-filled pen product. The sponsor was asked to provide this information to the BLA record. On 3-9-15, the sponsor provided a system risk analysis which established technical and use-related risks. This sponsor states that the risk analysis takes into consideration the specific medication to be delivered by using clinical expert input for the assessment of hazards and hazardous situations. To supplement the system risk analysis, a system failure modes and effects analysis (FMEA) was conducted to provide a more detailed analysis of technical risks associated with the device constituent parts.

Risk Management Plan

The risk management plan details the sponsor's approach to risk management in the context of their business relationship with the injector designer, (b) (4). The specific types of analyses conducted were a top-down analysis based on user tasks and a bottom-up analysis via FMEA.

The risk management plan, outlined within the figure below, demonstrates that sufficient guidance and responsibility for risk management activities in the context of the medication being delivered has been planned.

Risk Management Report

The system risk management report was inspected and found to contain and rely on ISO14971 methodology to evaluate risks of the product, where acceptable and not acceptable regions were established via a multiplication of probability of occurrence and severity. A third central region was established which relies on a risk benefit analysis of the product. The sponsor also conducted a residual risk analysis.

The specific risk analysis elements covered considerations of:

- Degradation of medicinal product
- No dose delivered
- Incorrect medicinal product delivered
- Clinically significant underdose (b) (4) % of dose)
- Clinically significant overdose (b) (4) % of dose)
- Delay of injection or injection which occurs too fast
- Incorrect injection site
- Traumatic injuries (swallowing of parts, sharp edges, bent needle)
- Biologic harm (re-use of device, bio incompatibility)

Each of the above high level harms were digested into design and use-specific hazards/causes and sub-causes. The sponsor then implemented and recorded mitigation activities present to reduce the associated risks of each hazard.

After mitigation strategies were employed, residual risks existed within the “yellow” region of the risk matrix. Risks remaining in this category receive a benefit risk assessment. The sponsor conducted this assessment with

12 residual risks. These risks included items such as the possibility of swallowing the pen cap, not refrigerating the product, administering too many injections per week, and confusing the pen with other injectors. Each of these risks is considered by the reviewer to be acceptable after consideration of the mitigations employed to date and the probable benefit of the product, however one residual risk, explained below, requires additional evaluation.

The sponsor included a residual risk of "device stalling during injection". This is the same issue as is described within the *Stability with respect to Aging* section of this memorandum. However, the sponsor does not appear to have updated the risk management documentation in parallel with the activities conducted to date to mitigate the issue, as the risk management report contains old information on the issue. Additional information has been requested by the sponsor regarding the risks of the product in the context of aging stability and its effect on injection time; however the argument of product benefit is still relevant and will be considered within this memorandum's final recommendation.

Information comparing the to-be-marketed Products with Studied products

The sponsor states that the commercial version of the pen injector product is substantially identical to the presentations tested under a number of clinical studies for the injector presentations. The table below summarizes the differences between the clinical and commercial versions of the pre-filled syringe and pre-filled pen products:

Components	Description	CLINICAL	COMMERCIAL
		75 mg/mL and 150 mg/mL	(b) (4)
	(b) (4)		(b) (4)

The consulting reviewer agrees with the sponsor that most features are substantially identical between the studied and to-be-marketed versions of the devices, however for a single change issue the 75mg injector (b) (4) there may be important differences between the clinical and commercial versions of the product.



Assessment of the safety and efficacy of the pre-filled pen system is deferred to responsible CDER review division; however this section contains a brief summary of relevant device events.

The pre-filled pen (PFP) is reported to have been used in all other studies except the LONG TERM study which used the syringe only. In the placebo-controlled pool of injections, 768 patients received the study drug and 386 received a placebo using the identical PFP. In the ezetimibe-controlled studies, 864 patients received alirocumab and 618 received ezetimibe (all through the pen).

The most frequent device-related events reported by the sponsor were 'Device is jammed', 'Activation difficulty / fault' and 'Click/click sound missing'. In the pool of ezetimibe-controlled phase 3 studies where all patients used a PFP, device-related events were reported in 72 (8.3%) and 17 (2.8%) patients using the PFP for alirocumab and the placebo of alirocumab, respectively. Twenty-three (2.7%) patients with alirocumab and 1 (0.2%) with the placebo of alirocumab reported more than one device-related event. 9.5% and 6.7% patients with the PFP of alirocumab and its placebo, respectively experienced local site reactions. No patients discontinued treatment due to local injection site reaction with the use of the PFP.

According to the sponsor, most of symptoms at the injection site were reported to be mild in intensity; severe redness and severe itching at the injection site were reported in 2 and 1 patients, respectively, with the PFP of alirocumab. No injection site reaction was reported to be serious with the PFP.

The following device-related adverse events were reported for the PFP products:

n/N(%)	Ezetimibe (N=618)	Alirocumab (N=864)
Any device-related event	18/10328 (0.17%)	105/16837 (0.62%)
Device is jammed	5/10328 (0.05%)	61/16837 (0.36%)
Activation difficulty / fault	9/10328 (0.09%)	31/16837 (0.18%)
Click/click sound missing	0/10328	5/16837 (0.03%)
Injection time / leakage	0/10328	2/16837 (0.01%)
Unknown	1/10328 (0.01%)	2/16837 (0.01%)
Broken component	0/10328	1/16837 (0.01%)
Leakage	0/10328	1/16837 (0.01%)
Other	1/10328 (0.01%)	1/16837 (0.01%)
Potential: dropped autoinjector	0/10328	1/16837 (0.01%)
No investigation	1/10328 (0.01%)	0/16837
Packaging issue	1/10328 (0.01%)	0/16837

For the clinical presentation the majority of events appear to be related to long injection times and incomplete injections, including "Device is jammed", "Activation difficulty / fault", and "Click/click sound missing". There was one reported instance of injection time / leakage; however the details regarding this event are not reported. Based on clinical experience with the injector, the risk of high injection times appears to be significantly greater than the risk of an injection associated with leakage or injection site pain. (b) (4)

(b) (4)

Review Update: Potential Consequences of Enacting Manufacturing Control Change (b) (4)

(b) (4)

Safety features

The pre-filled pen is designed so that, prior to the injection, the needle is contained in the prefilled pen body and covered by the yellow needle cover. The injection cannot be initiated until the yellow cover is pressed against the skin and pushed into the pen body. This safety feature prevents accidental activation of the injection. After the injection, the needle cover extends back over the needle and is locked in the extended position, which protects anyone from being pricked by the needle after the device has been used.

A clinical use study was done out in accordance with guidelines in the *FDA Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features*.

A validation study was conducted with the primary intended user groups (nurses and patients) of the device. Study participants performed injections, needle shield tests and answered post test questions. The study participants performed 520 injections and had zero failures. The alirocumab pre-filled pen experienced zero needle cover extension or locking failures and generated zero needle-stick injuries across the 520 injections performed by the intended users of the device, demonstrating the reliability of the pre-filled pen sharps injury prevention feature.

Information Request History

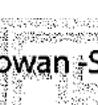
The CDRH consultant recommended IR questions be issued to the BLA sponsor on 3-27-2015 and a response was received on 3-9-2015. These response were accepted

The CDRH reviewer recommended IR questions be issued to the DMF holder (b) (4) on 2-27-2015 and a response was received on 3-9-2015. The responses were acceptable.

The CDRH reviewer recommended IR questions be issued to the DMF holder (b) (4) on 3-12-2015 and a response was received on 3-13-2015. The responses were acceptable.

The CDRH reviewer recommended IR questions be issued to the MAF holder on 2-27-2015 responses were received 4-10-2015. The responses were acceptable.

The CDRH reviewer assisted in crafting IR questions to the BLA sponsor on 4-22-2015 with regard to potential unintended impacts on manufacturing controls enacted to reduce injection time and the impact on the injection systems. The CDRH reviewer expressed that these were not issues under the purview of CDRH, but rather were issues for CMC and the clinical reviewers.

Digital Signature Concurrence Table	
Lead Reviewer Sign-Off	 <p>Janice L. Polacek -S Janice L. Polacek -S 2015.05.04 14:55:15 -04'00'</p>
Engineering Consultant Reviewer Sign-Off	 <p>Ryan J. McGowan -S Digitally signed by Ryan J. McGowan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=200035246 2, cn=Ryan J. McGowan -S Date: 2015.05.04 15:02:50 -04'00'</p>
Team Lead Sign-Off	 <p>Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130018921 1, cn=Alan M. Stevens -S Date: 2015.05.04 15:04:15 -04'00'</p>
Branch Sign-Off	 <p>Richard C. Chapman -S 2015.05.05 10:06:31 -04'00'</p>

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # BLA# 125559	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Praluent Established/Proper Name: alirocumab Dosage Form: subcutaneous injection Strengths: 75 and 150 mg		
Applicant: Sanofi-aventis U.S., LLC Agent for Applicant (if applicable):		
Date of Application: November 24, 2014 Date of Receipt: November 24, 2014 Date clock started after UN: NA		
PDUFA/BsUFA Goal Date: July 24, 2015		Action Goal Date (if different):
Filing Date: January 23, 2015		Date of Filing Meeting: January 7, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s): 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 or as monotherapy including in patients who cannot tolerate statins		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input checked="" type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
• <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i>	
• <i>The product is a Qualified Infectious Disease Product (QIDP)</i>	
• <i>A Tropical Disease Priority Review Voucher was submitted</i>	
• <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 105574

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> NA <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>		<input type="checkbox"/>	<input type="checkbox"/>		
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input type="checkbox"/>	XX		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	☒		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	☒		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Reviewed under the IND. No further assessment required
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC on 5/27/15

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not required in iPSP
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) syringe blisters			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Consulted to OSE/DMEPA,
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Device+IFU to CDRH – 11/24/14; all labeling to DDMAC 12/12/14 +1/19/15; PPI+IFU to PLT12/12/14
Meeting Minutes/SPAs	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): 2/21/2012 and 5/9/2012 (CMC only) <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9/4/2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): agreement: 7/13/12 (clinical); modifications: 8/17 and 10/1/12 and 11/8 and 12/17/13 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

ATTACHMENT
MEMO OF FILING MEETING

DATE: 1/7/15

BACKGROUND: Praluent is a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor developed to treat dyslipidemia. It is a biologic (monoclonal antibody) and new molecular entity (NME) being reviewed under “the Program.” The applicant, Sanofi Aventis, proposes that Praluent be indicated as an 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 or as monotherapy including in patients who cannot tolerate statins. The Applicant purchased a Pediatric Rare Disease Priority Review Voucher and has submitted it to the Agency for use when reviewing BLA 125559.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pat Madara	Y
	CPMS/TL:	Julie Van Der Waag	Y
Cross-Discipline Team Leader (CDTL)	Jim Smith		Y
Division Director/Deputy	Jim Smith, Deputy Director (Acting)		Y
Office Director/Deputy	Mary H. Parks, Deputy Director, ODE II		Y
Clinical	Reviewer:	Julie Golden (efficacy) Mary Roberts (safety)	Y
	TL:	Jim Smith	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Pharmacology	Reviewer:	Sang Chung	Y
	TL:	Jaya Vaidyanathan, acting	Y
Biostatistics	Reviewer:	Brad McEvoy	Y
	TL:	Mark Rothmann	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Lee Elmore	Y
	TL:	Karen Davis Bruno	Y
Statistics (carcinogenicity)	Reviewer:	NN	
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:	Richard Ledwidge (OBP)	Y
	TL:	Howard Anderson (OBP)	Y
Product Quality (CMC)	Reviewer:	Richard Ledwidge (OBP)	Y
	TL:	Howard Anderson (OBP)	Y
Biopharmaceutics	Reviewer	NN	
	TL:		
Quality Microbiology	Reviewer:	Maria Candauchacon Colleen Thomas	Y
	TL:	Patricia Hughes	N
CMC Labeling Review	Reviewer:	Jibril Abdus-Samad	Y
	TL:		
Facility Review/Inspection	Reviewer:	Michael Shanks (member of the team)	N
	TL:	Peter Zhihao Qiu	N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Mishele Mistry	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	Y
	TL:	Doris Auth	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NN	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	N
	TL:	Janice Pohlman	Y
Controlled Substance Staff (CSS)	Reviewer:	NN	
	TL:	NN	
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Bindi Nikhar, OCP Janice Polacek, CDRH Amy Rosenberg, OBP Twanda Scales, PLT Ankur Kalola, OPDP Ali Niak, DPV		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
New Molecular Entity (NDAs only) <ul style="list-style-type: none"> • Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: new system</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>none</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Office level sign off (ODE II director or deputy)</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 2/25/15</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). NA
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. NA
<input checked="" type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input checked="" type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

PATRICIA J MADARA
01/19/2015

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

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

Application: 125559

Application Type: New BLA

Name of Drug/Dosage Form: Praluent (alirocumab) injection for subcutaneous use

Applicant: Sanofi Aventis, U.S., Inc.

Receipt Date: November 24, 2014

Goal Date: July 24, 2014

1. Regulatory History and Applicant's Main Proposals

Praluent is a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor developed to treat dyslipidemia. It is a biologic (monoclonal antibody) and new molecular entity (NME) being reviewed under "the Program." The applicant, Sanofi Aventis, proposes that Praluent be indicated as an 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 or as monotherapy including in patients who cannot tolerate statins.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 60 or 74-day letter or an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 13, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

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

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

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

Comment:

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

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

***Comment:** Subsections 8.5, 8.6, and 8.7 all reference Subsection 12.3. The reference should cite SECTION 12 (CLINICAL PHARMACOLOGY) and the subsection identifier (12.3)*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

YES PATIENT COUNSELING INFORMATION Section in the FPI

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

PATRICIA J MADARA
01/19/2015