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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA	125559/S-014 (Seq No. 0172)
Submission Date(s)	October 24, 2017
Brand Name	PLALUENT
Generic Name	Alirocumab injection
Reviewers	Sang M. Chung, Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Sanofi
Submission Type	Prior Approval Supplement to include the use of alirocumab in HeFH patients undergoing apheresis
Formulation; Strength(s)	75 and 150 mg/mL in a single-use prefilled syringe or single-use pen
Indication	An adjunct to diet, for (b) (4) treatment of adult patients with (b) (4) hypercholesterolemia

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1 Executive Summary

Alirocumab is a monoclonal antibody (mAb) of human IgG1 isotype inhibiting proprotein convertase subtilisin kexin type 9 (PCSK9). The original Biologics License Application (BLA) was approved on July 24, 2015 and is indicated as 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 LDL-cholesterol (LDL-C) lowering. The recommended starting dose is 75 mg once every 2 weeks (Q2W) or 300 mg every 4 weeks (Q4W), and the dosage may be adjusted to 150 mg every 2 weeks (i.e., 75 mg Q2W/150 mg Q2W or 300 mg Q4W/150 mg Q2W) if the LDL-C response is inadequate.

This supplemental BLA is to pursue labeling update for the use of alirocumab in HeFH patients undergoing apheresis based on results of Study R727-CL-1216 (ESCAPE study). The sponsor proposed the labeling updates mainly in Indications and Usage (1), Dosage and Administration (2), Adverse Reactions (6), and Clinical Studies (14).

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the supplemental submission to BLA 125559 for PLALUENT™ and finds the clinical pharmacology data acceptable for approval.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Highlights of known alirocumab Pharmacokinetics (PK) and Pharmacodynamics (PD)

PCSK9 is shown to control trafficking of the hepatic LDL receptor (LDLR). Alirocumab reduces plasma free PCSK9 concentration as a PCSK9 inhibitor, and it leads to the increase of plasma LDL clearance as more LDLR are available to clear plasma LDL. For details of alirocumab PK and PD (free and total PCSK9 and LDL-C), refer to the clinical pharmacology review for the original BLA.

Primary results of supporting the proposed labeling: Study R727-CL-1216 (ESCAPE Study)

The ESCAPE Study was to evaluate the effect of alirocumab 150 mg Q2W compared to placebo on the frequency of LDL apheresis treatments in patients who had been undergoing LDL apheresis every 1 or 2 weeks in a randomized, double-blind, placebo-controlled, parallel-group design (Figure 1).

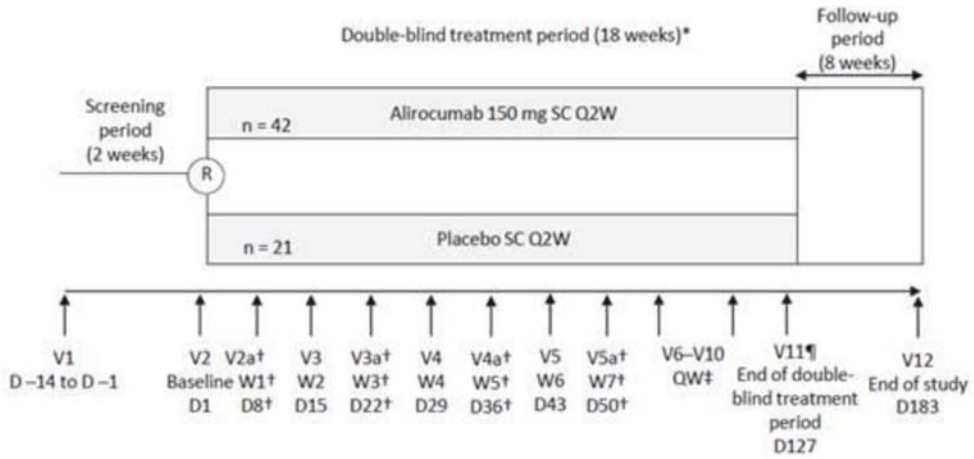

Figure 1 Schematic summary of the study design for the ESCAPE Study (Source: Figure 1, Section 2.5)

For the assessment of PK and PD (free and total PCSK9 and LDL-C), trough concentrations were measured at baseline, and at weeks 1, 2, 5, 6, 11, 12, 17, and 18 before and after the apheresis procedure, if scheduled. Sample collection at week 1, 5, 11, and 17 was mandatory for patients undergoing QW apheresis, and not applicable for patients undergoing bi-weekly apheresis. From week 7, for patients who did not undergo apheresis, the sample was drawn before study drug administration. Samples for LDL-C were collected at baseline and weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, and 26. For patients undergoing apheresis, samples were collected before and immediately following the apheresis procedure; for patients not undergoing apheresis, samples were collected before administration of study drug.

Primary efficacy endpoints

The study design was to evaluate if an average LDL-C following alirocumab would be similar to that of apheresis (Figure 2). The criterion used to determine the need for apheresis was whether a 30% reduction in LDL-C was achieved at the end of the dosing interval. The highest approved dose (i.e., 150 mg Q2W) was selected as the patients with apheresis would require the most potent dosing regimen due to life-long exposure to elevated LDL-C while on treatment with typical lipid modifying therapies.

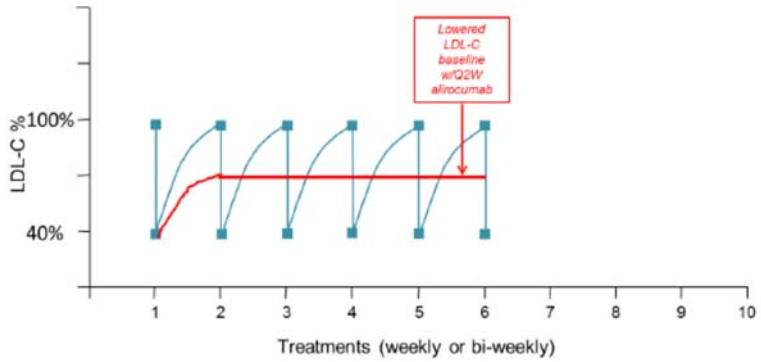

Figure 2 Schematic summary of typical effect of apheresis on LDL-C reduction and potential treatment effect of alirocumab (Source: Figure 1, Clinical Study Report)

The sponsor concluded that there was a significant decrease (75%) in the standardized rate of apheresis treatment from week 7 to week 18 following alirocumab compared with placebo group. In addition, reduction of LDL-C (percent change from baseline) following alirocumab ranged from -54.7% (week 4) to -42.3% (week 18) compared to 7.2% (week 14) following placebo. However, there were issues related to the efficacy analyses due to involvement different LDL-C measurement methods between baseline and treatment period. Please, refer details to the clinical and biostatistics reviewers by Dr. Julie Golden and Dr. Bradley McEvoy, respectively.

Apheresis significantly reduced LDL-C (Figure 3). There was significant alirocumab effect on LDL-C levels before apheresis compared to that of placebo group, whereas there was no significant difference in LDL-C levels after apheresis between treatment groups (Figure 3).

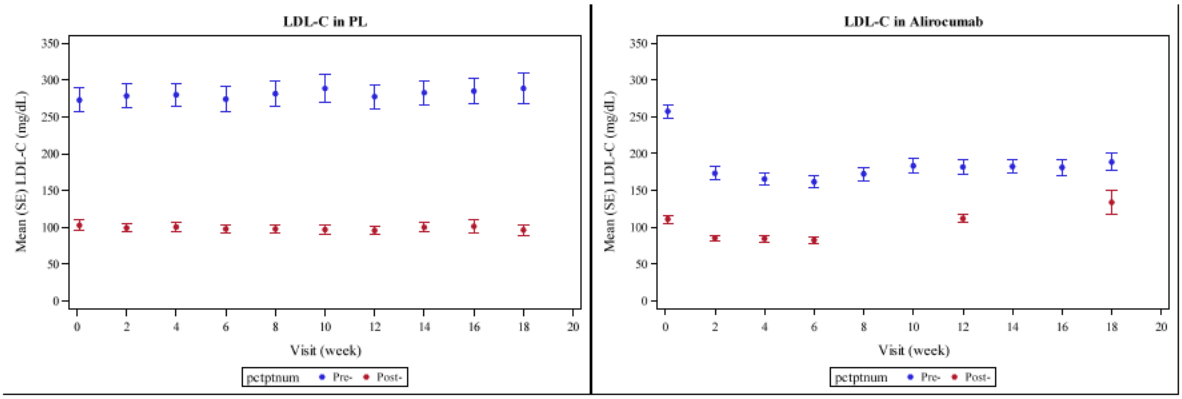

Figure 3 Mean (SE) LDL-C before (Pre-) and after (Post-) apheresis over the treatment period; placebo (left panel) vs. alirocumab (right panel)

Pharmacokinetic (PK) and Pharmacodynamic (PD) results

Alirocumab concentrations were reduced up to 37% by apheresis (Figure 4, Table 1). However, it is not considered clinically meaningful as free PCSK9 levels (PD) were negligible during alirocumab treatment regardless of apheresis (Figure 4). Total PCSK9 levels were reduced after apheresis compared to that of before apheresis. However, clinical relevance of the reduction is not known.

There was significant variability in alirocumab concentrations by different apheresis procedures (Table 2). However, clinical relevance of the variability is not clear as numbers of subjects were small in each group.

Immunogenicity

The sponsor monitored anti-drug antibody (ADA) and neutralizing antibody (NAb). There were 4 patients with positive ADA response (1 on placebo and 3 on alirocumab). All ADA levels were considered as transient with low titers and there was no positive NAb response among those 4 patients (Table 3). There was no significant effect of ADA response on PK. However, it should be cautious that the sample size was small for any quantitative analyses.

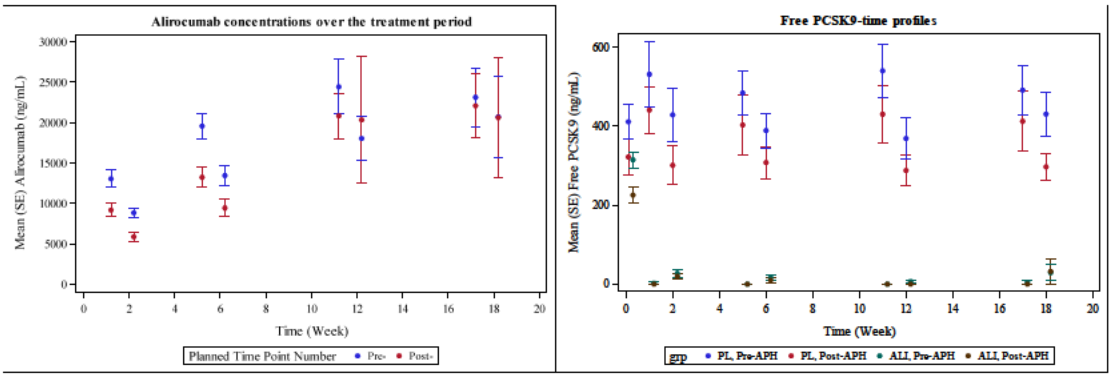

Figure 4 Mean (SE) alirocumab (left panel) and free PCSK9 (right panel) concentrations before (Pre-) and after (Post-) apheresis over the treatment period

Table 1 Difference in total alirocumab concentration (%) between pre- and post-apheresis

Clinical Study Day	Difference Pre- and Post-Apheresis (%)		
	150 mg Q2W SC		
	N	Mean	SD
Total Alirocumab			
Day 1	39	0.00	0.00
Day 8	18	-30.9	12.4
Day 15	40	-37.1	13.3
Day 36	16	-33.0	8.81
Day 43	37	-34.4	15.3
Day 78[a]	4	-20.0	10.6
Day 85	4	-23.0	7.95
Day 120	2	-17.9	0.864
Day 127	5	-31.2	20.8

Table 2 Descriptive summary of alirocumab concentrations by apheresis procedures

Visit (W)	Procedure*	N	Mean (ng/mL)	SE
2	1	4	7110	2040
	2	2	3375	1345
	3	18	6950	778
	4	11	5110	1063
	5	6	4208	879
6	1	4	10580	4639
	2	2	5650	1450
	3	14	10867	1994
	4	11	8851	1935
	5	6	7652	1574

* Procedure=1; DIRECT ADSORPTION OF LIPIDS, 2; DEXTRAN SULFATE ADSORPTION (WHOLE BLOOD, 3; DEXTRAN SULFATE ADSORPTION (PLASMA), 4; HEPARIN-INDUCED LDL PRECIPITATION, 5; DOUBLE MEMBRANE FILTRATION

Table 3 ADA titer category for patients who had ADA by treatment group (Source: Table 3, Section 2.7.2)

	Placebo		150 mg Q2W SC	
	N	%	N	%
All ADA Population	20	100	40	100
Low (<1,000)	1	5.0	3	7.5
Moderate (>=1,000 but <=10,000)	0	0	0	0
High (>10,000)	0	0	0	0

2 Labeling comment

(Red underlined text indicates addition and ~~strikethrough text~~ indicates deletion)
There was no proposed clinical pharmacology information by the sponsor

12.3 Pharmacokinetics

Absorption

After subcutaneous (SC) administration of 75 mg to 300 mg alirocumab, median times to maximum serum concentrations (t_{max}) were 3-7 days. The pharmacokinetics of alirocumab after single SC administration of 75 mg into the abdomen, upper arm, or thigh were similar. The absolute bioavailability of alirocumab after SC administration was about 85% as determined by population pharmacokinetics analysis. A slightly greater than dose proportional increase was observed, with a 2.1-fold to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose from 75 mg every 2 weeks to 150 mg every 2 weeks. Monthly dose normalized exposure with 300 mg every 4 weeks treatment was similar to that of 150 mg every 2 weeks. Steady state was reached after 2 to 3 doses with an accumulation ratio up to a maximum of about 2-fold.

Distribution

Following IV administration, the volume of distribution was about 0.04 to 0.05 L/kg indicating that alirocumab is distributed primarily in the circulatory system.

Metabolism and Elimination

Specific metabolism studies were not conducted, because alirocumab is a protein. Alirocumab is expected to degrade to small peptides and individual amino acids. In clinical studies where alirocumab was administered in combination with atorvastatin or rosuvastatin, no relevant changes in statin concentrations were observed in the presence of repeated administration of alirocumab, indicating that cytochrome P450 enzymes (mainly CYP3A4 and CYP2C9) and transporter proteins such as P-gp and OATP were not affected by alirocumab.

Two elimination phases were observed for alirocumab. At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination of alirocumab is largely through a non-saturable proteolytic pathway.

Based on a population pharmacokinetic analysis, the median apparent half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab at subcutaneous doses of 75 mg Q2W or 150 mg Q2W.

For patients with HeFH undergoing LDL apheresis, the apheresis procedure may reduce alirocumab concentrations up to 37%, but free PCSK9 levels do not significantly change. Thus, PRALUENT may be administered without regard to the timing of apheresis.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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07/31/2018

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07/31/2018