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RESEARCH**

APPLICATION NUMBER:

125559Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA	125559
Submission Date(s)	November 24, 2014
Brand Name	PLALUENT
Generic Name	Alirocumab injection
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OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Sanofi
Submission Type	Priority
Formulation; Strength(s)	75 and 150 mg/mL in a single-use prefilled syringe or single-use pen
Indication	An adjunct to diet, for long-term treatment of adult patients with primary hypercholesterolemia

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1 Executive Summary

Alirocumab is a monoclonal antibody (mAb) of human IgG1 isotype, and is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor, which controls the clearance of hepatic LDL receptor. Inhibition of PCSK9 is a new target for the treatment of primary hypercholesterolemia, (b) (4)

Clinical data of alirocumab were evaluated through total of 25 trials including 10 Phase 3 trials. Two doses were evaluated in pivotal trials; 75 and 150 mg administered once in every two weeks (Q2W) in patients with primary hypercholesterolemia (non-familial or heterozygous familial hypercholesterolemia). In addition, a titration scheme from 75 mg Q2W to 150 Q2W was evaluated by protocol in 8 of 10 pivotal trials.

Alirocumab pharmacokinetics is largely determined by its characteristics of being a mAb and PCSK9 inhibitor. Alirocumab demonstrates non-saturable proteolytic elimination, and the alirocumab-PCSK9 bound complex is known to have a saturable target-mediated elimination. Intrinsic or extrinsic factors do not affect alirocumab pharmacokinetics. In general alirocumab pharmacokinetics such as apparent effective half-life (e.g., 17-20 days), t_{max} (e.g., 3-7 days) and accumulation (e.g., about 2-fold) supports the proposed dosing regimen of subcutaneous injection once in every two weeks.

Alirocumab depletes free PCSK9 and decreases the low density lipoprotein cholesterol (LDL-C) concentrations in a dose-dependent manner.

Alirocumab exposure increased in a dose-dependent manner in patients and LDL-C reduction reached apparent nadir after 150 mg Q2W. In general, there were no known clinically important covariates for the dose/exposure-efficacy relationships. However, additional LDL-C reduction was noted among 6 of 8 trials with the titration scheme, which ranged from 1.5 to 23.1%, in patients who were titrated in the pivotal trials up to 150 mg Q2W, and baseline LDL-C values in the titrated patients were higher than those of 75 mg Q2W. Further, both 75 and 150 mg Q2W had superior efficacy compared to placebo. Therefore, it seems reasonable to consider 75 mg Q2W as the starting dose and alirocumab can be titrated up to 150 mg Q2W in patients needing additional LDL-C reduction.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed BLA 125559 for PLALUENT™ (alirocumab) for subcutaneous injection and recommends approval.

OCP recommends approval of both 75 mg and 150 mg doses given once every two weeks (Q2W). Both 75 and 150 mg Q2W doses demonstrated superior efficacy compared to placebo and active comparators in Phase 3 studies. Additional LDL-C reduction was noted, which ranged from 1.5 to 23.1%, in patients who were titrated in the pivotal trials up to 150 mg Q2W. Overall safety profile was comparable between two doses.

Therefore, we have the following recommendations:

- Initiate patients at 75 mg dose Q2W. Dose can be increased to 150 mg Q2W in patients who need additional LDL-C lowering and are able to tolerate the lower dose.
 - Alirocumab can be titrated up to 150 mg after 8 weeks as this scheme was evaluated in pivotal phase 3 trials. Alternatively, the dose can be titrated after 4 weeks as the maximum LDL-C reduction was attained in 2-3 weeks following alirocumab injection and LDL-C reduction reached apparent steady-state after the first dose.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

1.3.1 Highlights of Pharmacokinetics (PK)

Absorption, Distribution and Metabolism: Alirocumab shows typical PK characteristics of mAb in absorption, distribution and metabolism (Figure 1) as follows;

- Median time to maximum serum concentration (t_{max}): 3-7 days
- no apparent difference in alirocumab PK among injection sites (i.e., upper arm, abdomen and thigh)
- reached a steady-state after 2-3 doses with an accumulation ratio of about 2-fold
- mean of volume of distribution (Vd) with 0.04-0.05 L/kg indicating its distribution is limited to the circulatory system
- conventional metabolic or its concerted mechanisms (e.g., metabolic isozymes or hepatic transporters) are not involved in alirocumab clearance

Elimination: Alirocumab pharmacokinetics shows apparent non-linear pharmacokinetics primarily because of the following elimination aspects;

- two different pathways (i.e., proteolytic and target-mediated) are involved in its elimination
- proteolytic pathway is relatively slower than that of target mediated pathway
- their relative contribution to the overall clearance (mean: 3.1-6.2 mL/day/kg) is dependent on alirocumab concentration as the target-mediated pathway is saturable

Alirocumab pharmacokinetics including non-linearity in elimination can be adequately characterized within the proposed dosing range due to availability of sufficient concentration-time data. Median apparent effective terminal half-life ranged from 17 to 20 days and it was about 12 days in patients with statins co-administration as statins are known to induce PCSK9 and thus increase the clearance of alirocumab.

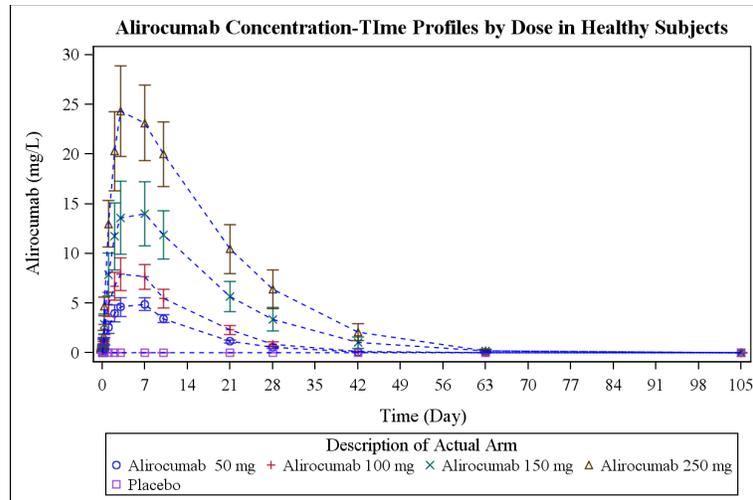


Figure 1 Mean (SE) alirocumab concentration-time profiles after single dose of 50, 100, 150 or 250 mg SC injection to healthy subjects

Intrinsic Factors: The effect of age, race, sex and body weight on alirocumab exposure and efficacy was evaluated using population analysis. There were no significant covariates of both alirocumab PK and efficacy for a dose adjustment.

Hepatic Impairment: Alirocumab PK tended to be lower in subjects with hepatic impairment with the ratios of geometric mean (90% CI) for C_{max} and AUC of 1.04 (0.74 to 1.48) and 0.9 (0.64 to 1.26), respectively, in mild, and 0.91 (0.66 to 1.24) and 0.82 (0.61 to 1.12), respectively, in moderate hepatic impairment groups, compared to those of healthy control group. Subjects with severe hepatic impairment were not included in the study.

The PK changes in the hepatic impairment sub-groups were considered not clinically significant for a dose adjustment.

Renal Impairment: Alirocumab PK change in subjects with renal impairment sub-groups was not studied because the kidney is not considered as the major eliminating organ for alirocumab.

There was no apparent correlation between alirocumab trough concentrations with eGFR in Phase 3 trials, which included healthy to moderate renal impaired patients as eGFR ranged from 19.4 to 167.9 mL/min/1.73m².

Extrinsic Factors: Alirocumab AUC was decreased by fenofibrate (36% in healthy subjects) and atorvastatin (39% in patients). However, these PK difference did not translate into meaningful clinical difference in LDL-C changes in the studies. Further, there was no apparent clinical significance of statins on alirocumab LDL-C.

There were no apparent associations between immunogenicity and PK or exposure-response according to the limited data from small number of patients with anti-drug antibody.

1.3.2 Highlights of Pharmacodynamics (PD)

Free PCSK9 concentrations are completely depleted during the initial period of alirocumab administration (Figure 2; Left). Total PCSK9 concentrations (free + bound to alirocumab) tend to reach the maximum at around 14 days after the alirocumab administration and its C_{max} increase was dose-dependent (Figure 2; Right).

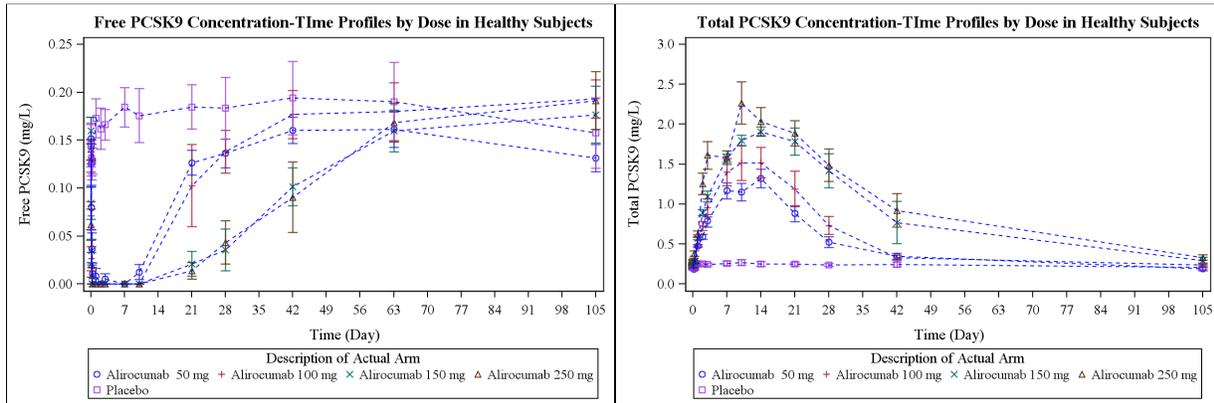


Figure 2 Mean (SE) Free (left) and total (right) PCSK9 concentration-time profiles after a single dose of 50, 100, 150 or 250 mg SC injection to healthy subjects

Free PCSK9 concentrations were zero for alirocumab concentrations above 5 mg/L, (Figure 2) which was approximately mean of C_{max} following the administration of 50 mg (Figure 1) and about 7-fold higher than IC_{50} of 0.6 mg/mL that was estimated using a simple E_{max} model with alirocumab and free PCSK9 concentrations. This indicates that 75 and 150 mg Q2W are anticipated to result in complete suppression of PCSK9. Concentrations of LDL-C reached a maximum reduction in a dose dependent manner at around 14-22 days (Figure 3).

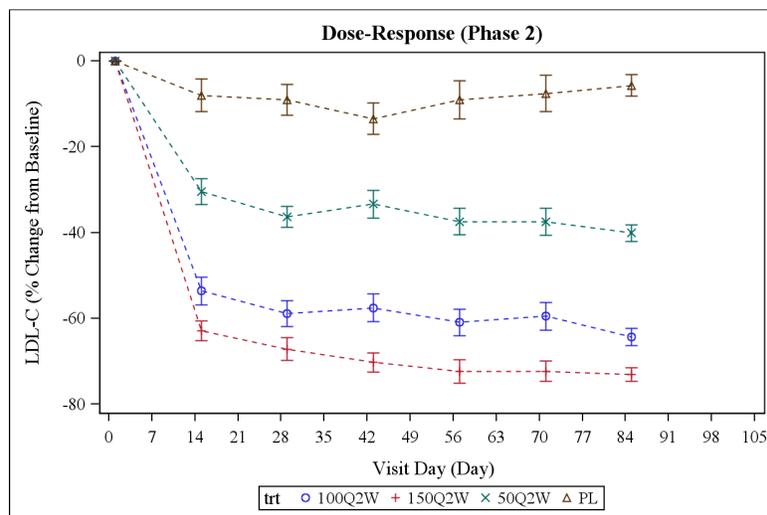


Figure 3 Mean (SE) LDL-C – time profiles by doses in non-FH subjects (Phase 2)

1.3.3 Highlights of dose/exposure-response relationship for efficacy

In dose-finding trials (Phase 2), alirocumab exposure increased in a dose dependent manner in patients and LDL-C reduction reached apparent maximum after 150 mg Q2W with mean reduction in LDL-C of 67.26% (Figure 4). In general, there were no known clinically important covariates for the exposure-efficacy relationships. Two doses were evaluated in Phase 3 trials based on the Phase 2 study results - 150 mg Q2W as it appeared to show a maximum efficacy, and 75 mg Q2W as it was estimated to show approximately 50% LDL-reduction from the sponsor's dose-response model with potential benefit(s) for some patients who may need less alirocumab.

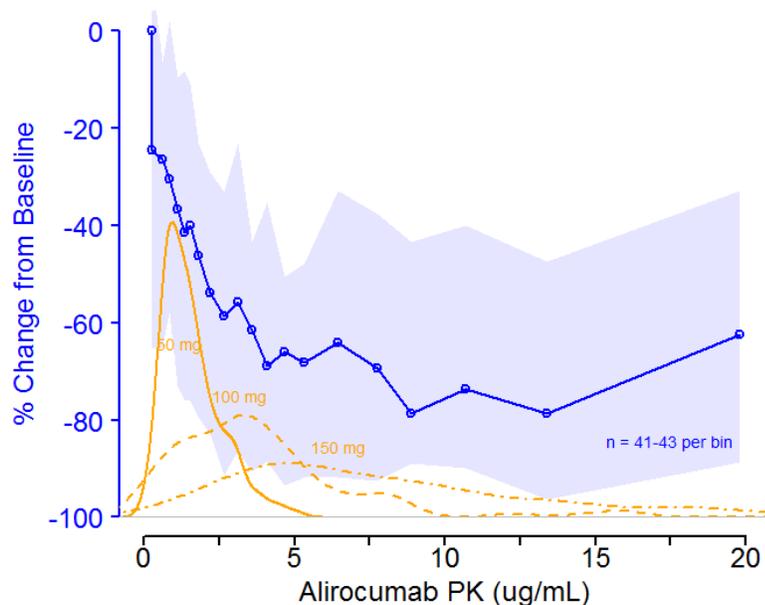


Figure 4 Exposure-response relationship for alirocumab PK concentrations and LDL-C change from baseline in study DFI11565 (Phase 2). (Mean LDL-C and the range of 5th – 95th percentiles at the corresponding median alirocumab concentrations are shown for each of 20 exposure bins by the solid line and shaded region. Solid orange lines depict the distribution of alirocumab concentrations for each respective dosing regimen.)

In eight of the ten pivotal Phase 3 trials conducted, alirocumab dose was titrated to 150 mg Q2W from 75 mg Q2W at Week 12 if their LDL-C did not reach a target (i.e., 70 mg/dL [1.81 mmol/L] or 100 mg/dL [2.59 mmol/L]) at Week 8. About 27% patients were titrated to 150 mg Q2W according to the criteria stated in the protocol and the titration showed additional efficacy benefit at Week 24 compared to that of 12 Week (Figure 5). This additional LDL-C reduction ranged from 1.5 to 23.1%, in patients who were titrated in the pivotal trials. The baseline LDL-C was significantly higher for patients who were titrated up to 150 mg Q2W compared to those patients who remained on the 75 mg Q2W dose (Figure 6). Other clinically important covariates such as body weight or age were not significantly different between two groups. Correlation of

statin co-therapy with alirocumab titration was not clear as number of patients was small in the titrated groups and LDL-C reduction was inconsistent among statins and their doses.

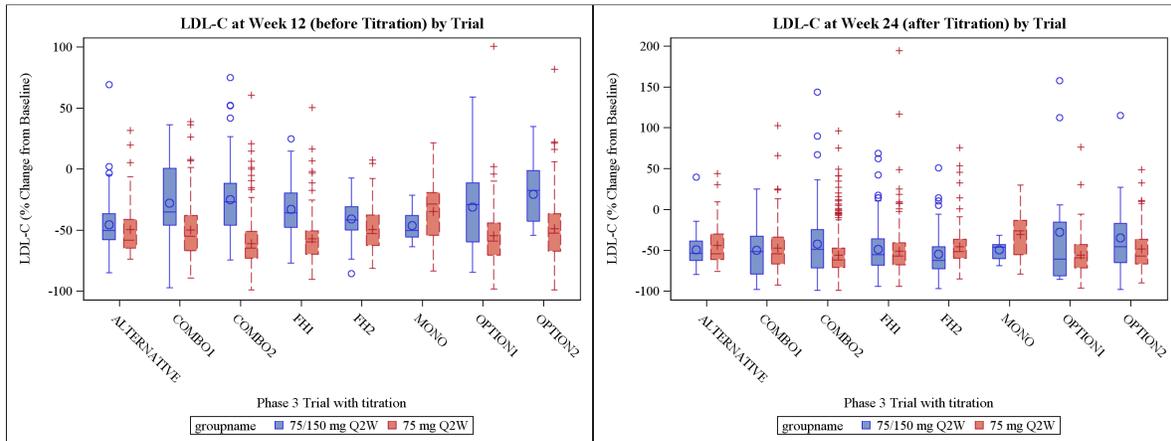


Figure 5 LDL-C (% change from baseline) at Week 12 (before titration; left) and 24 (after titration; right) by titration sub-groups across Phase 3 trials with titration. Patients either remained on 75 mg Q2W (75 mg Q2W group) or were titrated to 150 mg Q2W at Week 12 (75/150 mg Q2W group)

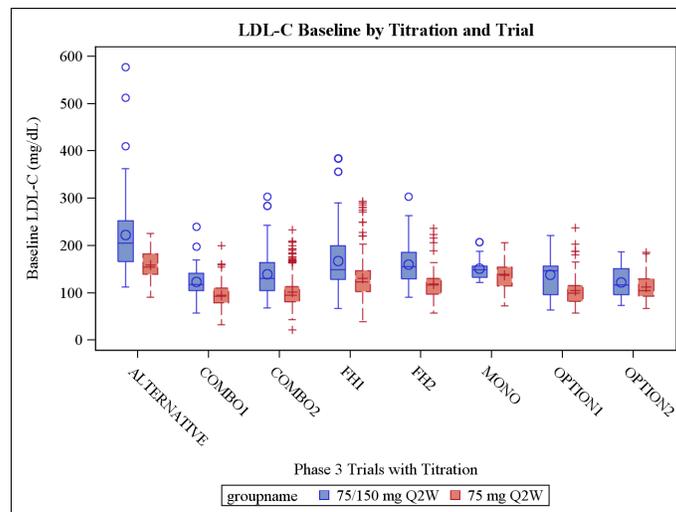


Figure 6 Baseline LDL-C by titration group among trials

2 Question-Based Review (QBR)

2.1 Brief Regulatory Background

The sponsor 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).

- BLA submitted on November 24, 2014.
- The application received the Priority Review designation as the sponsor uses the Rare Pediatric Disease Priority Review Voucher. (b) (4) and Sanofi acquired the voucher through the purchase agreement from BioMarin.
- Advisory committee meeting is scheduled for June 9, 2015.

The sponsor requested the following pediatric waivers as indicated in the Initial Pediatric Study Plan:

- (b) (4)
- a partial waiver (0 to (b) (4) years old) also requested for treatment of patients with heterozygous familial hypercholesterolemia

2.2 General Attributes

2.2.1 What are the highlights of the alirocumab drug product as they relate to clinical pharmacology review?

The final formulations were evaluated in the pivotal studies (Table 1).

Table 1 Alirocumab formulations used in clinical studies

Container Closure	Vial						Pre-filled syringe	
	Liquid	Lyophilized		Liquid		Liquid		
Formulation description								
Alirocumab concentration	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(150 mg/mL)	(150 mg/mL)	(75 mg/mL)
Histidine ^a	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	6 mM	6 mM	8 mM
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	-	-	-
Polysorbate 20	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucrose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
pH	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Clinical studies phase	Toxicology	Phase 1		Phase 2	Phase 2	Phase 2	Phase 2/3, intended commercial	Phase 2/3, intended commercial

There were significant changes with cell lines, manufacturing processes and formulations during the clinical development (Table 2). The applicant provided adequate PK/PD bridging for the

major changes (see review section 2.8.2). The final presentations of devices and formulations (Table 2) were evaluated in the pivotal clinical studies. Therefore, there was no need for a comparability study to bridge the to-be-marketed presentations to those of clinical studies.

Table 2 Overview on devices, cell lines, manufacturing processes, and formulations used in clinical studies

Device	Vial and syringe with needle gauge size 27				Pre-filled syringe with needle gauge	Pre-filled syringe with needle gauge size 27 in pre-filled pen	
Cell Line and Manufacturing process	(b) (4)				(b) (4)		
Formulation					Liquid Formulation (150 mg/mL)	Liquid Formulation (150 mg/mL, 75 mg/mL)	Liquid Formulation (150 mg/mL, 75 mg/mL)
Histidine*					6 mM	6 mM / 8 mM	6 mM (150 mg/mL), 8 mM (75 mg/mL)
(b) (4)					-	-	-
Polysorbate 20					(b) (4)		
Sucrose					(b) (4)		
pH	6.0	6.0	6.0	6.0	6.0	6.0	
Clinical studies	CL-0902 CL-0904 CL-1001 TDU12190	DFI11565 DFI11566 CL-1003 TDU12190 PKD12010	PKD12010 PKD12011	PKD12011 PKD12275	PKD12275 DFI12361	LTS11717 CL-1018 CL-1032	BDR13362 CL-1112 CL-1110 CL-1118 CL-1119 PKD12910 POP12671 EFC11568 EFC11569 EFC11570 EFC11716 EFC12492 EFC12732

2.2.2 What is the composition of to-be-marketed formulation of alirocumab?

The composition of the to-be-marketed formulation of alirocumab is shown below:

Table 3 Composition of alirocumab drug products

Component	Function / Characteristic	Reference to Quality Standard	75 mg/mL alirocumab		150 mg/mL alirocumab	
			Concentration	Amount per pre-filled pen or syringe (mg) ^a	Concentration	Amount per pre-filled pen or syringe (mg) ^a
alirocumab	active ingredient	In-house FDS specification	75 mg/mL	75.0	150 mg/mL	150.0
Histidine ^{b, c}	(b) (4)	USP, Ph. Eur., JP				
(b) (4)		Ph. Eur., JP	8 mM ^d	(b) (4)	6 mM ^d	(b) (4)
sucrose		NF, Ph. Eur., JP	(b) (4)			
Polysorbate 20		NF, Ph. Eur., JP				
Water for Injection	USP, Ph. Eur., JP					

2.2.3 What are the proposed mechanism of action and therapeutic indications?

Alirocumab is a monoclonal antibody (mAb) of human IgG1 isotype and PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor. PCSK9 controls trafficking of the hepatic LDL receptor (LDLR) as PCSK9 binding to LDLR promotes the degradation of LDLR. Inhibition of PCSK9 by alirocumab lowers LDL-C as free LDLRs are available for LDL particle clearance.

The proposed indication is, 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.

2.2.4 What are the proposed dosages and routes of administration?

The recommended alirocumab dose is 75 mg or 150 mg administered subcutaneously once every 2 weeks (Q2W).

The final presentation is supplied in (b) (4) 1 mL, pre-filled pens or single-use, 1 mL, pre-filled glass syringes. Each pre-filled pen or pre-filled syringe is designed to deliver 1 mL of 75 mg/mL or 150 mg/mL solution.

2.3 General Clinical Pharmacology

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

Alirocumab PK was evaluated in healthy subjects and patients after single or multiple doses, and its PK with 3-6 days of t_{max} , 17-22 days of effective half-life or about 2-fold accumulation generally supports the proposed dosing regimen.

Alirocumab was evaluated in patients with heterozygous familial hypercholesterolemia (heFH, see Appendix for diagnosis) and non-familial hypercholesterolemia (non-FH) (

Table 4). Patients with heFH participated in trials FH I, FH II, HIGH FH, and a stratum of LONG TERM, and heFH patients represented about 25% of the overall population. About 38% of patients had mixed dyslipidemia, which was defined as fasting baseline TG \geq 150 mg/dL [1.7 mmol/L] in addition to hypercholesterolemia. Alirocumab was evaluated in some patients who were not receiving statins (i.e., ALTERNATIVE and MONO)

Placebo-controlled trials were COMBO I, FH I, FH II, HIGH FH and LONG TERM, where a maximum tolerated statin dose and additional lipid-modifying therapy (LMT) were allowed. Ezetimibe (EZ) was the active comparator in the other 5 trials, where patients received a maximum statin dose without other LMT (COMBO II), a statin at less than maximal dose (OPTIONS I and II), or no statin (ALTERNATIVE, MONO).

Two doses, 75 and 150 mg, once every two weeks were evaluated in pivotal studies. An up-titration scheme at Week 12, if patients did not achieve a specified LDL-C target, was used in 8 trials (

Table 4). Two trials used the 150 mg Q2W dosing regimen without a titration.

Overall, design of clinical trials was reasonable to evaluate the proposed dosing regimen in the proposed patients for the proposed indication.

Table 4 Clinical studies with PK and/or PD information submitted in the NDA

Categories	Study information (e.g., study name, objectives, dose, duration or number of subjects)
Comparative BA & BE	<ul style="list-style-type: none"> • Formulation (PKD12010, 175 vs. 150 mg/mL, Dose=200 mg, n=24) • Cell line (PKD12011, C1 vs. C2, Dose=200 mg, n=24) • Formulation (PKD12275, 175 vs. 150 mg/mL + injection vol, Dose=300 mg, (n=36) • Injection sites (BDR13362, upper arm vs. thigh vs. abdomen, Dose=75 mg, n=60)
Healthy PK/PD	<ul style="list-style-type: none"> • IV (CL-0902, 0.3/1/3/6/12 mg/kg, n=40) • SAD (CL-0904, 50/100/150/250 mg, n=32) • Japanese (TDU12190, 100/150/250/300 mg, n=32)
Patient PK/PD	<ul style="list-style-type: none"> • CL-1001 (50/100/150 mg, 200 (n=10), n=62) • mono or add-on (PKD12910, 150 mg once every four weeks (Q4W), 8 weeks, n=72) • Hepatic impairment (POP12671, Dose=75 mg, n=25)
Population analyses	<ul style="list-style-type: none"> • POH0377 pop PK • POH0394 pop PK/PD (5 P1/4 P2/4 P3) • POH0500 TMDD (P1/4 P2/1 P3 (MONO))
Phase 2	<ul style="list-style-type: none"> • non-FH (add-on atorv) (DFI11565, 50/100/150 mg Q2W or 200/300 mg Q4W for 12 weeks, n=183) • heFH (add-on statin ± EZ) (CL-1003, 150 mg Q2W or 150/200/300 mg Q4W for 12 weeks, n=77) • Exploratory studies <ul style="list-style-type: none"> ○ Japanese, add-on statin (DFI12361, 50/75/150 mg Q2W for 12 weeks, n=100) ○ add-on ator 10/80 mg (DFI11566, 150 mg Q2W for 8 weeks, n=92) ○ mutation in PCSK9 gene (GOFm) / Apo B gene (LOFm) (CL-1018, 50 mg Q2W for 14 weeks, n=23, on-going)
Phase 3	<p>Trials with 150 mg Q2W dosing:</p> <ul style="list-style-type: none"> • LONG TERM (LTS11717, n=2341, 78WK)* heFH & high CV risk non-FH (add-on MTD statins± LMT vs. PL) • HIGH FH (EFC12732, n=107, 78W)* heFH (add-on to MTD statins ± LMT vs. PL); LDL-C>160 mg/dL (4.14 mmol/L) <p>Trials with 75 mg Q2W and up-titrated to 150 mg Q2W at WK12 dosing if LDL-C did not reach a goal at WK8:</p> <ul style="list-style-type: none"> • MONO (EFC11716, n=103, 24WK); mod CV risk (monotherapy vs. EZ) • FH I (EFC12492, n=486, 78WK)* / FH II (CL-1112, n=249, 78WK)* heFH (add-on to MTD statins ± LMT vs. PL) • COMBO I (EFC11568, n=316, 52WK) / COMBO II (EFC11569, n=720, 104WK)*; high CV risk non-FH (add-on to MTD statins ± LMT vs. PL or EZ) • OPTIONS I (CL-1110, n=355, 24WK) / OPTIONS II (CL-1118, n=305, 24WK) high CV risk (add-on to non-max atorv ± LMT vs. EZ/ator tit/rosu or rosu tit) • ALTERNATIVE (CL-1119, n=314, 24WK) • Statin intolerant (mono or add-on to non-statin LMT vs. EZ/atorv)

* Alirocumab trough concentrations were measured.

2.3.2 Are active moieties and response endpoints measured in pivotal clinical trials and clinical pharmacology studies appropriate to assess PK/PD parameters and exposure response relationships?

Yes: Total alirocumab trough concentrations were measured in 4 pivotal trials (i.e., LONG TERM, MONO, FH I and COMBO II) and Phase 2 trials (

Table 4). In addition, extensive alirocumab concentrations were measured in 10 Phase 1 trials in healthy subjects or patients.

Free and total PCSK9 concentrations were measured in all clinical trials. Both PCSK9 concentrations were measured at the same time-points as the alirocumab concentrations in the above mentioned trials (i.e., 10 Phase 1, 5 Phase 2, and 4 Phase 3 trials). Data of LDL-C were estimated at the time-points corresponding to PCSK9, and alirocumab concentrations if available. The primary efficacy endpoint in pivotal studies was the calculated LDL-C (see Appendix for the calculation) change from baseline at Week 24.

Therefore, available data adequately support the assessment of PK/PD and exposure-efficacy response.

2.4 Exposure/Dose - Response

2.4.1 What data from the Phase 2 studies contributed to the selection of the Phase 3 doses?

The 150 mg Q2W showed the largest decrease in LDL-C among Phase 2 dosing regimens in non-FH subjects (i.e., 50, 100, and 150 mg Q2W; 150, 200, and 300 mg Q4W add to atorvastatin) (Figure 4, Figure 7, Table 5). Although 300 mg Q4W presented the same total dose over 4 weeks as the 150 mg Q2W, the maximum treatment effect was not maintained during the dosing interval (Figure 7).

The 75 mg Q2W was selected for an alternative dose with approximately 50% LDL-C lowering from baseline based on sponsor's dose-response model.

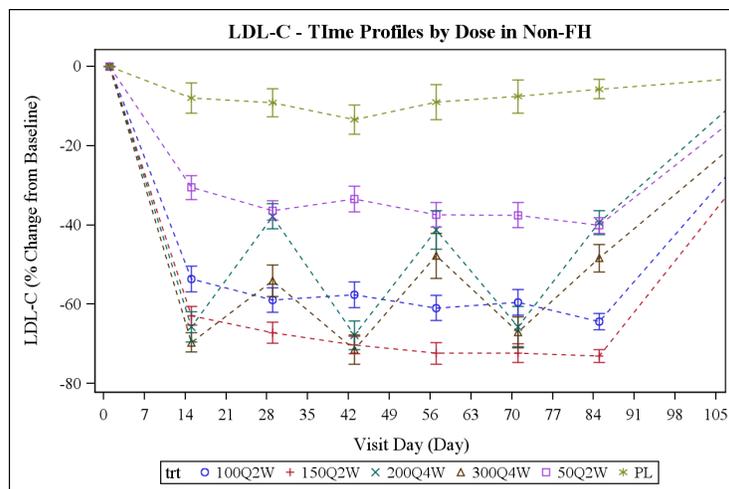


Figure 7 Mean (SE) LDL-C (% change from baseline) – time profiles by dosing regimen (Study DFI11565-Phase 2 trial)

Table 5 Percent LDL-C reduction at Week 12 (Study DFI11565)

LDL Cholesterol (mmol/L)	Placebo (n=31)	50 mg E2W (n=30)	100 mg E2W (n=31)	150 mg E2W (n=29)	200 mg E4W (n=28)	300 mg E4W (n=30)
W12-LOCF percent change from baseline						
Number	31	30	31	29	28	30
Mean (SD)	-5.70 (19.73)	-38.89 (15.24)	-64.15 (15.77)	-71.83 (13.54)	-43.54 (18.36)	-48.61 (22.85)
Median	-4.80	-39.19	-65.40	-74.19	-44.25	-53.97
Min : Max	-47.4 : 42.3	-65.1 : -8.6	-91.3 : -33.0	-91.8 : -31.9	-75.5 : -10.3	-81.8 : 8.0
LS Mean (SE)	-5.11 (3.12)	-39.62 (3.18)	-64.17 (3.11)	-72.37 (3.22)	-43.21 (3.28)	-47.74 (3.18)
LS Mean Difference (SE)		-34.50 (4.44)	-59.06 (4.39)	-67.26 (4.48)	-38.10 (4.51)	-42.62 (4.43)
95% CI		(-43.26 to -25.74)	(-67.73 to -50.39)	(-76.10 to -58.42)	(-47.00 to -29.20)	(-51.36 to -33.89)
p-value vs placebo		<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*

Note: LOCF: Last Observation Carried Forward

Least-squares (LS) means and p-values come from covariance analysis with treatment group and randomization strata of atorvastatin dose as fixed effects and baseline as covariate.

[a] p values are not adjusted for multiplicity and provided for descriptive purpose only

* indicates a statistically significant p value according to the hierarchical procedure

2.4.2 What are the characteristics of the dose/exposure-response relationships for effectiveness?

Efficacy was demonstrated for the two dosing regimens evaluated - 75 mg Q2W, with the option for titration to 150 mg at week 12, or 150 mg Q2W across different designs such as patient types or background lipid modifying therapy (LMT) (Figure 8).

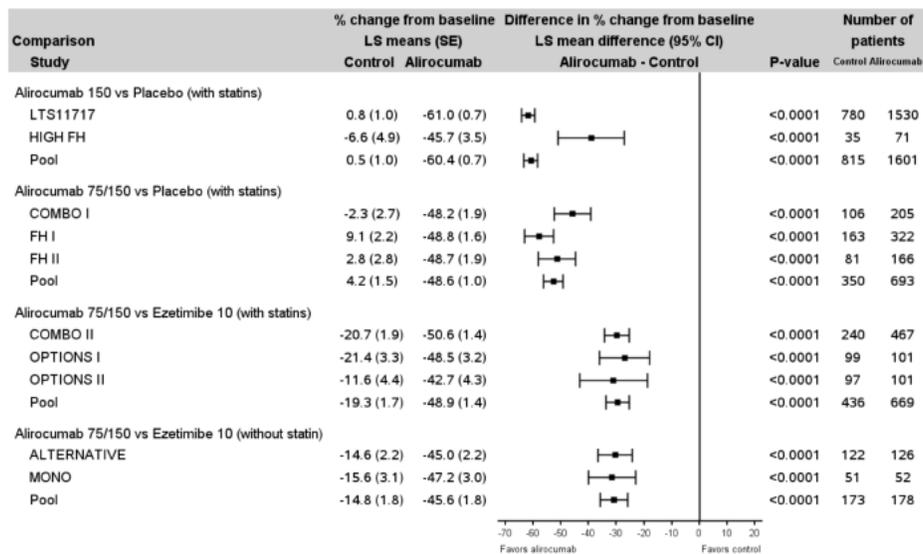


Figure 8 Mean differences between alirocumab and control for LDL-C reduction (% change from baseline) at Week 24 (Phase 3 trials)

Effect of various covariates such as age, sex, body weight, statin use as well as baseline PCSK9 levels were evaluated in the population analysis (refer details in Dr. Justin Earp’s review at section 4.4). There were no significant covariates for LDL-C reduction identified in this analysis (Figure 9).

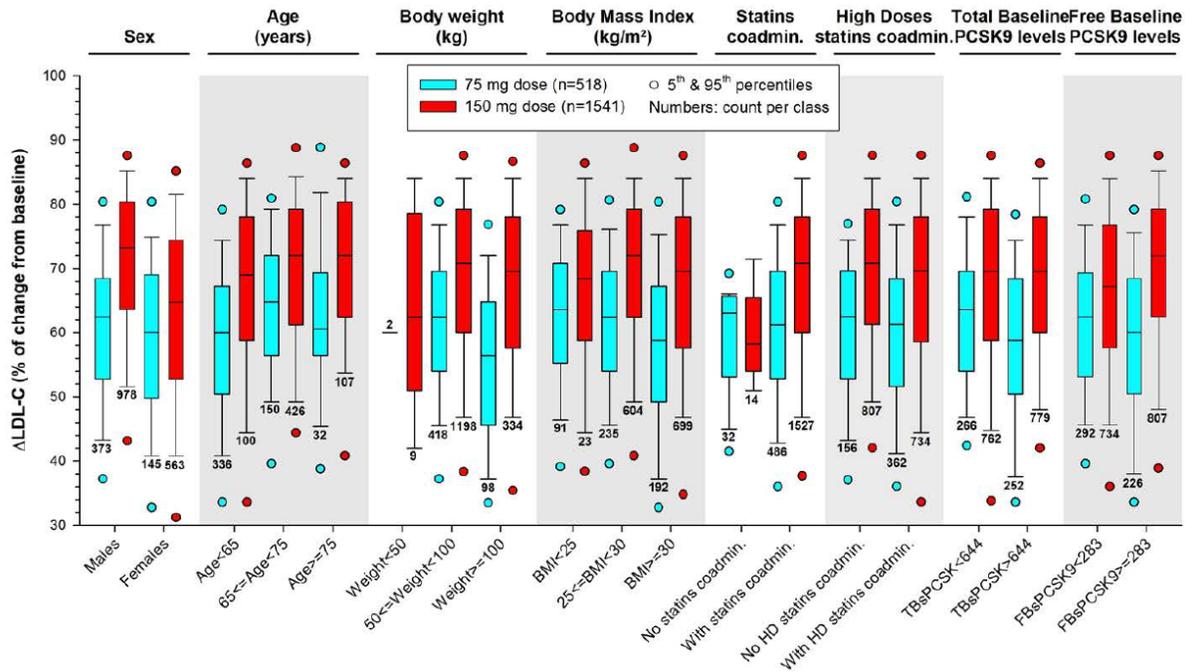


Figure 9 Relationship between LDL-C reduction and clinically significant covariates from the sponsor’s population analysis

2.4.2.1 Is there a benefit of titration of alirocumab dose from 75 mg Q2W to 150 mg Q2W?

Yes, there is a benefit of titration of alirocumab dose from 75 mg Q2W to 150 mg Q2W.

A titration scheme was evaluated in 8 of 10 pivotal trials. The starting dosing was 75 mg Q2W and the dose was up-titrated at Week 12 if patients did not achieve a specified LDL-C target (70 mg/dL at 8 weeks) in 8 trials (

Table 4, Figure 10).

About 27% patients were titrated up to 150 mg across 8 trials. Alirocumab trough concentrations were increased with increasing dose (Figure 11). There was no apparent difference in LDL-C reduction between patients who initiated and maintained after 75 or 150 mg Q2W (Figure 12, left)

The titration showed additional efficacy benefit at Week 24 compared to that of 12 Week (Figure 5, Figure 12 and Table 6), which ranged from 1.8 to 22.4% except OPTIONS1 where up-titration did not show the efficacy benefit. Further analysis to understand whether there were any demographic characteristics for the patients who showed benefit upon increasing the alirocumab dose indicated that the baseline LDL-C was significantly higher for these patients compared to those patients who remained on the 75 mg Q2W dose (Figure 6). Other clinically relevant baseline covariates (e.g., age, renal function or body weight) were not significantly different between patients who remained on 75 mg Q2W (75 mg Q2W) or were titrated up to 150 mg Q2W (75/150 mg Q2W) (Figure 13).

Correlation of statin co-therapy with alirocumab titration was not clear as patient numbers were small in the titrated groups and LDL-C reduction was inconsistent among statins and their doses.

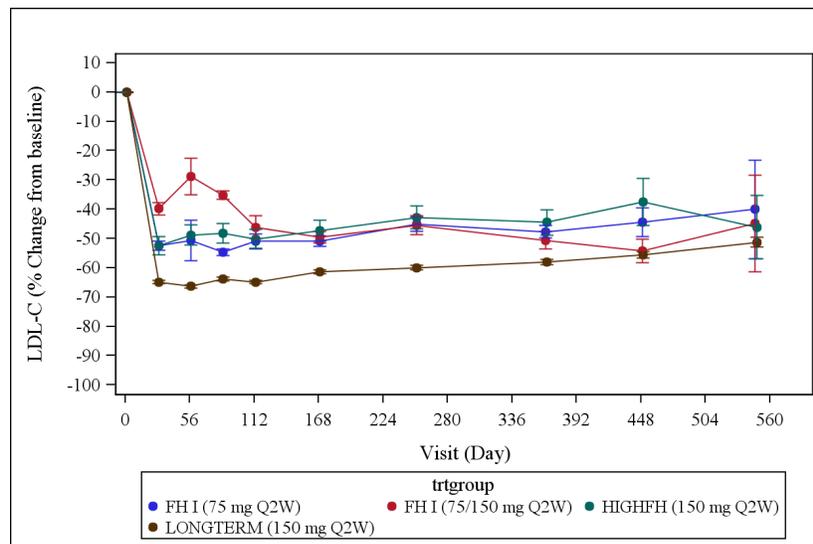


Figure 10 Mean (SE) of LDL-C (% Change from baseline) – time profiles over treatment periods in FH I (75 mg vs. 75/150 mg) compared to those of LONG TERM (150 mg) and HIGH FH (150 mg). (Credit to Dr. Bradley McEvoy)

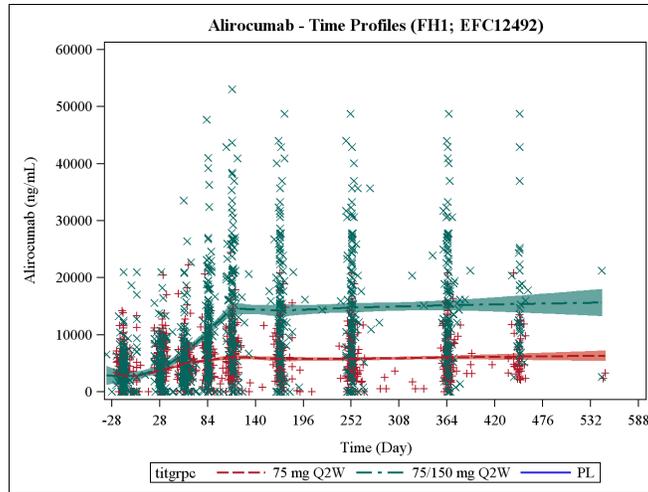


Figure 11 Alirocumab trough concentration – time profiles by titration groups (FH1) (Lowess fit with 90% CI)

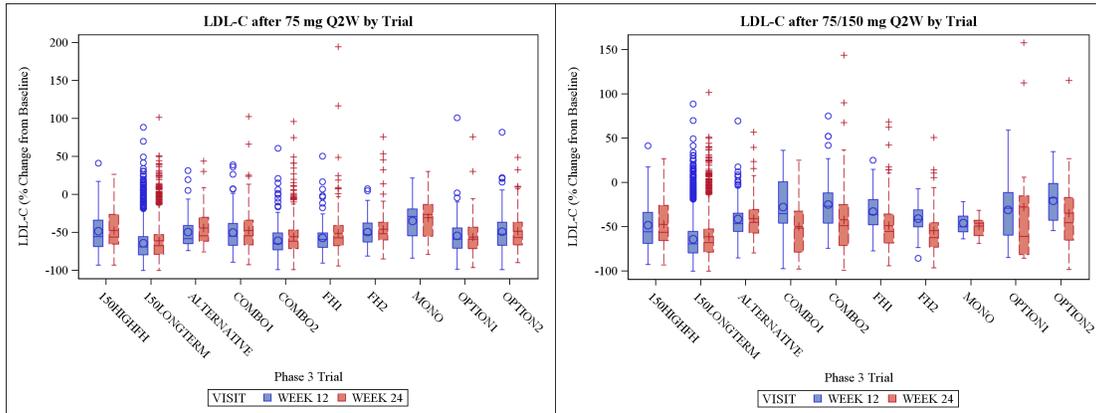


Figure 12 Reduction of LDL-C between Week 12 and 24 in patients who were titrated up to 150 mg (Right) or were not (Left).

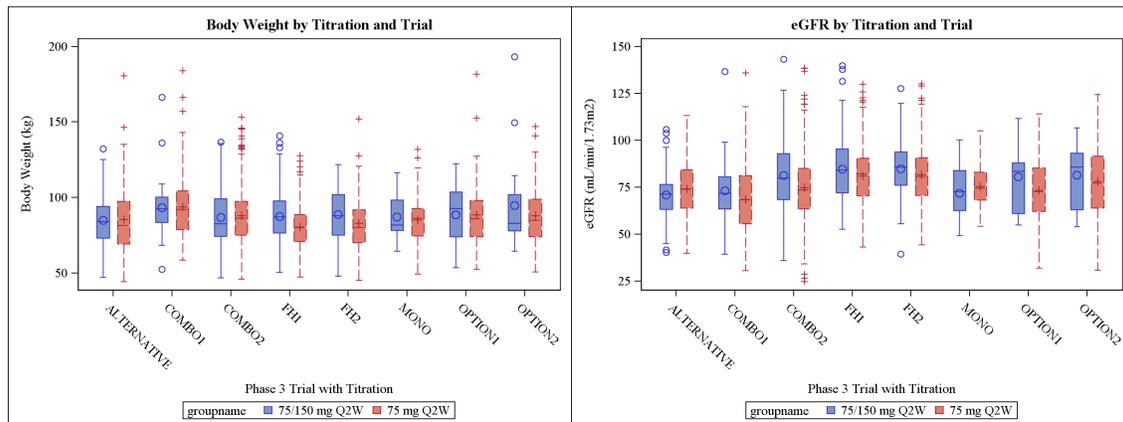


Figure 13 Body weight (left) or eGFR (right) by titration among trials

Table 6 Summary of difference in LDL-C reduction between Week 24 and Week 12 by titration among trials

Analysis Variable : Week 24 – Week 12 (% change from baseline)							
Study	Titration	N	Mean	Median	SD	Minimum	Maximum
ALTERNATIVE	75 mg Q2W	62	4.0	0.9	15.1	-30.8	54.8
	75/150 mg Q2W	62	-1.8	-1.2	15.2	-41.0	51.4
COMBO1	75 mg Q2W	166	2.0	-1.5	27.1	-70.0	165.3
	75/150 mg Q2W	31	-22.4	-29.4	27.4	-60.5	48.0
COMBO2	75 mg Q2W	474	3.7	1.8	23.5	-148.3	132.8
	75/150 mg Q2W	112	-17.9	-15.8	34.9	-104.5	81.3
FH1	75 mg Q2W	242	6.5	4.2	19.6	-45.6	134.2
	75/150 mg Q2W	183	-17.2	-17.6	25.7	-82.0	70.9
FH2	75 mg Q2W	101	4.3	2.7	23.5	-51.9	96.0
	75/150 mg Q2W	60	-14.1	-18.9	23.0	-53.7	67.0
MONO	75 mg Q2W	124	1.4	-0.7	15.9	-28.1	67.7
	75/150 mg Q2W	25	-2.5	-1.7	10.5	-21.1	18.0
OPTIONS1	75 mg Q2W	83	-1.2	-3.2	16.7	-65.7	55.2
	75/150 mg Q2W	13	3.7	-10.4	61.2	-67.5	168.8
OPTIONS2	75 mg Q2W	77	0.2	-4.9	30.0	-75.3	119.1
	75/150 mg Q2W	17	-13.0	-17.1	46.7	-108.9	132.5

2.4.3 Should alirocumab be dosed on a body-weight basis?

No, there is no need for dose adjustment in patients with lower body weight.

Patients with the lowest body weight exhibited the highest exposure of alirocumab (Table 7). Compared to a patient weighing the median weight (83 kg) the linear clearance component decreased 78% for a 50 kg individual and increased 40% for a 100 kg individual. Steady-state AUC and Cmax values are shown in Table 7 for both the 75 and 150 mg doses. These numbers are post hoc Bayesian estimates that also take into account the non-linear clearance pathway which body weight does not influence in the model. Additionally, there does not appear to be any safety reason that would suggest patients with lower body weight receive a lower dose of alirocumab. Despite the correlation of alirocumab PK with body weight, no safety events by system organ class were correlated with low body weight (See Section 4.4 for individual safety plots).

Table 7 Mean (CV%) - median (5th, 95th percentiles) of steady-state alirocumab exposure values as a function of body weight and dose.

Dose	Weight	n	AUC (mg·hr/L)	Cmax (mg/L)
75 mg	< 50 kg	3	4580 (52.7) - 3780 (2660, 7290)	- 3780 (2660, 7290) 14.9 (48.6)
75 mg	50 - <100 kg	450	2330 (42.3) - 2170 (1140, 4180)	- 2170 (1140, 4180) 8.52 (35.8)
75 mg	≥ 100 kg	101	1640 (34.8) - 1550 (747, 2690)	- 1550 (747, 2690) 6.23 (28.5)
150 mg	< 50 kg	11	12100 (33.5) - 12000 (7050, 20400)	- 12000 (7050, 20400) 40.2 (31.1)
150 mg	50 - <100 kg	1282	5450 (49.5) - 4940 (2030, 10500)	- 4940 (2030, 10500) 19.3 (43.6)
150 mg	≥ 100 kg	347	3460 (47.2) - 3150 (1440, 6620)	- 3150 (1440, 6620) 13.1 (39.6)

(Source: Applicant's Population PK Report POH0377, Tables 20 and 21)

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

There were no apparent dose related safety issues. In order to address whether there is any clinical safety concerns related to unusual LDL-C reduction, an analysis was conducted using 25 mg/dL as a potential LDL-C lower threshold. However, there was no dose related to signal in the analysis. Please, refer the clinical safety review by Dr. Mary Roberts for further details.

2.4.5 Does this drug prolong QT/QTc interval?

A through QT/QTc study was not conducted because alirocumab is a monoclonal IgG and the IgG is known to show no significant effect on QT interval.

2.5 What are the PK and PD characteristics of Alirocumab after subcutaneous administration and how do they relate to the dose?

2.5.1 Single Dose

After intravenous administration in healthy subjects (Study CL-902), AUC increase was greater than proportional to dose (Table 8), and the deviation was greater up to 3 mg/kg while dose-proportionality in AUC was apparent when the doses above 3 mg/kg. It indicates a target-mediated elimination and the pathway is saturated at doses of approximately 3 mg/kg and greater following IV administration. The mean clearance (CL), volume of distribution (V_{dss}) and terminal half-life (t_{1/2}) ranged from 3.1 to 6.2 mL/day/kg, 39 to 55 mL/kg and 4.75 to 7.97 hours, respectively (Table 8).

Table 8 Alirocumab PK parameters after intravenous administration in healthy subject (Study CL-902)

Parameter	Dose (mg/kg)									
	0.3		1		3		6		12	
	N	Mean	N	Mean	N	mean	N	Mean	N	Mean
T _{1/2} (day)	5	4.75	5	5.10	6	7.97	6	6.71	4	6.66
CL (L/day/kg)	5	0.00620	5	0.00516	6	0.00329	6	0.00314	4	0.00317
V _z (L/kg)	5	0.0422	5	0.0371	6	0.0362	6	0.0301	4	0.0304
V _{ss} (L/kg)	5	0.0388	5	0.0415	6	0.0399	6	0.0545	4	0.0545
C _{max} (mg/L)	5	8.66	5	27.0	6	100.0	6	172	4	331
AUC _{last} (mg/L*day)	5	47.9	5	194	6	939	6	1932	4	4368
MRT _{last} (day)	5	5.64	5	7.91	6	12.0	6	17.4	4	17.2

After subcutaneous administration in healthy subjects (Study CL-0904), alirocumab exposure (AUC and C_{max}) was apparently proportional to dose (50, 100, 150 and 250 mg) (Figure 14, Table 9). The mean of t_{1/2} ranged from 5.58 to 7.61 days (Table 9). Means of maximum LDL-C reduction were -40, -51, -58, and -58% for 50, 100, 150 and 250 mg, respectively.

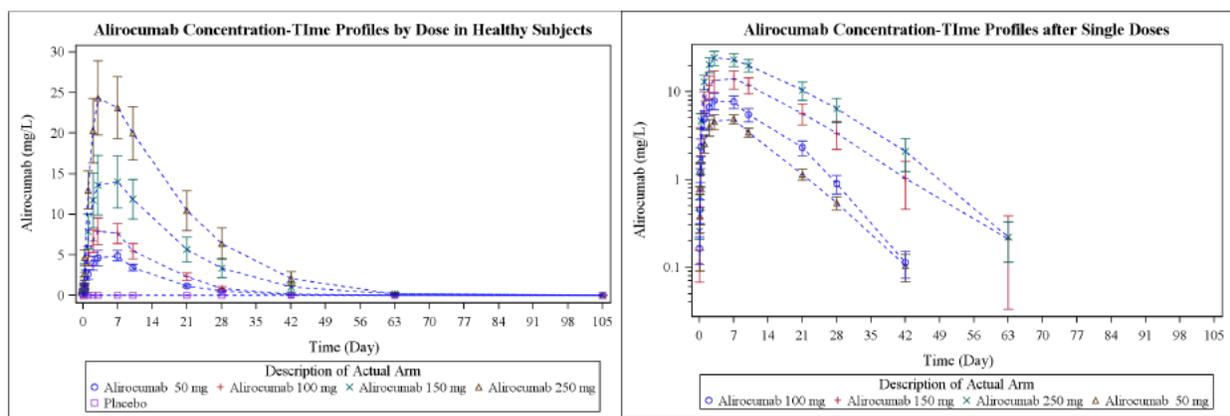


Figure 14 Mean (SE) alirocumab concentration-time profiles after single dose of 50, 100, 150 or 250 mg SC injection to healthy subjects; regular scale (left) and semi-log scale (right)

Table 9 alirocumab PK parameters after a single SC dose in healthy subjects (CL-0904)

Parameter	Dose (mg)											
	50			100			150			250		
	N	Mean	CV%	N	Mean	CV%	N	Mean	CV%	N	Mean	CV%
$t_{1/2}$ (day)	6	6.33	18.6	6	5.58	11.2	5	7.61	26.1	6	5.94	18.6
CL/F (L/day)	6	0.709	40.4	6	0.859	41.2	5	0.691	58.6	6	0.612	52.0
V _{ss} /F (L)	6	8.36	49.9	6	9.62	41.5	5	9.64	57.0	6	8.17	44.5
C _{max} (mg/L)	6	5.27	34.2	6	8.28	44.6	5	14.6	54.5	6	25.2	41.3
C _{max} /Dose (1/L)	6	0.105	34.2	6	0.0828	44.6	5	0.0973	54.5	6	0.101	41.3
T _{max} (day)	6	5.03	44.2	6	5.67	36.5	5	6.38	30.3	6	5.00	43.8
AUC _{0-∞} (day mg/L)	6	75.7	29.0	6	131	40.8	5	288	58.6	6	515	49.8
AUC _{0-t} (day mg/L)	6	78.0	29.7	6	135	42.6	5	293	58.7	6	517	49.8
AUC _{0-t} /Dose (day/L)	6	1.56	29.7	6	1.35	42.6	5	1.95	58.7	6	2.07	49.8
MRT _{0-∞} (day)	6	11.5	18.1	6	11.2	10.3	5	14.3	18.3	6	14.3	24.0

Free PCSK9 concentrations are completely depleted during the initial period of alirocumab administration (Figure 15). Total PCSK9 concentrations (free + bound to alirocumab) tend to reach the maximum at around 14 days after the alirocumab administration and its C_{max} increase was dose-dependent (Figure 15).

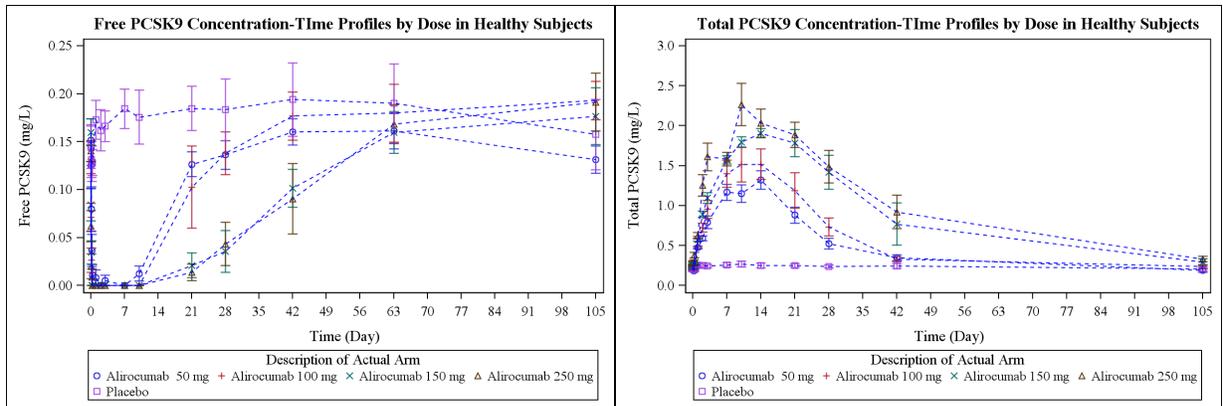


Figure 15 Mean (SE) free (left) and total (right) PCSK9 concentration-time profiles after a single dose of 50, 100, 150 or 250 mg SC injection to healthy subjects.

2.5.2 Multiple Dose

For the Q2W dosing regimen, the increase was only slightly more than dose proportional (2.86-fold increase in alirocumab concentrations for a 2-fold increase in dose). Graphically, steady-state for the Q2W dosing regimen appears to be reached after 3 or 4 doses, with a slight accumulation of less than 2-fold, as measured by concentrations in serum observed before treatment administration during repeated dosing (C_{trough}). There was no apparent accumulation of alirocumab or for free PCSK9 between 1st and 3rd dose during Q4W dosing (Figure 16).

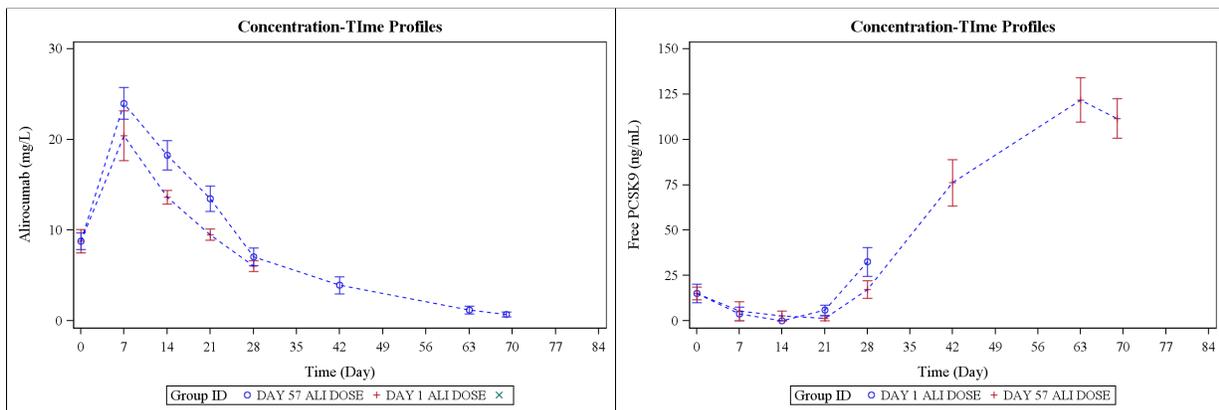


Figure 16 Mean (SE) alirocumab (left) or free PCSK9 (right) - time profiles after 150 mg Q4W in healthy subject (PKD12910; Day 1 and Day 57 doses indicate the 1st and 3rd dose, respectively)

2.5.3 Based on PK parameters, what is the degree of the linearity or nonlinearity of the dose-concentration relationship?

According to the sponsor's estimation, both target-mediated and typical IgG elimination mechanisms similarly contribute to the overall clearance in the typical C_{trough} range after 75 mg Q2W, and typical IgG elimination pathway is major clearance mechanism after 150 mg Q2W

(Figure 17). Overall, alirocumab PK is adequately characterized for the proposed dosing regimen.

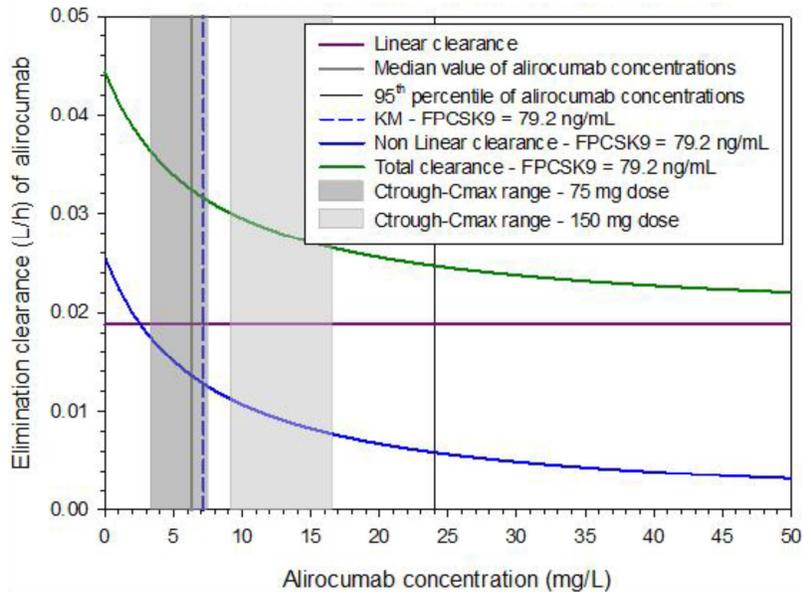


Figure 17 Dependence of total, linear and nonlinear clearance on alirocumab concentrations in patients co-administered with statins from phase 3 studies – (Study POH0377)

2.5.4 How do the pharmacokinetics and pharmacodynamics of alirocumab in patients with primary hyperlipidemia compare to that in healthy volunteers?

There was no significant difference in PK or PD in patients compared to those of patients. Alirocumab PK and PD were assessed in a randomized, placebo-controlled, ascending doses design study with and without concomitant atorvastatin in patients with primary hypercholesterolemia who were on stable doses of atorvastatin (10 to 40 mg/day for at least 28 days). (Study CL-1001) (Table 10).

Table 10 Study Cohorts (Study CL-1001)

Patient Cohort	FH Status	REGN727 Dose (mg)*	Screening LDL-C	Total number of patients (REGN727:Pbo)	Atorvastatin Dose (mg/day)
Part A					
1	FH	50	> 100 mg/dL	7 (5:2)	10-40
2	non-FH	50	> 100 mg/dL	10 (8:2)	10-40
3	FH	100	> 100 mg/dL	7 (5:2)	10-40
4	non-FH	100	> 100 mg/dL	10 (8:2)	10-40
5	FH	150	> 100 mg/dL	7 (5:2)	10-40
6	non-FH	150	> 100 mg/dL	10 (8:2)	10-40
7	non-FH	150	> 130 mg/dL	10 (8:2)	None ^a
Part B					
8	either	2	> 100 mg/dL	10 (8:2)	10-40

* Dosing: Day 1, Day 29, and Day 43 for cohorts 1-7, Day 1 and Day 29 for cohort 8

Alirocumab PK was more proportional to dose in patients with atorvastatin as seen in healthy subjects (Table 11); slopes were 1.2084 and 1.4199 for C_{max} and AUC₂₈, respectively, in a power model (PK parameter = a*Dose^{slope}). However, the proportionality assessment was confounded by atorvastatin because atorvastatin seemed to reduce alirocumab PK (

Table 12). Further, there were issues regarding patients' compliance taking atorvastatin during the trial period. There was no accumulation following the second dose after 4 weeks of the first dose.

Table 11 Alirocumab PK parameters in patients with primary hyperlipidemia + atorvastatin (Study CL-1001)

Parameter	Diagnosis / Atorvastatin / Dose (mg)															
	non-FH/Yes/050		FH/Yes/050		non-FH/Yes/100		FH/Yes/100		non-FH/Yes/150		FH/Yes/150		non-FH/Yes/200		FH/Yes*/200	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
t _{1/2} (day)	7	6.14	5	6.69	7	6.12	4	5.96	7	6.58	5	7.82	3	6.68	1	8.16
CL/F (L/day)	7	1.04	5	0.999	7	0.914	4	1.05	7	1.52	5	0.678	3	0.875	1	0.842
C _{max} (mg/L)	7	4.45	5	3.71	8	7.64	5	8.78	8	10.5	5	14.4	4	16.7	3	19.6
t _{max} (day)	7	3.74	5	5.20	8	4.76	5	4.80	8	3.80	5	5.24	4	7.45	3	6.39
AUC ₂₈ (day mg/L)	7	51.8	5	47.9	8	114	5	126	8	153	5	224	4	270	3	345
AUC _{inf} (day*mg/L)	7	54.8	5	52.4	7	115	4	98.1	7	154	5	267	3	259	1	238

*: Yes for atorvastatin co-administration

Table 12 Alirocumab PK parameters with and without atorvastatin (Study CL-1001)

Parameter	Diagnosis / Atorvastatin / Dose (mg)					
	non-FH/No/150		non-FH/Yes*/150		FH/Yes**/150	
	N	Mean	N	Mean	N	Mean
$t_{1/2}$ (day)	6	7.38	7	6.58	5	7.82
C_{max} (mg/L)	8	14.0	8	10.5	5	14.4
t_{max} (day)	8	5.65	8	3.80	5	5.24
AUC_{28} (day*mg/L)	8	252	8	153	5	224
AUC_{inf} (day*mg/L)	6	253	7	154	5	267

* non-FH patient numbers were 5 and 3 who were taking 10 and 20 mg atorvastatin, respectively.

** FH patient numbers were 1, 2 and 2 who were taking 10, 20 and 40 mg atorvastatin, respectively.

Free PCSK9 levels were higher in subjects with atorvastatin compared to those of without (Figure 18, left). It seems that there was atorvastatin dose related free PCSK9 difference within the same alirocumab dose (Figure 18, right). However, interpretation of atorvastatin dose related PCSK9 changes should be cautious because numbers of subjects were small. Changes of the primary PD variables (e.g., free and total PCSK9, LDL-C) were related to alirocumab dose. Maximum (SD) LDL-C reduction (Day 57) was -58.44 (12.75) after 150 mg without atorvastatin (n=8), and -41.67 (4.82), -55.75 (4.79) and -62.38 (4.77) for 50 (n=13), 100 (n=13), and 150 mg (n=13) with atorvastatin treatment groups, respectively.

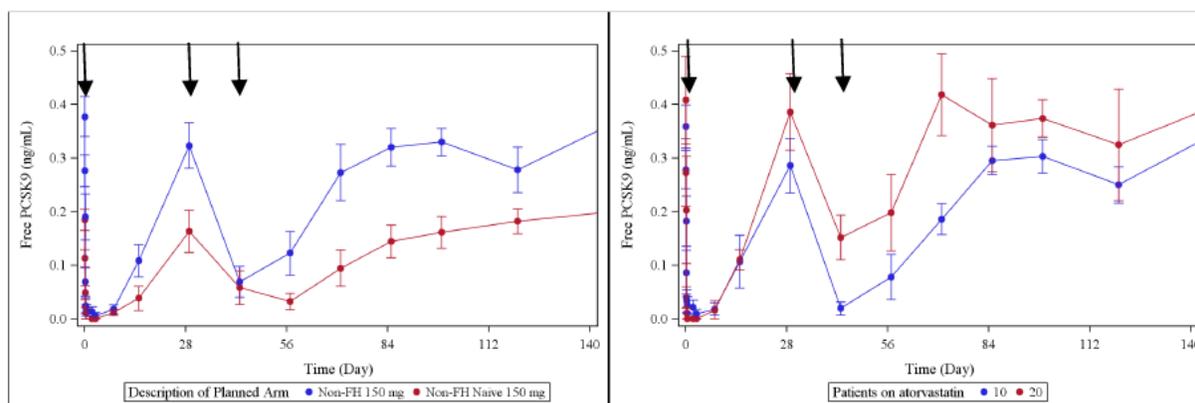


Figure 18 Mean (SE) free PCSK9 – time profiles after alirocumab 150 mg administration: left - with (blue; n=8) and without (red; n=8) atorvastatin (arrow indicates alirocumab 150 mg administration), right – atorvastatin 10 (blue; n=5) or 20 mg (red; n=3) among Non-FH 150 mg.

Free PCSK9 concentrations were completely depleted below after a single dose of 50 mg (Figure 19) as its C_{max} (5.27 mg/L, Table 9) was significantly higher than IC_{50} (0.7 mg/L in a simple Emax model).

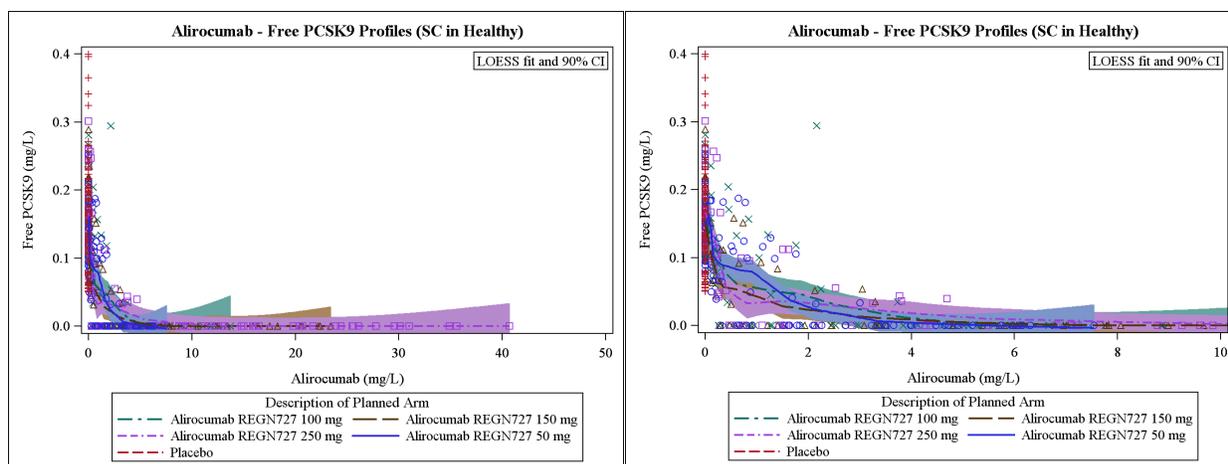


Figure 19 Free PCSK9 vs. Alirocumab concentrations after 50 to 250 mg SC in healthy subjects: full scale (left) and low concentration range (right)

2.5.5 What is the inter- and intra-subject variability of PK parameters, and what are the major causes of variability?

Variability of alirocumab PK (CV%) was about 30-31% and 28-39% for C_{max} and AUC, respectively, at different injection sites, and it indicates PK variability is not highly variable, which is defined by 30% intra-subject variability. The main intrinsic sources of PK variability identified in patients were age, body weight and free PCSK9, but they had a moderate effect with less than 1.6-fold change. Statins are known extrinsic factor for alirocumab PK.

2.6 Intrinsic Factors

2.6.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of age, race, sex and body weight on alirocumab exposure and efficacy was evaluated using population analysis (refer details in Dr. Justin Earp's review at section 4.4). There were no significant covariates for both alirocumab PK and efficacy.

There were no significant covariates for the alirocumab exposure in the sponsor's population analysis (Figure 20) other than body weight and statins, which were known. There was an apparent correlation between creatinine clearance (CL_{cr}; mL/min) and exposure. Body weight may attribute to this apparent correlation because there was significant correlation between body weight and CL_{cr} (Figure 21) as indicated by Cockcroft-Gault equation.

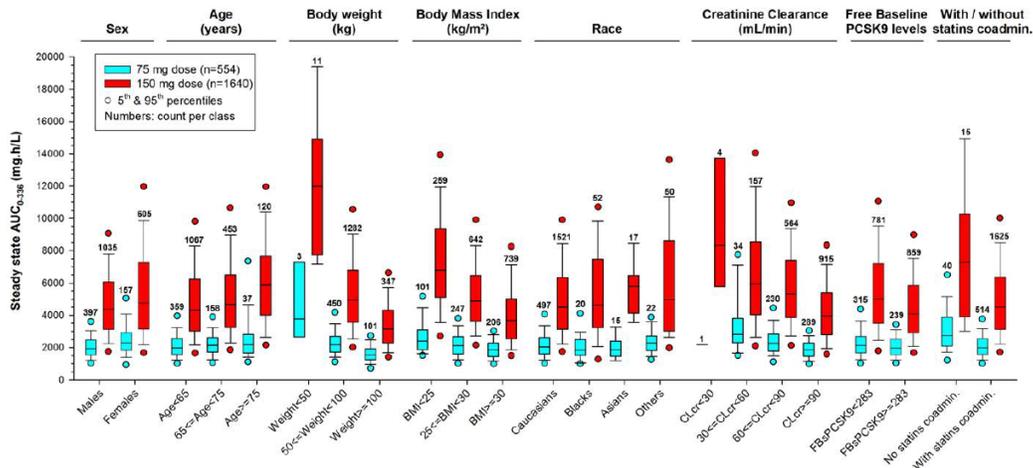


Figure 20 Relationship between steady state AUC and clinically significant covariates from the sponsor's population analysis

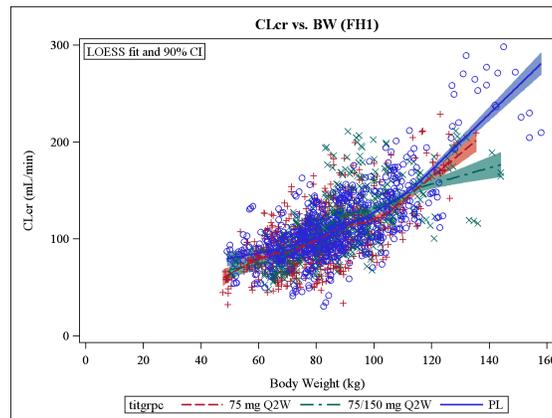


Figure 21 Relationship between CLcr (mL/min) vs. body weight (kg) (data from FH1)

There were no difference in age, gender, body weight between 75 mg Q2W and 75/150 mg Q2W dosing groups in pivotal trials, and it indicates that these covariates may not be significant factor for the titration.

There were sufficient elderly in trials where titration scheme was used; median age of subjects who received alirocumab for at least 24 weeks in the pivotal trials with titration design was 60 years with ages ranging between 21 to 88 years, and subjects with older than 65 and 76 years were 25% and 5% of subjects with alirocumab administration in pivotal studies with titration design (n=1817), respectively.

2.6.2 Does renal function affect alirocumab pharmacokinetics and pharmacodynamics?

A dedicated study to address the effect of renal function on alirocumab PK was not conducted because the renal elimination is considered not a major clearance mechanism for mAb. However, the effect of renal function was evaluated using the creatinine clearance (CLcr, mL/min) (Figure 18 and 19) or estimated glomerular filtration rate (eGFR, mL/min/m²) to determine whether they

are the significant covariate for alirocumab PK. There was no apparent correlation between eGFR and alirocumab PK (Figure 22).

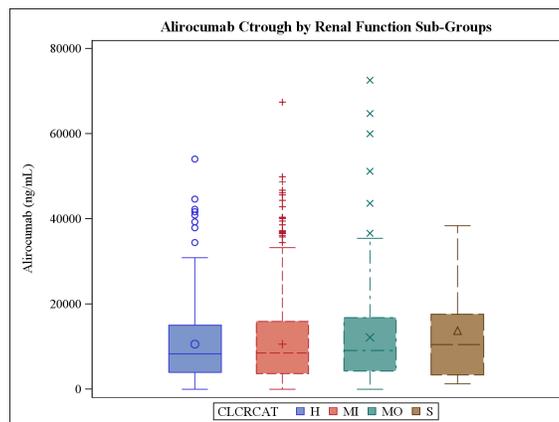


Figure 22 Alirocumab Ctrough Concentrations by renal function sub-groups based on eGFR

(CLCRCAT indicates the renal function subgroups by eGFR; n=3743 subjects with available data of both alirocumab Ctrough concentration and eGFR at Week 24 in Phase 3 studies; n=780, 2388, 561, and 14 for healthy (H), mild (MI), moderate (MO) and severe (S) sub-groups, respectively)

2.6.3 Does hepatic function affect alirocumab pharmacokinetics and pharmacodynamics?

The effect of hepatic function on alirocumab PK was assessed after 75 mg administration to subjects with mild (n=8) or moderate (n=8) hepatic impairment compared to that in healthy subjects (n=8).

PK parameters tended to be lower with hepatic impairment compared to those of healthy (Figure 23, Table 13 and Table 14). Although there was no statically significant difference among sub-groups (p=0.3256), means of baseline free PCSK9 concentrations in mild and moderate impairment sub-groups were lower than that of healthy subjects (Figure 24). Both free and total PCSK9 concentrations after alirocumab administration tended to be higher in the hepatic impaired subjects compared to those of healthy (Figure 25). The PCSK9 data indicate that PCSK9 change is not the main factor for alirocumab PK change with the hepatic impairment. The maximum LDL-C reduction in the hepatic impaired subjects (33.20% and 35.83% in mild and moderate hepatic impairment sub-groups, respectively), was somewhat less than that of healthy subjects (45.42%).

Overall, the PK and PD difference was not significant for a dose adjustment.

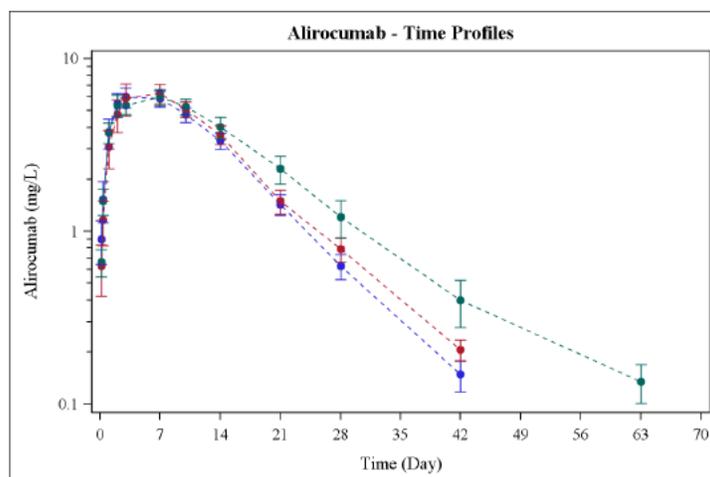


Figure 23 Mean (SE) alirocumab – time profiles (Study POP12671)
(green for control, blue for mild, and red for moderate sub-groups)

Table 13 Mean±SD (Geometric Mean) [CV%] serum PK parameters of alirocumab after 75 mg administration (Study POP12671)

	normal	mild H.I.	moderate H.I.
N	8	8	8
C _{max} (mg/l)	6.47 ± 1.52 (6.32) [23.5]	6.23 ± 2.09 (5.90) [33.6]	6.45 ± 3.16 (5.81) [49.1]
t _{1/2z} (day)	6.06 ± 1.89 (5.80) [31.2]	5.95 ± 0.977 (5.87) [16.4]	5.64 ± 1.95 (5.30) [34.5]
AUC _{0-D28} (mg•day/l)	104 ± 29.3 (99.7) [28.1]	92.1 ± 27.9 (88.3) [30.3]	88.7 ± 27.5 (84.6) [31.0]
AUC (mg•day/l)	119 ± 38.1 (112) [32.1]	98.4 ± 29.5 (94.3) [30.0]	95.2 ± 26.2 (91.8) [27.5]

Table 14 Point estimates of GM Ratio with 90% CI (Study POP12671)

Parameter	Comparison	Estimate	90% CI
C _{max}	Mild vs. Control	1.04	(0.74 to 1.48)
	Moderate vs. Control	0.90	(0.64 to 1.26)
AUC	Mild vs. Control	0.91	(0.66 to 1.24)
	Moderate vs. Control	0.82	(0.61 to 1.12)

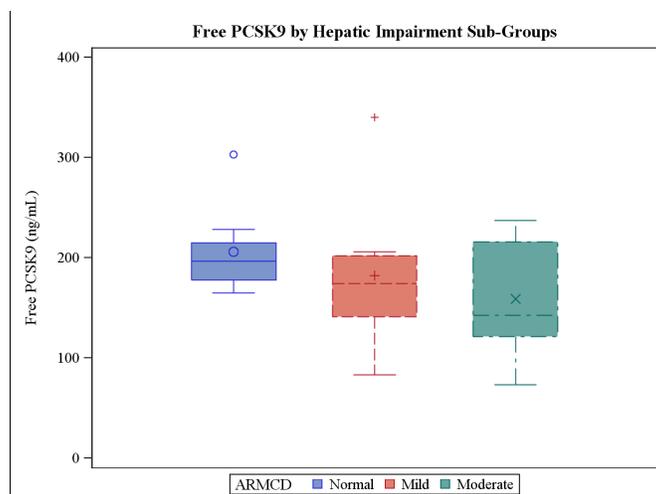


Figure 24 Free PCSK9 at baseline by hepatic impairment sub-groups (Study POP12671)

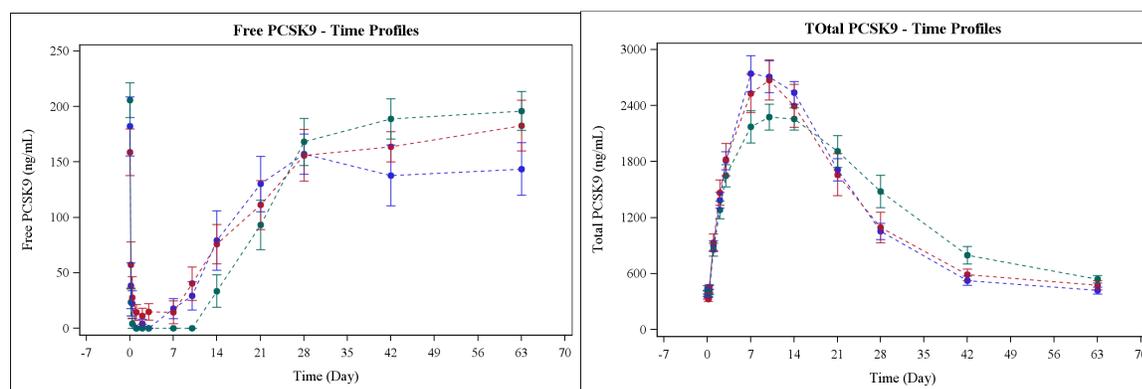


Figure 25 Mean (SE) free (left) and total (right) PCSK9 concentration – time profiles (Study POP12671) (green for control, blue for mild, and red for moderate sub-groups)

2.6.4 What is the incidence of formation of antibodies to alirocumab during and after the treatment?

The treatment-emergent positive anti-drug antibody (ADA) was reported in 4.8% of alirocumab-treated patients compared to 0.6% in the control group across Phase 3 trials (Table 15). Patients with neutralizing antibodies (Nab) were reported in 1.2%, and 10 patients (0.3%) had 2 or more Nab positive samples. In general, patients with ADA were not sufficient to do a formal analysis on the impact of it on PK or exposure-analysis. However, there were no apparent trends that PK was significantly different in the ADA positive patients compared to others.

Most of the ADA positive samples exhibited low titers (≤ 240). A few patients (21/3033) had an ADA response with maximum titers above 240 (and up to 3840), but ADA responses in these patients were either negative or exhibiting lower titers at subsequent visits.

Table 15 Summary of pre-existing and treatment-emergent anti-alirocumab antibodies positive response (Anti-alirocumab antibody population) – Global pool phase 3

Anti-alirocumab antibody (ADA) n (%)	Control (N=1708)	Alirocumab (N=3033)
Pre-existing ADA ^a [n/N1 (%)]	18/1708 (1.1%)	41/3033 (1.4%)
Treatment-emergent ADA positive response ^b [n/N1 (%)]	10/1708 (0.6%)	147/3033 (4.8%)
Persistent ^c [n/N2 (%)]	2/10 (20.0%)	39/147 (26.5%)
Transient ^d [n/N2 (%)]	2/10 (20.0%)	93/147 (63.3%)
Indeterminate ^e [n/N2 (%)]	6/10 (60.0%)	15/147 (10.2%)
Time to onset of treatment-emergent ADA response (week)		
Number	10	147
Mean (SD)	43.74 (23.74)	13.00 (10.99)
Median	52.14	12.14
Q1 : Q3	24.14 : 64.29	4.29 : 12.43
Min : Max	11.3 : 78.1	1.6 : 63.7

Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)

Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

Note: The denominator N1 (respectively N2) within a treatment group is the number of patients who had ADA assessed (respectively positive ADA status)

a patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period

b patients with no positive ADA response at baseline but with any positive response in the post-baseline period OR with a positive ADA response at baseline and at least 4-fold increase in titer in the post-baseline period

c at least 2 consecutive post-baseline samples with positive ADA separated by at least a 12-week period

d any treatment-emergent positive ADA response neither considered persistent nor indeterminate; *e* ADA positive response present only at the last sampling time point

In phase 3 studies, a treatment-emergent positive ADA response was defined as either no ADA positive response at baseline but with any positive response in the post-baseline period (up to follow-up visit) or a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (up to follow-up visit).

For treatment-emergent positive ADA, the duration of the ADA response was classified as 1) persistent when an ADA positive response was detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period, 2) indeterminate when ADA was present only at the last sampling time point, and 3) transient for a response that is neither considered persistent nor indeterminate.

Across phase 1 studies, positive low titer responses in the ADA assay were observed in a few subjects at baseline, suggesting a pre-existing reactivity. At the 75 mg dose and 150 mg dose, 22.4% and 16.7% of the subjects were positive in the ADA assay, respectively (Table 16). Most of the ADA positive samples exhibited a low titer response (≤ 240), except for a few subjects who presented titers up to 1920. However, titers diminished over time and were not associated with any specific safety findings.

Table 16 ADA status summary (safety population) in healthy subjects after SC single dose

Anti-alirocumab antibody (ADA) n (%)	Placebo (N=16)	Alirocumab						
		50 mg (N=6)	75 mg (N=85)	100 mg (N=12)	150 mg (N=12)	200 mg (N=48)	250 mg (N=12)	300 mg (N=42)
Pre-existing ADA ^a [n/N1 (%)]	0/16	1/6 (16.7%)	0/85	0/12	0/12	0/48	0/12	1/42 (2.4%)
Treatment-emergent ADA positive response ^b [n/N1 (%)]	0/16	0/6	19/85 (22.4%)	2/12 (16.7%)	2/12 (16.7%)	12/48 (25.0%)	4/12 (33.3%)	8/42 (19.0%)
Time to onset (week)								
Number	0	0	19	2	2	12	4	8
Mean (SD)			5.70 (2.50)	6.64 (3.54)	4.64 (2.12)	8.17 (2.57)	5.39 (2.87)	8.02 (3.77)
Median			4.14	6.64	4.64	9.14	4.64	9.07
Q1 : Q3			4.14 : 8.00	4.14 : 9.14	3.14 : 6.14	6.64 : 9.14	3.14 : 7.64	4.21 : 9.14
Min : Max			4.1 : 12.1	4.1 : 9.1	3.1 : 6.1	4.1 : 12.1	3.1 : 9.1	4.1 : 15.1

Pool of R727-CL-0904, PKD12010, PKD12011, PKD12275, TDU12190, BDR13362, POP12671 (including healthy subjects and hepatic impaired function patients) studies

a Subjects with positive ADA status at baseline with less than 4-fold versus baseline increase in titer values up to end-of-study visit

b Subjects with no positive ADA status at baseline but with any positive response in post-baseline period OR with positive ADA status at baseline and at least 4-fold increase in titer values up to end-of-study visit Note: the denominator N1 within a treatment group is the number of subjects who had ADA assessed

2.7 Extrinsic Factors

2.7.1 Drug-Drug Interactions

Pharmacokinetic drug interaction potentials of alirocumab were not formally evaluated because conventional mechanisms (e.g., CYP, conjugation enzymes or transporters) are known to be not involved in the IgG elimination.

2.7.1.1 What is the effect of lipid-modifying therapy on the pharmacokinetics and pharmacodynamics of Alirocumab?

Lipid-modifying therapy (LMT) may affect alirocumab PK and/or PD because it is known to increase PCSK9 concentration, which can result in inducing target-mediated elimination of alirocumab. However, there are no dose adjustments based on drug interaction.

2.7.1.1.1 Drug interaction between alirocumab and atorvastatin

The interaction potential between alirocumab and atorvastatin was evaluated as part of Study CL-1001. Alirocumab was administered to subjects with stable atorvastatin dose between 10 and 40 mg/day (see Section 2.5.4 for additional study design information). Atorvastatin reduced alirocumab PK with up to 40% lower exposure: mean ratios (with/without) were 0.89 and 0.61 for C_{max} and AUC, respectively (Table 12). However, the assessment of atorvastatin effect on alirocumab PK was not reliable because atorvastatin doses were not adequately maintained in some patients with during the study.

There was no apparent effect of alirocumab on atorvastatin PK (Table 17) as there was no alirocumab dose related atorvastatin PK changes, and some atorvastatin PK changes were similar to those of alirocumab placebo treatment group.

Table 17 Atorvastatin PK parameter ratios (Day 43 to Day -1) by alirocumab doses (Study CL-1001)

Atorvastatin PK Parameter	Alirocumab Dose (mg)	N	Mean	SD	SE	CV%	Min	Median	Max
C_{max} (ng/mL)	0	13	1.54	0.722	0.200	46.8	0.852	1.20	3.24
	50	12	1.05	0.492	0.142	46.8	0.412	1.01	1.96
	100	13	1.50	0.753	0.209	50.3	0.514	1.24	2.94
	150	13	1.54	1.02	0.282	66.1	0.712	1.24	4.57
	200	7	1.27	1.000	0.378	78.5	0.540	1.12	3.45
AUC_{last} (ng/mL*day)	0	13	1.22	0.369	0.102	30.3	0.672	1.10	1.82
	50	12	1.13	0.470	0.136	41.7	0.617	1.08	2.33
	100	13	1.32	0.384	0.106	29.0	0.672	1.31	1.87
	150	13	1.27	0.461	0.128	36.5	0.709	1.19	2.43
	200	7	1.24	0.755	0.285	60.9	0.726	1.05	2.92

2.7.1.1.2 Drug interaction between alirocumab and fenofibrate or ezitimibe

The effect of ezitimibe or fenofibrate on alirocumab PK and PD was evaluated in a randomized, 3 parallel groups study design following 150 mg Q4W administration for a total of 3 doses + placebo, EZ 10 mg/day or fenofibrate 160 mg/day to health subjects (Study PKD12910, see the study design in Figure 26).

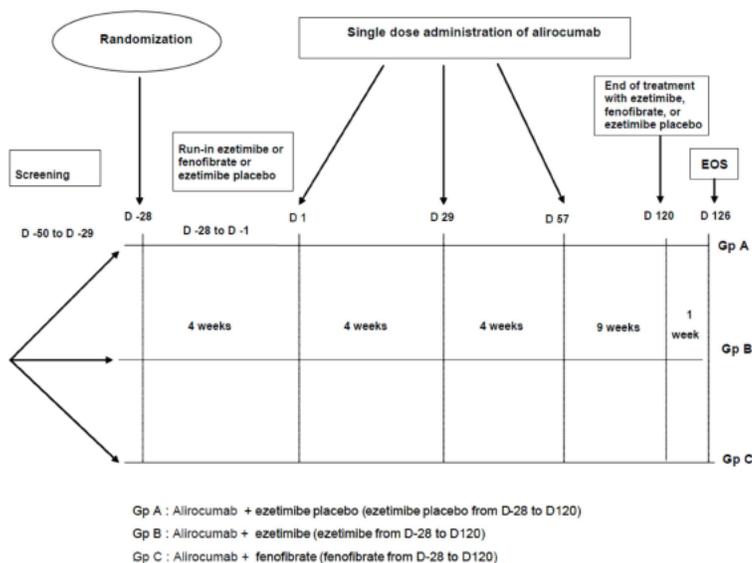


Figure 26 Study design (PKD12910)

Alirocumab C_{max} values were similar (point estimate=0.92), while AUC_{0-D28} was lower (point estimate=0.71) in the alirocumab coadministered with ezetimibe (10 mg/day) treatment group, compared to those of alirocumab alone.

However, alirocumab PK parameters were significantly reduced by the coadministration of fenofibrate (160 mg/day); point estimates of 0.71 (90% CI = 0.60 to 0.84) and 0.64 (90% CI = 0.53 to 0.77) for C_{max} and AUC_{0-D28}, respectively (Table 18,

Table 19).

There was no apparent effect of alirocumab on trough concentrations of total and unconjugated ezetimibe, or fenofibrate. However, trough concentration data may not adequately assess the absence of DDI potential.

Free PCSK9 concentrations were higher with fenofibrate treatment in the same study (Figure 27). The study results support that PCSK9 induction is correlated with the alirocumab exposure decrease. However, mean maximum LDL-C reduction with coadministration with ezetimibe (56.6%) or fenofibrate (54.3%) was greater than that of alirocumab alone (47.4%). Although there was the effect of fenofibrate on alirocumab PK through PCSK9 changes, the clinical significance of these changes are not clear based on the above observed LDL-C reduction. Further, LDL-C results in the study may not be adequate to assess the clinical consequence as the number of subjects per treatment was small and the study was conducted in healthy subjects, where PK/PD interactions maybe different from those in patients.

Table 18 Mean±SD (Geometric Mean) [CV%] serum PK parameters of alirocumab 150 mg Q4W in healthy subjects (PKD12910)

		Alirocumab+PL	Alirocumab+Feno	Alirocumab+EZ
	N	24	24	24
after the 1st administration				
	C _{max} (mg/L)	20.4 ± 13.5 (18.3) [66.2]	14.6 ± 4.06 (14.1) [27.7]	18.2 ± 5.68 (17.3) [31.2]
	t _{max} (day)	7.00 (6.96-7.01)	7.00 (6.97-7.01)	7.00 (6.97-7.19)
	AUC _{0-D28} (mg•day/L)	326 ± 125 (306) [38.4]	233 ± 75.5 (221) [32.3]	274 ± 87.4 (261) [31.8]
after the 3 rd administration				
	C _{max} (mg/L)	24.3 ± 8.61 (22.9) [35.5]	17.1 ± 6.66 (15.9) [38.9]	21.9 ± 8.91 (20.5) [40.6]
	t _{max} (day)	7.00 (0-7.00)	7.00 (6.97-7.99)	7.00 (6.96-13.98)
	t _{1/2z} (day)	8.76 ± 3.12 (8.37) [35.7]	7.07 ± 1.68 (6.88) [23.8]	6.72 ± 1.56 (6.55) [23.3]
	AUC _{0-D28} (mg•day/L)	445 ± 189 (414) [42.3]	292 ± 138 (259) [47.3]	364 ± 143 (338) [39.4]

Table 19 Point estimates of GM Ratio with 90% CI (PKD12910)

	Parameter	Comparison	Estimate	90% CI
after the 1 st administration	C _{max}	Alirocumab+EZ vs. alirocumab+PL	0.97	(0.82 to 1.14)
		Alirocumab+Feno vs. alirocumab+PL	0.78	(0.66 to 0.92)
	AUC _{0-D28}	Alirocumab+EZ vs. alirocumab+PL	0.88	(0.76 to 1.03)
		Alirocumab+Feno vs. alirocumab+PL	0.74	(0.64 to 0.86)
after the 3 rd administration	C _{max}	Alirocumab+EZ vs. alirocumab+PL	0.92	(0.78-1.09)
		Alirocumab+Feno vs. alirocumab+PL	0.71	(0.60-0.84)
	AUC _{0-D28}	Alirocumab+EZ vs. alirocumab+PL	0.85	(0.70-1.03)
		Alirocumab+Feno vs. alirocumab+PL	0.64	(0.53-0.77)

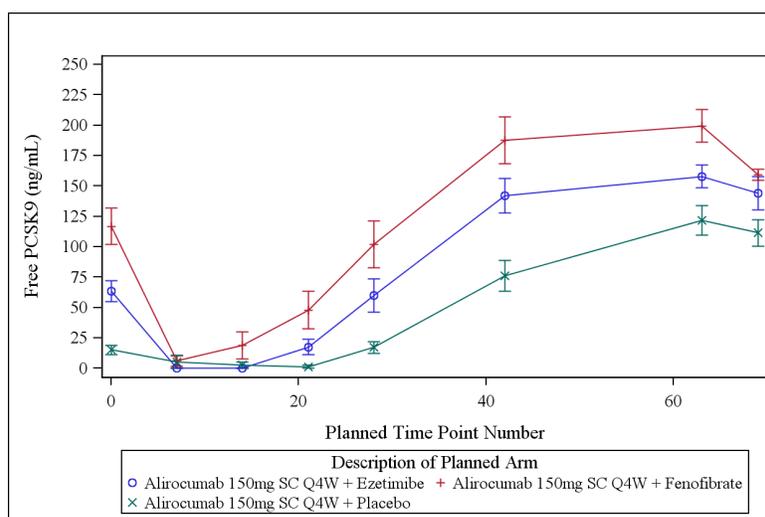


Figure 27 Mean (SE) free PCSK9 – time profiles by treatment arms

2.8 General Biopharmaceutics

2.8.1 Is there any significant difference in PK and PD after administration at different injection sites?

To evaluate impact of injection sites, relative BA of alirocumab and PD (PCSK9 and LDL-C) were assessed after 75 mg administration at abdomen, upper arm or thigh in a randomized, 3-parallel group study with healthy subjects (Study BDR13362).

Alirocumab PK parameters and statistical analysis on the relative bioavailability are summarized in Table 20 and Table 21. Relative BA of alirocumab administration after injection to upper arm or thigh tended to be lower than that of abdomen (e.g., AUC mean ratios were 0.92 and 0.84 for upper arm and thigh to abdomen, respectively, Table 21). However, maximum mean LDL-C reduction (% change from baseline) was not significantly different between thigh (45.55%) and

abdomen injection (48.38%) (Day 15) and LDL-C reduction tended to be less after upper arm injection (37.47%) compared to those of others. Overall, relative BA difference among injection sites does not appear to translate to any clinically significant changes in LDL-C.

Table 20 Mean±SD (Geometric Mean) [CV%] serum PK parameters of alirocumab after 75 mg administration at different injection sites (Study BDR13362)

	Abdomen	Upper arm	Thigh
N	20	20	20
C _{max} (mg/L)	8.14 ± 2.51 (7.79) [30.7]	6.77 ± 2.02 (6.45) [29.8]	7.13 ± 2.21 (6.77) [31.0]
t _{max} (day)	2.96 (1.95-7.01)	6.95 (1.96-10.08)	3.06 (2.15-8.11)
t _{1/2z} (day)	6.03 ± 1.11 (5.93) [18.5]	6.66 ± 0.967 (6.59) [14.5]	5.77 ± 1.59 (5.59) [27.6]
AUC _{0-D28} (mg·day/L)	119 ± 32.2 (115) [27.0]	116 ± 35.3 (111) [30.5]	105 ± 36.6 (98.7) [34.8]
AUC (mg·day/L)	129 ± 35.7 (124) [27.8]	130 ± 42.0 (124) [32.3]	115 ± 44.4 (107) [38.7]

Table 21 Point estimates of GM Ratio with 90% CI for injection sites (Study BDR13362)

Parameter	Comparison	Estimate	90% CI
C _{max}	Upper arm vs. Abdomen	0.79	(0.66 to 0.93)
	Upper arm vs. Thigh	0.90	(0.76 to 1.06)
	Thigh vs. Abdomen	0.88	(0.74 to 1.04)
AUC	Upper arm vs. Abdomen	0.92	(0.78 to 1.09)
	Upper arm vs. Thigh	1.09	(0.93 to 1.28)
	Thigh vs. Abdomen	0.84	(0.72 to 0.99)

2.8.2 Is comparability established between the to-be-marked and clinical trial presentations?

The to-be-marketed presentations including formulations (75 and 150 mg/mL) and device (pre-filled syringe and pre-filled pen) have been used in the pivotal clinical trials (Table 2). Therefore, there is no need for comparability studies with the to-be-marketed product. PK cross-study comparison was made to evaluate the comparability between two final presentations in clinical trials as a supplemental data, and it seems PK was comparable (Table 22).

Table 22 Alirocumab steady state exposures at 150 mg by drug presentation after 150 mg Q2W repeated administration to patients from phase 3 studies- Study POH0377 (Mean (CV%) [Median])

Drug presentation	Alirocumab 150 mg		
	N	C _{max} (mg/L)	AUC ₀₋₃₆₆ (mg/L*h)
Prefilled syringe	1437	18.0 (46.6%) [16.5]	5030 (53.6%) [4470]
Prefilled pen	203	19.0 (46.7%) [18.3]	5390 (52.4%) [5030]

There were some major process and formulation changes during the development, and the sponsor evaluated the comparability for those changes (Figure 28). Clinical pharmacology bridging information is summarized in review section of 2.9.3 and 2.9.4.



Figure 28 Summary of major changes in process or formulations, and clinical pharmacology bridging



Table 24 Point estimates of GM Ratio (175 vs. 150 mg/mL) with 90% CI (PKD12011)

Parameter	Estimate	90% CI
C _{max}	1.02	(0.85 to 1.22)
AUC	1.00	(0.81 to 1.23)

2.8.4 Is comparability evaluated between formulations?

To evaluate the comparability of two formulations (i.e., 175 mg/mL, which was used in early clinical development vs. 150 mg/mL, which was used in pivotal trials), relative BA of alirocumab was assessed after 200 mg injection in a randomized parallel design study with healthy subjects (Study PKD12010).

Relative BA of alirocumab was similar between two formulations (Table 25 and Table 26). Maximum means of LDL-C reduction (% change from baseline) (Day 15) were also similar between two formulations: 53.6 and 57.0% for 150 and 175 mg/mL, respectively.

Table 25 Mean±SD (Geometric Mean) [CV%] serum PK parameters of alirocumab after 200 mg administration (PKD12010)

	150 mg/mL (1.33 mL)	175 mg/mL (1.14 mL)
N	12	12
C _{max} (mg/L)	18.9 ± 5.70 (18.0) [30.2]	18.2 ± 4.40 (17.7) [24.2]
t _{max} (day)	3.00 (2.00-10.00)	5.00 (3.00-10.00)
t _{1/2z} (day)	6.88 ± 1.09 (6.80) [15.9]	6.14 ± 0.899 (6.08) [14.6]
AUC _{0-D28} (mg•day/L)	288 ± 82.7 (276) [28.7]	282 ± 72.3 (274) [25.6]
AUC (mg•day/L)	334 ± 98.4 (319) [29.5]	315 ± 83.9 (305) [26.6]

Table 26 Point estimates of GM Ratio (175 vs. 150 mg/mL) with 90% CI (PKD12010)

Parameter	Estimate	90% CI
C _{max}	0.95	(0.79 to 1.15)
AUC	0.92	(0.78 to 1.09)

The sponsor also evaluated injection tolerability of a single injection of 2 mL (150 mg/mL), a single injection of 1.71 mL, compared to that of two injection of 1 mL (150 mg/mL) in a randomized, parallel design study with healthy subjects (PKD12275).

The injection sites were to be at least 10 cm apart. Injection was to be completed in 10 and 20 seconds for twice (1 mL twice) and single (2 mL or 1.71 mL), respectively. The entire duration of all injections for each subject was to be within 2 minutes.

Alirocumab PK was similar among different injection volumes or times for the same dose (Table 27 and Table 28). Means of the maximum LDL-C reduction were 59.5% (Day 15) for 150 mg/mL single injection, 54.3% (Day 22) for 175 mg/mL single injection, and 52.6% (Day 15) for 150 mg/mL twice injection. Data indicate that there is no apparent difference in PK and PD among treatment groups.

Table 27 Mean±SD (Geometric Mean) [CV%] serum PK parameters of alirocumab after 300 mg administration (PKD12275)

	150 mg/mL single injection (2 mL)	175 mg/mL single injection (1.71 mL)	150 mg/mL twice injection (2mL)
N	12	12	12
C _{max} (mg/L)	29.6 ± 8.75 (28.2) [29.6]	32.7 ± 9.09 (31.3) [27.8]	29.9 ± 7.76 (28.9) [25.9]
t _{max} (day)	5.00 (3.00-14.00)	5.00 (2.00-10.00)	5.00 (2.00-7.00)
t _{1/2z} (day)	7.38 ± 1.33 (7.26) [18.0]	7.37 ± 1.51 (7.20) [20.5]	8.81 ± 5.50 (7.94) [62.4]
AUC _{0-D28} (mg·day/L)	476 ± 145 (456) [30.5]	562 ± 163 (541) [29.0]	538 ± 146 (515) [27.2]
AUC (mg·day/L)	580 ± 209 (547) [36.1]	713 ± 259 (677) [36.3]	678 ± 231 (637) [34.1]

Table 28 Point estimates of GM Ratio with 90% CI (PKD12275)

Parameter	Comparison	Estimate	90% CI
C _{max}	150 mg/mL (single) vs. 150 mg/mL (twice)	0.98	(0.79 to 1.21)
	175 mg/mL (single) vs. 150 mg/mL (twice)	1.07	(0.86 to 1.33)
AUC	150 mg/mL (single) vs. 150 mg/mL (twice)	0.80	(0.78 to 1.09)
	175 mg/mL (single) vs. 150 mg/mL (twice)	0.96	(0.76 to 1.22)

2.9 Analytical

2.9.1 Are the analytical methods for Alirocumab, LDL-C and PCSK9 appropriately validated?

Yes, analytical methods were validated. In addition, the long-term stability of total alirocumab in frozen human serum was demonstrated up to (b) (4) months when stored at (b) (4). The followings are excerpt from the sponsor's validation reports:

- Enzyme-linked immunosorbent assay to measure total alirocumab

Alirocumab has 2 binding sites and can form complexes with 1 or 2 molecules of PCSK9. The lower limit of quantification (LLOQ) of total alirocumab was 78 ng/mL in undiluted human serum and 1.56 ng/mL in the assay (2% human serum) (R727-CL-1001-SA-02V1).

The assay employs a (b) (4)



- Enzyme-linked immunosorbent assay to measure free PCSK9

The LLOQ was 15.6 ng/mL in the assay (50% human serum) and 31.2 ng/mL in undiluted human serum.



- Enzyme-linked immunosorbent assay to measure total PCSK9

The LLOQ was 1.56 ng/mL in the assay (2% human serum) and 78 ng/mL in undiluted human serum.

Bioanalytical studies associated with clinical trials are summarized in

Table 29.

Table 29 Summary of bioanalytical studies associated with clinical pharmacology studies and efficacy/safety clinical studies

Study method (Report Location)	Analyte	Matrix (MRD)	Calibration curve	LLOQ/Sensitivity (ng/mL)	Accuracy (%AR)	Within-run precision (CV%)	Between-run precision (CV%)	Clinical studies
REGN727-AV-09104-SA-01V2 (5 3 1 4)	alirocumab	human serum (1:50)	78 – 5000 ng/mL	78 ng/mL	99 – 113	≤10	≤9	CL-0902, CL-0904, CL-1001, TDU12190, CL-1003, DFI11565, DFI11566
REGN727-AV-11051-SA-01V3 (5 3 1 4)	alirocumab	human serum (1:50)	78 – 5000 ng/mL	78 ng/mL	92-101	≤5	≤12	PKD12910, POP12671, CL-1018, DFI12361, MONO, FH I, COMBO II, LONG TERM
REGN727-AV-10014-SA-01V3 (5 3 1 4)	Anti-alirocumab antibodies	human serum (1:30)	NA	1 7 ng/mL	NA	NA	NA	CL-0902, CL-0904, CL-1001, POP12671, PKD12910, TDU12190, CL-1003, CL-1018, DFI11565, DFI11566, DFI12361
				5 6 ng/mL				MONO, FH I, FH II, HIGH FH, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, LONG TERM, CL1032
REGN727-AV-10014-SA-01V3	Anti-alirocumab neutralizing antibodies	human serum (1:150)	NA	470 ng/mL	NjA	NA	NA	DFI12361, MONO, FH I, FH II, HIGH FH, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, LONG TERM
REGN727-AV-11081-SA-01V1 (5 3 1 4)	Total PCSK9	human serum (1:50)	156 – 10000 ng/mL	156 ng/mL	86-108	≤8	≤9	CL-0902, CL-0904, CL-1001, PKD12910, POP12671, TDU12190, CL-1003, CL-1018, DFI11565, DFI11566, MONO, FH I, COMBO II, LONG TERM
REGN727-AV-11084-SA-01V2 (5 3 1 4)	Free PCSK9	human serum (1:2)	31 2 – 2000 ng/mL	31 2 ng/mL	95 - 107	≤9	≤15	CL-0902, CL-0904, CL-1001, PKD12910, POP12671, TDU12190, CL-1003, CL-1018, DFI11565, DFI11566, MONO, FH I, COMBO II, LONG TERM

LLOQ: lower limit of quantification; AR: analyte recovery; CV: coefficient of variation

3 Labeling Comments (Preliminary)

The following are the labeling recommendations relevant to clinical pharmacology for BLA 125522. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

12.3 Pharmacokinetics

Absorption

After subcutaneous (SC) administration of ~~(b) (4)~~ mg to ~~(b) (4)~~ 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- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose. Steady state was reached after 2 to 3 doses with an accumulation ratio 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.

Elimination

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 ~~(b) (4)~~ at subcutaneous doses of 75 mg Q2W or 150 mg Q2W. ~~(b) (4)~~

~~(b) (4)~~

~~(b) (4)~~

Specific Populations

A population PK analysis was conducted on data from 2799 subjects (b) (4). Age, gender, race, and creatinine clearance were found not to influence alirocumab PK (b) (4). No dose adjustments are recommended for these demographics.

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Renal Impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of alirocumab. (b) (4)

No data are available in patients with severe renal impairment.

Hepatic Impairment

(b) (4) administration of a single 75 mg SC dose, alirocumab pharmacokinetic profiles in subjects with mild and moderate hepatic impairment were similar (b) (4) to subjects with normal hepatic function.

No data are available in patients with severe hepatic impairment.

(b) (4)

(b) (4)

(b) (4)

4 APPENDIX

4.1 OCP Filing Memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	125559	SDN	
Applicant	Sanofi/Regeneron	Submission Date	11/24/2014
Generic Name	Alirocumab	Brand Name	PRALUENT
Drug Class	Proprotein Convertase Subtilisin Kexin Type 9 inhibitor		
Indication	Treatment of hypercholesterolemia and mixed dyslipidemia		
Dosage Regimen	75 or 150 mg every 2 weeks		
Dosage Form	75 mg/mL and 150 mg/mL pre-filled pens or pre-filled syringe	Route of Administration	Subcutaneous injection
OCP Division	DCP2	OND Division	DMEP
OCP Review Team	Primary Reviewer(s)		Secondary Reviewer/ Team Leader
Division	Sang Chung		Jayabharathi Vaidyanathan
Pharmacometrics	Sang Chung / Justin Earp		Nitin Mehrotra
Genomics			
Review Classification	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	1/7/2015	74-Day Letter Date	2/6/2015
Review Due Date	2/24/2015	PDUFA Goal Date	7/24/2015
Application Fileability			
Is the Clinical Pharmacology section of the application fileable? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes list comment(s)			
Is there a need for clinical trial(s) inspection? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes explain			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies		<input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Clinical Pharmacology Summary <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No Bioanalytical and Analytical Methods <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No Labeling <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	
In Vitro Studies			
<input type="checkbox"/> Metabolism Characterization			
<input type="checkbox"/> Transporter Characterization			
<input type="checkbox"/> Distribution			
<input type="checkbox"/> Drug-Drug Interaction			

In Vivo Studies				
Biopharmaceutics				
<input type="checkbox"/> Absolute Bioavailability	1	CL-0902 vs CL-0904		
<input type="checkbox"/> Relative Bioavailability				
<input type="checkbox"/> Bioequivalence	4	Comparability studies; PKD12010, PKD12011, PKD12275, BDR13362		
<input type="checkbox"/> Food Effect		Subcutaneous injection		
<input type="checkbox"/> Other				
Human Pharmacokinetics				
Healthy Subjects	<input checked="" type="checkbox"/> Single Dose	3	CL-0902 / CL-0904 / TDU12190	
	<input type="checkbox"/> Multiple Dose			
Patients	<input checked="" type="checkbox"/> Single Dose	1	CL-1001 (Part A)	
	<input checked="" type="checkbox"/> Multiple Dose	2	PKD12910 / CL-1001 (Part B)	
<input type="checkbox"/> Mass Balance Study				
<input type="checkbox"/> Other (e.g. dose proportionality)				
Intrinsic Factors				
<input type="checkbox"/> Race		Pop PK		
<input type="checkbox"/> Sex		Pop PK		
<input type="checkbox"/> Geriatrics		Pop PK		
<input type="checkbox"/> Pediatrics				
<input checked="" type="checkbox"/> Hepatic Impairment	1	POP12671		
<input type="checkbox"/> Renal Impairment		Pop PK		
<input checked="" type="checkbox"/> Genetics	1	CL-1018		
Extrinsic Factors				
<input checked="" type="checkbox"/> Effects on Primary Drug		CL-1001 (atorvastatin on alirocumab)		
<input checked="" type="checkbox"/> Effects of Primary Drug		CL-1001 (alirocumab on atorvastatin or rosuvastatin) CL-1003 (rosuvastatin); DDI was evaluated as part of PK/PD.		
Pharmacodynamics				
<input checked="" type="checkbox"/> Healthy Subjects		All clinical pharmacology studies in healthy subjects (PCSK9)		
<input checked="" type="checkbox"/> Patients		All clinical pharmacology studies in patients (PCSK9)		
Pharmacokinetics/Pharmacodynamics				
<input checked="" type="checkbox"/> Healthy Subjects		All clinical pharmacology studies in healthy subjects (PCSK9)		
<input checked="" type="checkbox"/> Patients		All clinical pharmacology studies in healthy subjects (PCSK9)		
<input type="checkbox"/> QT		No TQT study as this is a biologic		
Pharmacometrics				
<input checked="" type="checkbox"/> Population Pharmacokinetics	2	POH0377/POH0500		
<input type="checkbox"/> Exposure-Efficacy	1	POH0394		
<input type="checkbox"/> Exposure-Safety				
Total Number of Studies		In Vitro	In Vivo	28
Total Number of Studies to be Reviewed				28

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	TBM presentations have been evaluated in P3 studies.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Filing Memo

Alirocumab is a humanized monoclonal antibody (IgG1) that binds to the proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 controls trafficking of the hepatic low-density lipoprotein receptors (LDLRs). Alirocumab lowers LDL-C levels by inhibiting the binding of PCSK9 to LDLRs.

The proposed indication is for the treatment of primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus. The applicant requested the priority review designation using Priority Review Voucher. There was a navigation session of the submission formats with the application dated on 12/10/2014.

Pediatric Study Plan was submitted to IND 105574 and finalized through the Agency's letter dated on 7/25/2014 as follows:

- [REDACTED] (b) (4)
- A partial waiver for treatment of patients with heterozygous familial hypercholesterolemia in the following age categories:
[REDACTED] (b) (4)
- A deferral of the initiation of the clinical studies in [REDACTED] (b) (4) until safety and efficacy in adults has been established.

Clinical trials supporting the clinical pharmacology information are summarized in Table 1.

Key review questions are identified as follows:

- Proposed dosing is 75 or 150 mg Q2W
 - Should dose titration be considered for labeling?
 - Are there any baseline patients characteristics to be considered for the decision on choosing the dosing regimen (75 or 150 mg Q2Q)?
 - Are there any baseline patient characteristics that correlate to whether patients respond to the treatment?
- Is there a need of dose adjustment for patients with renal impairment?
- Is there any effect of immunogenicity on PK, efficacy and/or safety?

Tentative review timelines are as follows:

- Filing/Planning Meeting: 1/7/2015
- File / RTF Application: 1/23/2015
- Issue 74-day letter: 2/6/2015
- OCP Scoping meeting: 2/9/2015
- MCM: 2/25/2015
- Label planning meeting: 3/15/2015
- Labeling/PMRs/REMS: 3/15-4/15/2015
- Primary Review in DARRTS: 4/24/2015

- Secondary Review: ~5/1/2015
- Pre-LCM: 5/14/2015
- Briefing package due to application: ~5/21/2015
- LCM with applicant: ~5/28/2015
- AC: 6/9//2015
- WU: 6/17/2015
- Div Director: 6/24-7/10/2015
- ODE review: 7/10-7/24/2015
- PDUFA Date: 7/24/2015

Table 1 Summary of clinical trials supporting clinical pharmacology information

Comparative BA & BE	P2 (5 completed + 2 on-going)	P3 (5 completed + on-going*) (n=5296; 3188 to alirocumab)
<ul style="list-style-type: none"> • PKD12010 (n=24) 175 vs. 150 mg/mL • PKD12011 (n=24) Cell line C1 vs. C2 • PKD12275 (n=36) 175 vs. 150 mg/mL • BDR13362 (n=60) 75 mg/mL inj sites 	<ul style="list-style-type: none"> • DFI11565 (n=183, 12WK) 50/100/150 mg Q2W 200/300 mg Q4W non-FH (add-on atorv 10/20/40) • CL-1003 (n=77, 12WK) 150 mg Q2W 150/200/300 mg Q4W heFH (add-on statin ± EZ) • DFI12361 (n=100, 12WK) 50/75/150 mg Q2W Japan, add-on atorv • DFI11566 (n=92, 8WK) 150 mg Q2W add-on ator 10/80 mg • CL-1018 (n=23, 14WK) 50 mg Q2W mutation in PCSK9 gene / Apo B gene 	<p>150 mg Q2W</p> <ul style="list-style-type: none"> • LTS11717 (LONG TERM, n=2341, 78WK)* heFH & high CV risk non-FH (add-on MTD statins± LMT vs. PL) • EFC12732 (HIGH FH, n=107, 78W)* heFH (add-on to MTD statins ± LMT vs. PL) LDL-C>160 mg/dL (4.14 mmol/L) <p>75 mg Q2W, up-titrated 150 mg Q2W at WK12</p> <ul style="list-style-type: none"> • EFC11716 (MONO, n=103, 24WK) mod CV risk (monotherapy vs. EZ) • EFC12492 (FH I, n=486, 78WK)* heFH (add-on to MTD statins ± LMT vs. PL) • CL-1112 (FH II, n=249, 78WK)* heFH (add-on to MTD statins ± LMT vs. PL) • EFC11568 (COMBO I, n=316, 52WK) high CV risk non-FH (add-on to MTD statins ± LMT vs. PL) • EFC11569 (COMBO II, n=720, 104WK)* High CV risk non-FH (add-on to MTD statins vs. EZ) • CL-1110 (OPTIONS I, n=355, 24WK) high CV risk (add-on to non-max atorv ± LMT vs. EZ/ator tit/rosu) • CL-1118 (OPTIONS II, n=305, 24WK) high CV risk (add-on to non-max atorv ± LMT vs. EZ/rosu tit) • CL-1119 (ALTERNATIVE, n=314, 24WK) Statin intolerant (mono or add-on to non-statin LMT vs. EZ/atorv)
Healthy PK/PD		
<ul style="list-style-type: none"> • CL-0902 (n=40) IV: 0.3/1/3/6/12 mg/kg • CL-0904 (n=32) 50/100/150/250 mg • TDU12190 (n=32) 100/150/250/300 mg 		
Patient PK/PD		
<ul style="list-style-type: none"> • CL-1001 (n=62) 50/100/150 200 (n=10) • PKD12910 (n=72) 150 mg Q4W, 8 wk (mono or add-on) • POP12671 (n=25) 75 mg, hepatic (n=17) 		
Population analyses		
<ul style="list-style-type: none"> • POH0377 pop PK • POH0394 pop PK/PD 5 P1/4 P2/4 P3 • POH0500 TMDD P1/4 P2/1 P3 (MONO) 		

4.2 Heterozygous Familial Hypercholesterolemia

Diagnosis of heFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the Simon Broome criteria with a criteria for definite FH or the WHO/Dutch Lipid Network criteria with a score >8 points.

4.2.1 Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia

Definite familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/l (260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

PLUS

- Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR

- DNA-based evidence of an LDL receptor mutation or familial defective apo B-100

Possible familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/l (260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

And at least one of the following:

- Family history of MI below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
- Family history of raised cholesterols >7.5 mmol/l (290 mg/dL) in adult 1st or 2nd degree relative or >6.7 mmol/l (260 mg/dL) in child or sibling under 16 years of age.

4.2.2 WHO Criteria (Dutch Lipid Network clinical criteria) for diagnosis of Heterozygous Familial Hypercholesterolemia (heFH)

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia			
Family history			
a	First degree relative with known premature (men <55 yrs, women <60 yrs) coronary and vascular disease.		1
b	First degree relative with known LDL-cholesterol >95th percentile for age and sex.		
and/or			
a	First degree relative with tendon xanthomata and/or arcus cornealis.		2
b	Children below 18 yrs. with LDL-cholesterol >95th percentile for age and sex.		
Clinical history			
a	Patient has premature (men <55 yrs, women <60 yrs) coronary artery disease		2
b	Patient has premature (men <55 yrs, women <60 yrs) cerebral or peripheral vascular disease.		1
Physical examination			
a	Tendon xanthomata		6
b	Arcus cornealis below the age of 45 yrs.		4
Laboratory analysis			
		mmol/L	mg/dL
a	LDL-cholesterol	>8.5	>330
b	LDL-cholesterol	6.5-8.4	250-329
c	LDL-cholesterol	5.0-6.4	190-249
d	LDL-cholesterol	4.0-4.9	155-189
(HDL-cholesterol and triglycerides are normal)			
DNA-analysis			
a	Functional mutation low-density lipoprotein receptor gene present		8
Diagnosis of heFH is:			
Certain When			>8 points
Probable When			6-8 points
Possible When			3-5 points

4.3 The Friedewald Equation for LDL calculation

The ultracentrifugal measurement of LDL is time consuming and expensive and requires specialist equipment. For this reason, LDL-cholesterol is most commonly estimated from quantitative measurements of total and HDL-cholesterol and plasma triglycerides (TG) using the empirical relationship of Friedewald et al. (1972).

- $[\text{LDL-cho}] = [\text{Total chol}] - [\text{HDL-cho}] - ([\text{TG}]/2.2)$ where all concentrations are given in mmol/L (note that if calculated using all concentrations in mg/dL then the equation is $[\text{LDL-cho}] = [\text{Total chol}] - [\text{HDL-cho}] - ([\text{TG}]/5)$)
- the quotient $([\text{TG}]/5)$ is used as an estimate of VLDL-cholesterol concentration. It assumes, first, that virtually all of the plasma TG is carried on VLDL, and second, that the TG:cholesterol ratio of VLDL is constant at about 5:1 (Friedewald et al. 1972). Neither assumption is strictly true.

Limitations of the Friedewald equation

The Friedewald equation should not be used under the following circumstances:

- when chylomicrons are present
- when plasma triglyceride concentration exceeds 400 mg/dL (4.52 mmol/L)
- in patients with dysbetalipoproteinemia (type III hyperlipoproteinemia)

4.4 Pharmacometric Review

Office of clinical Pharmacology: Pharmacometric review

4.4.1 Summary of Findings

4.4.2 Key Review Questions

The purpose of this review is to address the following key questions.

2.4.2.2 The proposed dosing suggests that either 75 or 150 mg can be given once every two weeks. Are there certain baseline patient characteristics that suggest either the 75 mg or 150 mg dose be given to specific populations?

No clinically meaningful covariates were identified to suggest one regimen would be better than the other for certain patients. However, the exposure-response analysis below and the titration analyses conducted by clinical pharmacology and statistics (see the reviews by Dr. Sang Chung and Dr. Bradley McEvoy) suggest that it is reasonable to start at 75 mg and then up-titrate to 150 mg if the desired LDL-C response is not achieved with the 75 mg dose.

Exposure-response analyses was conducted to evaluate the appropriateness of the doses selected. Dose-ranging data from the phase three program were not used as they were confounded by titration. In the phase 3 studies, only those patients whose response was inadequate at the 75 mg dose up-titrated to 150 mg alirocumab. In the phase 2 trial DFI11565 there was a fixed dose comparison between 50 mg, 100 mg, and 150 mg twice-monthly. Figure 29 shows the exposure-response relationship for this study and the corresponding distribution of alirocumab concentrations at each dose. It appears that a 150 mg dose is just inside the plateau of response and that additional lowering may be attained for patients that receive less than 100 mg twice-weekly.

Figure 29. Exposure-response relationship for alirocumab PK concentrations and LDL-C change from baseline in study DFH11565 (Phase 2). (Mean LDL-C and the range of 5th – 95th percentiles at the corresponding median alirocumab concentrations are shown for each of 20 exposure bins by the solid line and shaded region. Solid orange lines depict the distribution of alirocumab concentrations for each respective dosing regimen.)

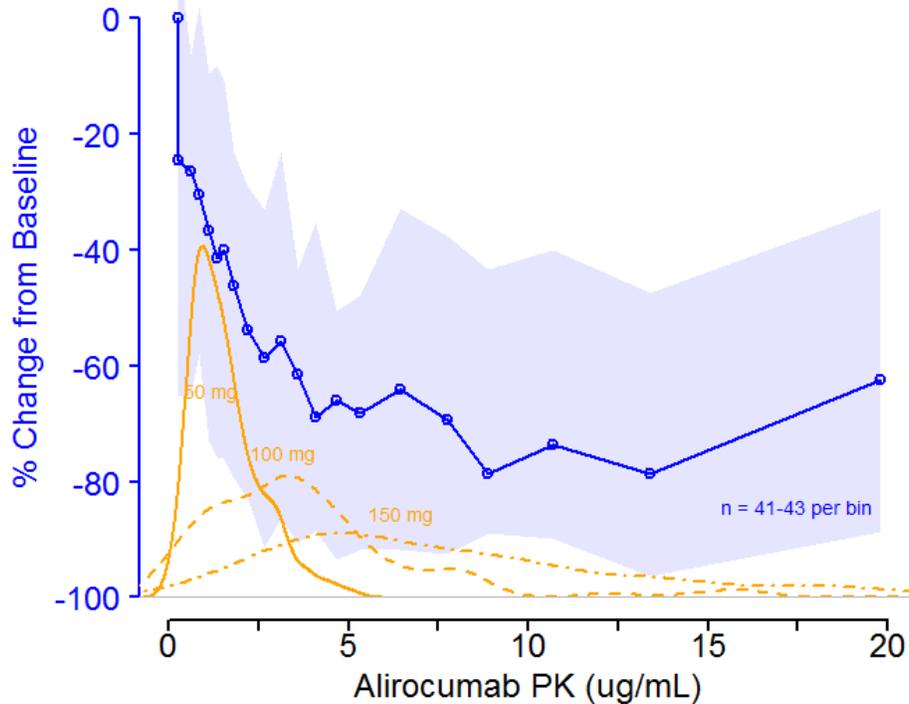
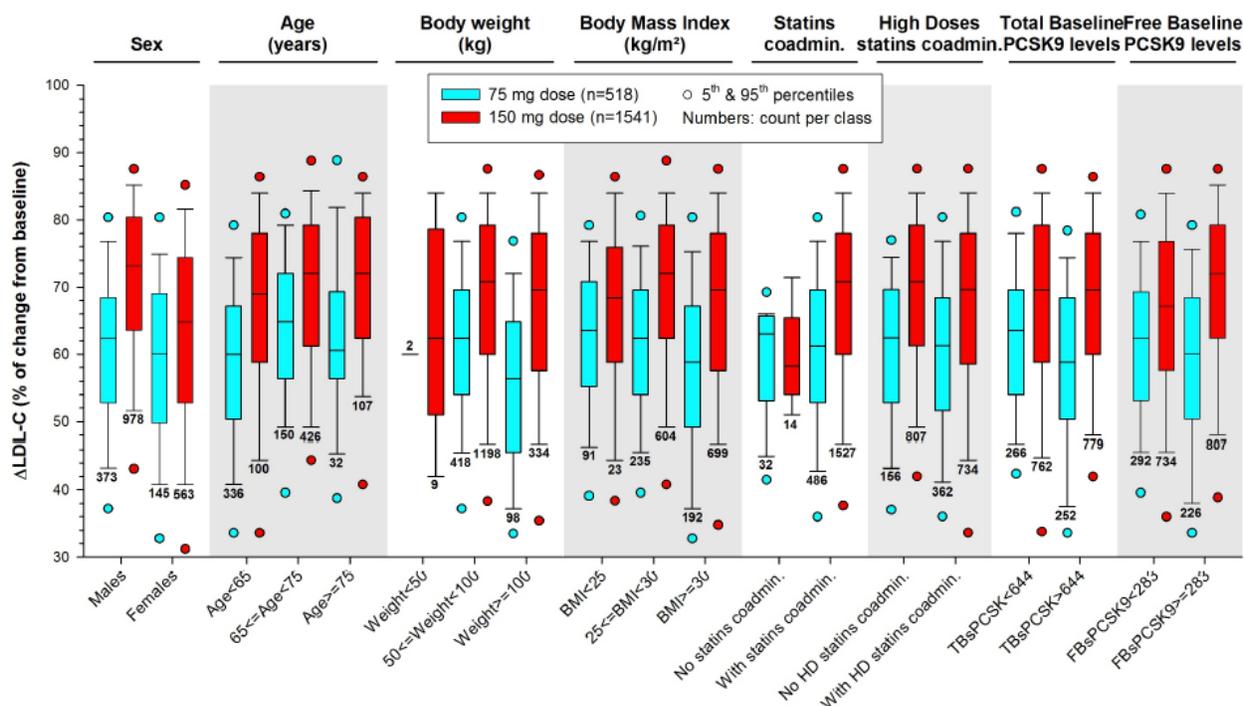


Figure 30 shows the change from baseline in trough LDL-C measurements at week 22-24. In general there does not appear to be a trend across any of the patient characteristics that would suggest certain individuals perform better. It is important to note this consideration is made in light of the large extent of LDL-C lowering with this product at either dose. When comparisons are made across doses it is apparent that the 150 mg dose tends to lower LDL-C more compared to the 75 mg dose. This is consistent with Figure 29 and supports starting at 75 mg alirocumab and increasing the dose to 150 mg if the desired LDL-C reduction is not achieved with the 75 mg dose. The titration is supported by the phase three trial design which incorporated this dose titration paradigm and by the reviews of Dr. Sang Chung and Dr. Bradley McEvoy.

Figure 30. Box plot of Δ LDL-C on Week 22-24 (% change from baseline) in phase 3 patients.



(Source: Applicants Population PK/PD Report, Figure 19)

2.4.2.3 Should alirocumab be dosed on a body-weight basis?

No, there is no need for dose adjustment in patients with lower body weight. Additionally at lower exposures in patients with the highest body weight, efficacy was not compromised so there is no need for dose adjustment for higher body weights as well.

Patients with the lowest body weight exhibited the highest exposure of alirocumab (Table 1). Compared to a patient weighing the median weight (83 kg) the linear clearance component decreased 78% for a 50 kg individual and increased 40% for a 100 kg individual. Steady-state AUC and Cmax values are shown in Table 1 for both the 75 and 150 mg doses. Additionally, there does not appear to be any safety reason that would suggest patients with lower body weight receive a lower dose of alirocumab. Despite the correlation of evolocumab PK with body weight, no safety events by system organ class were correlated with low body weight (See Section 4 for individual safety plots).

Table 30 Mean (CV%) - median (5th, 95th percentiles) of steady-state alirocumab exposure values as a function of body weight and dose.

Dose	Weight	n	AUC (mg·hr/L)	Cmax (mg/L)
75 mg	< 50 kg	3	4580 (52.7) - 3780 (2660, 7290)	- 3780 (2660, 7290) 14.9 (48.6)
75 mg	50 - <100 kg	450	2330 (42.3) - 2170 (1140, 4180)	- 2170 (1140, 4180) 8.52 (35.8)
75 mg	≥ 100 kg	101	1640 (34.8) - 1550 (747, 2690)	- 1550 (747, 2690) 6.23 (28.5)
150 mg	< 50 kg	11	12100 (33.5) - 12000 (7050, 20400)	- 12000 (7050, 20400) 40.2 (31.1)
150 mg	50 - <100 kg	1282	5450 (49.5) - 4940 (2030, 10500)	- 4940 (2030, 10500) 19.3 (43.6)
150 mg	≥ 100 kg	347	3460 (47.2) - 3150 (1440, 6620)	- 3150 (1440, 6620) 13.1 (39.6)

(Source: Applicant's Population PK Report POH0377, Tables 20 and 21)

2.4.2.4 Is dose adjustment needed for age, gender, or renal impairment?

No dose adjustments are needed based on age, gender or renal impairment owing to the LDL-C response across these categories along with the correlation between CrCL and body weight. Despite the differences in exposures observed for age and gender (Figure 35), no appreciable differences in LDL-C lowering were observed for these patient demographic categories (Figure 30). With regards to CrCL, it is likely that the changes in alirocumab exposure are a reflection of differing body weights, gender, and age as CrCL is calculated as a function of serum creatinine and these three demographics. CrCL was not a significant factor in the population PK model after the inclusion of the more significant factor body weight.

4.4.3 Recommendations

The Division of Pharmacometrics, Office of Clinical Pharmacology has reviewed this application and found it acceptable from a clinical pharmacology perspective.

- Since the efficacy of two doses were comparable relative to the extent of reduction in LDL-C it is recommended that patients start with the 75 mg dose and up-titrate to 150 mg if the desired LDL-C lowering was not attained with the 75 mg dose.
- Minor recommendations for the labeling of alirocumab pharmacokinetics (See Section 1.3 below).

4.4.4 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

12.3 Pharmacokinetics

Absorption

After subcutaneous (SC) administration of (b) (4) mg to (b) (4) 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- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose. Steady state was reached after 2 to 3 doses with an accumulation ratio 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.

(b) (4)

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 (b) (4) at subcutaneous doses of 75 mg Q2W or 150 mg Q2W. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Specific Populations

A population PK analysis was conducted by combining (b) (4) from 2799 subjects (b) (4). Age, gender, race, and creatinine clearance were not found to influence alirocumab PK, (b) (4). No dose adjustments are recommended for these demographics.

(b) (4)

(b) (4)

Pediatric (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Renal Impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of alirocumab.

(b) (4)

No data are available in patients with severe renal impairment.

Hepatic Impairment

(b) (4) administration of a single 75 mg SC dose, alirocumab pharmacokinetic profiles in subjects with mild and moderate hepatic impairment were similar (b) (4) to subjects with normal hepatic function.

No data are available in patients with severe hepatic impairment.

(b) (4)

[Redacted]

(b) (4)

[Redacted]

4.4.5 Pertinent regulatory background

Alirocumab is a new molecular entity NDA being submitted for the treatment of primary hypercholesterolemia or mixed dyslipidemia. Alirocumab is a first-in-class PCSK9 inhibitor that acts to prevent the lysosomal degradation of the LDL receptor which clears LDL-cholesterol from the bloodstream.

4.4.6 Results of Sponsor's Analysis

4.4.6.1 Population PK Analysis

The applicant's population PK model for alirocumab was developed from a combination of phase I, phase II, and phase III PK data. The total dataset included 16153 samples from 2799 subjects in 13 clinical trials.

Parameter estimates and covariate relationships for the applicant's final population PK model are described in Table 31.

Table 31 Population PK Parameter Estimates before (PSM) and after inclusion of the covariates (Final Model).

Parameter	PSM		Final model with covariates		
	Estimate	% RSE	Estimate	% RSE	[95%CI]
Typical value of CLL (θ_1 , L/h) ^a	0.0114	9.07%	0.0124	2.99%	[0.0116; 0.0131]
Effect of WT on CLL (θ_{12}) ^a	NA	NA	2.92.10 ⁻⁴	3.24%	[2.73.10 ⁻⁴ ; 3.11.10 ⁻⁴]
Effect of STATIN on CLL (θ_{13}) ^a	NA	NA	6.44.10 ⁻³	6.08%	[5.66.10 ⁻³ ; 7.22.10 ⁻³]
Typical value of V2 (θ_2 , L)	2.66	6.54%	3.19	3.63%	[2.95 ; 3.42]
Typical value of Ka (θ_3 , h ⁻¹)	0.0129	5.44%	7.68.10 ⁻³	2.45%	[7.31.10 ⁻³ ; 8.06.10 ⁻³]
Typical value of V3 (θ_4 , L) ^b	1.81	5.21%	2.79	2.95%	[2.62 ; 2.95]
Effect of AGE on V3 (θ_{15}) ^b	NA	NA	0.310	12.3%	[0.233 ; 0.386]
Typical value of Q (θ_5 , L/h)	0.0156	7.29%	0.0185	4.95%	[0.0166 ; 0.0203]
Typical value of Vm (θ_6 , mg.h/L)	0.172	11.1%	0.183	4.96%	[0.165 ; 0.202]
Typical value of Km (θ_7 , mg/L) ^c	9.49	11.3%	7.73	6.39%	[6.74 ; 8.72]
Effect of FPCSK on Km (θ_{14}) ^c	NA	NA	-0.541	8.97%	[- 0.638 ; -0.444]
Typical value of F (θ_{10})	0.590	5.44%	0.862	0.13%	[0.860 ; 0.865]
Typical value of LAG (θ_{11} , h)	0.643	2.76%	0.641	2.58%	[0.608 ; 0.674]

F: bioavailability %RSE: Percentage of Relative Standard Error (100% * SE / Estimate) 95%CI: 95% confidence interval

θ and ω are the PopPK parameters (θ) and the variance of their associated inter-individual variability (ω).

a: the expression of linear elimination clearance including covariates effects is:

$$CLL = TVCLL + COV1 \times (WT - 82.9) + COV2 \times STATIN$$

where WT is weight with a median value of 82.9 in the available data. STATIN was coded as 0 if no coadministration, and 1 if coadministration of rosuvastatin (dose < 20 mg/day) or atorvastatin (dose < 40 mg/day) or simvastatin whatever the dose.

b: the expression of the distribution volume of the peripheral compartment is:

$$V3 = TVV3 \times (AGE / 60)^{COV4}$$

where 60 is the median value of age in the available data

c: the expression of Michaelis-Menten parameter Km is:

$$Km = TVKM + COV3 \times (FPCSK / 72.9)$$

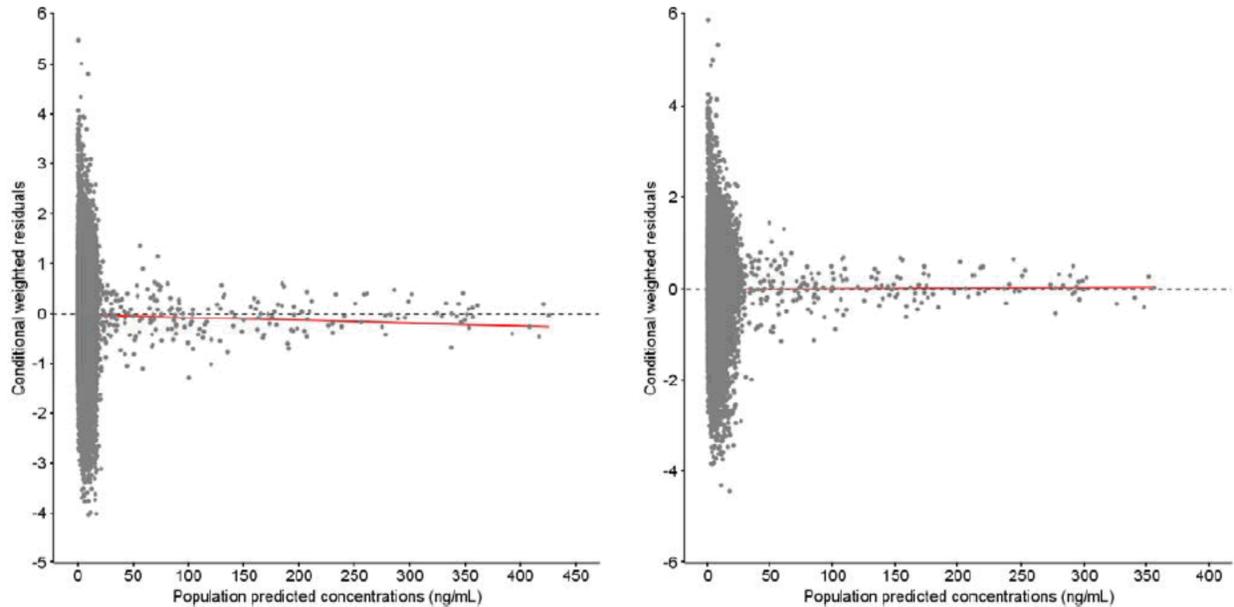
where FPCSK is the Time-varying Free anti-PCSK9 concentration with a median value of 72.9 in the available data

d: the value presented here is the correlation coefficient (r)

(Source: Applicant's Population PK Report POH0377, Table 9)

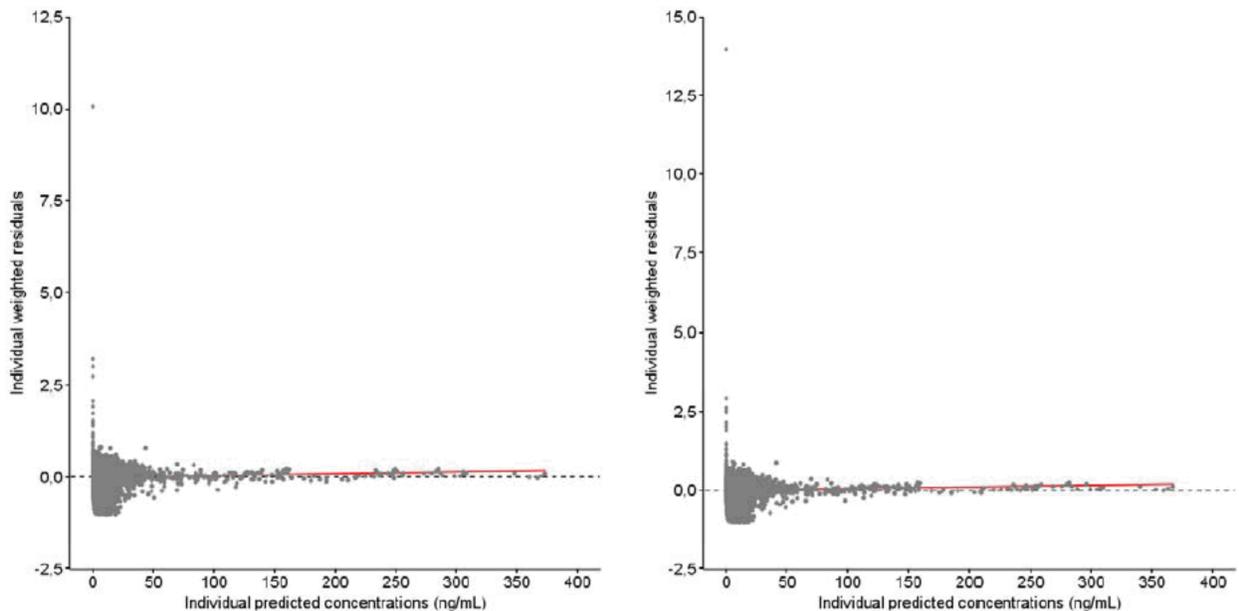
The applicant's diagnostic plots for the final model before and after covariate inclusion are shown in Figure 31 - Figure 34. In general the model appeared to fit the data with minimal bias, capturing the central tendency of the observations. Additionally, bias was not introduced and in some cases it decreased with the inclusion of the covariates in the final model.

Figure 31. Relationship between conditional weighted residuals and population predicted concentrations before (left panel) and after (right panel) covariate inclusion. Scatter points depict observations, while the red line depicts the tendency of the data.



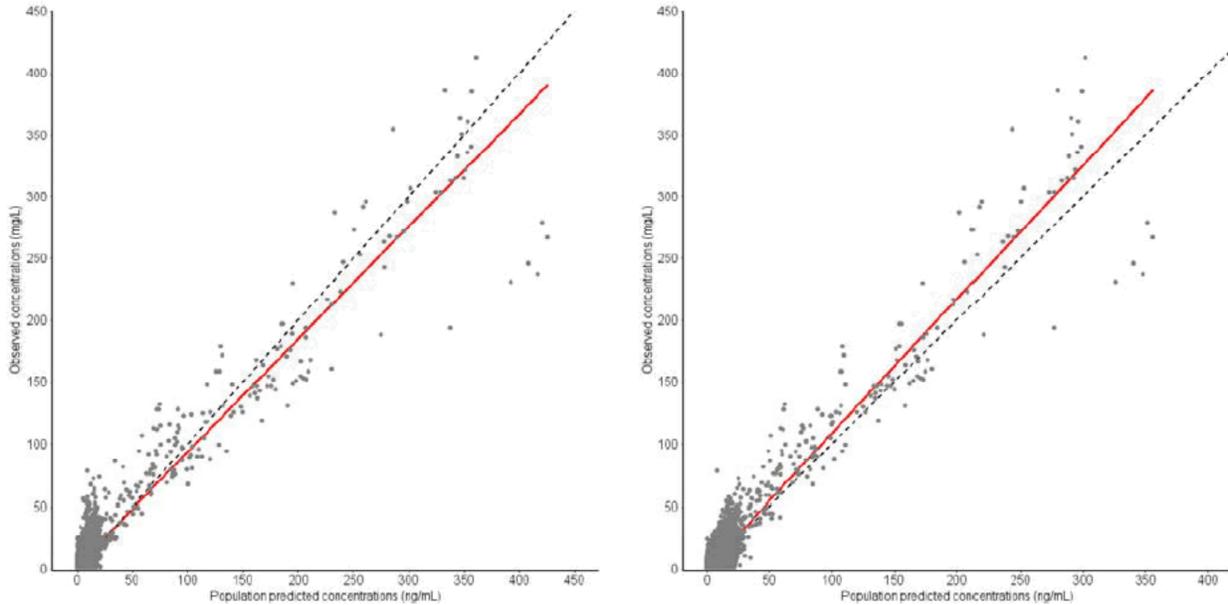
(Source: Applicant's Population PK Report POH0377, Figure 11)

Figure 32. Relationship between individual weighted residuals and individual predicted concentrations before (left panel) and after (right panel) covariate inclusion. Scatter points depict observations, while the red line depicts the tendency of the data.



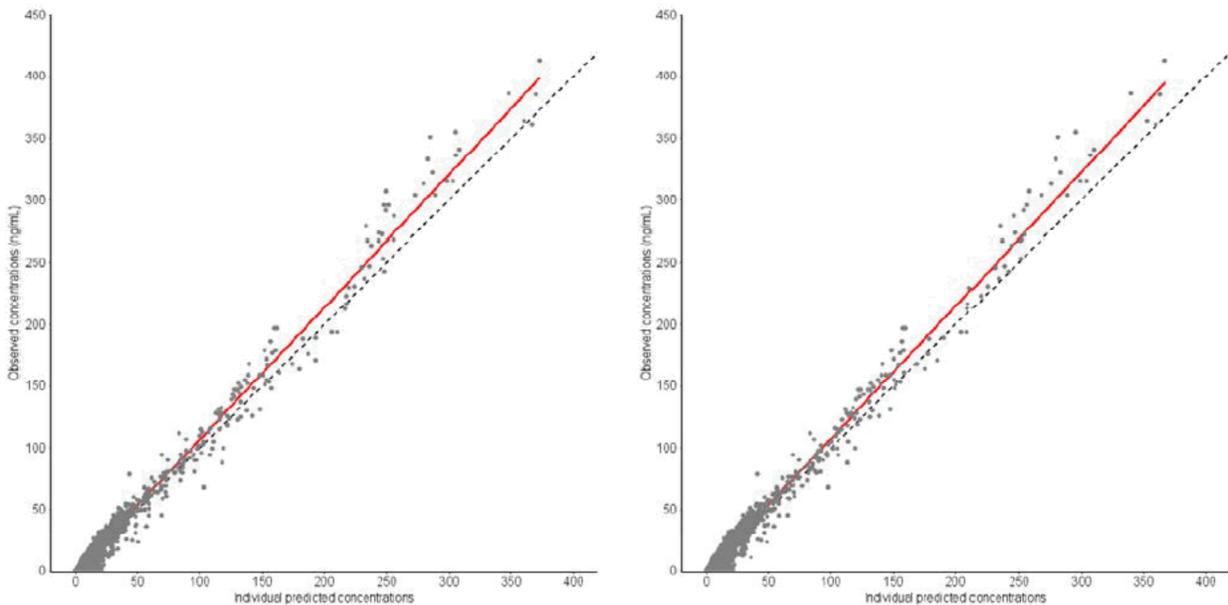
(Source: Applicant's Population PK Report POH0377, Figure 12)

Figure 33. Relationship between population predicted and observed concentrations before (left panel) and after (right panel) covariate inclusion. Scatter points depict observations, while the red line depicts the tendency of the data.



(Source: Applicant's Population PK Report POH0377, Figure 13)

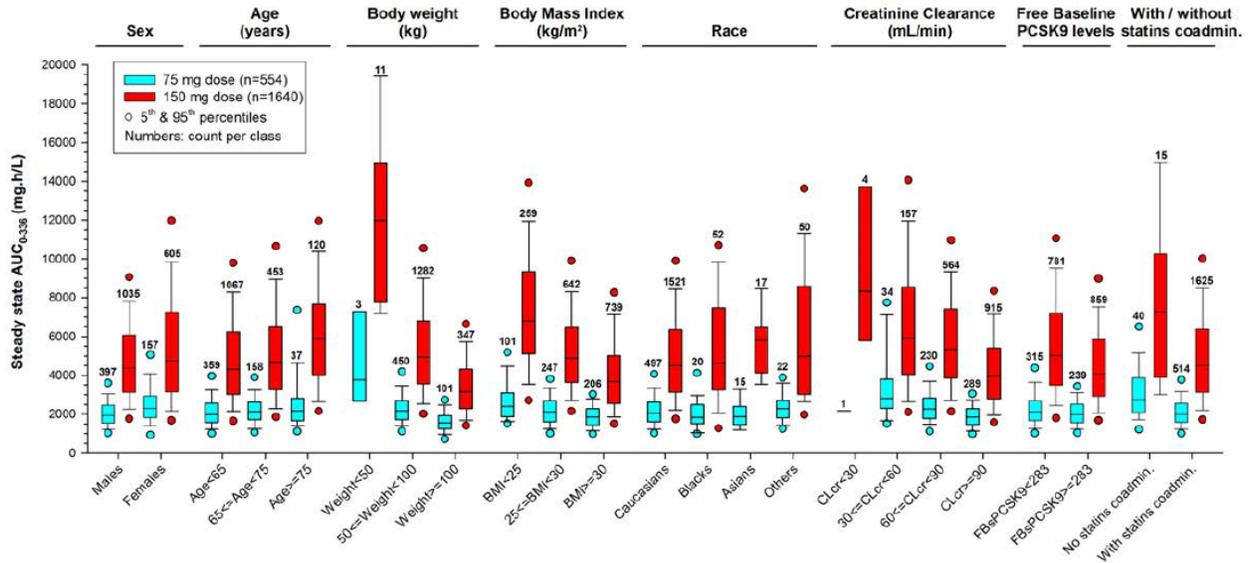
Figure 34. Relationship between individual predicted and observed concentrations before (left panel) and after (right panel) covariate inclusion. Scatter points depict observations, while the red line depicts the tendency of the data.



(Source: Applicant's Population PK Report POH0377, Figure 14)

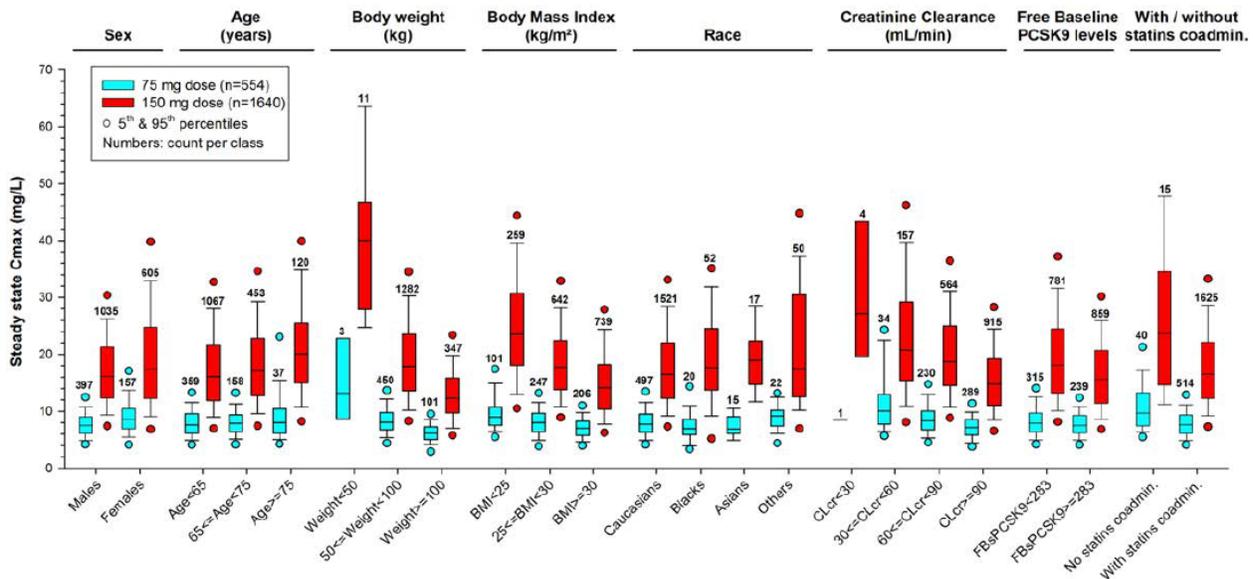
Plots of steady-state AUC and Cmax values (Figure 35 and Figure 36) depict the general range of exposures that each demographic exhibited in the phase III program. Not all covariates were included in the final model due to inter covariate correlations (e.g. body weight and CRCL).

Figure 35. Box plot of AUC values for the patients included in the Phase III study as a function of several covariates.



(Source: Applicant's Population PK Report POH0377, Figure 16)

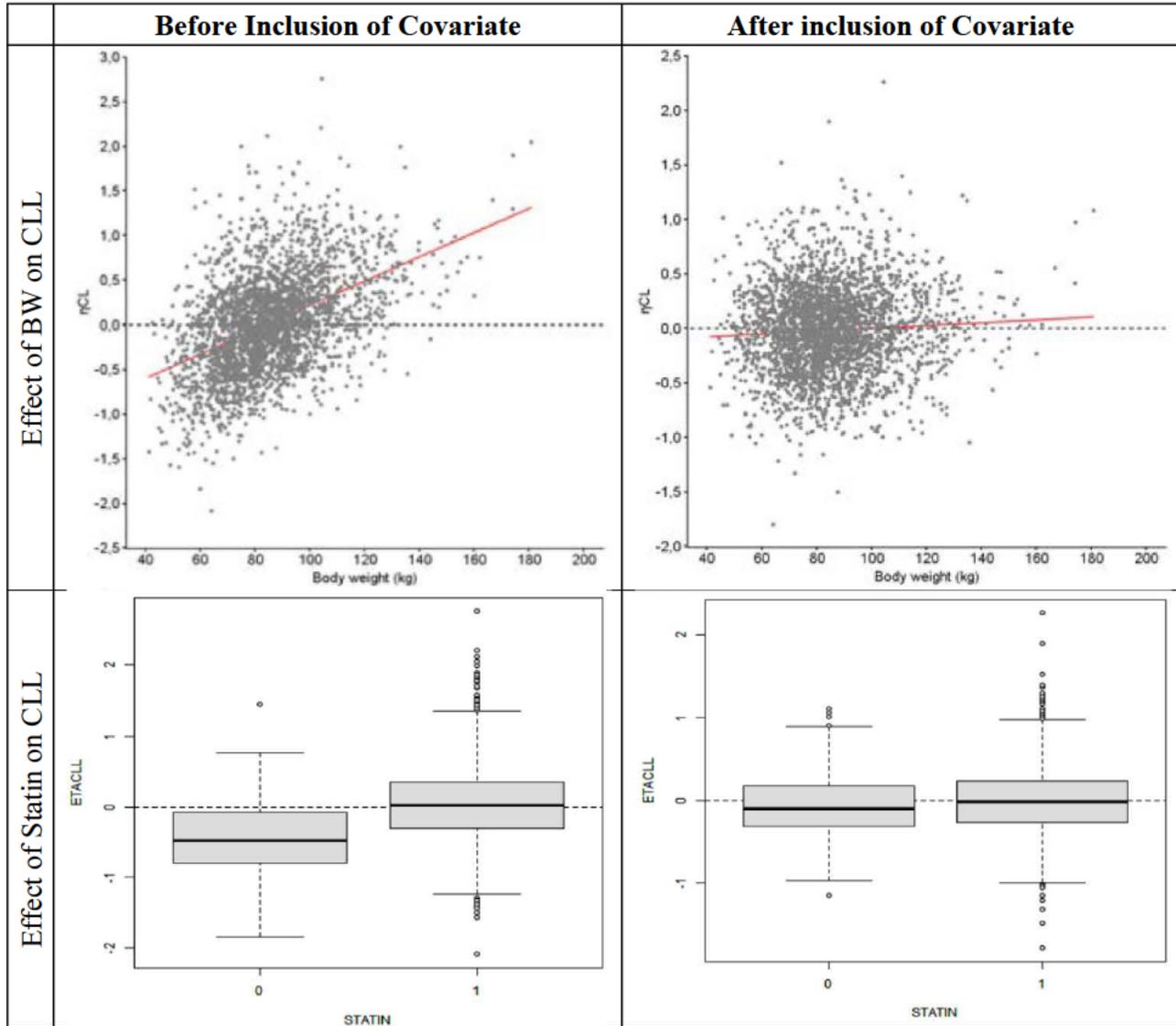
Figure 36. Box plot of C_{max} values for the patients included in the Phase III study as a function of several covariates.

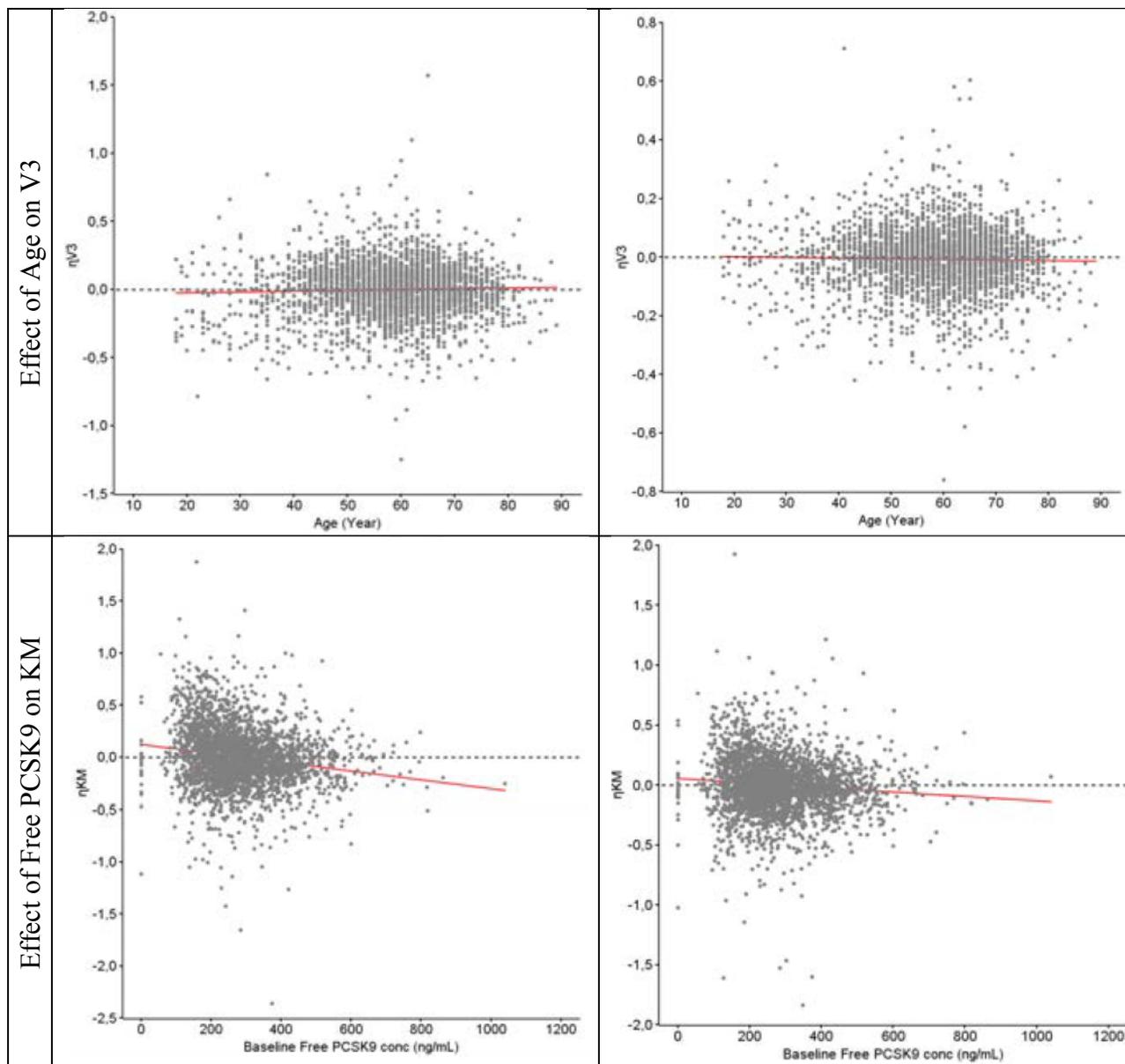


(Source: Applicant's Population PK Report POH0377, Figure 17)

Figure 37 shows the distribution of etas across each covariate that was included in the final model before and after covariate inclusion. In all cases the slope for the line of tendency (red line in each plot) appears to approach zero with the inclusion of the covariate.

Figure 37. Applicants plots of etas for each relevant covariate relationship in the final model before (left panel) and after (right panel) inclusion in the model.





(Source: Applicant's Population PK Report POH0377, Figures 19, 20, 24, 27, 36, 37, 42, 44)

The final model covariates reduced the between subject variability (BSV) and objective function value. These metrics for the respective parameter and covariate are shown below. Eta shrinkage was reported to be 18.5% for CLL.

Table 32 Difference in Objective Function Value (Δ OBF^{*}) and the Reduction in BSV^{} for each covariate effect. Objective function values and CV% were compared before and after the backward deletion step for each covariate. Reduction in BSV refers to after inclusion in the final model.**

Covariate	Δ OBF	Reduction in BSV (%)
Age on V3	156	1.70
PCSK9 on KM	402	6.32
Statin on CLL	176	2.23
BW on CLL	231	38.03

* Δ OBF = Model Minus Covariate Objective Function – Final Model Objective Function

**Reduction in BSV = (SQRT(Model without Covariate ω_{CLL})-SQRT(Final Model ω_{CLL}))·100%

Reviewer’s Comments:

The population PK model appears acceptable to label covariate effects of age, (b) (4)
 statin use, and PCSK9.

4.4.7 Reviewer’s Analysis

4.4.7.1 Introduction

This review aims to determine whether the safety data support use of alirocomab at the higher exposures in those patients with lower body weight. Additionally, there was a hypothetical concern that LDL-C could be suppressed too low for some organs in the body (i.e. nervous system, cell membrane, etc) and that adverse events may originate from low LDL-C levels. Thus safety analyses were conducted for each system organ class by the lowest LDL-C levels in each individual.

4.4.7.2 Objectives

Analysis objectives are:

- Determine relationship between body weight and adverse events by system organ class.
- Determine relationship between the average of the three lowest LDL-C values and adverse events by system organ class.

4.4.7.3 Methods

4.4.7.1.1 Data Sets

Data sets used are summarized in

Table 33.

Table 33 Analysis Data Sets

Study Number	Name	Link to EDR
ISS	adsl.xpt	\\cdsesub1\evsprod\BLA125559\0000\m5\datasets\iss\analysis\legacy\datasets\adsl.xpt
ISS	adae.xpt	\\cdsesub1\evsprod\BLA125559\0000\m5\datasets\iss\analysis\legacy\datasets\adae.xpt
ISS	adlbf.xpt	\\cdsesub1\evsprod\BLA125559\0000\m5\datasets\iss\analysis\legacy\datasets\adlbf.xpt
DFI11565	adpc.xpt	\\cdsesub1\evsprod\BLA125559\0000\m5\datasets\dfi11565\analysis\legacy\datasets\adpc.xpt
DFI11565	adlbf.xpt	\\cdsesub1\evsprod\BLA125559\0000\m5\datasets\dfi11565\analysis\legacy\datasets\adlbf.xpt

4.4.7.1.2 Software

The statistical software R (version 2.15) was used for all plots and figures. NONMEM (Version 7.3) was used for rerunning the applicant’s population PK models.

4.4.7.1.3 Models

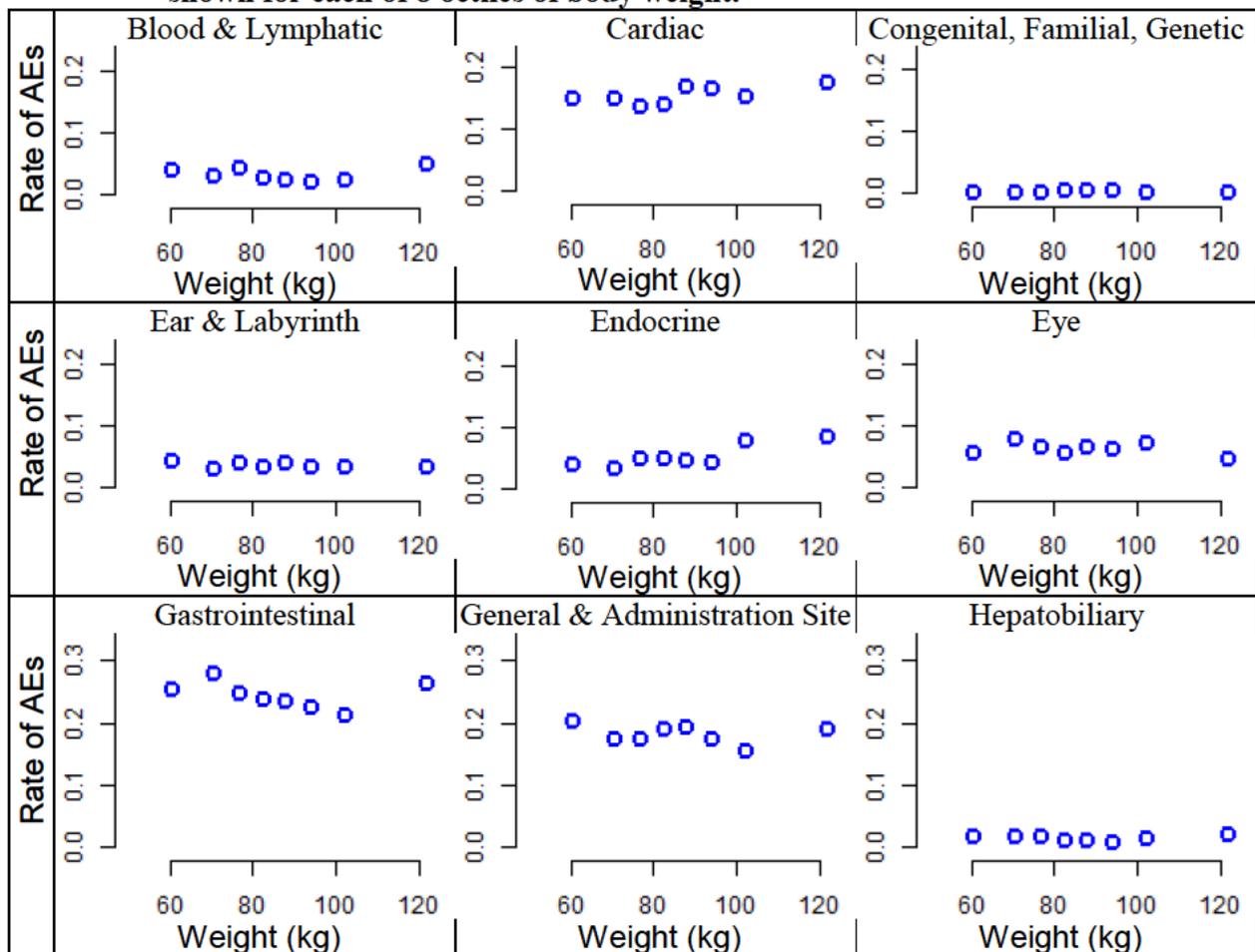
No original modeling was performed by the FDA.

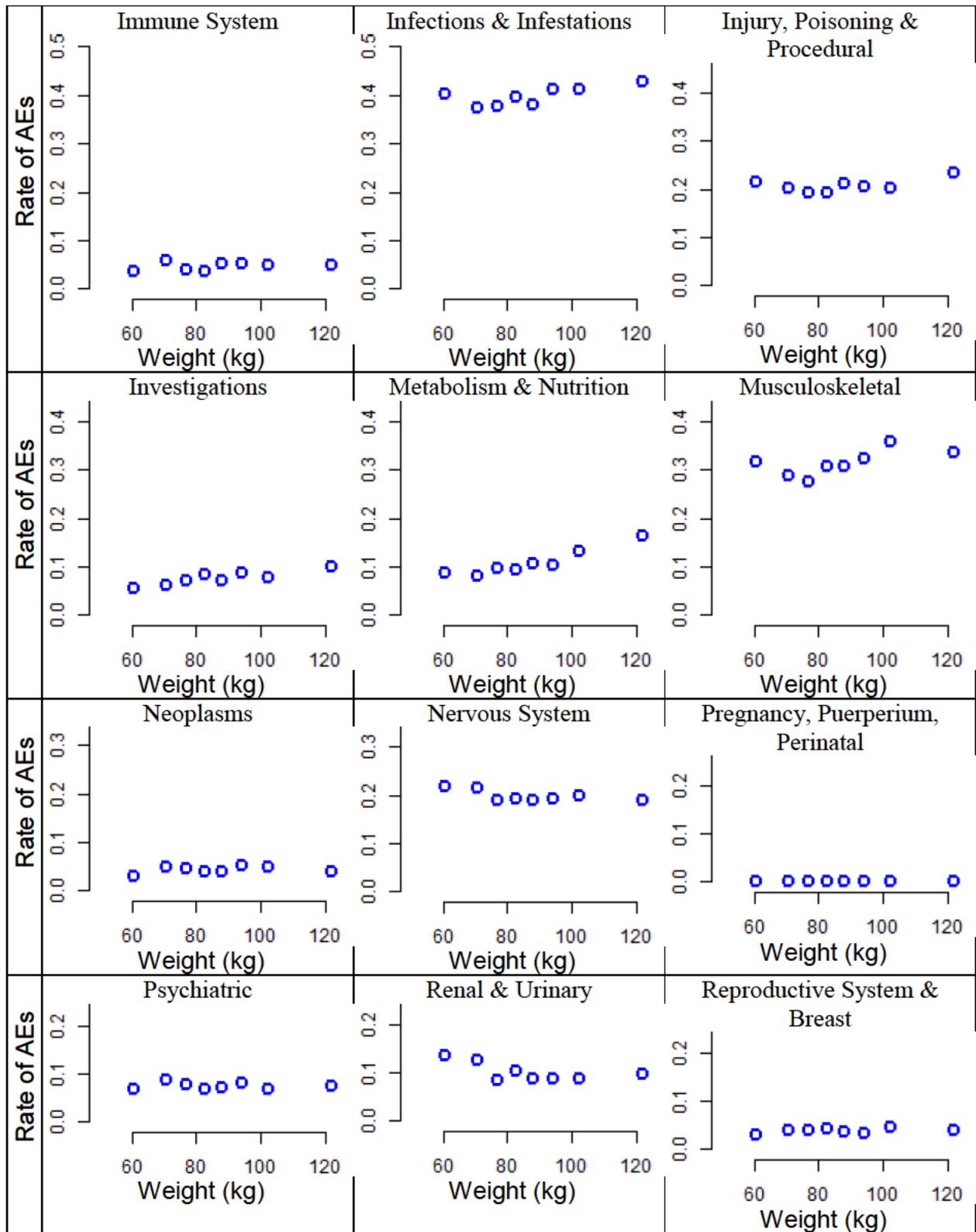
4.4.7.4 Results

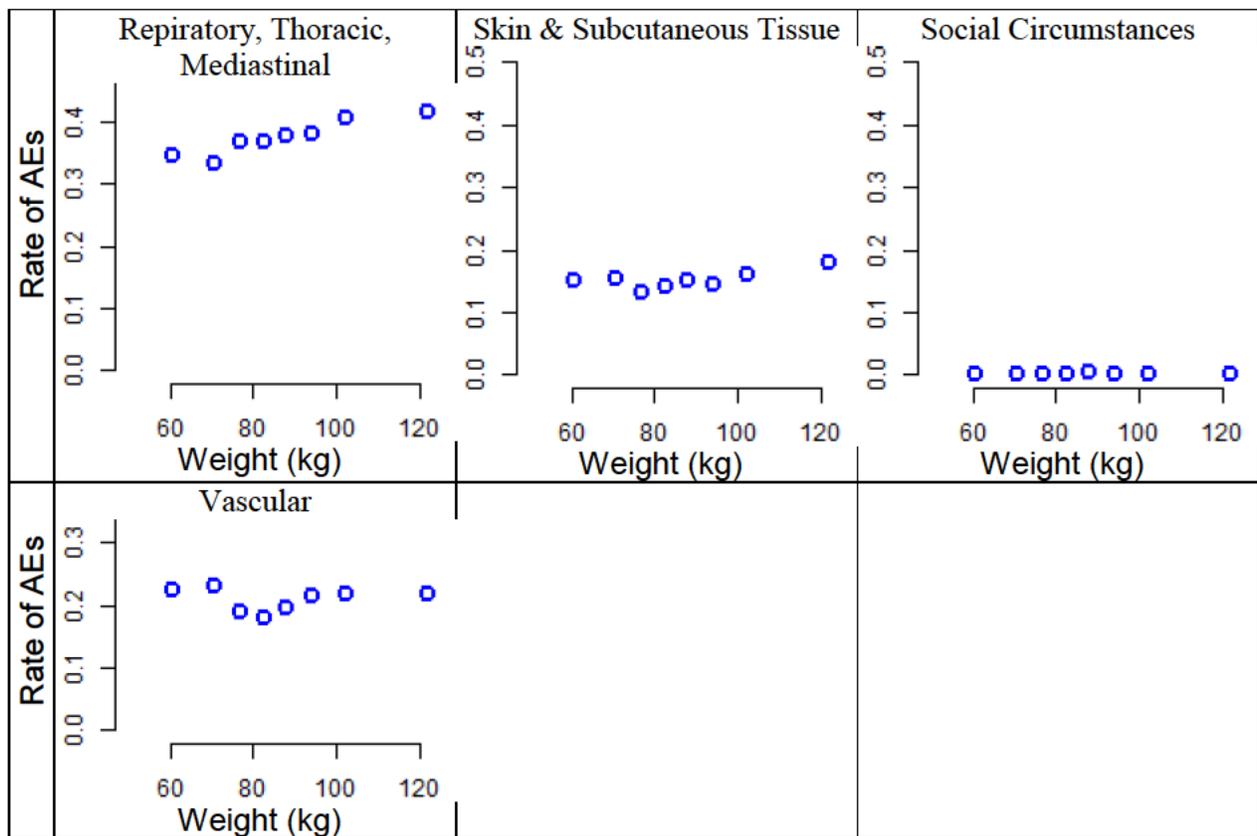
4.4.7.1.4 Body Weight – Adverse Event Analysis

All grade adverse events were evaluated by system organ class in order to determine if there was a correlation with body weight. The 78% reduction in alirocumab clearance for a 50 kg individual compared to the clearance of an 83 kg individual (median) raised concern regarding higher exposures in patients with lower weight. **Error! Not a valid bookmark self-reference.** shows the rate of adverse events per octile of body weight. In general there do not appear to be any meaningful increases in adverse events at lower body weights. This combined with the assessment by the clinical reviewer (Dr. Mary Roberts) suggests the safety profile of this product was well tolerated across the range of body weights and that dose-reduction for low body weight is probably not necessary.

Figure 38 There does not appear to be an increase in any grade adverse events and Low Body Weight by System Organ Class Disorder Type. The y-axis is the event rate in the integrated summary of safety population. The x-axis is body weight (kg). The proportion of those in the ISS database with an adverse event are shown for each of 8 octiles of body weight.



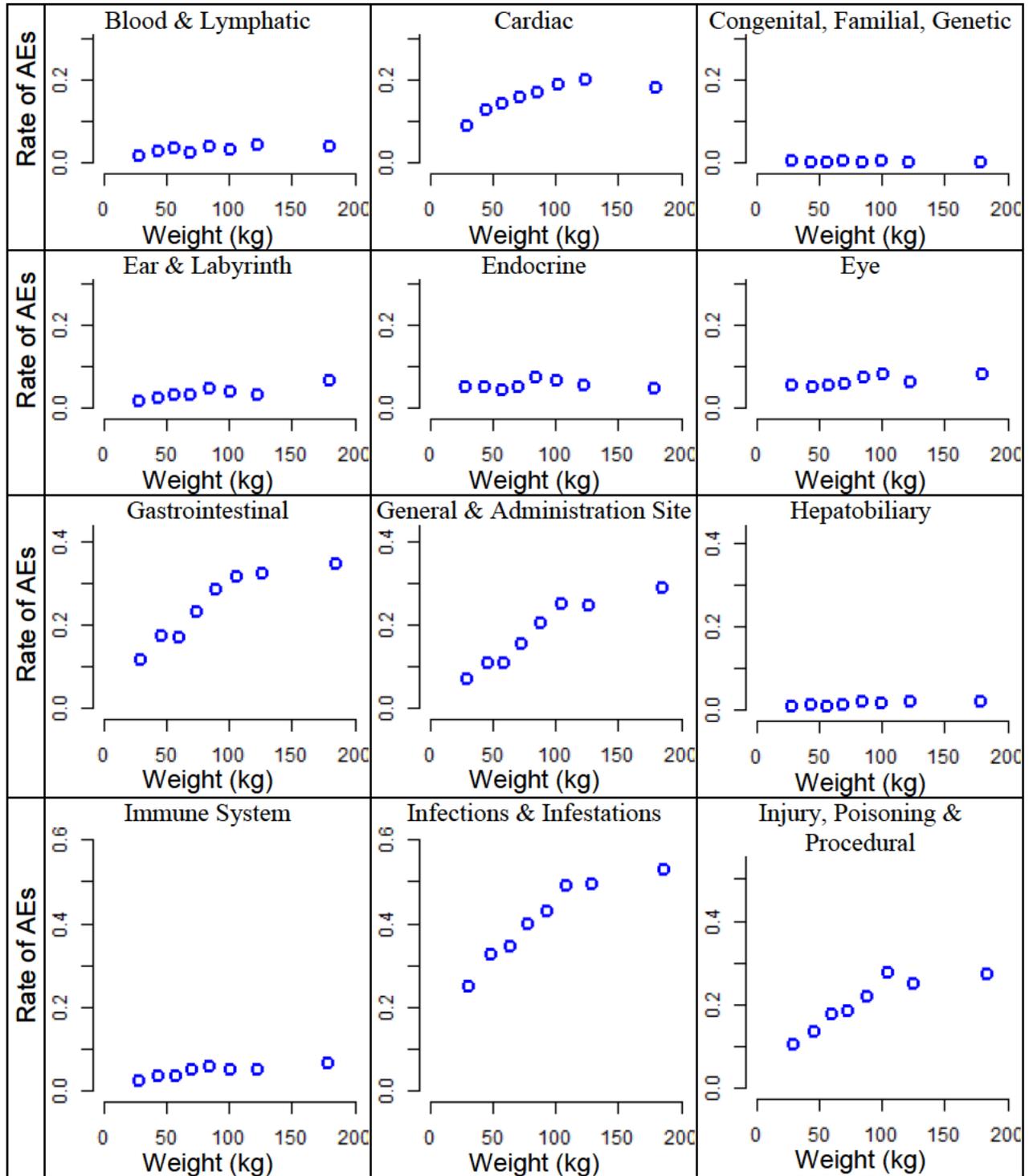


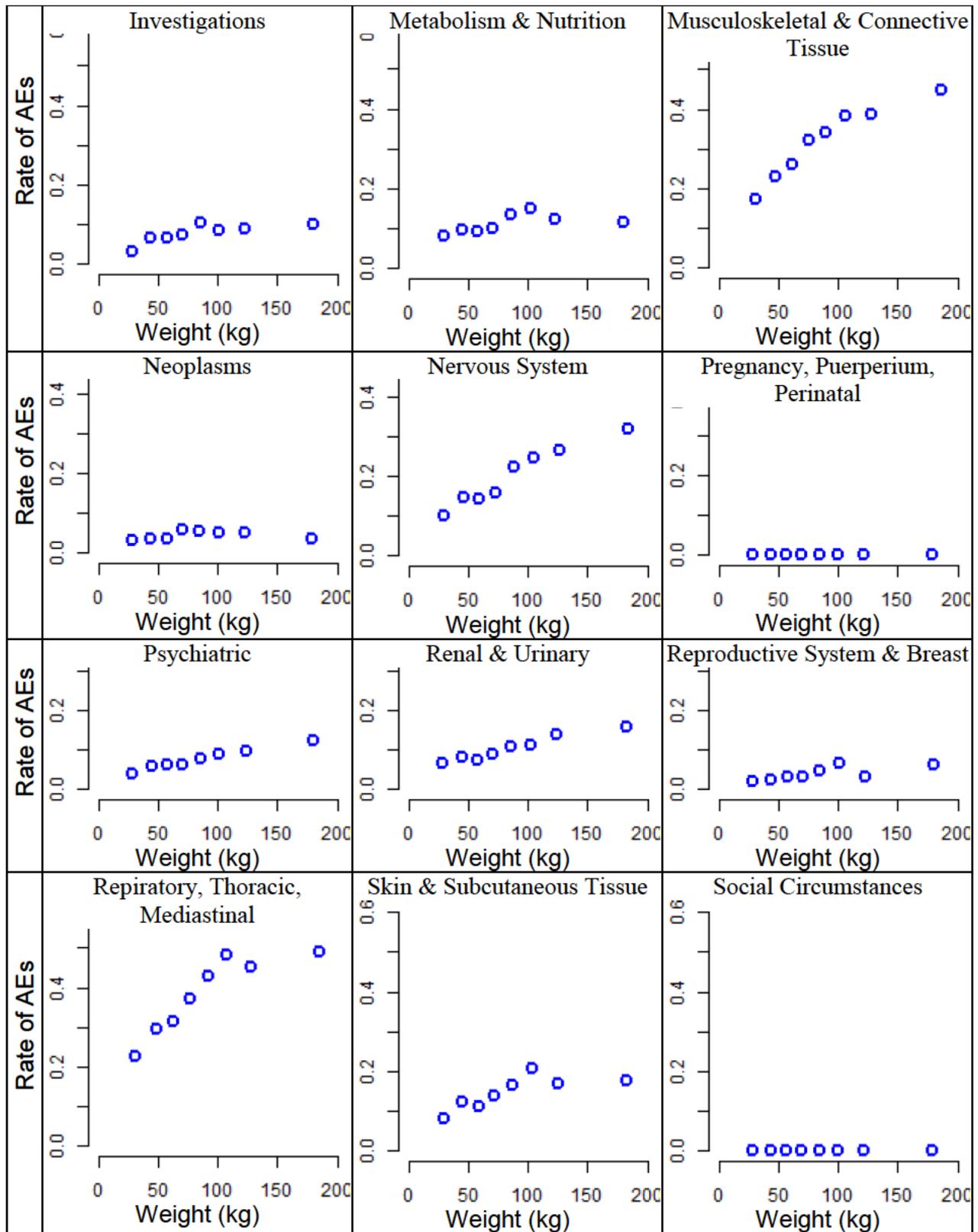


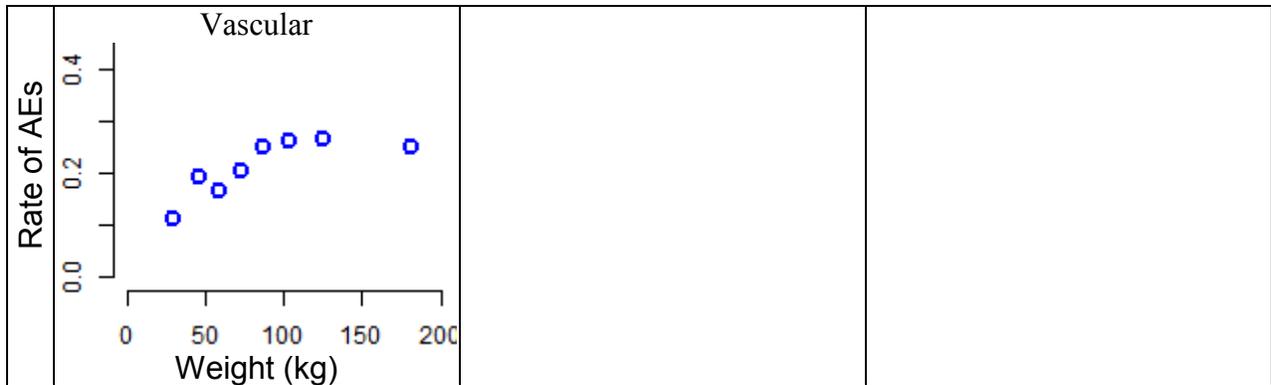
4.4.7.1.5 LDL-C – Adverse Event Analysis

All grade adverse events were evaluated by system organ class in order to determine if there was a correlation with low LDL-C levels. Based on the body's intrinsic need for some degree of LDL-C, there was concern that if LDL-C levels were reduced too much, physiological processes that require cholesterol such as cell membranes and the nervous system might show detrimental results. Thus, the LDL-C values prior to the adverse event were averaged and used as the low LDL-C metric for each individual. The adverse event rate was then determined for each low LDL-C octile and is shown in Figure 39. Low LDL-C was not correlated with higher rates of adverse events in any of the system organ classification of adverse events. It was interesting; however, that there was apparent increase in adverse events with higher LDL-C in at least several categories. It should be noted that this is univariate analysis and should not be interpreted as suggesting there is a causal relationship between LDL-C and AEs.

Figure 39. Low LDL-C does not appear to be correlated with any grade adverse events by System Organ Class. The y-axis is the event rate in the integrated summary of safety population. The x-axis is the average of the lowest 3 LDL-C values prior to the adverse event. The proportion of those in the ISS database with an adverse event are shown for each of 8 octiles of LDL-C averages. Points that lie left of zero on the x-axis depict the rate in patients who did not have LDL-C levels.







4.4.8 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
ISS_BW-AEalirocumab.R	Analysis file for BW-AE or LDL-C – AE correlations	..\Reviews\PM Review Archive\2015\Alirocumab_BLA125559_JCE\ER Analyses
*.tif	Output plots for safety analyses	..\Reviews\Ongoing PM Reviews\Alirocumab_BLA125559_JCE\ER Analyses\LDLC-AE_alirocumab
Alirocumab_ER.R	Analysis file for Exposure Response of Study DF111565	..\Reviews\PM Review Archive\2015\Alirocumab_BLA125559_JCE\ER Analyses
Ali_ExpResp_PChg.tif	Final Exposure-Response Graphic for study DF111565	..\Reviews\PM Review Archive\2015\Alirocumab_BLA125559_JCE\ER Analyses

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

/s/

SANG M CHUNG
06/01/2015

JUSTIN C EARP
06/01/2015

NITIN MEHROTRA
06/01/2015

JAYABHARATHI VAIDYANATHAN
06/01/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	125559	SDN	
Applicant	Sanofi/Regeneron	Submission Date	11/24/2014
Generic Name	Alirocumab	Brand Name	PRALUENT
Drug Class	Proprotein Convertase Subtilisin Kexin Type 9 inhibitor		
Indication	Treatment of hypercholesterolemia and mixed dyslipidemia		
Dosage Regimen	75 or 150 mg every 2 weeks		
Dosage Form	75 mg/mL and 150 mg/mL pre-filled pens or pre-filled syringe	Route of Administration	Subcutaneous injection
OCP Division	DCP2	OND Division	DMEP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Sang Chung	Jayabharathi Vaidyanathan	
Pharmacometrics	Sang Chung / Justin Earp	Nitin Mehrotra	
Genomics			
Review Classification	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	1/7/2015	74-Day Letter Date	2/6/2015
Review Due Date	2/24/2015	PDUFA Goal Date	7/24/2015

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

- Yes
 No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

- Yes
 No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

- Yes
 No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
<input type="checkbox"/> Metabolism Characterization		
<input type="checkbox"/> Transporter Characterization		
<input type="checkbox"/> Distribution		
<input type="checkbox"/> Drug-Drug Interaction		

In Vivo Studies				
Biopharmaceutics				
<input type="checkbox"/> Absolute Bioavailability	1	CL-0902 vs CL-0904		
<input type="checkbox"/> Relative Bioavailability				
<input type="checkbox"/> Bioequivalence	4	Comparability studies; PKD12010, PKD12011, PKD12275, BDR13362		
<input type="checkbox"/> Food Effect		Subcutaneous injection		
<input type="checkbox"/> Other				
Human Pharmacokinetics				
Healthy Subjects	<input checked="" type="checkbox"/> Single Dose	3	CL-0902 / CL-0904 / TDU12190	
	<input type="checkbox"/> Multiple Dose			
Patients	<input checked="" type="checkbox"/> Single Dose	1	CL-1001 (Part A)	
	<input checked="" type="checkbox"/> Multiple Dose	2	PKD12910 / CL-1001 (Part B)	
<input type="checkbox"/> Mass Balance Study				
<input type="checkbox"/> Other (e.g. dose proportionality)				
Intrinsic Factors				
<input type="checkbox"/> Race		Pop PK		
<input type="checkbox"/> Sex		Pop PK		
<input type="checkbox"/> Geriatrics		Pop PK		
<input type="checkbox"/> Pediatrics				
<input checked="" type="checkbox"/> Hepatic Impairment	1	POP12671		
<input type="checkbox"/> Renal Impairment		Pop PK		
<input checked="" type="checkbox"/> Genetics	1	CL-1018		
Extrinsic Factors				
<input checked="" type="checkbox"/> Effects on Primary Drug		CL-1001 (atorvastatin on alirocumab)		
<input checked="" type="checkbox"/> Effects of Primary Drug		CL-1001 (alirocumab on atorvastatin or rosuvastatin) CL-1003 (rosuvastatin); DDI was evaluated as part of PK/PD.		
Pharmacodynamics				
<input checked="" type="checkbox"/> Healthy Subjects		All clinical pharmacology studies in healthy subjects (PCSK9)		
<input checked="" type="checkbox"/> Patients		All clinical pharmacology studies in patients (PCSK9)		
Pharmacokinetics/Pharmacodynamics				
<input checked="" type="checkbox"/> Healthy Subjects		All clinical pharmacology studies in healthy subjects (PCSK9)		
<input checked="" type="checkbox"/> Patients		All clinical pharmacology studies in healthy subjects (PCSK9)		
<input type="checkbox"/> QT		No TQT study as this is a biologic		
Pharmacometrics				
<input checked="" type="checkbox"/> Population Pharmacokinetics	2	POH0377/POH0500		
<input type="checkbox"/> Exposure-Efficacy	1	POH0394		
<input type="checkbox"/> Exposure-Safety				
Total Number of Studies		In Vitro	In Vivo	28
Total Number of Studies to be Reviewed				28

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	TBM presentations have been evaluated in P3 studies.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist

Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Filing Memo

Alirocumab is a humanized monoclonal antibody (IgG1) that binds to the proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 controls trafficking of the hepatic low-density lipoprotein receptors (LDLRs). Alirocumab lowers LDL-C levels by inhibiting the binding of PCSK9 to LDLRs.

The proposed indication is for the treatment of primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus. The applicant requested the priority review designation using Priority Review Voucher. There was a navigation session of the submission formats with the application dated on 12/10/2014.

Pediatric Study Plan was submitted to IND 105574 and finalized through the Agency's letter dated on 7/25/2014 as follows:

- [REDACTED] (b) (4)
- A partial waiver for treatment of patients with heterozygous familial hypercholesterolemia in the following age categories:
[REDACTED] (b) (4)
- A deferral of the initiation of the clinical studies in the [REDACTED] (b) (4) until safety and efficacy in adults has been established.

Clinical trials supporting the clinical pharmacology information are summarized in Table 1.

Key review questions are identified as follows:

- Proposed dosing is 75 or 150 mg Q2W
 - Should dose titration be considered for labeling?
 - Are there any baseline patients characteristics to be considered for the decision on choosing the dosing regimen (75 or 150 mg Q2Q)?
 - Are there any baseline patient characteristics that correlate to whether patients respond to the treatment?
- Is there a need of dose adjustment for patients with renal impairment?
- Is there any effect of immunogenicity on PK, efficacy and/or safety?

Tentative review timelines are as follows:

- Filing/Planning Meeting: 1/7/2015
- File / RTF Application: 1/23/2015
- Issue 74-day letter: 2/6/2015
- OCP Scoping meeting: 2/9/2015
- MCM: 2/25/2015
- Label planning meeting: 3/15/2015
- Labeling/PMRs/REMS: 3/15-4/15/2015
- Primary Review in DARRTS: 4/24/2015

- Secondary Review: ~5/1/2015
- Pre-LCM: 5/14/2015
- Briefing package due to application: ~5/21/2015
- LCM with applicant: ~5/28/2015
- AC: 6/9//2015
- WU: 6/17/2015
- Div Director: 6/24-7/10/2015
- ODE review: 7/10-7/24/2015
- PDUFA Date: 7/24/2015

Table 1 Summary of clinical trials supporting clinical pharmacology information

Comparative BA & BE	P2 (5 completed + 2 on-going)	P3 (5 completed + on-going*) (n=5296; 3188 to alirocumab)
<ul style="list-style-type: none"> • PKD12010 (n=24) 175 vs. 150 mg/mL • PKD12011 (n=24) Cell line C1 vs. C2 • PKD12275 (n=36) 175 vs. 150 mg/mL • BDR13362 (n=60) 75 mg/mL inj sites 	<ul style="list-style-type: none"> • DF11565 (n=183, 12WK) 50/100/150 mg Q2W 200/300 mg Q4W non-FH (add-on atorv 10/20/40) • CL-1003 (n=77, 12WK) 150 mg Q2W 150/200/300 mg Q4W heFH (add-on statin ± EZ) • DF112361 (n=100, 12WK) 50/75/150 mg Q2W Japan, add-on atorv • DF11566 (n=92, 8WK) 150 mg Q2W add-on ator 10/80 mg • CL-1018 (n=23, 14WK) 50 mg Q2W mutation in PCSK9 gene / Apo B gene 	<p><u>150 mg Q2W</u></p> <ul style="list-style-type: none"> • LTS11717 (LONG TERM, n=2341, 78WK)* heFH & high CV risk non-FH (add-on MTD statins± LMT vs. PL) • EFC12732 (HIGH FH, n=107, 78W)* heFH (add-on to MTD statins ± LMT vs. PL) LDL-C>160 mg/dL (4.14 mmol/L) <p><u>75 mg Q2W, up-titrated 150 mg Q2W at WK12</u></p> <ul style="list-style-type: none"> • EFC11716 (MONO, n=103, 24WK) mod CV risk (monotherapy vs. EZ) • EFC12492 (FH I, n=486, 78WK)* heFH (add-on to MTD statins ± LMT vs. PL) • CL-1112 (FH II, n=249, 78WK)* heFH (add-on to MTD statins ± LMT vs. PL) • EFC11568 (COMBO I, n=316, 52WK) high CV risk non-FH (add-on to MTD statins ± LMT vs. PL) • EFC11569 (COMBO II, n=720, 104WK)* High CV risk non-FH (add-on to MTD statins vs. EZ) • CL-1110 (OPTIONS I, n=355, 24WK) high CV risk (add-on to non-max atorv ± ± LMT vs. EZ/ator tit/rosu) • CL-1118 (OPTIONS II, n=305, 24WK) high CV risk (add-on to non-max atorv ± ± LMT vs. EZ/rosu tit) • CL-1119 (ALTERNATIVE, n=314, 24WK) Statin intolerant (mono or add-on to non-statin LMT vs. EZ/atorv)
Healthy PK/PD		
<ul style="list-style-type: none"> • CL-0902 (n=40) IV: 0.3/1/3/6/12 mg/kg • CL-0904 (n=32) 50/100/150/250 mg • TDU12190 (n=32) 100/150/250/300 mg 		
Patient PK/PD		
<ul style="list-style-type: none"> • CL-1001 (n=62) 50/100/150 200 (n=10) • PKD12910 (n=72) 150 mg Q4W, 8 wk (mono or add-on) • POP12671 (n=25) 75 mg, hepatic (n=17) 		
Population analyses		
<ul style="list-style-type: none"> • POH0377 pop PK • POH0394 pop PK/PD 5 P1/4 P2/4 P3 • POH0500 TMDD P1/4 P2/1 P3 (MONO) 		

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/s/

SANG M CHUNG
02/27/2015

JAYABHARATHI VAIDYANATHAN
02/27/2015