

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125522Orig1s000

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA:	125522
Submission Date(s):	August 27, 2014
Brand Name	Repatha™
Generic Name	Evolocumab
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Amgen
Submission Type; Code	351(a) - Standard
Formulation; Strength(s)	<p>Injection:</p> <ul style="list-style-type: none"> • 140 mg single-use prefilled syringe; supplied as a 1-pack^{(b)(4)} <ul style="list-style-type: none"> ○ 1 ml of a 140 mg/mL solution of evolocumab • 140 mg single-use prefilled SureClick® Autoinjector; supplied as a 1-pack, 2-pack, and 3-pack^{(b)(4)} <ul style="list-style-type: none"> ○ 1 ml of a 140 mg/mL solution of evolocumab
Proposed Indication	<p>Adjunct therapy to diet to:</p> <ul style="list-style-type: none"> • Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia <ul style="list-style-type: none"> ○ in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or ○ alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or ○ alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate. • Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia
Dosage & Administration	<ul style="list-style-type: none"> • Primary hyperlipidemia or mixed dyslipidemia: Administer 140 mg every 2 weeks or 420 mg once monthly in the upper arm, thigh, or the abdomen • Homozygous familial hypercholesterolemia: Administer 420 mg either once monthly or every 2 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule
Clinical Pharmacology Review Team	Suryanarayana Sista, Justin Earp, Nitin Mehrotra, Jaya Vaidyanathan

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1 Executive Summary

The pharmacokinetics of Evolocumab (proposed trade name: Repatha™, being developed by Amgen), a proprotein convertase subtilisin kexin (PCSK9) inhibitor, are largely determined by its characteristics of being a monoclonal antibody (immunoglobulin2 subtype). Evolocumab demonstrates non-saturable proteolytic elimination. Evolocumab -PCSK9 bound complex is known to have a saturable target-mediated elimination. There are no known significant intrinsic or extrinsic factors affecting the pharmacokinetics of Evolocumab. The single-dose study in healthy volunteers comparing the to-be-marketed formulation (drug substance manufactured using Process 1) to the earlier formulation (drug substance manufactured using Process 2) demonstrated that the evolocumab pharmacokinetics and pharmacodynamics were comparable between the two formulations.

Evolocumab depletes free PCSK9 and thus decreases the low density lipoprotein cholesterol (LDL-C) concentrations in a dose-dependent manner. Evolocumab exposure increased in a dose-dependent manner in patients and LDL-C reduction reached apparent nadir after 140 mg administered once every two weeks (Q2W), or 420 mg administered once every month (QM). Increasing the exposures may not decrease LDL-C concentrations further based on the observations that the Q2W and QM regimens produce concentrations that fall near the nadir of these exposure response relationships. In general, there were no known clinically important covariates for the exposure-efficacy relationships.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 08/27/14 under BLA 125522 and recommend approval with the following comments.

- Primary Hyperlipidemia and Mixed Dyslipidemia: The sponsor's proposed dosing of either 140 mg every two weeks or 420 mg once monthly is acceptable.
- Homozygous Familial Hypercholesterolemia: The sponsor has proposed two regimens - 420 mg once monthly or 420 mg every two weeks. The 420 mg every two weeks dose appeared to offer little additional benefit (~6% additional reduction in LDL-C). Based on the exposure-response relationship in the Heterozygous familial Hypercholesterolemia population, the exposures from the once monthly dose are already in the plateau of the response curve and dosing higher amounts will not likely provide additional benefit. Further, from a safety perspective, there may be an insufficient amount of data in patients who received 420 mg every two weeks.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Evolocumab is available in the following configurations:

- 140 mg Repatha™ Single-Use pre-filled syringe (PFS); supplied as a 1-pack, containing one (1) mL of a 140 mg/mL solution of evolocumab

- 140 mg Single-Use Prefilled Repatha™ SureClick® Autoinjector; supplied as a 1 pack, 2-pack, and 3-pack, containing one (1) mL of a 140 mg/mL solution of evolocumab

Sponsor proposed the following dosing regimen:

Primary Hyperlipidemia (heterozygous familial and nonfamilial) and Mixed Dyslipidemia (collectively referred as HeFH in the document): Subcutaneous administration of 140 mg every 2 weeks (Q2W) or 420 mg once monthly (QM)

Homozygous Familial Hypercholesterolemia (HoFH): Subcutaneous administration of 420 mg either once monthly or every 2 weeks

Key pharmacokinetic and pharmacodynamic properties of Evolocumab are summarized in [Table 1](#).

Table 1 Highlights of Pharmacokinetics

Pharmacokinetics	
Absorption	<ul style="list-style-type: none"> • Non-linear pharmacokinetics up to 140 mg, and linear pharmacokinetics between 140 mg and 420 mg • Median T_{max} - 3 – 4 days • Estimated absolute bioavailability: 72%. • C_{max}: 18.6 ± 7.3 µg/mL following 140 mg dose; 59.0 ± 17.2 µg/mL following 420 mg dose • AUC_{last}: 188 ± 98.6 day·µg/mL following 140 mg dose; 924 ± 346 day·µg/mL following 420 mg dose • Mean C_{min} at weeks 12, 24, 36, and 52 were stable, and ranged between 8.23 ± 9.05 µg/mL to 10.3 ± 11.2 µg/mL following 420 mg QM over 52 weeks.
Distribution	<ul style="list-style-type: none"> • Mean (SD) steady-state volume of distribution estimated to be 3.3 ± 0.5 L, following a single 420 mg intravenous dose, suggesting evolocumab has limited tissue distribution
Metabolism and Elimination	<ul style="list-style-type: none"> • Mean systemic clearance estimated to be 12 ± 2 mL/hr • An approximate two- to three-fold accumulation was observed in serum C_{min} (7.21 ± 6.6) following 140 mg doses every 2 weeks or C_{min} (11.2 ± 10.8) following 420 mg doses administered monthly; serum trough concentrations approached steady state by 12 weeks of dosing. • Estimated effective half-life of evolocumab is 11 to 17 days • As a fully human IgG2 antibody, the clearance of evolocumab is mediated by specific binding and complex formation with its target ligand, PCSK9, as well as by typical IgG clearance processes in the reticuloendothelial system. Evolocumab is expected to be degraded into small peptides and amino acids via these catabolic pathways. • An approximately 20% increase in the clearance of evolocumab was observed in patients co-administered with statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9 • Population pharmacokinetic analysis indicated no appreciable differences in evolocumab serum concentrations in hypercholesterolemic patients (non- FH or FH) taking concomitant statins
Pharmacodynamics	
Primary Hyperlipidemia and Mixed Dyslipidemia	<ul style="list-style-type: none"> • LDL-C reduction of approximately 55% to 75% achieved as early as 1 week. Maximal response generally achieved within 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly, respectively, and maintained during long-term therapy
Homozygous Familial Hypercholesterolemia	<ul style="list-style-type: none"> • Approximately 20% to 30% in patients with HoFH not on apheresis and approximately 15% to 25% in patients with HoFH on apheresis showed reduction of LDL- after 12-week treatment of Evolocumab 420 mg once monthly and 420 mg once every 2 weeks • No overall differences in safety or efficacy of Evolocumab were observed between adolescents and adult patients with HoFH.

1.3.1 Dose/exposure-response relationship for efficacy

There is a clear exposure-response relationship between evolocumab trough concentrations and LDL-C response at week 10/12 as seen in trials 20110114 and 20110115 (Figure 1). A univariate exposure-response analysis performed using data from patients with primary hyperlipidemia and mixed dyslipidemia to ascertain the relationship between evolocumab concentrations and LDL-C lowering in order to evaluate the appropriateness of the dosing regimen suggested that increasing the exposures may not decrease

LDL-C concentrations further. The Q2W and QM regimens produce concentrations that fall near the nadir (5 µg/mL) of these exposure response relationships. The applicant's proposed dosing of either 140 mg Q2W or 420 mg QM in patients with HeFH appears reasonable.

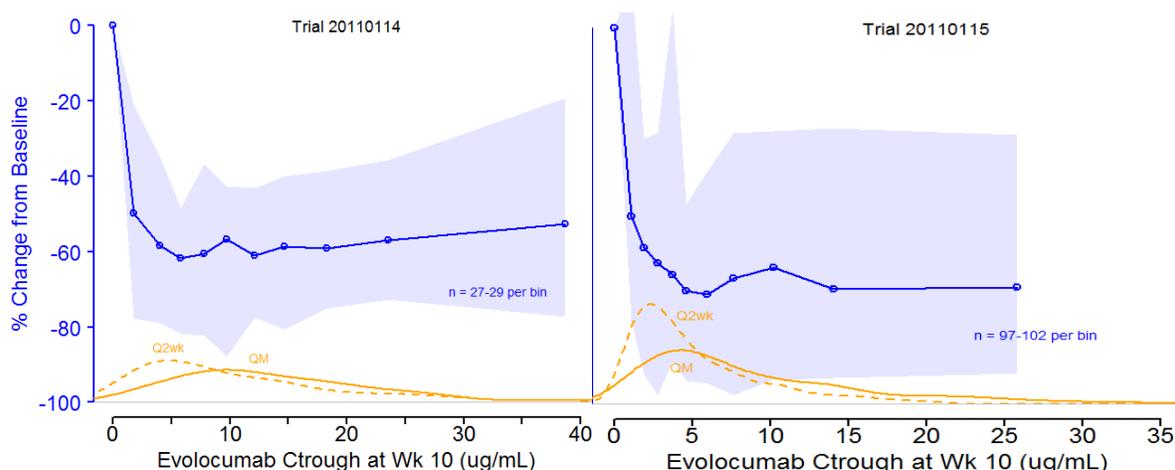


Figure 1 Exposure-response relationships for evolocumab trough concentrations at week 10 and LDL-C change from baseline in studies 20110114 (left panel) and 20110115 (right panel). Mean LDL-C and the range of 5th - 95th percentiles at the corresponding median Ctrough are shown for each of 10 exposure bins in Trial 20110114 and Trial 20110115 by the blue solid lines and shaded region. Solid orange lines depict the distribution of evolocumab Ctrough with each respective dosing regime

The 420 mg Q2W regimen appears to offer little additional benefit (~6% additional reduction in LDL-C) to HoFH patients. An analysis of the distribution of the average LDL-C concentrations over the duration of the treatment for (a) those patients that did not switch, (b) before the switch and (c) after the switch for those patients that changed their dosing frequency, showed that patients that did not up-titrate were responding better than those that required titration. There was a mild numerical lowering (6%) in the mean LDL-C concentrations in patients who up-titrated. At the individual level there was a sustaining of effect, but not much improvement was noted. Further, exposure-response data were not available in the HoFH populations. However, the relationship in the HeFH population suggests that the exposures from the QM dose are already in the plateau of the response curve and that dosing higher amounts will not likely provide additional benefit. From an efficacy perspective, the 420 mg Q2W regimen does not appear to offer much additional benefit and from a safety perspective, there may be an insufficient amount of data in patients who received 420 mg Q2W.

1.3.2 *Intrinsic Factors*

- **Age, Race and Gender:** Based on population PK of evolocumab, no dose adjustments are necessary based on age, race or gender.
- **Body Weight:** The pharmacokinetics of evolocumab were influenced by body weight, however, there were no notable effects on LDL-C lowering based on body weight.

1.3.3 *Drug-Drug Interactions:*

Since evolocumab is a monoclonal antibody, the sponsor did not conduct any *in vitro* permeability, *in vitro* metabolism, or *in vitro* metabolic drug-drug interaction studies that used human biomaterials in this program.

1.3.3.1 *Specific Population*

1.3.3.1.1 *Hepatic Impairment*

Following single 140 mg subcutaneous doses of evolocumab, the exposure to evolocumab was found to be 40% to 50% lower compared to healthy patients. However, baseline PCSK9 levels and the magnitude and time course of PCSK9 inhibition were found to be similar between patients with mild or moderate hepatic impairment and healthy patients. This resulted in similar time course and extent of absolute LDL-C lowering. No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A or B). Patients with severe hepatic impairment (Childs-Pugh C) have not been studied.

1.3.3.1.2 *Renal Impairment*

Population pharmacokinetic analysis of integrated data from the evolocumab clinical studies did not reveal a difference in pharmacokinetics in patients with mild or moderate renal impairment relative to non-renally impaired patients. No dose adjustment is recommended in patients with mild to moderate renal impairment. Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) have not been studied.

1.3.3.1.3 *Geriatric Population*

Approximately 30% of the patients studied in clinical studies of evolocumab were ≥ 65 years old, while approximately 4% were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients. No dose adjustment is recommended in geriatric patients.

1.3.3.1.4 *Pediatric Population*

The safety and effectiveness of evolocumab has not been established in pediatric patients with primary hyperlipidemia and mixed dyslipidemia. No overall differences in safety or efficacy were observed between 14 adolescent patients aged 12 years and adult patients with HoFH.

2 Question-Based Review (QBR)

2.1 General Attributes

Evolocumab is a PCSK9 inhibitor indicated as an adjunct therapy to diet to:

- Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia.
 - in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
 - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
 - alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.
- Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Date	Action
15 May 2009	The sponsor submitted the initial IND (IND 105188) to develop evolocumab for the treatment of hypercholesterolemia.
10 June, 2009	Partial clinical hold (PCH) was imposed on multiple-dose studies until the sponsor provided repeated-dose toxicity in a second pharmacologically relevant rodent species (e.g. hamster). This was based on the findings related to immune system perturbation in monkeys.
9 April, 2010	PCH removed following review of the toxicity study.
12 September, 2013	Orphan drug designation (designation # 13-4041) was granted for the treatment of HoFH.
10 July 2012	An EOP2 meeting was held to discuss the development program for evolocumab. Items discussed were: <ul style="list-style-type: none"> (a) requirement of cardiovascular outcomes trial (CVOT) data for monotherapy and superiority to ezetimibe/statin claims (b) concerns regarding only taking two dosing regimens (Q2W and Q4W) into phase 3 that seemed to yield approximately the same degree of LDL-C lowering, (c) disagreement with sponsor's proposed definition of statin-intolerance of failing 1 or more statins, (d) Agency's concerns with some of the proposed study populations who may not be taking the maximum tolerated dose of statin. (e) the design of the proposed CVOT, (f) accrual of a minimum of 25% of the planned first secondary endpoint events in the CVOT prior to BLA submission, (g) waiver of dedicated drug-drug interaction studies in lieu of collection of systemic exposure data, (h) waiver of a thorough QT study in lieu of collection of safety ECGs at baseline and at steady state and (i) Agency's agreement that the nonclinical data package should be sufficient.
10 April 2014	A pre-BLA meeting was held with the sponsor. The items discussed this meeting included the following: <ul style="list-style-type: none"> (a) The Agency will accept the evolocumab BLA file, even if less than 25% of potential events have been accrued and adjudicated in the CVOT (FOURIER

	<p>study) prior to filing of the BLA</p> <ul style="list-style-type: none"> (b) It was reconfirmed that the Agency had not shifted its position to consider a monotherapy indication or an indication explicitly referencing “statin-intolerant” patients for evolocumab without positive outcomes data. It was the expectation of the Agency that in the absence of outcomes data, the approvability of a PCSK9 inhibitor would be a topic for discussion with the Endocrine and Metabolic Drugs advisory committee (EMDAC) (c) The Agency expressed concerns about the sufficiency of the safety database and duration of exposure to support the proposed indications; (d) The Agency informed the sponsor that a different cutoff for the safety database was required, as the current estimates for the 1-year exposure would not constitute a complete file (e) The Agency requested the sponsor to submit all available PK data from the entire clinical program (phase 1, 2 and 3 studies). The inclusion of data from phase 3 studies in the population PK analysis was encouraged (f) A safety database cutoff date of 01 April 2014, including updates to all case study reports (CSRs) and affected summaries, was agreed upon between the Agency and the sponsor.
27 August 2014	The sponsor submitted the BLA (125522)

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting to discuss the BLA 125522 application is scheduled for June 10, 2015.

2.1.2 What are the highlights of the Evolocumab drug product as they relate to clinical pharmacology review?

Evolocumab consists of 2 heavy chains and 2 light chains that are covalently linked by a total of 18 disulfide bonds with a theoretical molecular weight of (b) (4). The physical and chemical properties of evolocumab are summarized in the [Table 2](#) below.

Table 2 Physicochemical Properties of Evolocumab

Evolocumab	
Immunoglobulin subclass	IgG2
Sequence	Human sequence
Biological target	Specific binding to human PCSK9
Physical Description	Clear to opalescent; colorless to yellowish; liquid, practically free from particles
Molecular Formula	(b) (4)
Molecular Mass^a	(b) (4)
Structural Formula	<p>Heavy chains are shown in blue and light chains are shown in orange V_H is the variable domain of the heavy chain C_H1, C_H2, and C_H3 are the constant domains of the heavy chain V_L is the variable domain of the light chain C_L is the constant domain of the light chain</p>
Cysteines	(b) (4)
Number of Disulfide Bonds	18
Extinction Coefficient	Theoretical: (b) (4) Determined: (b) (4)
Isoelectric Point	Theoretical: (b) (4) Determined: (b) (4)
T_m (melting temperatures)^c	(b) (4)

^a Experimentally determined molecular mass

^b Theoretical isoelectric point (b) (4)

^c Experimentally determined melting temperatures

2.1.3 What is the composition of to-be-marketed formulation of Evolocumab?

The sponsor provided description of evolocumab drug product is shown in the highlighted box below:

The drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous injection in a prefilled syringe (PFS).

The PFS contains a 1 mL syringe with 1.0 mL deliverable volume of 140 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The primary container closure consists of a 1 mL Type I glass syringe with a staked-in-place stainless steel needle covered with an (b) (4) needle shield and

a (b) (4) plunger-stopper (b) (4). The (b) (4) needle shield is made from (b) (4) and may be (b) (4) supplemented with an outer plastic rigid cover (b) (4).

The autoinjector/pen (AI/pen) is a prefilled, single-use, disposable, handheld, mechanical (spring-based) injection device that is provided ready-to-use, pre-assembled with a prefilled syringe containing a sterile, preservative-free solution of drug product. The AI/pen is used for subcutaneous administration of a fixed dose of 1.0 mL of 140 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0.

Each AI/pen contains a glass prefilled syringe. (b) (4)

The formulation composition is shown in [Table 3](#).

Table 3 Quantitative and Qualitative Composition of 140 mg/mL Prefilled Syringe

Component	Grade	Function	Concentration	Quantity (per dose)
Evolocumab	In house ^a	Active ingredient	140 mg/mL	140 mg
Proline	USP, PhEur, JP	(b) (4)	220 mM	25 mg
Acetic acid, glacial	USP, PhEur, JP	(b) (4)	20 mM	1.2 mg
Polysorbate 80	NF, PhEur, JP	(b) (4)	0.01% (w/v)	0.10 mg
Sodium hydroxide ^b	NF, PhEur, JP	(b) (4)	Titrate to pH 5.0	Titrate
Water for injection	USP, PhEur, JP	(b) (4)	(b) (4)	(b) (4)

^a Tested to internal specifications (3.2.S.4.1, Specification).

^b Sodium hydroxide may be used to adjust pH. The supplier tests sodium hydroxide (b) (4) to NF, PhEur, and JP standards.

(Source: Evolocumab BLA eCTD module 3.2.P.1; Description and Composition of the Drug Product [140 mg/mL PFS] Table 1, page 1)

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

The sponsor provided description of the mechanism of action for evolocumab is shown in the highlighted box below:

Recycling of the hepatic cell surface low-density lipoprotein receptor (LDLR) plays a critical role in the maintenance of cellular and whole body cholesterol balance by regulating plasma LDL-C concentrations. It has been shown that PCSK9 plays an important role in the recycling and regulation of LDLR. PCSK9 is a member of the subtilisin family of serine proteases and is expressed predominantly in the liver, kidney, and intestine. Following secretion, it causes post-translational down-regulation of hepatic cell surface LDLR by binding to the LDLR and targeting it for lysosomal destruction. This reduces the levels of LDLR available for LDL-C clearance from the bloodstream. Downregulation of hepatic LDLR in turn leads to increased concentrations of circulating LDL-C.

Evolocumab binds selectively and with high affinity to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

The mechanism of action of evolocumab is depicted in [Figure 2](#) below:



Figure 2 Mechanism of action for evolocumab

2.1.5 What are the proposed dosages and routes of administration?

Evolocumab is available as a subcutaneous injection. The following dosing recommendations are proposed by the sponsor:

- **Primary Hyperlipidemia and Mixed Dyslipidemia:** 140 mg every 2 weeks or 420 mg once monthly.
- **Homozygous Familial Hypercholesterolemia:** 420 mg either once monthly or every 2 weeks.

2.1.6 Was any OSIS (Office of Study Integrity and Surveillance) inspection requested for any of the clinical studies?

On 24 October 2014, the Agency held a teleconference with the sponsor to discuss the lack of bridging data between an earlier formulation (Process 1) used in Phase 1 and Phase 2 studies, and the to-be marketed formulation (Process 2) used in most of the Phase 3 studies. The Agency pointed out that the long-term safety database relied heavily on the phase 2 studies of the evolocumab clinical program. Additionally, long-term phase 3 studies (Studies 20110109, 20110110, 20120138) also used Process 1 material. Only 16 patients completed Year 1 (the control period) of the phase 3 extension study, using process 2 material. The Agency indicated to the sponsor that a strong bridge between process 1 and process 2 drug substance that provides a head-to-head data comparison data between the two processes will be needed (b) (4)

The sponsor was informed that the very low amount of long-term safety data for the intended to-be-marketed formulation was a substantial review issue. . The Agency strongly recommended that the sponsor design a bridging PK/PD comparability study to compare the two processes.

Based on the Agency's recommendation, the sponsor conducted a bridging PK/PD comparability study (Study 20110167). Since the pivotal Phase 3 trials used the to-be-marketed product, it was determined that an OSIS inspection was not needed for this bridging PK/PD comparability study.

2.2 General Clinical Pharmacology

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

The clinical pharmacology program included 26 completed or ongoing clinical studies (based on a data cutoff date of 01 April 2014) providing information on the safety, tolerability, pharmacokinetic, and pharmacodynamic properties of evolocumab or providing information on the tolerability and delivery performance of drug product presentations. Eight of the 26 studies were primarily designed as clinical pharmacology studies subcategorized as healthy subject pharmacokinetics and initial tolerability, patient pharmacokinetics and initial tolerability, and intrinsic factor pharmacokinetics. Two biopharmaceutic studies and 16 efficacy and safety studies provided supportive data on the safety, tolerability, pharmacokinetic, and pharmacodynamic properties of evolocumab.

A list of all completed clinical pharmacology studies is provided in [Table 4](#).

Table 4 Overview of studies with pharmacokinetic and pharmacodynamic assessments relevant to the clinical pharmacology of Evolocumab

Study Identifier	Study Design	Study Objective(s)	Number of Subjects/ Treatment
Healthy Subject Pharmacokinetics and Initial Tolerability Studies			
20080397	Phase 1, double-blind, randomized, placebo-controlled (ascending single dose)	To assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of evolocumab at 5 ascending SC doses and 2 ascending IV doses	42/evolocumab (7, 21, 70, 210, or 420 mg SC; or 21 or 420 mg IV) 14/placebo
20110121	Phase 1, double-blind, randomized, placebo-controlled (ascending single dose)	To assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of evolocumab at 3 ascending SC doses in Japanese subjects; and to compare the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles between Japanese and white subjects	Japanese subjects: 18/evolocumab (70, 210, or 420 mg SC) 6/placebo White subjects: 6/evolocumab (210 mg SC) 2/placebo
20120136	Phase 1, open-label, crossover (intra-subject variability)	To determine intra-subject variability in the pharmacokinetic and pharmacodynamic profiles of evolocumab following 140 mg SC dose administration in healthy adult subjects; and to evaluate safety, tolerability, and immunogenicity of evolocumab	20/evolocumab (140 mg SC, 2 doses separated by 56 days)
Patient Pharmacokinetics and Initial Tolerability			
20080398	Phase 1, double-blind, randomized, placebo-controlled (ascending multiple dose)	To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of multiple SC doses of evolocumab	43/evolocumab (14 or 35 mg SC QWx6; 140 or 280 mg SC Q2Wx3; 420 mg SC QMx2) 14/placebo
Intrinsic Factor Pharmacokinetics			
20120341	Phase 1, open-label (hepatic impairment)	To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of a single SC dose of evolocumab in subjects with mild or moderate hepatic impairment	24/evolocumab (140 mg SC single dose)
Biopharmaceutics Studies			
20110167	Phase 1, randomized, open-label, single-dose study	To demonstrate PK equivalence of Process 1 and Process 2 material	350 total (175 Process 1 175 Process 2)
20110168	Phase 1, randomized,	To demonstrate PK equivalence of the AMD	289 total

Study Identifier	Study Design	Study Objective(s)	Number of Subjects/ Treatment
	open-label, single-dose study	to the prefilled AI/pen	(145 AI/pen 144 AMD)
20120133	Phase 1, randomized, open-label, crossover study	To demonstrate PK equivalence of PFS to AI/pen	96 total (48 AI/pen:PFS 48 PFS:AI/pen)
Phase 2 Studies of Primary Hyperlipidemia and Mixed Dyslipidemia			
20101154	Phase 2, randomized, placebo- and ezetimibe-controlled, dose-ranging study	To evaluate the efficacy, safety, tolerability, and PK of evolocumab administered SC as monotherapy every 2 weeks (Q2W) or every 4 weeks (QM) for 12 weeks in subjects with low risk hypercholesterolemia	Total: 406 (136 evolocumab Q2W overall; 135 evolocumab QM overall; 90 placebo overall; 45 ezetimibe) 12 weeks: evolocumab SC Q2W (70, 105, 140 mg) evolocumab SC QM (280, 350, 420 mg) Placebo SC Q2W; Placebo SC QM; or Ezetimibe 10 mg PO QD
20101155	Phase 2, double-blind, randomized, placebo-controlled, dose-ranging study	To evaluate the safety, tolerability, and efficacy of evolocumab administered SC once Q2W or once QM in combination with statin therapy over a 12-week period in subjects with hypercholesterolemia.	Total: 629 (236 evolocumab Q2W overall 238 evolocumab QM overall 155 placebo overall) 12 weeks: evolocumab SC Q2W (70, 105, 140 mg) evolocumab SC QM (280, 350, 420 mg) Placebo SC Q2W Placebo SC QM
20090158	Phase 2, double-blind, randomized, placebo-controlled, study	To evaluate the safety and efficacy of 12 weeks of Evolocumab SC, compared with placebo, on the percent change from baseline in LDL-C in subjects with heterozygous familial hypercholesterolemia (HeFH).	Total: 167 (111 Evolocumab QM 56 placebo) 12 weeks: Evolocumab SC QM (350, 420 mg) Placebo SC QM
20090159	Phase 2, randomized, study	To evaluate the efficacy, safety, and tolerability of 12 weeks of Evolocumab SC compared with ezetimibe in subjects with hypercholesterolemia who are unable to tolerate an effective dose of a statin	Total: 157 (95 Evolocumab QM 30 Evolocumab plus ezetimibe 32 ezetimibe) 12 weeks: Evolocumab SC QM (280, 350, 420 mg) Evolocumab SC QM (280, 350, 420 mg) + ezetimibe 10 mg PO QD Placebo SC QM + ezetimibe 10 mg PO QD
20110231	Double-blind, randomized, placebo-controlled, multicenter study	To evaluate tolerability and efficacy of Evolocumab on LDL-C in combination with stable statin therapy in Japanese subjects with hypercholesterolemia and high cardiovascular risk	Total: 310 (101 Evolocumab Q2W 104 Evolocumab QM 52 placebo Q2W 50 placebo QM) 12 weeks: Evolocumab SC Q2W (70, 140 mg) Evolocumab SC QM (280, 420 mg) Placebo SC Q2W Placebo SC QM
20110110	multicenter, controlled, open-label extension study	to assess the long-term safety and efficacy of evolocumab (interim analysis)	Total: 1324 (882 Evolocumab + SOC 442 SOC alone) Year 1: Evolocumab 420 mg SC QM + standard of care (SOC) SOC alone Years 2-5: Evolocumab 420 mg SC QM + SOC
Phase 3 Studies of Primary Hyperlipidemia and Mixed Dyslipidemia			

Study Identifier	Study Design	Study Objective(s)	Number of Subjects/ Treatment
20110114	Phase 3, double-blind, randomized, double-dummy, placebo- and ezetimibe-controlled, parallel-group study	To evaluate the efficacy, safety, tolerability, and PK of Evolocumab administered SC as monotherapy Q2W or QM for 12 weeks in subjects with primary hyperlipidemia and mixed dyslipidemia and a 10-year Framingham Risk score of 10% or less	Total: 614 (153 Evolocumab Q2W 153 Evolocumab QM 76 placebo Q2W 78 placebo QM 77 ezetimibe [Q2W] 77 ezetimibe [QM]) 12 weeks: Evolocumab 140 mg SC Q2W (+placebo PO QD) Evolocumab 420 mg SC QM (+placebo PO QD) Placebo SC Q2W (+placebo PO QD) Placebo SC QM (+placebo PO QD) Ezetimibe 10 mg PO QD (+ placebo SC Q2W) Ezetimibe 10 mg PO QD (+ placebo SC QM)
20110115	Double-blind, randomized, placebo and ezetimibe controlled, multicenter study	To evaluate safety, tolerability and efficacy of Evolocumab on LDL-C in combination with statin therapy in subjects with primary hypercholesterolemia and mixed dyslipidemia	Total: 1899 (557 Evolocumab Q2W 562 Evolocumab QM 281 placebo Q2W 278 placebo QM 112 ezetimibe [Q2W] 109 ezetimibe [QM]) 12 weeks (with statin ^a): Evolocumab 140 mg SC Q2W (+placebo PO QD) Evolocumab 420 mg SC QM (+placebo PO QD) Placebo SC Q2W (+placebo PO QD) Placebo SC QM (+placebo PO QD) Ezetimibe 10 mg PO QD (+ placebo SC Q2W) Ezetimibe 10 mg PO QD (+ placebo SC QM)
20110116	Double-blind, randomized, multicenter study	To evaluate safety and efficacy of Evolocumab, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor (statin)	Total: 307 (103 Evolocumab Q2W 102 Evolocumab QM 51 ezetimibe [Q2W] 51 ezetimibe [QM]) 12 weeks: Evolocumab 140 mg SC Q2W (+placebo PO QD) Evolocumab 420 mg SC QM (+placebo PO QD) Ezetimibe 10 mg PO QD (+ placebo SC Q2W) Ezetimibe 10 mg PO QD (+ placebo SC QM)
20110117	Double-blind, randomized, placebo-controlled, multicenter study	To evaluate safety, tolerability and efficacy of Evolocumab on LDL-C in subjects with HeFH	Total: 331 (111 Evolocumab Q2W 110 Evolocumab QM 55 Placebo Q2W 55 Placebo QM) 12 weeks: Evolocumab 140 mg SC Q2W Evolocumab 420 mg SC QM Placebo SC Q2W Placebo SC QM
20110109	Double-blind, randomized, placebo-controlled, multicenter study	To evaluate long-term tolerability and durable efficacy of Evolocumab on LDL-C in subjects with primary hyperlipidemia and mixed dyslipidemia	Total: 905 (602 Evolocumab QM 303 placebo QM) 12 weeks:

Study Identifier	Study Design	Study Objective(s)	Number of Subjects/ Treatment
			Evolocumab 420 mg SC QM Placebo SC QM
20120138	Multicenter, controlled, open-label extension study	To assess the long-term safety and efficacy of evolocumab (interim analysis)	Total: 645 ^c (432 Evolocumab + SOC 213 SOC alone) Year 1: Evolocumab 140 mg SC Q2W + SOC Evolocumab 420 mg SC QM + SOC SOC alone Years 2-5: Evolocumab 420 mg SC QM + SOC
20110233	2 part, phase 2/3 study	To assess the safety, tolerability and efficacy of Evolocumab in subjects with HoFH: Part A – open-label, single-arm, multicenter pilot study; Part B – double-blind, randomized, placebo- controlled, multicenter study	Part A: 8 Part B: 50 (33 Evolocumab, 16 placebo) 12 weeks: Part A (open-label): Evolocumab 420 mg SC QM Part B (randomized): Evolocumab 420 mg SC QM Placebo SC QM
20110271	Multicenter, open-label study	To assess the long-term safety, tolerability, and efficacy of Evolocumab on LDL-C in subjects with severe familial hypercholesterolemia	Total: 198 (198 Evolocumab) Up to 5 years: Evolocumab 420 mg SC QM (Q2W as clinically indicated)
20120348	Multi-center, Randomized Study in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia	To assess subjects' ability to administer a full dose of evolocumab in home-use, using either a prefilled syringe or a prefilled autoinjector/pen	Total: 149 (75 PFS 74 AI/pen) 6 weeks: Evolocumab 140 mg SC Q2W (by PFS) Evolocumab 140 mg SC Q2W (by AI/pen)
20120356	Multi-Center, Randomized Study in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia	To assess subjects' ability to administer a full dose of evolocumab in home-use, using either a 3.5 mL personal injector or a prefilled autoinjector/pen.	Total: 164 (82 AI/pen 82 AMD) 12 weeks: Evolocumab 420 mg SC QM (by AI/pen) Evolocumab 420 mg SC QM (by AMD)

AI/pen = autoinjector/pen; AMD = automated mini-doser; AUEC = area under the effect curve; CHD = coronary heart disease; C_{min} = minimum concentration;

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamics; PFS = prefilled syringe; PK = pharmacokinetics; PO = per os (orally); Q2W = once every 2 weeks; QM = once monthly (every 4 weeks); SC = subcutaneous(ly); SOC = standard of care.

^a Atorvastatin 10 or 80 mg QD, rosuvastatin 5 or 40 mg QD, or simvastatin 40 mg.

^b Atorvastatin cohorts only.

(b) (4)

2.2.2 Are the active moieties in plasma/serum appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes.

PK:

Measurement of evolocumab using enzyme-linked immunosorbent assay (ELISA) was used in clinical pharmacology studies, phase 2 and phase 3 trials.

PD:

In each study, serum LDL-C concentrations and other lipid parameters were quantified using standard laboratory procedures. A direct measure of LDL-C by ultracentrifugation (UC) was also used in each study. A validated ELISA was used to quantify unbound PCSK9 serum concentrations. Since the mechanism of action for evolocumab is inhibition of PCSK9 thereby lowering LDL-C levels, it is appropriate to monitor LDL-C and PCSK9 levels.

Efficacy:

Besides LDL-C, the efficacy studies also evaluated total cholesterol, apolipoprotein B (ApoB), non-HDL-C, total cholesterol (TC)/HDL-C, and ApoB/apolipoprotein A1 (ApoA1) very low-density lipoprotein cholesterol (VLDL-C), triglycerides, lipoprotein(a) (Lp[a]), and increasing HDL-C and ApoA1.

2.3 Exposure Response

2.3.1 What data from the phase 2 studies contributed to the selection of the phase 3 doses?

Dose selection for the phase 3 studies was supported by results from the phase 1 and phase 2 single-dose and multiple dose studies (Studies 20080397, 20080398, 20090158, 20090159, 20101154, and 20101155). The selection of 140 mg and 420 mg originated from the dose-ranging phase 1 studies 20080397 and 20080398 (Figure 3 and Figure 4, respectively). The dose-ranging studies in phase 2 evaluated evolocumab dosed as 70 mg, 105 mg, and 140 mg Q2W and 280 mg, 350 mg, and 420 mg QM. In all cases, the efficacy was the greatest with the highest doses (i.e. 140 mg Q2W and 420 mg QM). The applicant noted that increased adverse events were not associated with increased evolocumab dose. These doses were carried forward into the phase 3 program and tested in a randomized parallel comparison with placebo and ezetimibe.

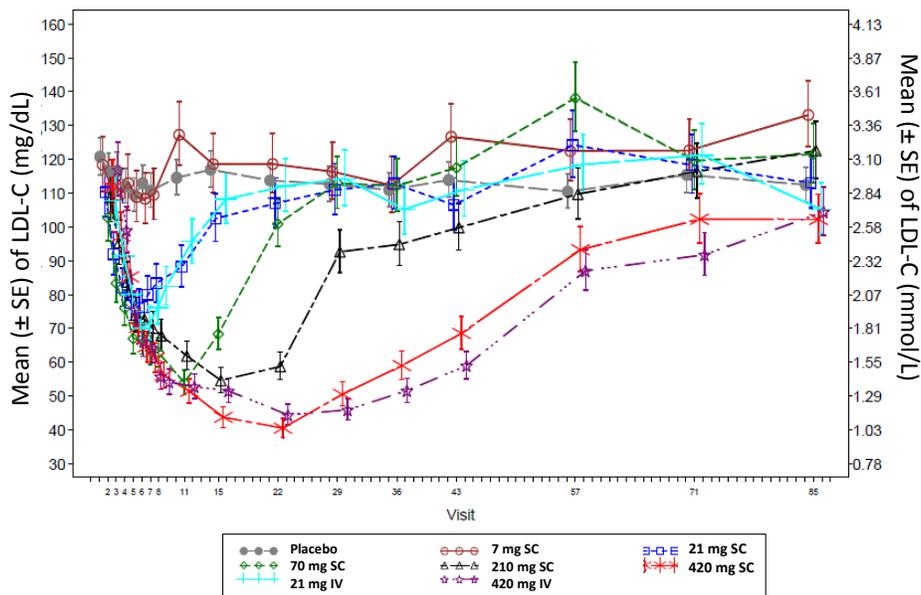


Figure 3. Geometric Mean (SE) of LDL-C over time (Study 20080397)

(Source Applicant's Summary of Clinical Pharmacology Studies, Figure 3)

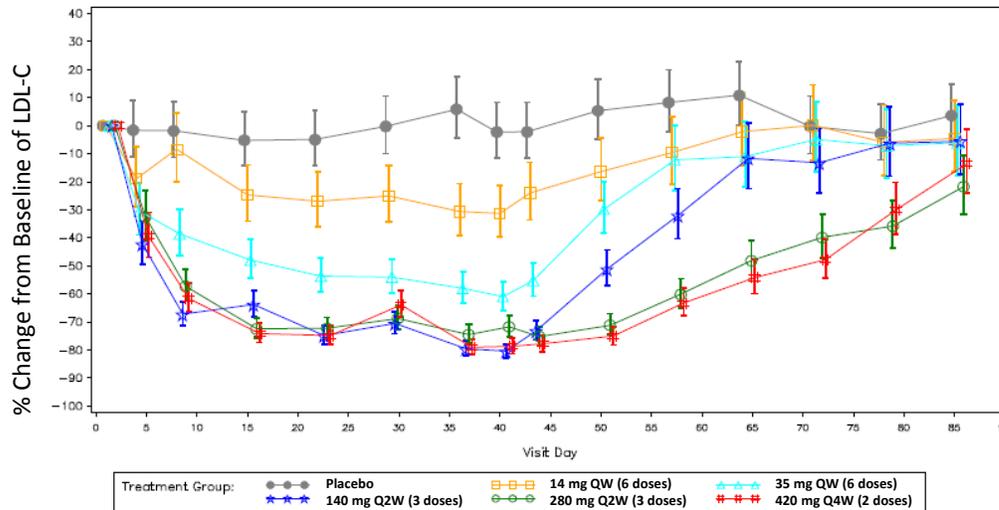


Figure 4. Percent Change from Baseline (\pm SE) of LDL-C over time on low-moderate statins (Study 20080398)

(Source Applicant's Summary of Clinical Pharmacology Studies, Figure 10)

2.3.2 What are the characteristics of the exposure-response relationships for effectiveness?

There is a clear exposure-response relationship between evolocumab trough concentrations and LDL-C response at week 10/12 in trials 20110114 and 20110115. The mean change from baseline LDL-C for each of 10 exposure bins were plotted against the median evolocumab trough concentration for the respective exposure bin in studies 20110114 (Figure 5, left panel) and 20110115 (Figure 5, right panel). The shape of the curves between the two studies appears similar with the nadirs occurring close to 5 μ g/mL.

This univariate analysis would suggest that increasing the exposures may not decrease LDL-C concentrations further. The Q2W and QM regimens produce concentrations that fall near the nadir of these exposure response relationships, as seen by comparing the peaks of the orange density plots for each dosing regimen in Figure 5. This was consistent with the applicant's findings.

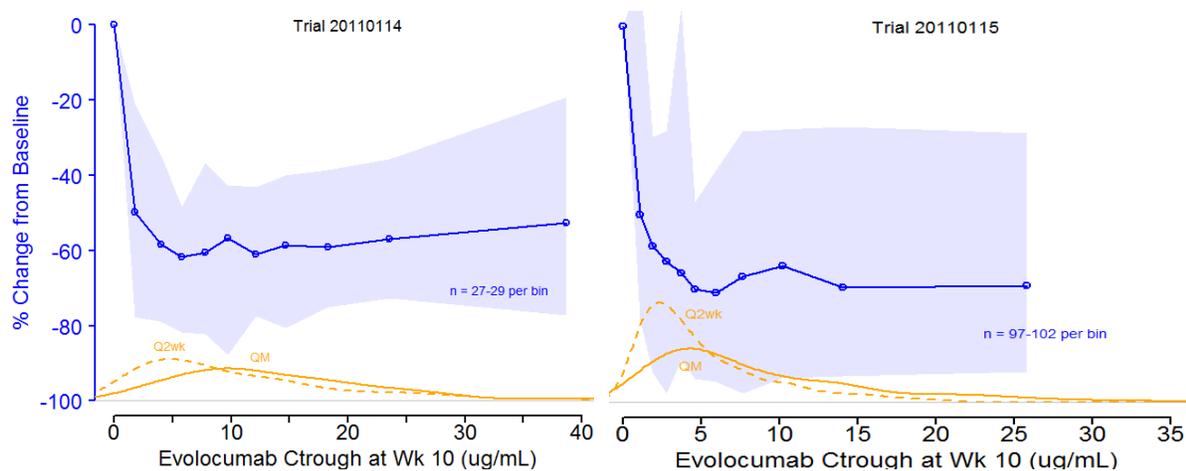


Figure 5. Exposure-response relationships for evolocumab trough concentrations at week 10 and LDL-C change from baseline in studies 20110114 (left panel) and 20110115 (right panel).

(Mean LDL-C and the range of 5th – 95th percentiles at the corresponding median C_{trough} are shown for each of 10 exposure bins in Trial 20110114 and Trial 20110115 by the blue solid lines and shaded region. Solid orange lines depict the distribution of evolocumab C_{trough} with each respective dosing regimen.)

Additionally, the LDL-C change from baseline and percent change from baseline at weeks 10 and 12 were evaluated against different baseline demographic factors. No clinically meaningful correlations between baseline PCSK9, baseline LDL-C, age, sex, race, weight, and statin use were found to influence LDL-C for either evolocumab dosing regimen.

As the responses appeared to be similar between regimens and no baseline demographic factors were identified that might inform which dosing regimen to give. The applicant's proposed dosing of either 140 mg Q2W or 420 mg QM in patients with HeFH appears reasonable.

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

Dose-response was not evident for adverse events by evolocumab dose in the phase three trials. Refer to the clinical review by Dr. Eileen Craig for a comparison of the adverse events across the phase 3 trials (with the exception of trial 20110109) between ezetimibe, evolocumab 140 Q2W and evolocumab 420 mg QM. No differences in adverse event rate were identified by dose in this table.

Indirect exposure-response analysis was considered due to the relationship between evolocumab AUC and body weight. There is a 6-7 fold change in evolocumab AUC across the range of studied body weights (40 – 140 kg) or a change of 2-3 fold at either end when compared to the AUC at the median weight. The pharmacometric review describes in more detail an attempt to correlate the rate of adverse events of each system organ class by body weight. No clinically meaningful relationships were identified (Section 4.1).

Given the well-tolerated safety profile, the lack of any correlation between AEs and body weight and that there were no major specific events of concern, no direct exposure response analyses were performed.

2.3.4 Does this drug prolong QT/QTc interval?

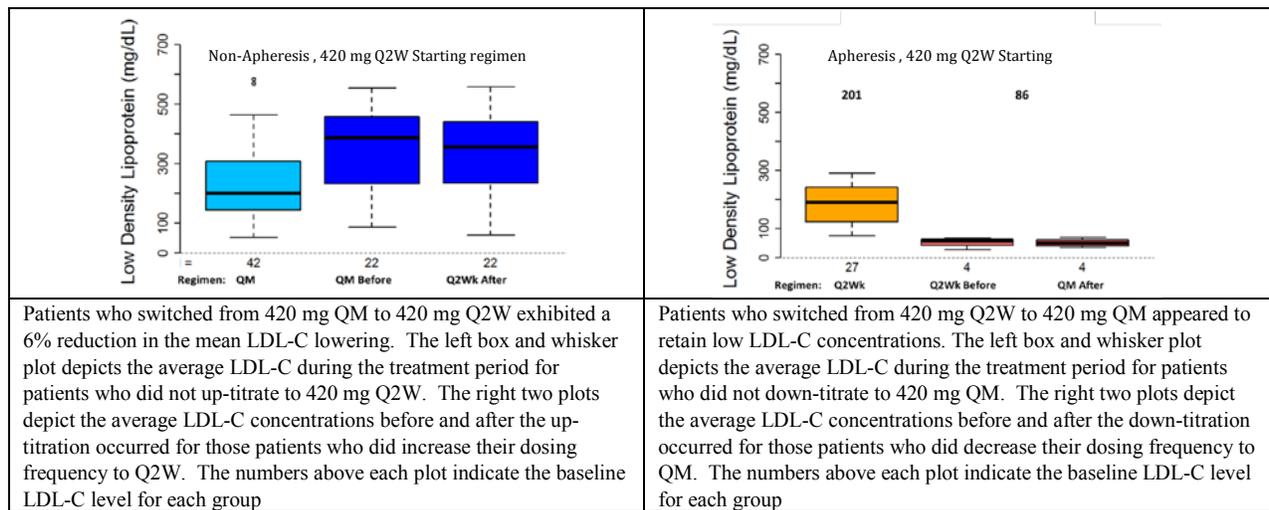
Evolocumab does not prolong QT/QTc interval. A thorough QT study is not required for a monoclonal antibody. Refer to clinical review on QTc related information from phase 3 trials. No major concerns were noted.

2.3.5 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Primary Hypercholesterolemia: Yes, the proposed dosing regimen of 140 Q2W or 420 QM in patients with primary hypercholesterolemia is acceptable. The exposures achieved from the 140 mg Q2W and 420 mg QM dosing regimens, produce exposures that fall near the nadir of the exposure response curves for LDL-C lowering ([Figure 5](#)) as seen by comparing the peaks of the density plots for each dosing regimen.

Additionally, the LDL-C change from baseline and percent change from baseline at weeks 10 and 12 were evaluated against different baseline demographic factors. No clinically meaningful correlations between baseline PCSK9, baseline LDL-C, age, sex, race, weight, and statin use were found to influence LDL-C for either evolocumab dosing regimen. Based on the results of the phase 3 studies 20110114 and 20110115, it is not anticipated that higher doses or one of the studied regimens will offer more benefit. See the pharmacometric review (Section 4.1, [page 76](#)) for further details on the assessment of response by dose group for different baseline demographics.

Homozygous Hypercholesterolemia: The 420 mg Q2W regimen appears to offer little additional benefit (~6% additional reduction in LDL-C) to HoFH patients.



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

Details of the PK/PD characteristics of evolocumab are discussed below:

2.4.1 Single Dose

Single-dose pharmacokinetics of Evolocumab in healthy subjects are available from 2 studies. A dose range of 7 mg to 420 mg administered subcutaneously were investigated in studies 20080397 and

20110121. Study 20080397 also investigated doses of evolocumab 21 mg and 420 mg administered intravenously.

(a) Study 20080397:

IV Administration: Data from cohorts receiving intravenous dose in this study were used to estimate systemic clearance (CL) and steady-state volume of distribution (V_{ss}) of evolocumab. Estimated values for mean systemic clearance were 68.3 ± 16 mL/hr and 11.6 ± 2.26 mL/hr for the 21 mg and 420 mg intravenous doses, respectively. Corresponding V_{ss} values were 3340 ± 558 mL and 3340 ± 460 mL, approximating plasma volume of 4L. Clearance declining as a function of dose was indicative of non-linear elimination, as was also observed following sub-cutaneous dosing.

SC Administration: Mean apparent clearance (CL/F) values following SC dosing ranged from 101 ± 129 mL/hr to 24.2 ± 12.5 mL/hr for the 70 mg and 420 mg dose groups, respectively. Similarly, the median time to maximum concentration (t_{max}) for evolocumab ranged from 48 hours in the 21-mg SC group to 168 hours in the 420-mg SC group, increasing with increasing dose. These observations are consistent with drugs that exhibit target-mediated disposition. At low doses, elimination was mediated by evolocumab binding to its ligand, PCSK9. At doses ≥ 210 mg SC, CL/F plateaued with disposition characteristic of endogenous IgG2, indicating that at these concentrations for the majority of time observed antibody elimination was not mediated by binding to PCSK9.

Representative mean plasma concentration-time profiles of Evolocumab following single-dose administrations are illustrated in [Figure 6](#) below for normal healthy volunteers.

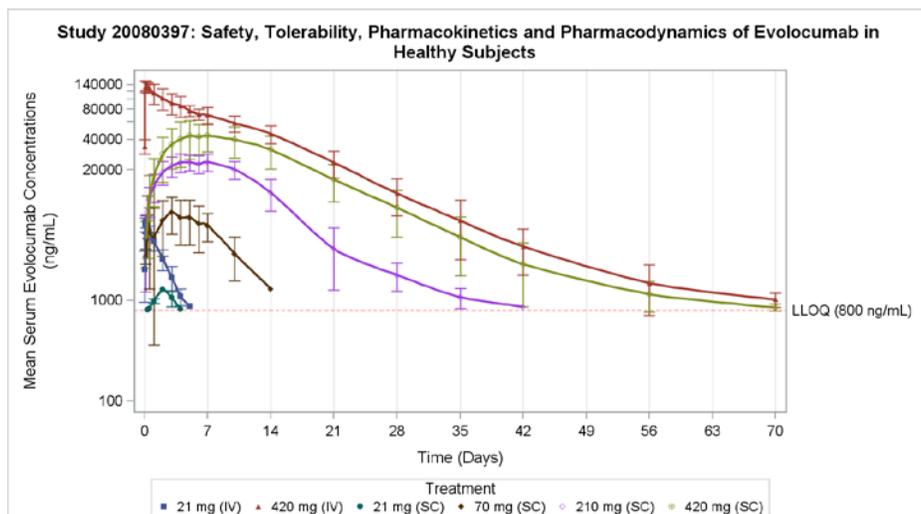


Figure 6 Mean serum concentration-time profile of Evolocumab following single-dose administration

The sponsor used a power model to assess dose proportionality in the SC groups, and observed that the slopes of the model for all parameters exceeded unity; the C_{max} and AUC_{0-inf} point estimates of the slope (90% confidence interval) were 1.23 (1.06, 1.40) and 1.63 (1.29, 1.96), respectively, over a 20-fold range of doses (21 mg to 420 mg), indicating that evolocumab serum concentrations increased in a greater-than-dose-proportional manner with increasing dose.

LDL-C: Following single-dose administrations of evolocumab, mean LDL-C reductions from baseline were dose related with respect to magnitude of decrease, time to nadir, and overall duration of decrease (Figure 7). For the doses that were administered both SC and IV (21 mg and 420 mg), little difference between groups as a function of route of administration was apparent. For the 21 mg SC and 21 mg IV groups, LDL-C nadirs were approximately 70 to 76 mg/dL and were reached at approximately day 5 or day 6 after dosing, with subsequent returns to baseline by approximately day 15 to day 22. Mean LDL-C decrease over time in the 420-mg SC and 420-mg IV groups were more pronounced and were similar between the 2 groups; nadirs of 40 to 44 mg/dL were reached at approximately day 22 after dosing, with subsequent returns to near baseline by approximately day 71. Nadirs of approximately 54 to 55 mg/dL were reached at approximately day 11 and day 15 after dosing, respectively, with subsequent returns to baseline by approximately day 29 and day 43 to day 57, were seen for the 70 mg SC and 210 mg SC dose groups.

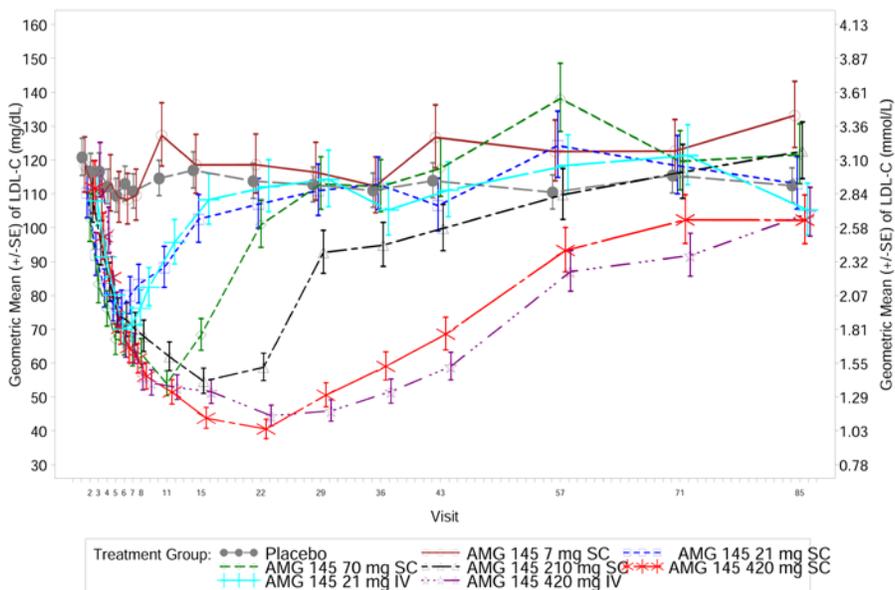


Figure 7 Mean LDL-C-time profile for LDL-C following single-dose administration

PCSK9: Baseline mean values for PCSK9 were in the range of 219 to 320 ng/mL for all groups. In all dose groups except the 7-mg SC group and the 21-mg SC group, mean PCSK9 rapidly decreased to below the LLOQ of 15 ng/mL (Figure 8). The duration of decrease to below LLOQ and the rate of return to baseline were dose dependent.

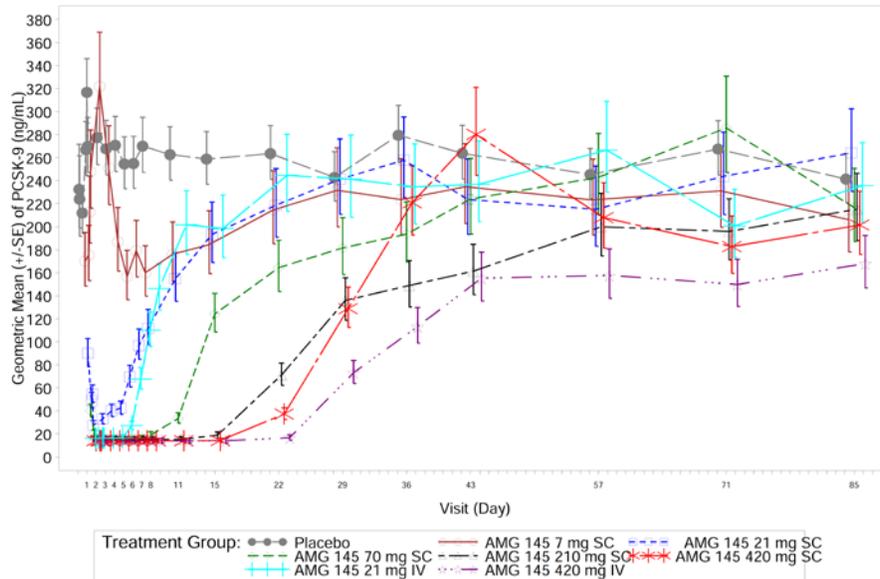


Figure 8 Mean PCSK9-time profile or % Change from Baseline for PCSK9 following single-dose administration

(b) Study 20110121

Study 20110121 evaluated the single-dose PK of evolocumab in Japanese population at doses ranging from 70 mg to 420 mg, and compared the PK at a 210 mg dose between Japanese and Caucasian subjects. The mean C_{max} in the Japanese cohorts who received evolocumab ranged from 9.53 $\mu\text{g/mL}$ at the 70 mg SC dose to 104 $\mu\text{g/mL}$ at the 420 mg SC dose. Evolocumab serum concentration-time profile and AUC_{inf} showed that nonlinear pharmacokinetic behavior of evolocumab seen in study [20080397](#) was also observed in Japanese subjects. A short terminal elimination phase and a less than dose proportional change in mean AUC_{inf} was observed in subjects receiving the 70 mg SC dose. A greater than dose proportional mean AUC_{inf} change was observed in subjects receiving 210 mg SC and 420 mg SC compared with subjects who received 70 mg SC dose. The C_{max} and AUC_{inf} changes were approximately dose proportional between the 210 mg and 420 mg SC doses indicating linearity of pharmacokinetics at these doses.

Representative mean plasma concentration-time profiles of Evolocumab following single-dose administrations are illustrated in [Figure 9](#) below for normal healthy volunteers. At a SC dose of 210 mg, Japanese subjects had a similar evolocumab profile compared with Caucasian subjects. Point estimate comparisons for Japanese subjects vs. Caucasian subjects for C_{max} and AUC_{inf} ratios were 0.955 and 0.947, respectively. The median t_{max} for evolocumab was 6.5 days in Japanese subjects compared to 6.0 days in Caucasian subjects.

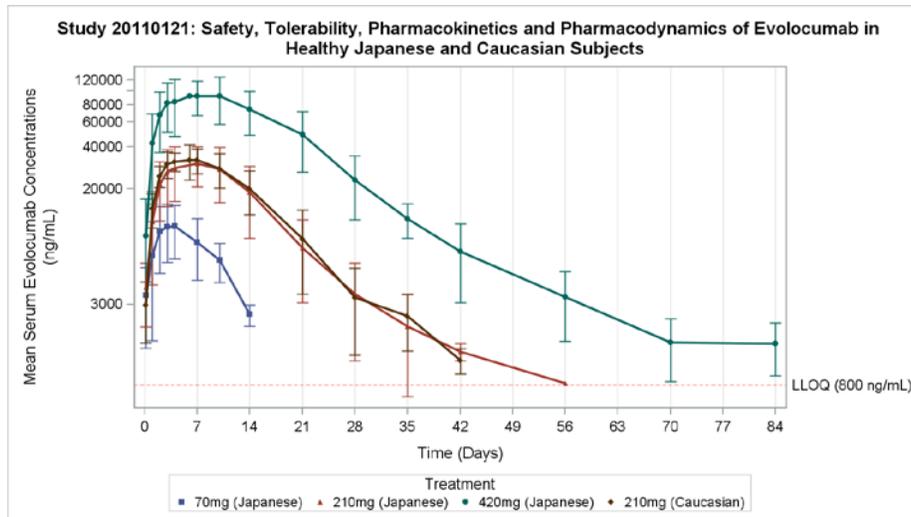


Figure 9 Mean serum concentration-time profile of Evolocumab following single-dose administration

LDL-C: Reduction in LDL-C was observed by day 3 for the 210 mg dose group and by day 4 for the 70 mg and 420 mg dose groups. Over time LDL-C levels gradually returned to baseline, or near baseline, levels thereafter but remained significantly lower than placebo though day 29 for the 70 mg treatment group, day 36 for the 210 mg group and through day 57 for the 420 mg group (Figure 10). Relative to placebo, the maximum mean percent reductions of LDL-C were 40.7%, 60.3% and 57.6% in the 70 mg, 210 mg and 420 mg evolocumab dose groups, respectively. The time course of LDL-C for Caucasians followed a pattern similar to that seen in Japanese subjects. The mean maximum percent reduction in LDL-C, relative to placebo, after the single 210 mg dose was 60.3% in Japanese subjects and 66.3% in Caucasian subjects.

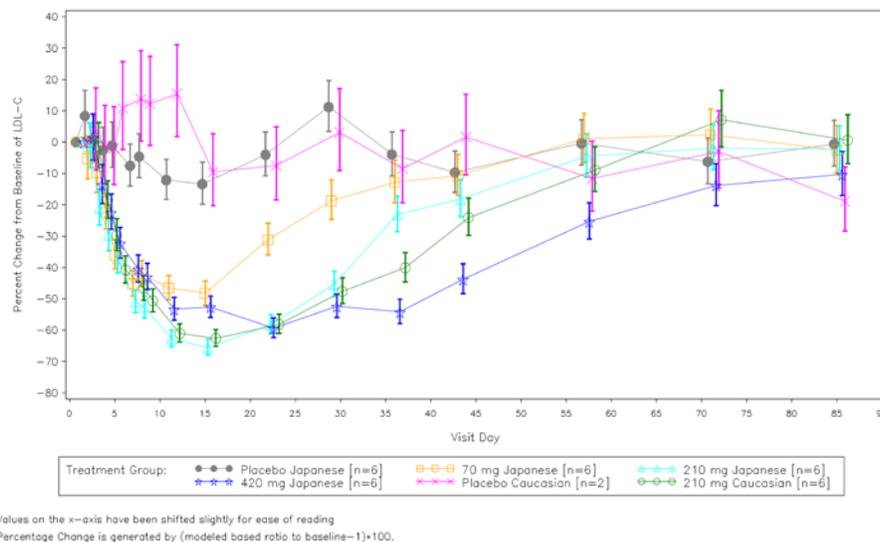
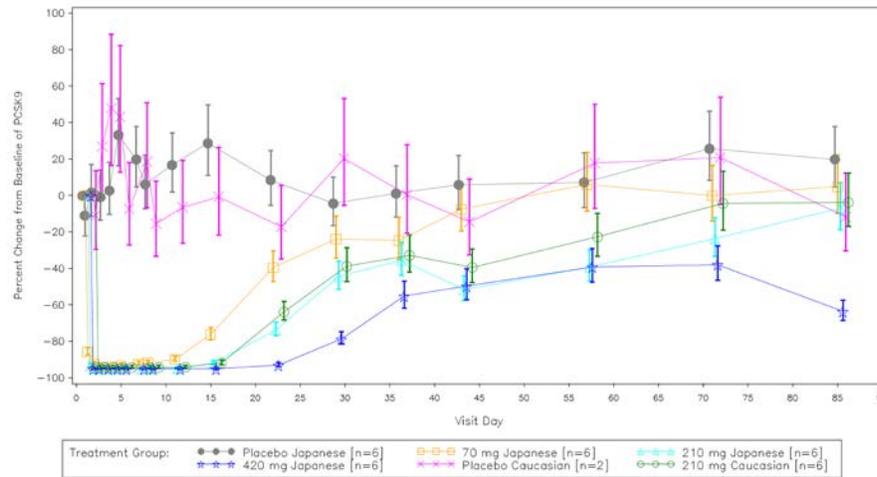


Figure 10 Mean LDL-C % Change from Baseline for LDL-C following single-dose administration

PCSK9: Within the Japanese study population, a lowering of mean PCSK9 to near complete suppression in all treatment groups at day 2 was observed following treatment with evolocumab (Figure 11). PCSK9 levels returned toward baseline gradually, remaining below baseline levels through day 43 for the 70 mg group and through the end of study (day 85) for the 210 mg and 420 mg groups.



Values on the x-axis have been shifted slightly for ease of reading
 Percentage Change is generated by (modeled based ratio to baseline-1)*100.
 BDL of PCSK9 is set of low limit level of 15 ng/mL.

Figure 11 Mean PCSK9-time profile or % Change from Baseline for PCSK9 following single-dose administration

The mean and SD of pharmacokinetic parameters for evolocumab across the single-dose studies are presented in [Table 5](#) and [Table 6](#) below.

Table 5 Mean (SD) Pharmacokinetic Parameter Estimates of Evolocumab Following IV or SC Administration of Evolocumab in Healthy Subjects

Treatment Description	N	t_{max} (hr) ^a	C_{max} (µg/mL)	AUC_{0-t} (day·µg/mL)	CL (mL/hr)	V_{ss} (mL)	CL/F (mL/hr)
AMG 145 7 mg SC	6	NC	0 (0)	0 (0)	NC	NC	NC
AMG 145 21 mg SC	6	48.00 (24.00-72.00)	0.526 (0.590)	0.771 (1.06)	NC	NC	NC
AMG 145 70 mg SC	6	96.00 (72.00-120.00)	7.19 (3.54)	48.1 (29.9)	NC	NC	101 (129)
AMG 145 210 mg SC	6	132.00 (96.00-240.00)	24.7 (4.27)	343 (94.1)	NC	NC	26.5 (6.86)
AMG 145 420 mg SC	6	168.00 (96.00-168.00)	46.0 (17.2)	842 (333)	NC	NC	24.2 (12.5)
AMG 145 21 mg IV	6	NR	6.11 (0.864)	10.7 (3.28)	68.3 (16.0)	3340 (558)	NC
AMG 145 420 mg IV	6	NR	139 (16.0)	1550 (348)	11.6 (2.26)	3340 (460)	NC

^a t_{max} (hr) is median (min-max); t_{max} not reported (NR) for IV administration

Abbreviations: AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; CL = serum clearance after IV administration; CL/F = apparent serum clearance after SC administration; C_{max} = maximum observed concentration; IV = intravenous; NC = not calculated; NR = not reported; SC = subcutaneous; SD = standard deviation; t_{max} = time of C_{max} ; V_{ss} = volume of distribution at steady state after IV administration

Summary of Slopes for Evolocumab Dose/Exposure Analyses					
Route	PK Parameter	N	Intercept	Slope	90% Confidence Interval of Slope
SC	C _{max}	21	-3.52	1.23	(1.06, 1.40)
	AUC _{0-last}	21	-5.63	2.09	(1.80, 2.38)
	AUC _{0-inf}	18	-3.04	1.63	(1.29, 1.96)
IV	AUC _{0-last}	12	-2.76	1.67	(1.57, 1.77)
	AUC _{0-inf}	12	-2.25	1.59	(1.51, 1.66)

Slope is calculated from a linear regression model with log-transformed PK parameter as a dependent variable and log-transformed dose level as an independent variable.

Abbreviations: AUC_{0-inf} = area under the concentration-time curve from time 0 to infinity; AUC_{0-last} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; IV = intravenous; PK = pharmacokinetics; SC = subcutaneous

(source: eCTD Module 5.3.4.1, Report of Study 20080397; Table 10-5, Page 83 and Table 10-6, page 84)

Table 6 Mean Pharmacokinetic Parameter Estimates of Evolocumab Following SC Administration of Evolocumab in Healthy Japanese and Caucasian Subjects

Parameter	Descriptive Statistic	70 mg SC Japanese Subjects	210 mg SC Japanese Subjects	210 mg SC Caucasian Subjects	420 mg SC Japanese Subjects
AUC _{last} (day*µg/mL)	n	6	6	6	6
	Mean	76.3	501	504	1970
	SD	58.0	218	139	749
	CV%	75.9	43.5	27.7	38.1
	Median	80.6	541	516	1910
	Min	0.00	235	303	1220
AUC _{inf} (day*µg/mL)	n	5	6	6	6
	Mean	108	511	542	2510
	SD	51.5	220	160	1250
	CV%	47.8	43.1	29.4	49.9
	Median	118	551	552	2500
	Min	30.6	244	312	1250
C _{max} (µg/mL)	n	6	6	6	6
	Mean	9.53	31.9	33.0	104
	SD	6.37	11.1	7.06	31.4
	CV%	66.8	34.8	21.4	30.2
	Median	10.3	34.3	35.4	121
	Min	0.00	15.8	23.7	60.2
t _{max} (day)	n	5	6	6	6
	Mean	NR	NR	NR	NR
	SD	NR	NR	NR	NR
	CV%	NR	NR	NR	NR
	Median	3.0	6.5	6.0	6.5
	Min	2.0	4.0	3.0	3.0
	Max	4.0	9.0	7.0	10

AUC_{last} = Area of the AMG 145 concentration-time curve from time = 0 to the last measurable concentration

AUC_{inf} = Area of the AMG 145 concentration concentration-time curve from time = 0 extrapolated to infinity

C_{max} = Maximum observed AMG 145 concentration

t_{max} = Time of maximum observed AMG 145 concentration reported only as median to 2 significant figures

NR = Not reported

(source: eCTD Module 5.3.4.1, Study Report 20110121; Table 10-3, page 60)

2.4.2 Multiple Once Daily Doses

Multiple-dose pharmacokinetics of evolocumab are available from one Phase 1 study. Additional supportive pharmacokinetic data are available from several Phase 2 and 3 studies. The Phase 1 study was a placebo-controlled, ascending, multiple-dose study in subjects with hyperlipidemia taking a stable dose of a statin. The primary objective of the study was to evaluate the safety, tolerability, and immunogenicity profile of evolocumab following multiple SC doses of evolocumab in subjects taking a stable dose of a statin. Several dose of evolocumab were evaluated as shown in the matrix below:

Dose Cohorts (Study 20080398)

Cohort	Inclusion Criterion	Evolocumab Dose (mg)	Frequency	Total Dose (mg)	Planned N	Evolocumab: Placebo
1	Hypercholesterolemia, low- or moderate-dose statin	14	QWx6	84	8	3:1
2		35	QWx6	210	8	3:1
3		140	Q2Wx3	420	8	3:1
4		280	Q2Wx3	840	8	3:1
5		420	QMx2	840	8	3:1
6	Hypercholesterolemia, high-dose statin	140	Q2Wx3	420	12	3:1
7	HeFH	140	Q2Wx3	420	6	2:1

Note: Evolocumab (in 1 mL, 70 mg/mL vials) and placebo were administered by subcutaneous injection. Within each cohort, the volume of placebo injected was matched to active investigational product injected (range: 0.2 mL [cohort 1] to 6.0 mL [cohort 5]). HeFH = heterozygous familial hypercholesterolemia; QW = once weekly; Q2W = once every 2 weeks; QM = once monthly (every 4 weeks).

Evolocumab C_{max} was observed approximately 1 week following SC dosing after the first and last doses. Unbound evolocumab serum concentrations demonstrated accumulation during the Q2W regimens but less accumulation occurred with the 420 mg SC dose administered QM, as is expected with less frequent administration. Unbound evolocumab exhibited nonlinear pharmacokinetics following multiple doses up to 140 mg. Doses of evolocumab greater than 140 mg SC resulted in concentrations associated with near complete suppression of its ligand, PCSK9, and in this dose range, unbound evolocumab exhibited principally linear pharmacokinetics.

In subjects receiving a high-dose statin, the C_{max} and AUC_{last} of unbound evolocumab were slightly lower compared with subjects receiving lower statin doses. However, unbound PCSK9 and LDL-C responses between subjects on lower doses of statins compared with subjects on high doses of statins, indicating that differences in pharmacokinetics did not translate to changes in PCSK9 and LDL-C response. The C_{max} of unbound evolocumab in subjects with HeFH was slightly lower compared with subjects without HeFH on low- to moderate-dose statins receiving the same evolocumab dose regimen (140 mg SC Q2W × 3). The AUC_{last} values, unbound PCSK9 and LDL-C responses were comparable between subjects with and without HeFH.

Representative mean plasma concentration-time profiles of evolocumab following multiple-dose SC administration of evolocumab are illustrated in [Figure 12](#) below.

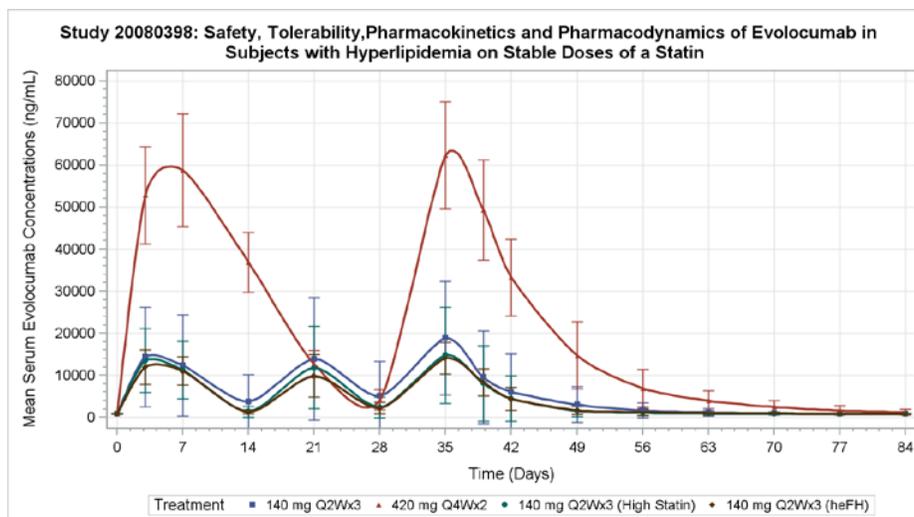


Figure 12 Mean plasma concentration time profile of Evolocumab after multiple-dose SC administration

A comparison of trough values at week 10 with those at week 2 from Phase 3 studies (Studies 20101154 and 20101155), showed 3-fold accumulation in mean unbound evolocumab serum concentration for 140 mg SC Q2W after the sixth dose (Figure 13). For the same time frame, a less than 2-fold accumulation was seen for 420 mg SC QM after the third dose. Similar accumulation was observed in Studies 20110114 and 20110115 for the 140 mg SC Q2W regimen based on trough samples collected at weeks 2, 10, and 12, and for the 420 mg SC QM regimen based on samples collected at weeks 2 and 10.

In the long-term safety, tolerability, and efficacy of evolocumab in subjects with primary hyperlipidemia and mixed dyslipidemia (Study 20110109), following administration of evolocumab 420 mg SC QM over 52 weeks, mean trough serum concentrations of unbound evolocumab at weeks 12, 24, 36, and 52 were stable and ranged from 8.23 $\mu\text{g/mL}$ to 10.3 $\mu\text{g/mL}$. The mean evolocumab C_{max} values at weeks 13 and 37 were 47.4 $\mu\text{g/mL}$ and 49.4 $\mu\text{g/mL}$, respectively.

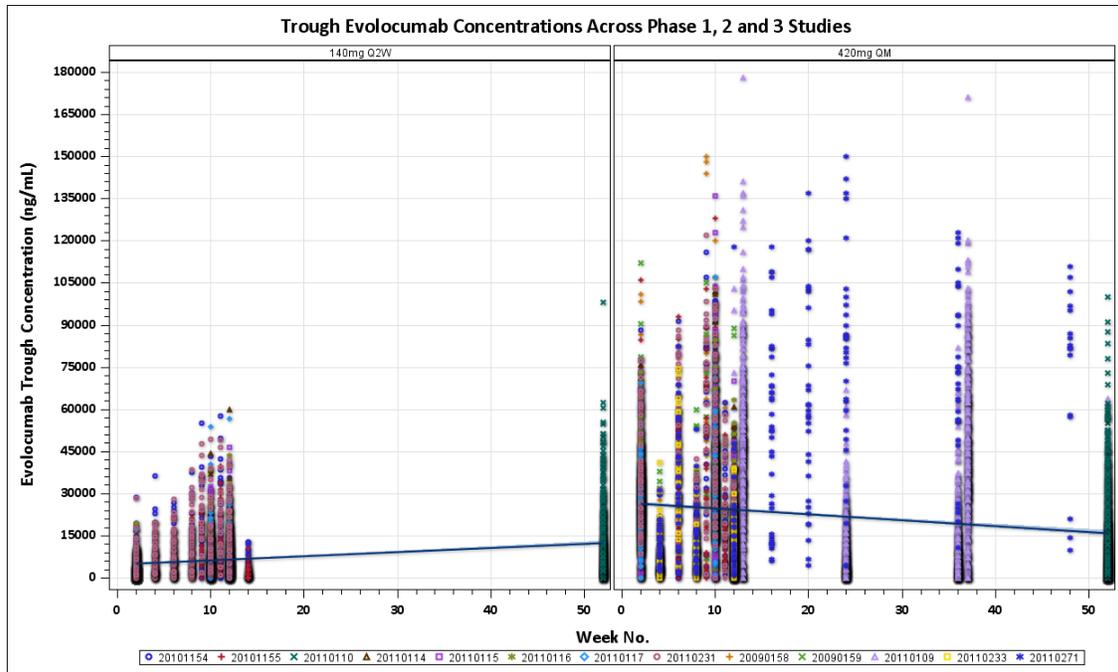


Figure 13 Trough evolocumab concentrations in Phase 1, 2 and 3 studies

In the ongoing long term safety and efficacy study (20110110), the trough concentrations are essentially unchanged between weeks 52 and 260 ([Figure 14](#)).



Figure 14 Trough Evolocumab Concentrations at Weeks 52 and 260 in Study 20110110

LDL-C:

Dose-dependent decreases in LDL-C levels were seen following treatment with evolocumab. Mean LDL-C decreases from baseline at end-of-treatment time point for 140 mg SC Q2W (day 43) and 420 mg SC QM (day 57) were 73%, and 63%, respectively (Figure 15). The analysis of LDL-C data showed statistically significant decreases ($p < 0.001$) in normalized AUC of LDL-C in both evolocumab dose-escalation cohorts versus placebo. In subjects without HeFH, statistically significant decreases ($p \leq 0.05$) in LDL-C versus placebo were observed as early as the first post-baseline time point (day 4) and continued through the day 71 time points for subjects receiving evolocumab at doses of 420 mg SC QM. In subjects with HeFH, statistically significant decreases ($p \leq 0.05$) in LDL-C versus placebo were observed from the second post-baseline time point (day 8) and continued through the day 50 time point for subjects receiving evolocumab 140 mg SC Q2W.

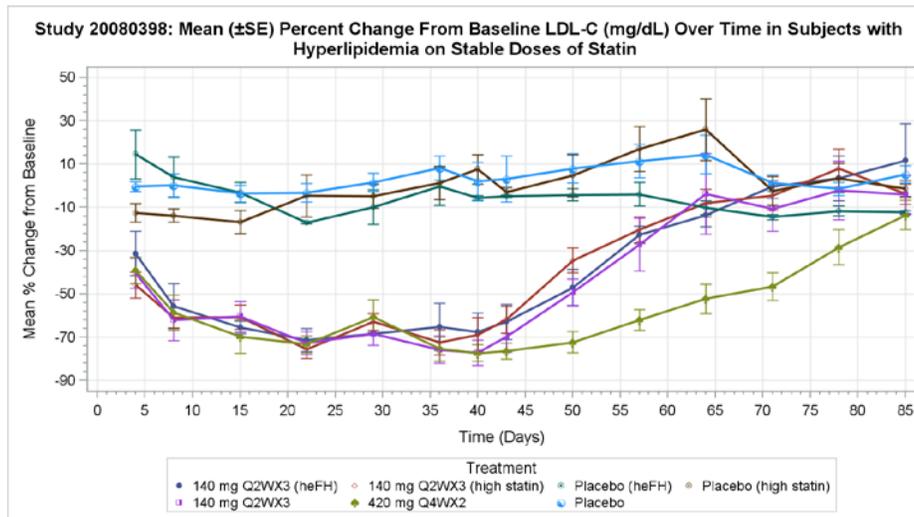


Figure 15 Mean % change from baseline for LDL-C of Evolocumab after multiple-dose SC administration

PCSK9:

Dose-dependent decreases in unbound PCSK9 was observed following treatment with evolocumab (Figure 16). Mean unbound PCSK9 decreases for 140 mg SC Q2W and 420 mg SC QM were 77% and 36%, respectively, at the end-of-treatment time point (day 43 for 140 mg and day 57 for 420 mg). Maximum mean observed unbound PCSK9 reductions from baseline at any time point during the study were $\geq 96\%$ for both treatment regimens. The sponsor reported statistically significant decreases (all $p < 0.001$) in normalized AUC of unbound PCSK9 in all evolocumab dose-escalation cohorts versus placebo. No differences were observed when comparing subjects on high-dose statins versus subjects on low- to moderate-dose statins receiving the same evolocumab dose regimen.

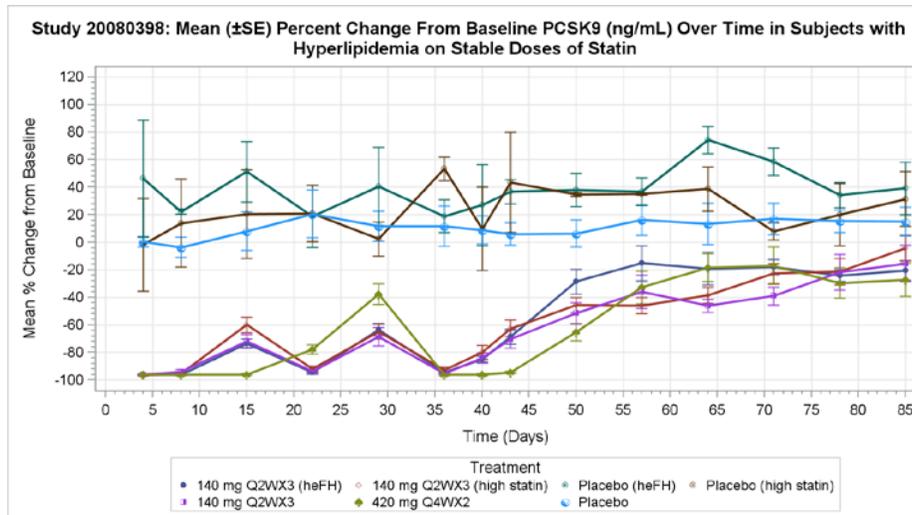


Figure 16 Mean % change from baseline for PCSK9 of Evolocumab after multiple-dose SC administration

2.4.3 What is the intra-subject variability for the pharmacokinetics and pharmacodynamics of evolocumab in healthy volunteers?

The intra-subject variability in the pharmacokinetic and pharmacodynamic profiles of evolocumab following 140 mg SC dose administration in healthy adult subjects was evaluated in study 20120136. Subjects were dosed 140 mg evolocumab subcutaneously on 2 occasions separated by a 56-day period. Mean evolocumab concentration-time profiles are shown in [Figure 17](#).

The mean C_{max} for period 1 and period 2 were 13.0 $\mu\text{g/mL}$ and 11.7 $\mu\text{g/mL}$, respectively; mean AUC_{last} for period 1 and period 2 were 96.5 $\mu\text{g}\cdot\text{day/mL}$ and 97.7 $\mu\text{g}\cdot\text{day/mL}$, respectively. Median t_{max} occurred 4 days after each dose.

Between subjects variability was greater than within subject variability for unbound evolocumab pharmacokinetics. For C_{max} , inter-subject and intra-subject variability, reported as percent coefficient of variation (%CV), was 78.8% (95% CI, 54.8% to 148.4%) and 32.6% (95% CI, 24.1% to 50.7%), respectively. For AUC_{last} , inter-subject and intra-subject %CV was 129.3% (95% CI, 84.3% to 308.5%) and 45.1% (95% CI, 33.1% to 72.5%), respectively.

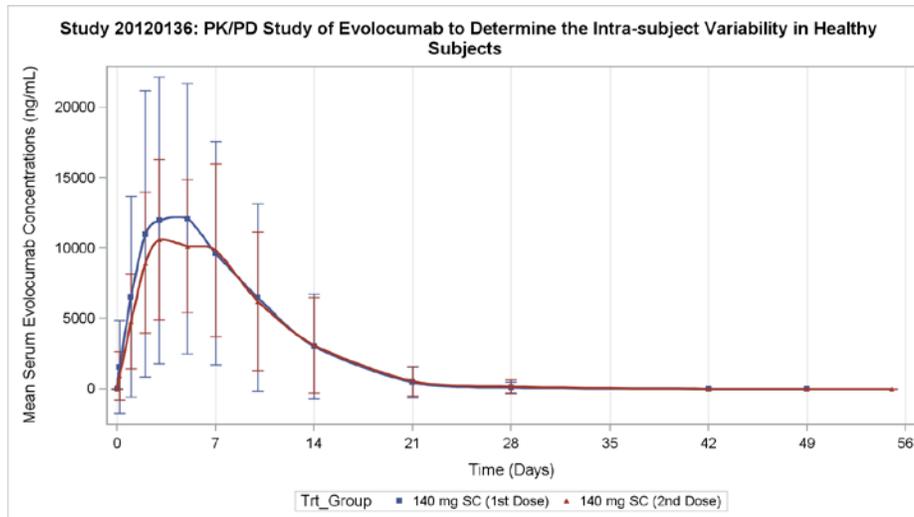


Figure 17 Mean plasma concentration time profile of Evolocumab by Period

LDL-C:

Similar to the observation for evolocumab concentrations, variability for LDL-C was also greater between subjects than within a subject. For LDL-C, inter-subject and intra-subject %CV was 18.7% (95% CI, 12.3% to 38.9%) and 7.5% (95% CI, 5.1% to 14.0%), respectively. Mean % change in LDL-C from baseline is presented in [Figure 18](#).

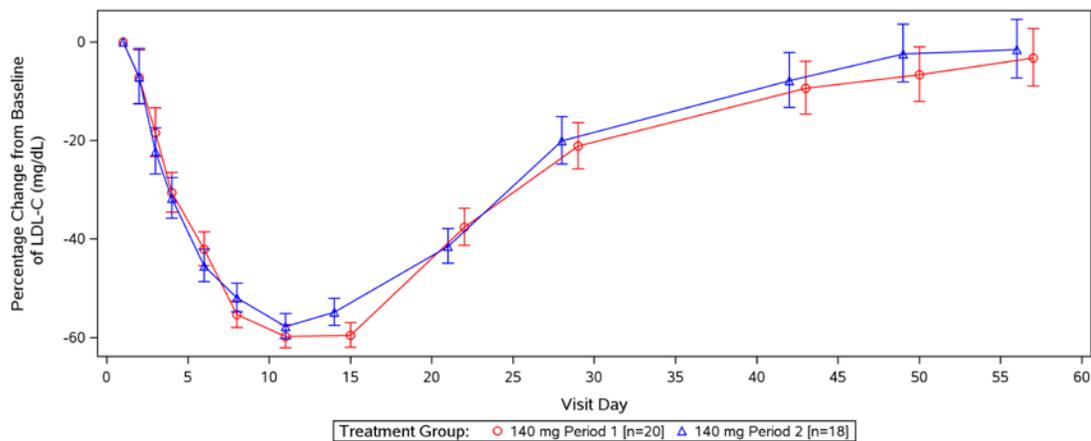


Figure 18 Mean Percentage Change from Baseline (\pm SE) of LDL-C over Time by Period

2.4.4 Is major route of elimination in humans identified?

Since evolocumab is a monoclonal antibody, no mass balance studies were conducted. Evolocumab. Unbound evolocumab has likely two mechanisms of elimination ([Figure 19](#)): (a) a target-mediated (nonlinear) pathway that predominates at low doses or serum concentrations of evolocumab and becomes saturated as serum evolocumab concentrations increase, and (b) a non-saturable mechanism (linear) through a nonspecific pathway via the reticuloendothelial system that governs the rate of elimination at higher doses or serum evolocumab concentrations.

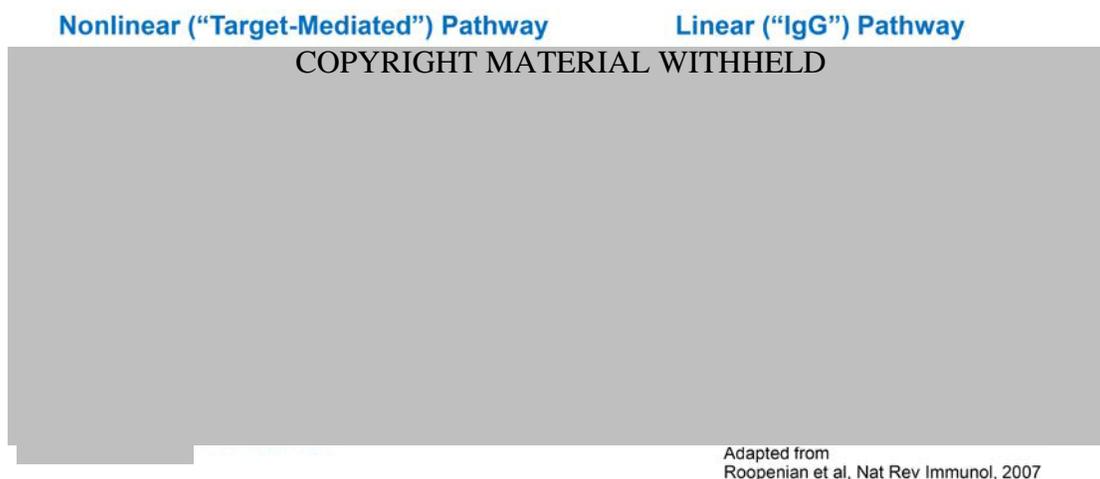


Figure 19 Mechanism of Evolocumab clearance

2.5 Intrinsic Factors

2.5.1 *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?*

Information on the intrinsic factors affecting the pharmacokinetics of Evolocumab was pooled from several Phase 1, Phase 2 and Phase3 studies. The PK/PD of evolocumab in patients with hepatic impairment was investigated in a dedicated Phase 1 study. Based on pooled analysis, no notable differences in evolocumab exposure were observed across age groups, between sexes, or across race groups. Body weight appeared to influence the exposure of evolocumab. Lower evolocumab exposure was observed with higher total body weight; however, there appeared to be no clinically meaningful effect of body weight on LDL-C reduction.

2.5.1.1 Age

Data pooled from 9 studies indicated that there was no relationship between age and unbound evolocumab week 12 trough concentration in patients 18 – 80 years of age ([Figure 20](#)). Additionally, population PK analysis did not identify age as a significant covariate.

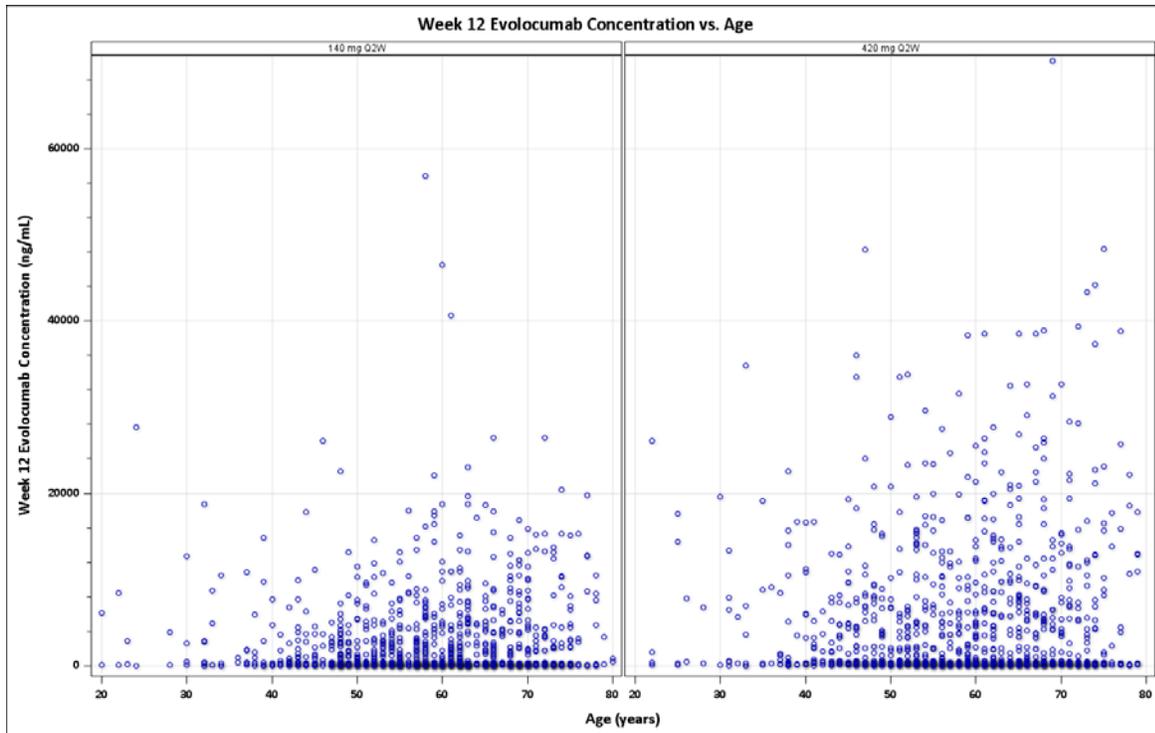


Figure 20 Scatter Plot for Week 12 Trough Concentration vs. Age for Evolocumab

2.5.1.2 Gender and Race

Gender:

Gender differences were noted in the pharmacokinetics of evolocumab. Following 140 mg SC Q2W, the difference between female and male patients in median unbound evolocumab trough serum concentrations at week 12 were approximately 48%. The difference was 18% for evolocumab 420 mg SC QM (Figure 21). Since female patients had lower body weight than male patients, higher trough concentrations were expected in female patients. Population PK analysis did not identify gender to be a significant covariate, explaining the variability in PK of evolocumab after adjusting for body weight.

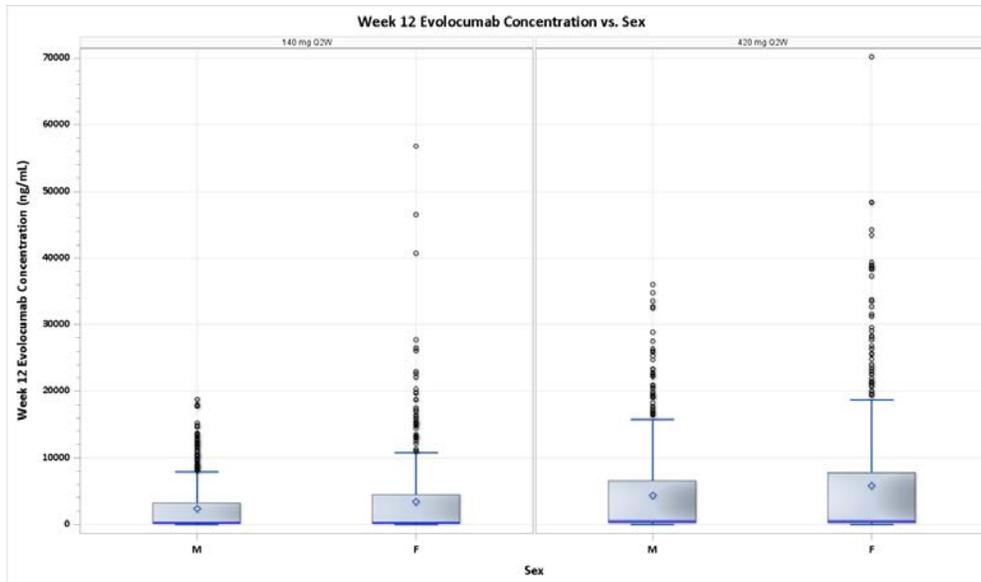


Figure 21 Boxplot of Week 12 Trough Concentration vs. Gender for Evolocumab

Race:

Median unbound evolocumab trough serum concentrations at week 12 for white patients were similar to those for black patients and to those for Asian patients, though due to the larger number of enrolled subjects, the spread appeared to be larger in white patients (Figure 22). Additionally, population PK analysis did not identify race as a significant covariate.

These results suggest that race does not have a substantial effect on the pharmacokinetic and pharmacodynamic profiles of evolocumab.

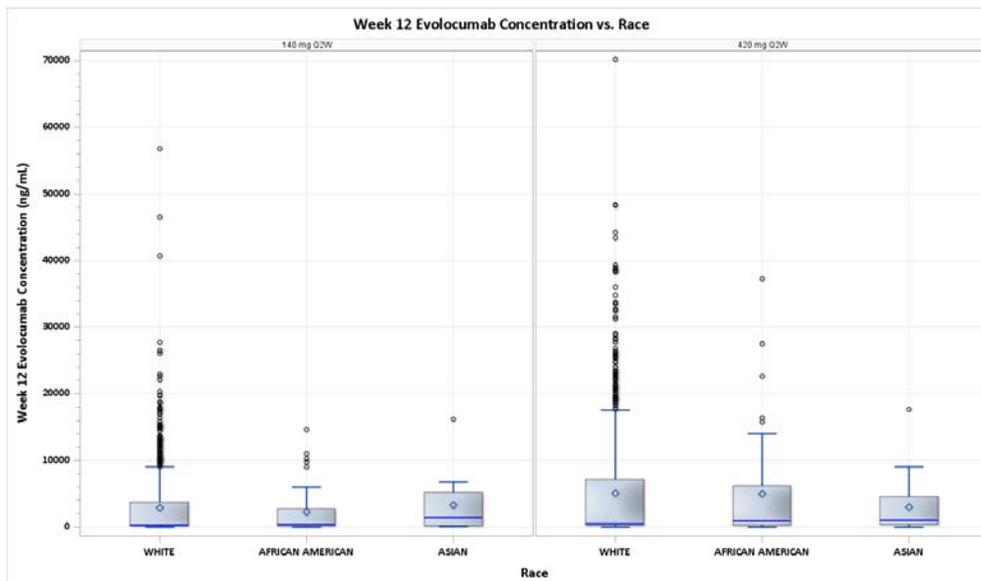


Figure 22 Boxplot of Week 12 Trough Concentration vs. Race for Evolocumab

2.5.1.3 Body Weight

Population analysis of phase 1 and phase 2 studies indicated that body weight emerged as a statistically significant covariate on unbound evolocumab pharmacokinetics. (Figure 23). An approximately three-fold increase in the AUC of someone who is 40 kg was observed compared to an 80 kg individual (~median weight for studies 20110114, 20110115, 20110116, 20110117) and a two-fold decrease in AUC when comparing 140 kg individual to an 80 kg individual. Despite the correlation of evolocumab PK with body weight, no safety events by system organ class were correlated with low body weight.

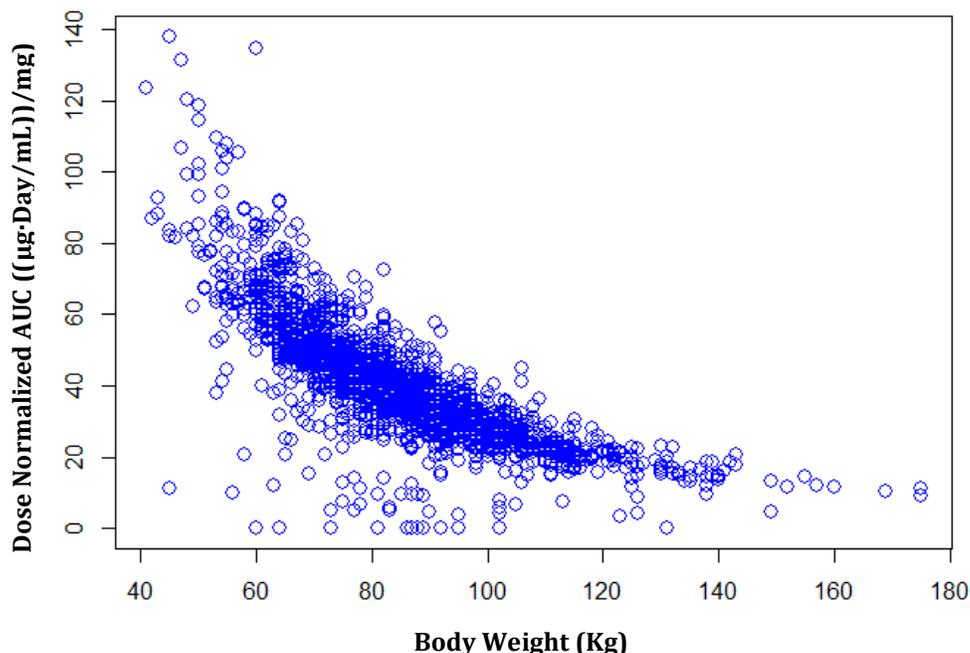


Figure 23 Scatter Plot for Dose Normalized Evolocumab AUC vs. Body Weight

Reviewer's Comments: Regarding special populations, the applicant concluded that that no dose adjustments based on age, race, gender, and body weight are needed. This conclusion appears to be reasonable, since any effects of these population characteristics were minor compared to the extent of LDL-C reduction achieved at the population level for each dose.

2.5.2 Does renal function affect Evolocumab pharmacokinetics?

Since diminished renal function is not expected to modify the pharmacokinetics of monoclonal antibodies, a dedicated study to evaluate the pharmacokinetics of evolocumab in patients with renal impairment was not conducted by the sponsor. The effect of renal function on the PK of evolocumab was evaluated in a population PK model. Data from 243 patients were pooled from 4 studies (studies 20090158, 20090159, 20101154, and 20101155) for this analysis. The effect of renal impairment on the pharmacokinetics of evolocumab was compared across these studies using both Cockcroft-Gault creatinine clearance (CrCL) and the Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) measures. Based on MDRD eGFR, there were 95 patients with normal renal function (eGFR \geq 90 mL/min), 131 mild renally impaired patients (eGFR 60-89 mL/min), and 17 moderate renally impaired patients (eGFR 30-59 mL/min). Renal function did not appear to influence the pharmacokinetics of evolocumab (see Figure 24).

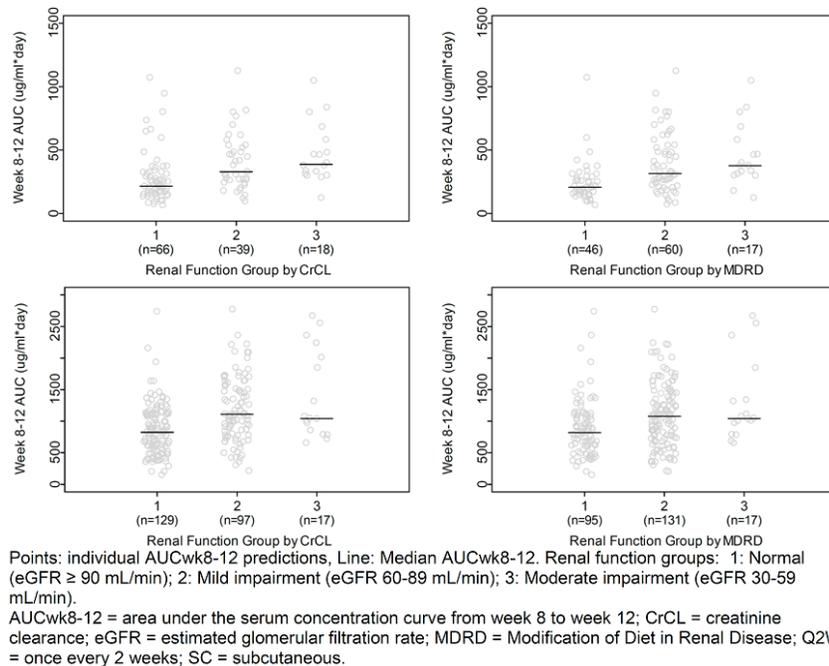


Figure 24 Base Model Evolocumab AUCwk8-12 Prediction for 140 mg Q2W Renal Function Covariate Plots

(source: Module 1.11.3, Efficacy Amendment, response to 16 April 2015 Information Request., pages 3 and 4)

2.5.3 Does hepatic dysfunction affect Evolocumab pharmacokinetics?

The pharmacokinetics, pharmacodynamics, and safety of evolocumab in subjects with mild to moderate hepatic impairment were investigated in study 20120341. Mean plasma evolocumab concentrations following a single dose of 140 mg administered subcutaneously are shown in [Figure 25](#).

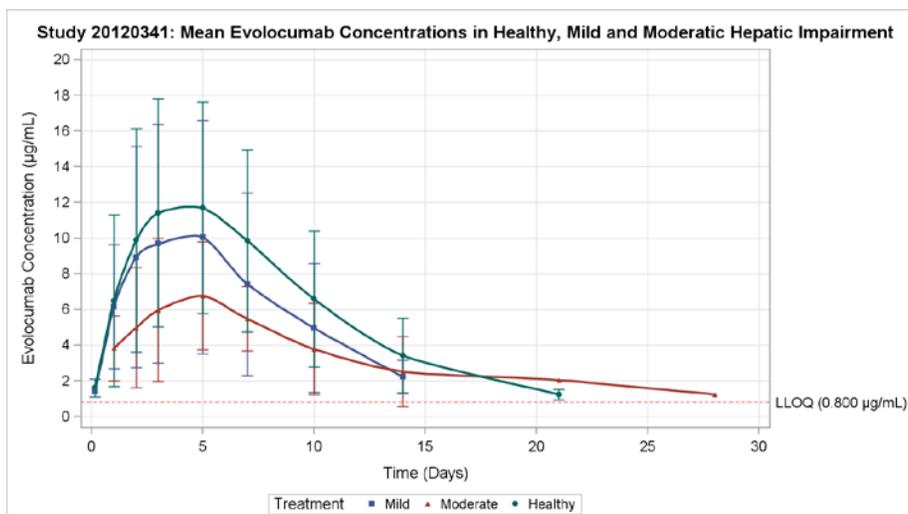


Figure 25 Mean evolocumab concentrations in mild and moderately impaired hepatic patients compared to healthy subjects

Following a single 140 mg SC dose of evolocumab, AUC_{last} and C_{max} , decreased with increasing hepatic impairment. Median t_{max} was 4.5 - 5.0 days in both hepatically impaired (mild or moderate) and healthy subjects. As seen in [Figure 26](#) (histogram plots), compared with healthy subjects with no hepatic impairment, subjects with mild and moderate hepatic impairment had least squares mean AUC_{last} values that were 39% and 47% lower, respectively ($p = 0.090$) and least squares mean C_{max} values that were 21% and 34% lower, respectively ($p = 0.18$). A summary of pharmacokinetic parameters is provided in Table 7, and statistical comparison shown in Table 8.

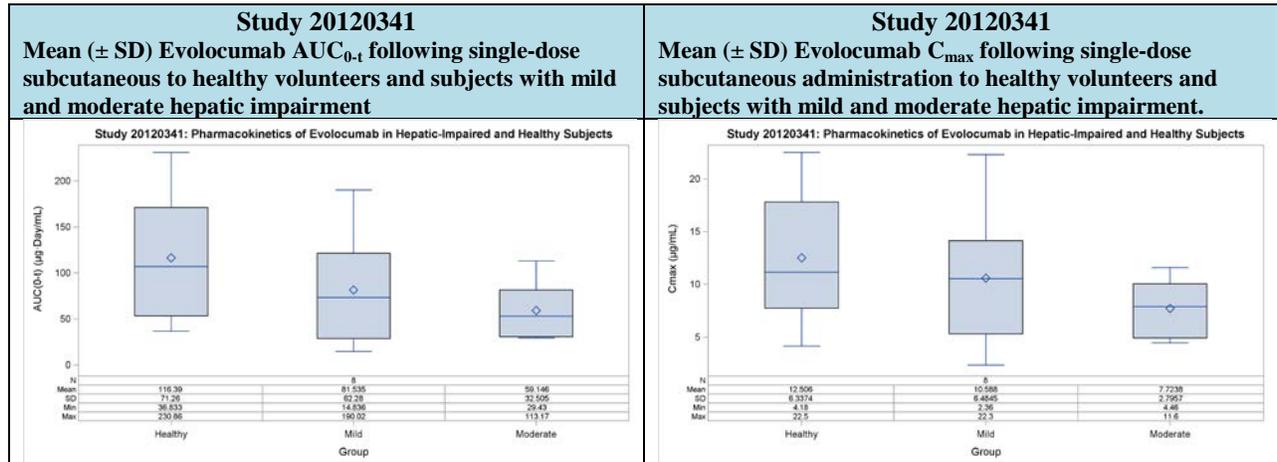


Figure 26 Histogram plots of evolocumab AUC_{0-t} and C_{max} in mild and moderately impaired hepatic patients compared to healthy subjects

Table 7 Pharmacokinetic Parameter Estimates of Evolocumab after Single Subcutaneous Administration of 140 mg Evolocumab to Hepatically Impaired or Healthy Subjects

Parameter	Descriptive Statistics	Mild Impairment (N = 8)	Moderate Impairment (N = 8)	Healthy (N = 8)
t_{max} (day)	Median	5.0	4.5	5.0
	(Min - Max)	(1.0 - 5.0)	(3.0 - 10)	(3.0 - 7.0)
C_{max} ($\mu\text{g/mL}$)	Mean \pm SD	10.6 \pm 6.48	7.72 \pm 2.80	12.5 \pm 6.34
	(Min - Max)	(2.36 - 22.3)	(4.46 - 11.6)	(4.18 - 22.5)
AUC_{last} (day $\cdot\mu\text{g/mL}$)	Mean \pm SD	81.5 \pm 62.3	59.1 \pm 32.5	116 \pm 71.3
	(Min - Max)	(14.8 - 190)	(29.4 - 113)	(36.8 - 231)

t_{max} = time to reach C_{max} ; C_{max} = maximum observed drug concentration; SD = standard deviation; AUC_{last} = area under the drug concentration-time curve from time zero to time of last quantifiable concentration.

Table 8 Least Squares Geometric Means of Pharmacokinetic Parameter Estimates of Evolocumab from Hepatic Impaired and Healthy Subjects

Parameter (unit)	Statistics	AMG 145 140 mg			Jonckheere-Terpstra Test p-value
		Mild Impairment (Test 1) (N = 8)	Moderate Impairment (Test 2) (N = 8)	Healthy (Reference) (N = 8)	
AUC _{last} (day·µg/mL)	n	8	8	8	0.090
	LS Mean ^a	58.8	51.5	96.8	
	Ratio (Test/Ref) ^b	60.8	53.2	-	
	90% CI of Ratio ^b	(32.1, 115.3)	(28.1, 100.9)	-	
C _{max} (µg/mL)	n	8	8	8	0.18
	LS Mean ^a	8.6	7.3	11.0	
	Ratio (Test/Ref) ^b	78.5	66.0	-	
	90% CI of Ratio ^b	(47.8, 129.1)	(40.1, 108.4)	-	

AUC_{last} = area under the serum concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum concentration; LS = least squares; CI = confidence interval.

^a LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

^b Ratio and CI are multiplied by 100 to express the hepatic impairment group response as a percentage of the healthy.

P-value from Jonckheere-Terpstra test conducted on log scale.

LDL-C concentrations reached nadir by day 11 in each of the study groups. Maximum mean LDL-C percent change from baseline were -57%, -70%, and -53% in the healthy, mild hepatic impairment, and moderate hepatic impairment groups, respectively. Mean percent change in LDL-C over time in each hepatic impairment group is shown in [Figure 27](#).

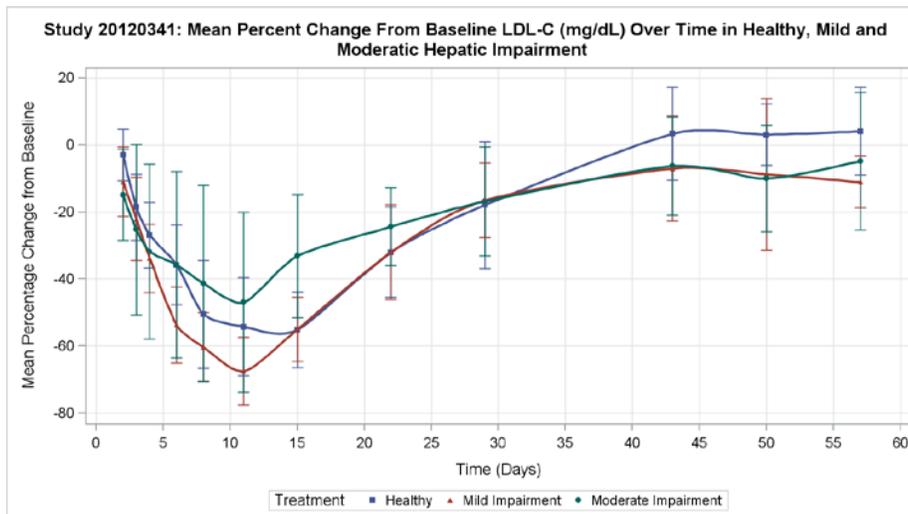


Figure 27 Mean LDL-C percent change from baseline in mild and moderately impaired hepatic patients compared to healthy subjects

Following a single dose of evolocumab 140 mg, mean PCSK9 concentrations decreased rapidly in each group. Four (4) hours after dose, reductions from baseline were 84% or greater in each group and from

study day 2 through study day 8, the reduction from baseline was 94% or greater in each group. Mean percent changes in PCSK9 from baseline by visit are shown in [Figure 28](#).

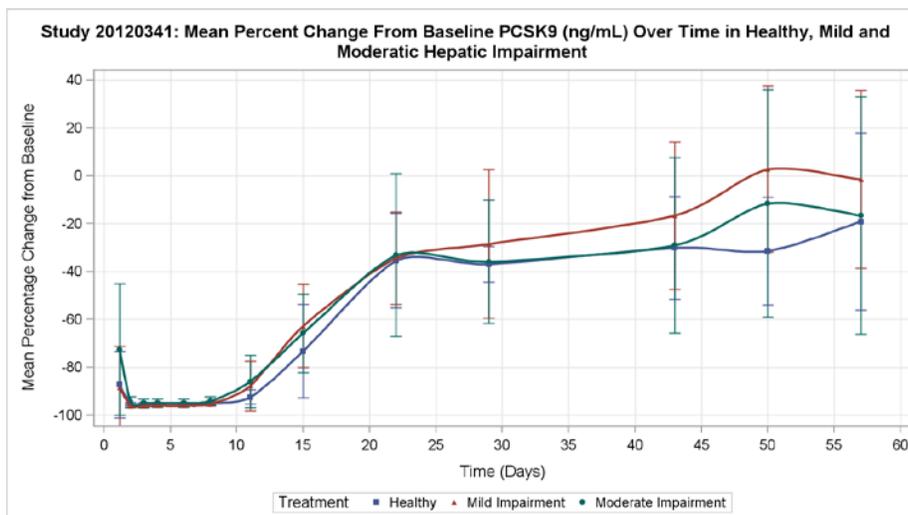


Figure 28 Mean PCSK9 percent change from baseline in mild and moderately impaired hepatic patients compared to healthy subjects

The pharmacodynamic profiles and the adverse event safety profile in subjects with mild or moderate hepatic impairment were similar to those seen in healthy subjects. Statistical analysis of the LDL-C percent change from baseline indicated that there were no differences in the area under the effect concentration (AUEC_{day1-57}) between the 3 groups ([Table 9](#)).

Table 9 Comparison of LDL-C (mg/dL) AUEC_{day1-57} for Hepatically Impaired and Healthy Subjects

Statistics	AMG 145 140 mg			Trend ^c
	Mild Impairment (N = 8)	Moderate Impairment (N = 8)	Healthy (N = 8)	
Model Including Baseline Covariate^a				
n	8	8	8	0.56
LS Geometric Mean	4320.2	4687.2	4683.7	
Ratio to Healthy with 95% CI	0.92 (0.82, 1.04)	1.00 (0.88, 1.14)		
p-value ^b	0.18	0.99		
Model Excluding Baseline Covariate^a				
n	8	8	8	0.56
LS Geometric Mean	4491.6	4017.5	5256.0	
Ratio to Healthy with 95% CI	0.85 (0.60, 1.21)	0.76 (0.54, 1.08)		
p-value ^b	0.36	0.12		

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^a Baseline covariate refers to log-transformed baseline value for UC LDL-C
^b p-value is associated with each level of impairment versus healthy subjects
^c p-value from trend test conducted by Jonckheere-Terpstra test on log scale

Evolocumab is not eliminated by liver enzymes and transporters, rather, it is eliminated through nonspecific elimination via the reticuloendothelial system (linear process) and specific target-mediated clearance (nonlinear process). Due to these reasons, hepatic impairment is not expected to affect evolocumab clearance.

Pharmacokinetics and safety in subjects with severe hepatic impairment (Child-Pugh Class C) were not evaluated.

2.5.4 What is the incidence of formation of antibodies to evolocumab during and after the treatment? What is the impact of antibodies on PK, efficacy and safety?

Since administration of any therapeutic protein has the potential to elicit an immune response, the sponsor developed and validated sensitive and specific assays to characterize the immune response against evolocumab in clinical studies. The procedure undertaken by the sponsor is listed in the highlighted box below:



The incidence of anti-evolocumab binding antibodies was low in the clinical program. The overall incidence of anti-evolocumab binding antibody development after at least 1 dose of evolocumab was 0.1% (7 out of 4846 subjects) in the integrated phase 2 and phase 3 primary hyperlipidemia and mixed dyslipidemia studies. In addition, neutralizing antibodies were not detected in any subject, while a 0.3% incidence was observed in placebo or other control groups.

PK Studies:

[Table 10](#) lists the unbound evolocumab and unbound PCSK9 serum concentrations at the time of positive anti-evolocumab antibody results. The pharmacokinetics and pharmacodynamics of evolocumab for any evaluable subject were not influenced by the presence of anti-evolocumab binding antibodies. Available data indicated that the serum evolocumab concentrations and unbound PCSK9 concentrations for the antibody positive subjects were all within the ranges observed for the other subjects in the studies. There appears to be no evidence to suggest that the occurrence of binding antibodies to evolocumab alters its pharmacokinetic profile.

Safety and Efficacy Studies:

A review of adverse events for the subjects with binding antibodies indicated that there were no hypersensitivity reactions that were determined to be due to the presence of a binding antibody. No serious adverse events were temporally associated with a positive antibody result.

Of the 80 HoFH subjects evaluated, none developed anti-evolocumab antibodies after receiving at least 1 dose of evolocumab. Two subjects had tested positive for pre-existing anti-evolocumab binding antibodies at baseline (prior to receiving evolocumab).

An ongoing open-label extension study to assess the long-term safety and efficacy of evolocumab (OSLER-1, study 20110110) looked at the interim data for (b) (4) subjects receiving evolocumab. No binding or neutralizing anti-evolocumab antibodies were detected in any subjects over 2 years of therapy.

Table 10 Unbound Evolocumab and Unbound PCSK9 Serum Concentrations at the Time of Positive Anti-evolocumab Antibody Results

Study	Subject ID	Treatment	Time of Positive Ab Result	Evolocumab Serum Concentration (µg/mL)	Evolocumab Serum Concentration Range ^a (µg/mL)	PCSK9 Concentration (ng/mL)	PCSK9 Concentration Range ^a (ng/mL)
20110109	10916301002	EvoMab 420 mg SC QM	Day 1	BQL	0-0	386	0-1140
20110109	10957207052	EvoMab 420 mg SC QM	Week 12	9.06	0-73.1	112	0-755
20110109	10957207052	EvoMab 420 mg SC QM	Week 36	22.7	0-81.9	19.4	0-850
20110109	10966402019	EvoMab 420 mg SC QM	Day 1	BQL	0-0	860	0-1140
20110115	11522001087	EvoMab 140 mg SC Q2W	Day 1	BQL	0-0	390	0-964
20110115	11551690003	EvoMab 420 mg SC QM	Day 1	BQL	0-0	254	0-964
20110115	11551690003	EvoMab 420 mg SC QM	Week 12	8.88	0-79.7	138	0-1040
20110115	11559002012	EvoMab 420 mg SC QM	Day 1	BQL	0-0	341	0-964
20101154	15413012005	EvoMab 105 mg SC Q2W	Week 4	14.0	0-18.5	23.8	0-268
20101154	15466039020	Placebo SC QM	End of study	NR	0-0	343	29-940 (Week 14)
20110110	(b) (6)	SOC ONLY	Week 4	NR	0-0	491	47.6-1020
20110110	(b) (6)	SOC ONLY	Week 4	NR	0-0	455	47.6-1020
20110110	(b) (6)	EvoMab + SOC	Week 4	7.23	0-77.9	142	0-854
20110110	(b) (6)	EvoMab + SOC	Week 12	29.0	0-91.3	39.8	0-995
20110110	(b) (6)	EvoMab + SOC	Week 48	7.6	0-87.6	171	15.8-965
20110231	23134079012	Placebo SC Q2W	Week 12	NR	0-0	973	273-849
20110110	(b) (6)	EvoMab + SOC	Day 1	BQL	0-0	564	22.4-1030
20110233	23356001018	EvoMab 420 mg SC QM	Day 1	BQL	0-0	565	<15-1190
20110271	23356001018	EvoMab 420 mg SC QM	OLE Week 12	18.1	0-45.8	244	57.1-981
20110271	27116007008	EvoMab 420 mg SC QM	OLE Day 1	NR	0-0	401	210-1820

Ab = antibody; EvoMab = Evolocumab (AMG 145); NR = not reported; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q2W = once every 2 weeks; QM = once monthly (every 4 weeks); SC = subcutaneous; SOC = standard of care. Lower limits of quantification: evolocumab, 800 ng/mL; PCSK9, 15 ng/mL.

Includes Studies 20090158, 20090159, 20101154, 20101155, 20110109, 20110110, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356, 20110233, and 20110271. Evolocumab and PCSK9 concentrations were not measured in Study 20120138.

^a For antibody negative subjects.

2.6 Extrinsic Factors

2.6.1 Drug-Drug Interactions

Since evolocumab is a monoclonal antibody, the sponsor did not conduct any *in vitro* permeability, *in vitro* metabolism, or *in vitro* metabolic drug-drug interaction studies that used human biomaterials for this BLA.

2.6.1.1 What is the effect of Statin co-administration on the pharmacokinetics and pharmacodynamics of Evolocumab?

It has been reported that statins upregulate PCSK9^{1,2}. Dong et al³ reported that rosuvastatin increased the expression of sterol response element binding protein 2 (SREBP2) and also increased the liver expression of hepatocyte nuclear factor 1 α (HNF1 α), a key transactivator for PCSK9 gene expression. Welder et al⁴ reported that atorvastatin (80 mg) caused a rapid 47% increase in serum PCSK9 at 4 weeks that was sustained throughout 16 weeks of dosing. They put forth an explanation for why proportional LDL-C lowering was not achieved with increasing doses of statin.

Based on the mechanism, it would be expected that statins by increasing circulating PCSK9 levels, would reduce the effectiveness of evolocumab.

The safety, tolerability, pharmacokinetics and immunogenicity profile of evolocumab following multiple SC doses of evolocumab was evaluated in subjects on a stable dose of statin in one Phase 1 and several Phase 2 and 3 studies.

Phase 1 Study:

The safety, tolerability, and immunogenicity profile of evolocumab following multiple SC doses of evolocumab was evaluated in subjects on a stable dose of statin (simvastatin, atorvastatin or rosuvastatin) in study 20080398. Cohort 6, the high-dose statin group received either atorvastatin 80 mg/day or rosuvastatin 40 mg/day). Seven cohorts of subjects were selected and were dosed according to the matrix shown below:

Cohort Assignments and Dose Regimens

Cohort	AMG 145 Dose (mg)	Frequency	Total Dose (mg)	Planned N	AMG 145: Placebo	Subjects With Hypercholesterolemia
1	14	QWx6	84	8	3:1	On low- to moderate-dose statins
2	35	QWx6	210	8	3:1	
3	140	Q2Wx3	420	8	3:1	
4	280	Q2Wx3	840	8	3:1	
5	420	Q4Wx2	840	8	3:1	On high-dose statins
6	140	Q2Wx3	420	12	3:1	
7	140	Q2Wx3	420	6	2:1	

QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; HeFH = heterozygous familial hypercholesterolemia

Note: AMG 145 and placebo were administered by subcutaneous injection. Within each cohort, the volume of placebo injected was matched to active investigational product injected (range: 0.2 mL [cohort 1] to 6.0 mL [cohort 5]).

Pharmacokinetics:

- Cohorts 1-2: Following repeated dosing of evolocumab at doses of 14 mg weekly for 6 weeks, there were no detectable concentrations of evolocumab (LOQ = 0.8 μ g/mL). Following doses of 35 mg weekly for 6 weeks, only 2 out of 6 subjects had detectable levels of evolocumab.
- Cohorts 3-5 (dose-escalation): Multiple dosing of evolocumab resulted in nonlinear kinetics for the lower doses (up to 140 mg SC). Doses of evolocumab greater than 140 mg SC resulted in concentrations associated with near complete suppression of its ligand, PCSK9. At these concentrations, evolocumab exhibited principally linear pharmacokinetics. T_{max} was observed

¹ Dubuc, G., A. Chamberland, H. Wassef, J. Davignon, N. G. Seidah, L. Bernier, and A. Prat. 2004. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated convertase-1 implicated in familial hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.* **24**: 1454 - 1459.

² Careskey HE, Davis RA, Alborn WE, Troutt JS, Cao G, Konrad RJ. Atorvastatin increases human serum levels of proprotein convertase subtilisin/kexin type 9. *J Lipid Res.* 2008;**49**:394-398.

³ Dong, B., M. Wu, H. Li, F. B. Kraemer, K. Adeli, N. G. Seidah, S. W. Park, and J. Liu. 2010. Strong induction of PCSK9 gene expression through HNF1 α and SREBP2: mechanism for the resistance to LDL-cholesterol lowering effect of statins in dyslipidemic hamsters. *J. Lipid Res.* **51**: 1486 - 1495.

⁴ Welder, G., I. Zineh, M. A. Pacanowski, J. S. Troutt, G. Cao, and R. J. Konrad. High-dose atorvastatin causes a rapid, sustained increase in human serum PCSK9 and disrupts its correlation with LDL cholesterol. *J. Lipid Res.* 2010. **51**: 2714-2721

approximately 1 week following SC dosing after the first and last doses. The pharmacokinetic profiles of evolocumab for the highest dose groups (140 mg Q2W, 280 mg Q2W, and 420 mg Q4W) were similar to the pharmacokinetic profiles of evolocumab in the phase 1 single dose FIH study. Compared to the 140 mg Q2W regimen, less accumulation occurred with the 420-mg dose administered Q4W as expected with frequency of administration. Trough concentrations following a dose of 140 mg administered Q2W x 3 were 3480 ng/mL, 5130 ng/mL, and 6110 ng/mL following the first, second, and third doses, respectively. Trough concentrations following the first and second doses of 420-mg Q4W x 2, were 4180 ng/mL and 6920 ng/mL, respectively.

- (c) **Cohort 6 (subjects on high-dose statin):** Administration of evolocumab at a dose of 140 mg every 2 weeks for 3 weeks to subjects who were on a higher dose of statin resulted in lower C_{max} and AUC_{last} values for evolocumab compared to subjects receiving lower doses of statin. The point estimates for the ratio of C_{max} and AUC_{last} of evolocumab in subjects receiving a high-dose statin compared with subjects receiving low and moderate statin doses were 0.73 and 0.74, respectively. These differences, however, did not result in a difference in either PCSK9 or LDL-C lowering at the dosing regimen employed.
- (d) **Cohort 7 (subjects with HeFH):** Administration of evolocumab at a dose of 140 mg every 2 weeks for 3 weeks to HeFH subjects resulted in C_{max} values of 14.5 $\mu\text{g/mL}$ that were slightly lower compared to the C_{max} of 17.5 $\mu\text{g/mL}$ in subjects without HeFH. Mean AUC_{last} value of 152 $\mu\text{g}\cdot\text{day/mL}$ in HeFH patients was comparable to the mean AUC_{last} value of 161 $\mu\text{g}\cdot\text{day/mL}$ in non-HeFH patients. There were no differences in LDL-C and PCSK9 response between the two groups.

Mean serum evolocumab concentration-time profiles for the cohorts receiving 140 mg and 420 mg doses are shown in [Figure 29](#). Mean pharmacokinetic parameters are shown in [Table 11](#).

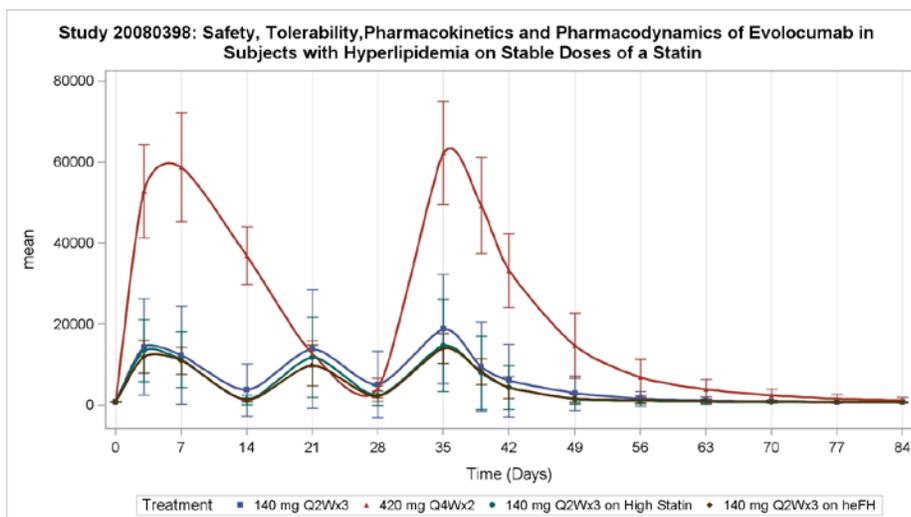


Figure 29 Mean (+ SD) Unbound Evolocumab Serum Concentrations versus Time by Treatment in Subjects with Hyperlipidemia on Stable Doses of a Statin

Table 11 Summary of Evolocumab Pharmacokinetic Parameter Estimates by Treatment in Subjects with Hyperlipidemia on Stable Doses of a Statin

Parameter	Descriptive Statistics	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7
		(140 mg Q2W x 3)	(280 mg Q2W x 3)	(420 mg Q4W x 2)	(140 mg Q2W x 3)	(140 mg Q2W x 3)
C _{max} (µg/mL)	n	6	6	6	9	4
	Mean	20.3	62.8	63.6	16.3	14.7
	SD	13.2	22.7	11.2	10.8	2.88
	CV %	65.0%	36.2%	17.6%	65.9%	19.5%
	Min	9.06	36.0	49.0	2.96	12.2
	Median	17.1	59.4	63.0	17.3	14.2
	Max	45.3	104	82.4	37.0	18.3
t _{max} (day)	n	6	6	6	9	4
	Mean	24	31	21	16	27
	SD	17	7.0	15	16	16
	CV %	68%	23%	73%	100%	59%
	Min	2.9	21	6.9	2.9	3.0
	Median	35	35	21	3.0	35
	Max	35	35	35	35	35
AUC _{last} (day·µg/mL)	n	6	6	6	8	4
	Mean	226	1200	903	181	165
	SD	249	634	280	157	69.1
	CV %	110%	52.8%	31.0%	86.9%	41.9%
	Min	76.1	530	576	16.7	75.2
	Median	119	1070	840	151	172
	Max	725	2370	1400	472	240
AUC _{0-t_{max}} (day·µg/mL)	n	6	6	6	9	4
	Mean	168	749	823	137	128
	SD	156	312	224	119	35.8
	CV %	92.7%	41.7%	27.2%	86.9%	27.9%
	Min	67.0	394	560	8.24	75.2
	Median	98.4	682	771	122	142
	Max	479	1310	1230	362	154

AUC_{last} = area under the unbound AMG 145 serum concentration-time curve from time of last dose to time of last quantifiable concentration following the last AMG 145 dose; AUC_{0-t_{max}} = area under the unbound AMG 145 serum concentration-time curve over the dosing interval following the last AMG 145 dose; C_{max} = maximum observed drug concentration; CV % = coefficient of variation; SD = standard deviation; t_{max} = time to C_{max}.

Pharmacodynamics:

LDL-C:

- (a) Dose-escalation Cohorts (Cohorts 1 to 5): Mean LDL-C decreases from baseline were 73%, 75%, and 63%, respectively following administration of the 3 highest dose-escalation cohorts (140 mg, 280 mg, and 420 mg). Maximum mean observed LDL-C reductions from baseline at any time point during the study for the 3 highest dose-escalation cohorts were 81% (day 40), 75% (days 36 and 43), and 79% (days 36 and 40), respectively. Mean LDL-C reductions from baseline of 24% and 55% were observed for subjects in the 14-mg and 35-mg dose-escalation cohorts, respectively, at the end-of-treatment time point.
- (b) High-dose Statin Cohort (Cohort 6): Mean LDL-C decrease from baseline for subjects on high-dose statin therapy receiving evolocumab was 65%, similar to the 73% mean percent reduction observed for subjects in the 140 mg dose group of the dose-escalation cohort on low- to moderate-dose statins. Maximum mean observed LDL-C reductions from baseline at any time point during the study, 78% on day 22 for the high-dose statin group compared to 81% on day 40 for the low- to moderate-dose statin, were similar between these 2 groups. Duration of effect was also comparable between the 2 groups, with mean LDL-C reduction from baseline values of ≥ 50% continuing through day 43 for subjects on high-dose statin therapy receiving evolocumab and through day 50 for subjects on low- to moderate-dose statins that received the same evolocumab dose of 140 mg.

(c) Cohort 7 (HeFH): Maximum mean observed LDL-C reductions from baseline at any time point during the study, 73% on day 22 for the HeFH group compared to 81% on day 40 for the low- to moderate-dose statin, were similar between these 2 groups.

Profiles of mean LDL-C decrease from baseline for the cohorts receiving 140 mg, 420 mg doses and corresponding placebo is shown in [Figure 30](#).

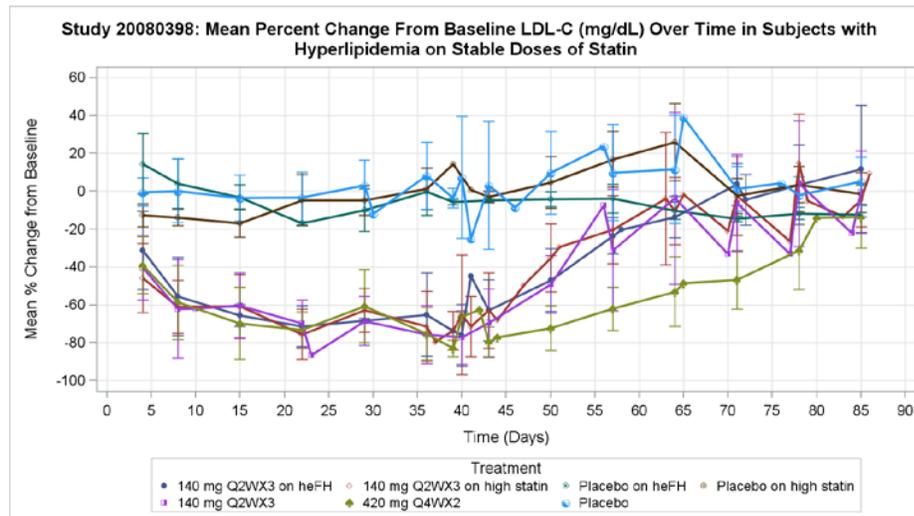


Figure 30 Mean Percent Change (\pm SD) from Baseline of LDL-C Over Time by Treatment in Subjects with Hyperlipidemia on Stable Doses of a Statin

PCSK9:

Mean unbound PCSK9 decreases from baseline were greatest in the 140-mg and 280-mg dose-escalation cohorts (77% and 94%, respectively), and were similar in the high-dose statin therapy and HeFH cohorts (70% each in both cohorts). Maximum mean observed unbound PCSK9 reductions from baseline at any time point during the study were also similar ($\geq 96\%$ between days 4-36) between the low to moderate dose statin, high dose statin and HeFH cohorts. For the 420-mg dose-escalation cohort, mean unbound PCSK9 reductions at the end-of-treatment time point (day 57) were lower (36%); however, the maximum mean observed unbound PCSK9 reduction at any time during the study was identical ($\geq 96\%$; full inhibition) to the 140-mg and 280-mg dose-escalation cohorts, occurring on days 4, 8, 15, 36, and 40.

Profiles of mean PCSK9 decrease from baseline for the cohorts receiving 140 mg, 420 mg doses and corresponding placebo is shown in [Figure 31](#).

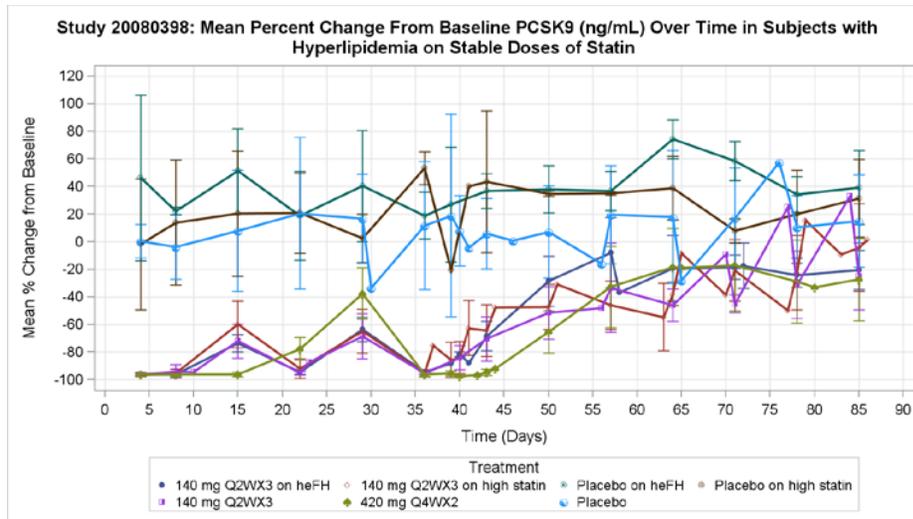


Figure 31 Mean Percent Change (\pm SD) from Baseline of PCSK9 Over Time by Treatment in Subjects with Hyperlipidemia on Stable Doses of a Statin

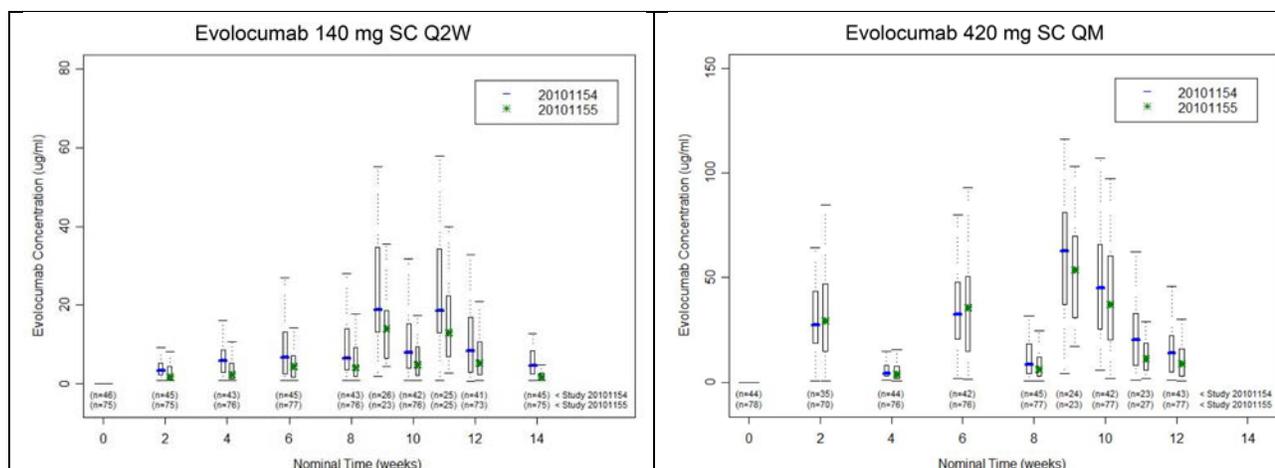
Phase 2 and 3 Studies:

The pharmacokinetics and pharmacodynamics of evolocumab were also characterized in Phase 2 and 3 studies in patients with primary hyperlipidemia and mixed dyslipidemia who received evolocumab alone as monotherapy with or without a low/atypical dose statin in statin-intolerant patients, or in combination with a statin with or without other lipid-lowering therapy. Studies 20101154 (Phase 2) and 20101155 (Phase 3) also included pharmacokinetic sub-studies, with sample collection at weeks 8, 9, 10, 11, and 12, to characterize unbound evolocumab AUC and C_{max} following Q2W or QM dosing.

Serum concentrations of unbound evolocumab and LDL-C at each study assessment, as well as AUC and C_{max} for unbound evolocumab were available from studies 20101154 and 20101155 for cross-study comparison.

Similarly, phase 3 studies, 20110114, 20110115, and 20110116 included serum concentrations of unbound evolocumab, LDL-C, and unbound PCSK9 at week 12, enabling cross-study comparison. The week 12 trough concentrations from phase 3 Study 20110109 are considered to represent steady-state concentrations of unbound evolocumab, LDL-C, and unbound PCSK9.

Comparison of unbound evolocumab serum concentrations from the monotherapy Phase 2 study 20101154 and the statin combination Phase 2 study 20110115, showed considerable overlap of evolocumab concentrations (see [Figure 32](#)). However, compared with monotherapy patients, patients who received evolocumab with a statin had mean unbound evolocumab serum concentrations at week 12 that were 32% lower for the 140 mg SC Q2W dose or 26% lower for the 420 mg SC QM dose. Pharmacokinetic comparison showed that evolocumab AUC over weeks 8 to 12 were also overlapping between the two studies, but appeared to be 21% and 22% lower after the 140 mg SC and 420 mg SC doses, respectively, in patients who received evolocumab with a statin compared with patients who received evolocumab monotherapy (see [Table 12](#)). Similarly, C_{max} values over weeks 8 to 12 were overlapping, but were 26% and 13% lower after the 140 mg SC and 420 mg SC doses, respectively, in patients treated with a statin ([Table 12](#)).



Boxes: median observed concentration with 25th and 75th percentiles and upper and lower observed, without outliers; Q2W = once every 2 weeks; QM = once every month; SC = subcutaneously.

Figure 32 Unbound Evolocumab Serum Concentrations Over 12 to 14 Weeks from Phase 2 Studies 20101154 and 20101155

(source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Figure 24, page 94)

Table 12 Unbound Evolocumab Pharmacokinetic Parameters in Pharmacokinetic Sub-study (Phase 2 Studies 20101154 and 20101155)

	140 mg SC Q2W		420 mg SC QM	
	Primary Hyperlipidemia and Mixed Dyslipidemia: Monotherapy (Study 20101154) ^a	Primary Hyperlipidemia and Mixed Dyslipidemia: With a Statin (Study 20101155) ^a	Primary Hyperlipidemia and Mixed Dyslipidemia: Monotherapy (Study 20101154) ^a	Primary Hyperlipidemia and Mixed Dyslipidemia: With a Statin (Study 20101155) ^a
AUC^a (µg·day/mL)				
N	21	19	21	21
Mean	387	304	962	746
SD	271	200	459	342
Min	42.9	61.5	306	211
Median	288	231	954	791
Max	1010	845	1890	1310
%CV	70.0	65.8	47.7	45.9
C_{max} (µg/mL)				
N	21	19	21	21
Mean	23.7	17.6	62.9	54.6
SD	14.7	9.06	24.3	23.8
Min	1.98	4.36	27.8	17.3
Median	18.9	15.3	63.3	54.6
Max	55.0	39.8	116	103
%CV	61.7	51.3	38.6	43.5

^a%CV = coefficient of variation; AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; QM = once monthly (every 4 weeks); QW = once weekly; SC = subcutaneous; SD = standard deviation.

^aAUC in PK substudy patients from weeks 8 to 12 after dosing on weeks 8 and 10 for Q2W and after dosing on week 8 for QM.

(source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Table 14, page 96)

In phase 3 studies, unbound evolocumab trough serum concentrations at week 12 with 140 mg SC Q2W or 420 mg SC QM dosing were overlapping between evolocumab monotherapy and evolocumab treatment in statin intolerant patients, with a 55% and 41% lower concentrations in patients on concomitant statin therapy for the 140 mg Q2W and 420 mg QM doses, respectively.

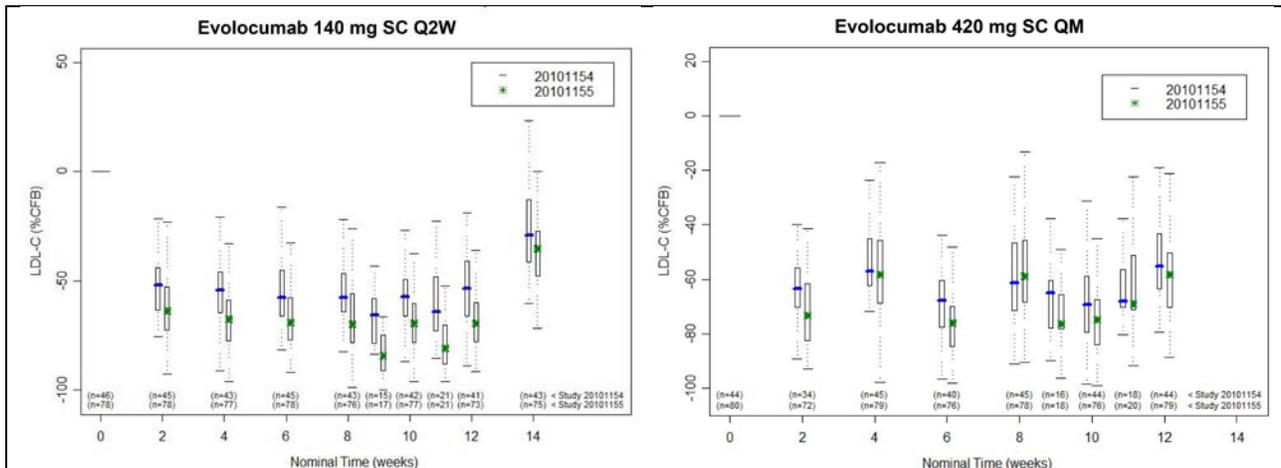
Following concomitant administration with a low dose (10 mg) or high dose (80 mg) of atorvastatin, the trough evolocumab concentrations at week 12 were 24% and 30% lower for the concomitant administration with the high dose atorvastatin compared to concomitant administration with the low dose

atorvastatin for the 140 mg and 420 mg doses, respectively. Similar findings of 50% and 34% lower week 12 trough evolocumab concentrations were observed when co-administered with rosuvastatin 5 mg and 40 mg for the 140 mg and 420 mg doses, respectively.

LDL-C:

Comparison of LDL-C responses, measured as percent change from baseline over weeks 2 to 14 of evolocumab 140 mg SC Q2W dosing or weeks 2 to 12 of evolocumab 420 mg SC QM dosing from the monotherapy Phase 2 study 20101154 and the statin combination Phase 2 study 20101155, showed considerable overlap (see [Figure 33](#)). Median percent reduction from baseline for LDL-C was modestly more for evolocumab combination with statins than with evolocumab monotherapy.

The mean percent reduction from baseline in LDL-C at week 12 and at the mean of weeks 10 and 12 was comparable between evolocumab monotherapy, evolocumab treatment in statin intolerant patients, and evolocumab treatment with a statin in phase 3 studies, for patients with primary hyperlipidemia and mixed dyslipidemia treated with evolocumab 140 mg SC Q2W (see [Table 13](#)). Similar comparable percent reduction from baseline LDL-C between monotherapy and statin combination therapy was observed for evolocumab 420 mg SC Q2W (see [Table 13](#)).



Boxes: median observed LDL-C percent change from baseline with 25th and 75th percentiles and upper and lower observed, without outliers. CFB = change from baseline; Q2W = once every 2 weeks; QM = once monthly; SC = subcutaneous.

Figure 33 Calculated LDL-C Percent Change From Baseline Over 14 Weeks for Studies 20101154 and 20101155

(source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Figure 25, page 100)

Table 13 LDL-C Concentrations (Percent Change From Baseline) Following Evolocumab 140 mg SC Q2W or 420 mg SC QM as Monotherapy (Study 20110114), in Statin Intolerant Patients (Study 20110116), or With a Statin (Study 20110115)

140 mg SC				420 mg SC QM			
	Monotherapy (Study 20110114)	Statin Intolerance (Study 20110116)	With Statin (Study 20110115)		Monotherapy (Study 20110114)	Statin Intolerance (Study 20110116)	With Statin (Study 20110115)
Week 12				Week 12			
N	133	98	517	N	136	96	514
Mean	-58.17	-56.25	-61.80	Mean	-56.44	-54.26	-57.74
SD	13.34	-	18.84	SD	10.74	-	22.39
SE	1.16	1.82	0.83	SE	0.92	1.37	0.99
Min	-84.5	-82.9	-94.0	Min	-84.3	-76.2	-96.9
Median	-59.86	-59.50	-64.20	Median	-57.29	-56.91	-61.14
Max	-11.8	10.4	44.1	Max	-22.0	-12.9	146.0
Mean of weeks 10 and 12				Mean of weeks 10 and 12			
N	140	101	539	N	150	100	545
Mean	-57.65	-56.39	-61.57	Mean	-59.00	-56.70	-63.06
SD	-	-	-	SD	-	-	-
SE	1.09	1.69	0.74	SE	0.89	1.32	0.94
Min	-79.2	-83.5	-93.0	Min	-84.5	-78.4	-94.3
Median	-60.04	-60.50	-63.89	Median	-60.59	-59.60	-66.07
Max	-16.4	8.9	38.7	Max	-22.0	-12.4	146.0

LDL-C = low-density lipoprotein cholesterol; min = minimum; max = maximum; Q2W = once every 2 weeks; SC = subcutaneous; SD = standard deviation; SE = standard error.
When the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available.

LDL-C = low-density lipoprotein cholesterol; min = minimum; max = maximum; QM = once monthly (every 4 weeks); SC = subcutaneous; SD = standard deviation; SE = standard error.
When the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available.

(source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Tables 19 and 20, pages 101-102)

PCSK9:

In phase 3 studies, for patients with primary hyperlipidemia and mixed dyslipidemia, mean percent reduction of unbound PCSK9 at week 12 was comparable between evolocumab monotherapy, evolocumab treatment in statin intolerant patients, and evolocumab treatment with a statin treated following evolocumab doses of 140 mg Q2W or 420 mg QM (see Table 14).

Table 14 Unbound PCSK9 Concentrations (Percent Change From Baseline) at Week 12: Evolocumab 140 mg SC Q2W Monotherapy (Study 20110114), in Statin Intolerant Patients (Study 20110116), or With a Statin (Study 20110115)

140 mg SC Q2W			
	Monotherapy (Study 20110114)	Statin Intolerance (Study 20110116)	With Statin (Study 20110115)
N	123	93	99
Mean	-69.00	-61.09	-56.64
SE	2.26	3.50	2.74
Min	-100	-100.0	-95.2
Median	-77.21	-69.17	-61.08
Max	31.7	80.7	48.6
420 mg SC QM			
	Monotherapy (Study 20110114)	Statin Intolerance (Study 20110116)	With Statin (Study 20110115)
N	130	85	94
Mean	-39.17	-27.16	-33.35
SE	3.07	17.78	3.64
Min	-100	-100.0	-91.8
Median	-45.31	-45.03	-38.14
Max	66.7	1436.7	59.9

max = maximum; min = minimum; QM = once monthly (every 4 weeks); SC = subcutaneous; SE = standard error.

(source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Tables 21 and 22, pages 103-104)

In the Phase 3 program, study 20110115 evaluated the effect of 12 weeks of evolocumab administered subcutaneously every 2 weeks and monthly when used in combination with a statin, compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with primary hypercholesterolemia and mixed dyslipidemia. In subjects with high-dose statins, mean baseline PCSK9 were relatively elevated compared to subjects on low-dose statins. For patients with primary hyperlipidemia and mixed dyslipidemia treated with evolocumab in combination with atorvastatin or rosuvastatin, mean unbound PCSK9 serum concentrations at week 12 were 12% to 53% higher with high doses of statins than with low doses of statins ([Table 15](#)).

Table 15 Unbound PCSK9 Serum Concentrations (ng/mL) at Baseline and Week 12- Evolocumab in Combination With Atorvastatin or Rosuvastatin(Study 20110115)

	Evolocumab 140 mg SC Q2W				Evolocumab 420 mg SC QM			
	Baseline		Week 12		Baseline		Week 12	
	Atorvastatin 10 mg QD	Atorvastatin 80 mg QD						
N	104	96	102	99	92	93	90	93
Mean	348	363	150	168	313	357	209	270
SD	115	96.5	95.1	100	96.0	121	122	116
Min	106	132	16.1	17.4	121	0.00	0.00	16.6
Median	329	357	136	161	291	361	193	273
Max	772	707	451	542	608	816	607	620
%CV	33.2	26.6	63.6	59.6	30.7	33.8	58.4	42.9

	Evolocumab 140 mg SC Q2W				Evolocumab 420 mg SC QM			
	Baseline		Week 12		Baseline		Week 12	
	Rosuvastatin 5 mg QD	Rosuvastatin 40 mg QD	Rosuvastatin 5 mg QD	Rosuvastatin 40 mg QD	Rosuvastatin 5 mg QD	Rosuvastatin 40 mg QD	Rosuvastatin 5 mg QD	Rosuvastatin 40 mg QD
N	99	94	100	96	99	92	100	90
Mean	344	392	163	220	339	405	249	301
SD	101	115	130	102	98.1	120	139	114
Min	19.2	197	0.00	31.6	137	34.7	0.00	62.2
Median	344	384	140	213	330	387	231	300
Max	621	802	946	566	643	867	1040	635
%CV	29.4	29.3	80.0	46.5	28.9	29.7	55.9	37.9

%CV = coefficient of variation; max = maximum; min = minimum; QD = once daily; Q2W = once every 2 weeks; QM = once monthly (every 4 weeks); SC = subcutaneous; SD = standard deviation.

(source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Tables 23 and 24, pages 105-106)

Reviewer comments: As pointed out by Welder et al, circulating PCSK9 levels were expected to increase based on the mechanism of action of statins, thereby reducing the levels of unbound evolocumab in cohorts receiving statin therapy.

Despite the up-regulation of PCSK9 with higher doses of statin, it is possible that at a dose level of 140 mg Q2W or 420 mg QM, PCSK9 is nearly completely suppressed, resulting in no difference in PCSK9 or LDL-C lowering between evolocumab administered alone, on a background of low or moderate dose statin or a background of high-dose statin. The implication of this finding is that no dose adjustment is recommended for patients on a background therapy of statins.

2.7 General Biopharmaceutics

2.7.1 Is bioequivalence established between Process 1 formulation and Process 2 formulation (the to-be-marketed formulation) and how does it relate to the overall product development?

Background: Drug substance for Phase 1 (n=4) and Phase 2 (n=6) and limited phase 3 (n=2) clinical studies was initially manufactured using a manufacturing process referred to as Process 1. Drug substance for the majority of the subsequent Phase 1 (n=3) and Phase 3 studies (n = 8) was manufactured using the proposed commercial manufacturing process referred to as Process 2.

The sponsor conducted Study 20110167 as a parallel design study in 350 healthy subjects to formally evaluate the pharmacokinetic equivalence, safety, tolerability, immunogenicity, and changes in LDL-C and PCSK9 following a single dose of evolocumab manufactured by Process 1 and Process 2, in healthy subjects. For Process 1 material, evolocumab was administered as a 2.0 mL injection by syringe and for Process 2, as a 1.0 mL administration by AI/pen. Comparison of the formulation for Process 1 and Process 2 material are shown in Table 16. The main differences in the two processes are (b) (4)

Table 16 Comparison of Drug Product Presentations Used in Clinical Studies

Parameter	Phase 1 Phase 2 Phase 3 (Limited)	Phase 3		Phase 3 (b) (4)
Primary container	Glass vial	Glass PFS		(b) (4)
Clinical administration	Syringe	PFS or prefilled AI/pen		AMD
Dose	70 mg to 420 mg	140 mg	420 mg	(b) (4)
Injections	Up to three 2.0 mL injections	One 1.0 mL injection	Three 1.0 mL injections	One 3.5 mL Injection
Protein concentration	70 mg/mL	140 mg/mL		120 mg/mL
(b) (4)	(b) (4)	20 mM acetate		(b) (4)
pH	(b) (4)	5.0		(b) (4)
(b) (4)	(b) (4)	220 mM proline		(b) (4)
(b) (4)	(b) (4)	0.01% (w/v) polysorbate 80		(b) (4)
Recommended storage temperature	(b) (4)	2°C to 8°C		(b) (4)

PFS = prefilled syringe; (b) (4) AI/pen = autoinjector/pen, AMD = automated mini-doser
(source: module 3.2.P.2, Pharmaceutical Development, Formulation Development Overview, Table 1, Page 2)

Mean serum unbound evolocumab concentration-time profiles following subcutaneous administration from either syringe (Process 1 material) or autoinjector/pen (Process 2 material) were similar (Figure 34).

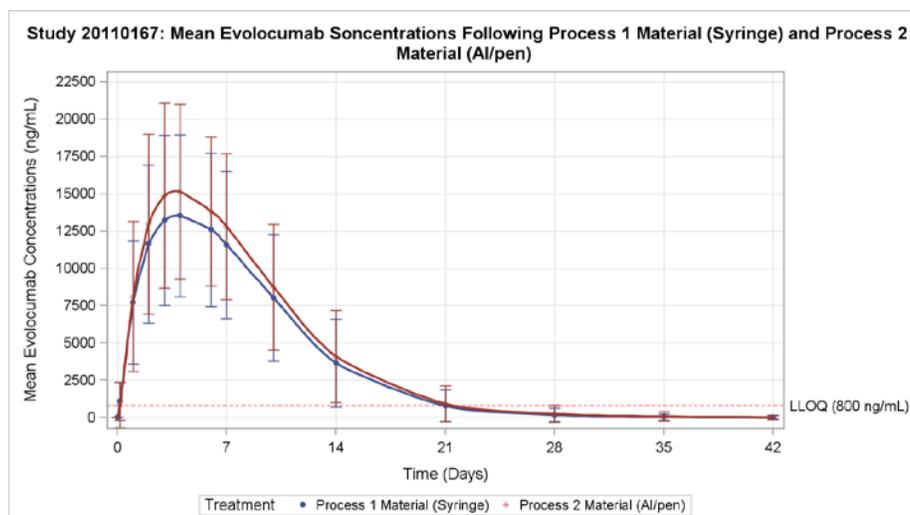


Figure 34 Mean Evolocumab Concentrations Following Subcutaneous Administration of Evolocumab Process 1 Material (Syringe) and Process 2 Material (AI/pen) to Healthy Volunteers

Following single-dose 140 mg subcutaneous administration of evolocumab, C_{max} of 13.01 $\mu\text{g/mL}$ at a median T_{max} of 3.98 days for Process 1 material and a C_{max} of 14.83 $\mu\text{g/mL}$ at a median T_{max} of 3.96 days for Process 2 material were observed. The corresponding AUC_{last} were 125.41 $\mu\text{g}\cdot\text{day/mL}$ and 142.60 $\mu\text{g}\cdot\text{day/mL}$ for Process 1 and Process 2 material, respectively. Corresponding values for area under the curve extrapolated to infinity (AUC_{inf}) were 140.21 $\mu\text{g}\cdot\text{day/mL}$ and 158.11 $\mu\text{g}\cdot\text{day/mL}$ for Process 1 and Process 2 material, respectively (Table 17).

Statistical evaluation of the pharmacokinetic data by this reviewer using PROC MIXED routine in SAS indicated that the two formulations are comparable. The 90% confidence intervals based on the two-one sided test were (105.70 – 123.03), and (102.91 – 123.57) for C_{max} , and AUC_{inf} respectively (Table 17).

Table 17 Summary of Statistical Evaluation of PK Parameter Estimates of Evolocumab (140 mg) Between Test (Process 2 Material Prefilled Autoinjector/Pen) and Reference (Process 1 Material Syringe)

PK Parameter	Test (Process 2 Material)			Reference (Process 1 Material)			Ratio of Test/Reference	
	n	LS Mean	90% CI	n	LS Mean	90% CI	LS Mean	90% CI ^a
AUC_{inf} ($\mu\text{g}\cdot\text{day/mL}$)	164	158.11	(148.73, 168.08)	170	140.21	(130.95, 150.14)	1.13	(102.91 – 123.57)
AUC_{last} ($\mu\text{g}\cdot\text{day/mL}$)	172	142.60	(133.18, 152.58)	175	125.41	(116.28, 135.27)	1.14	(102.71 – 125.87)
C_{max} ($\mu\text{g/mL}$)	172	14.83	(14.08, 15.63)	175	13.01	(12.30, 13.75)	1.14	(105.70 – 123.03)
T_{max} (days)	172	3.96 ^b (1.94 – 6.98)		175	3.98 ^b (1.98 – 6.99)			

CI = Confidence Interval

LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

^aRatio and CI are based on natural log scale data converted back to the original scale

^bMedian (Range)

PD Results:

LDL-C:

Mean reduction of LDL-C over time following subcutaneous administration from either syringe (Process 1 material) or autoinjector/pen (Process 2 material) are shown in [Figure 35](#). The reduction in LDL-C over time between the 2 groups was nearly identical.

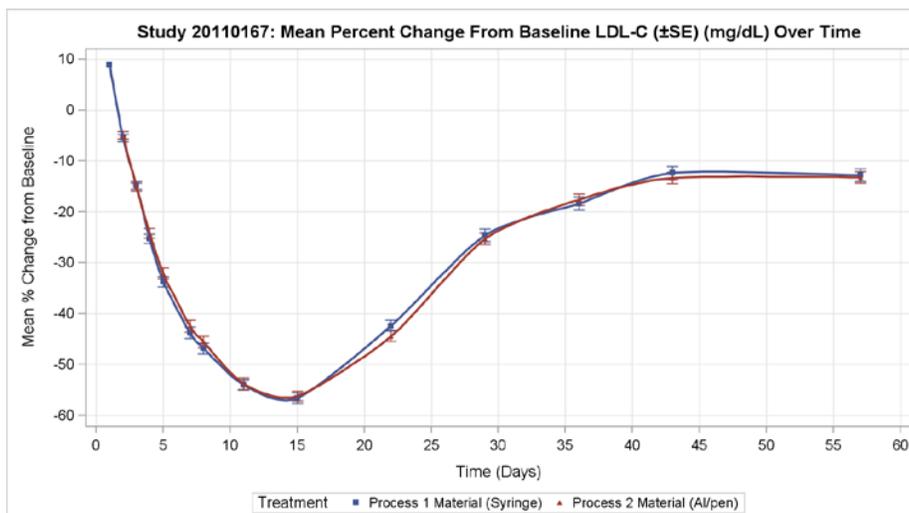


Figure 35 Geometric Mean Percent Change from Baseline (+/- SE) of LDL-C over Time Following Subcutaneous Administration of Evolocumab Process 1 Material (Syringe) and Process 2 Material (AI/pen) to Healthy Volunteers

The LDL-C AUEC_{day1-day57} LS means for the Process 1 and Process 2 groups were 5288.04 mg·day/dL and 5247.93 mg·day/dL, respectively. The geometric LS mean point estimate for the ratio (95% CIs) of Process 2 group to Process 1 group for LDL-C AUEC_{day1-day57} was 0.99 (0.97-1.02), indicating PD bioequivalence ([Table 18](#)).

Table 18 Summary of Statistical Evaluation of AUEC_{day1-day57} for LDL-C Between Test (Process 2 Material Prefilled Autoinjector/Pen) and Reference (Process 1 Material Syringe)

PK Parameter	Test (Process 2 Material)			Reference (Process 1 Material)			Ratio of Test/Reference	
	n	LS Mean	95% CI	n	LS Mean	90% CI	LS Mean	90% CI ^a
AUEC (mg·day/dL)	172	5248	(5148, 5350)	174	5288	(5188, 5390)	0.99	(0.97, 1.02)

CI = Confidence Interval

LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

^aRatio and CI are based on natural log scale data converted back to the original scale

PCSK9:

Within 4 hours of dosing, PCSK9 concentrations decreased steeply with a mean approximate reduction of 93% and 92% from baseline in the Process 1 and Process 2 groups, respectively. The PCSK9 percent change over time was nearly identical for both treatment groups during the study ([Figure 36](#)). There was about 94% percent mean reductions from baseline in PCSK9 concentrations between days 1 to 8, when PCSK9 reached the LLOQ (15 ng/mL) of the assay. Mean percent reduction from baseline in PCSK9 concentrations was approximately 83% for both groups by day 15, and by end of the study, the mean

percent reductions from baseline were approximately 19.5% and 17.3% for the Process 1 and Process 2 groups, respectively.

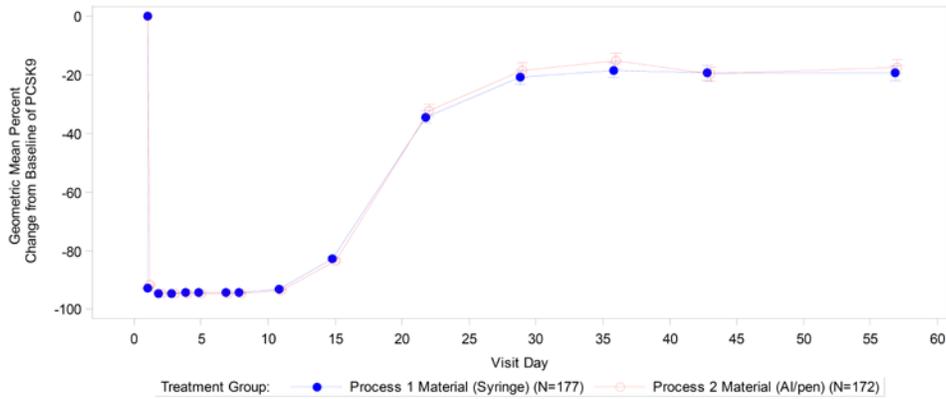


Figure 36 Geometric Mean Percent Change from Baseline (+/- SE) of PCSK9 over Time Following Subcutaneous Administration of Evolocumab Process 1 Material (Syringe) and Process 2 Material (AI/pen) to Healthy Volunteers

2.7.2 Is bioequivalence established between formulations in different presentations (PFS, AI/pen, AMD)?



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(b) **Pre-filled syringe (PFS) vs. Auto-Injector Pens (AI/pens) – Study 20120133:** This study evaluated the bioequivalence of a dose of 140 mg evolocumab delivered either via a pre-filled syringe or an AI/Pen in healthy volunteers. Similar mean unbound evolocumab serum concentration time profiles were observed after a 140 mg SC dose of evolocumab when delivered using the PFS or AI/pen. Median t_{max} was 3.0 days for both the PFS (range = 2.0 to 7.0 days) and the AI/pen (range = 0.97 to 7.1 days). The geometric least square mean ratios (90% CI) of the PFS to AI/pen for C_{max} and AUC_{last} were 1.02 (0.98 - 1.07) and 1.01 (0.95 - 1.08), respectively, indicating bioequivalence between the formulations from the two devices.

Mean serum evolocumab concentration profiles for the two treatments are shown in [Figure 40](#). Mean pharmacokinetic parameters are shown in [Table 21](#), and statistical comparison of pharmacokinetic parameters is shown in [Table 22](#).

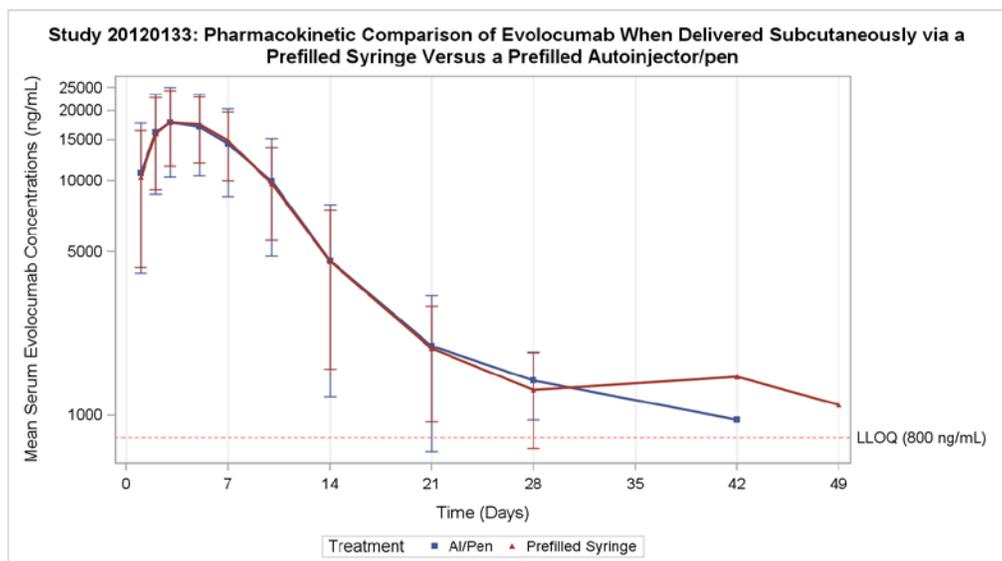


Figure 40 Mean unbound serum evolocumab concentration following subcutaneous administration of a 140 mg dose delivered either via a pre-filled syringe or AI/Pen to Healthy Volunteers

Table 21 Serum Evolocumab Pharmacokinetic Parameter Estimates After a Single Injection of Evolocumab Delivered Subcutaneously via a Prefilled Syringe Versus a Prefilled Autoinjector/Pen in Healthy Subjects

Descriptive Statistic	EvoMab 140 mg SC Autoinjector/pen (Reference)			EvoMab 140 mg SC Prefilled Syringe (Test)		
	t _{max} (day)	C _{max} (µg/mL)	AUC _{last} day·µg/mL)	t _{max} (day)	C _{max} (µg/mL)	AUC _{last} (day·µg/mL)
Period 1						
N	46	46	42	47	47	43
Mean	NR	18.8	188	NR	18.0	176
SD	NR	7.45	95.6	NR	6.08	74.1
Min	2.0	7.35	69.8	2.0	10.5	66.6
Median	3.0	18.7	169	3.0	16.4	162
Max	7.1	45.3	535	7.0	35.3	400
CV%	NR	39.7	51.0	NR	33.7	42.0
Period 2						
N	39	39	32	40	40	31
Mean	NR	18.4	188	NR	19.9	197
SD	NR	7.16	104	NR	6.62	100
Min	0.97	7.72	49.3	2.0	11.3	92.7
Median	3.0	17.6	159	3.1	18.4	163
Max	5.1	42.7	540	7.0	43.3	484
CV%	NR	38.9	55.4	NR	33.3	50.9
Both Periods Combined						
N	85	85	74	87	87	74
Mean	NR	18.6	188	NR	18.9	185
SD	NR	7.28	98.6	NR	6.36	86.0
Min	0.97	7.35	49.3	2.0	10.5	66.6
Median	3.0	18.1	167	3.0	17.0	163
Max	7.1	45.3	540	7.0	43.3	484
CV%	NR	39.1	52.5	NR	33.7	46.4

AUC_{last} = area under the curve from time zero to time of last quantifiable concentration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; EvoMab = evolocumab; NR = not reported; SC = subcutaneous; SD = standard deviation; t_{max} = time to reach C_{max}

(source: report for study 20120133, table 11-1, page 44)

Table 22 Summary of Comparison of Least Square Mean Values After a Single Injection of Evolocumab Delivered Subcutaneously via a Prefilled Syringe Versus a Prefilled Autoinjector/pen in Healthy Subjects

Treatment Parameter(unit)	PFS (N = 87)			AI/pen (N = 85)			Ratio of PFS:AI/pen ^a	
	n	LS Mean	90% CI	n	LS Mean	90% CI	LS Mean	90% CI
AUC _{last} (day·µg/mL)	74	170.29	(156.46, 185.33)	74	168.32	(154.68, 183.16)	1.01	(0.95, 1.08)
C _{max} (µg/mL)	87	17.78	(16.75, 18.88)	85	17.36	(16.34, 18.44)	1.02	(0.98, 1.07)

AI/pen = autoinjector/pen; AUC_{last} = area under the curve from time zero to time of last quantifiable concentration; CI = Confidence Interval; C_{max} = maximum observed drug concentration; LS = least square; PFS = prefilled syringe

LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

^a Ratio and CI are based on the natural log scale data converted back to original scale

(source: study report 20120133, table 11-2, page 45)

Analysis of LDL-C and PCSK9 data indicated that the reductions over time in LDL-C and PCSK9 were nearly identical between groups. The geometric LS mean ratio (90% CIs) of the PFS to AI/pen for LDL-C AUEC_{day1-day85} was 1.00 (0.97 - 1.03), indicating PD equivalence.

Between days 2 to 6 following administration of evolocumab 140 mg with the PFS or the AI/pen, unbound PCSK9 serum concentrations reached the LLOQ (15 ng/mL) of the assay (> 93% mean reductions from baseline). By day 15 of each period, the mean percent reduction from baseline in unbound PCSK9 serum concentrations had receded to approximately 77%, returning to baseline levels by day 43 of each period.

Mean LDL-C and PCSK9 profiles are shown in [Figure 41](#), and [Figure 42](#), respectively.

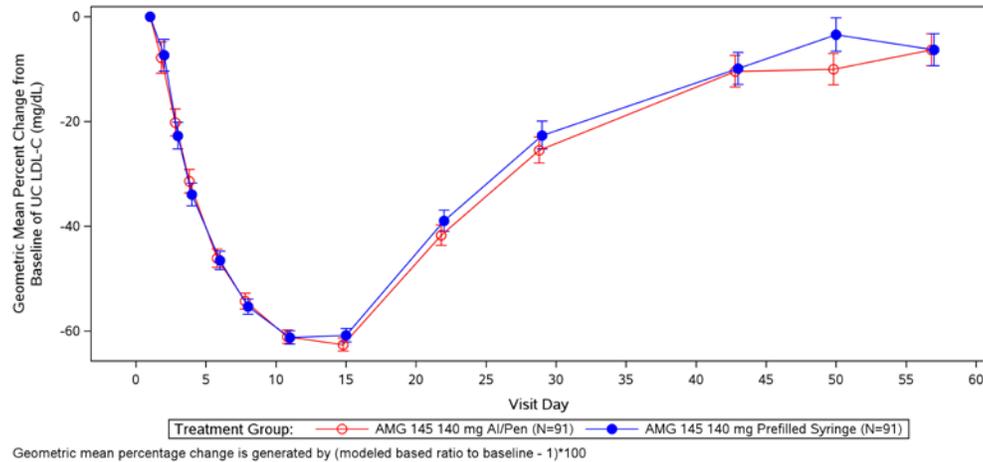


Figure 41 Geometric Mean Percent Change from Baseline (\pm SE) of LDL-C (mg/dL) over Time After a Single Injection of Evolocumab Delivered Subcutaneously via a Prefilled Syringe Versus a Prefilled Autoinjector/Pen in Healthy Subjects

(source: report for study 20120133, Figure 11-2, page 49)

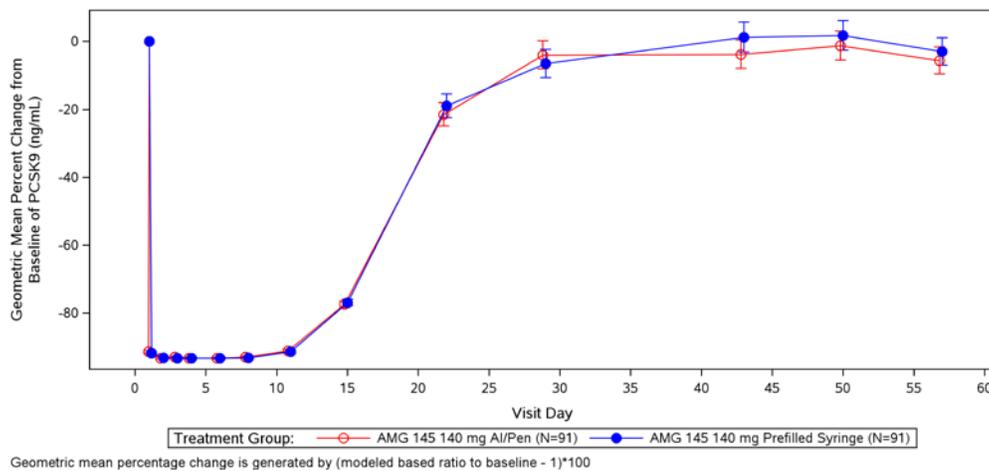


Figure 42 Geometric Mean Percent Change from Baseline (\pm SE) of PCSK9 over Time After a Single Injection of Evolocumab Delivered Subcutaneously via a Prefilled Syringe Versus a Prefilled Autoinjector/Pen in Healthy Subjects

(source: report for study 20120133, Figure 11-3, page 51)

2.7.3 What percentage of Evolocumab, if any, is cleared by the apheresis procedure?

The mean serum unbound evolocumab concentrations assessed at trough (ie, 2 weeks after administration) in 31 subjects with HoFH on apheresis were approximately 20% to 30% lower as a result of apheresis, representing an estimated to be 30 to 60 mg of evolocumab (8% to 15% of the dose). The mean (SD) post-apheresis, pre-dose trough concentration of 61.3 (26.1) was associated with a corresponding unbound PCSK9 mean (SD) level of 25.1 (29.0) ng/mL [0.18 (0.20) nM].. This amount of evolocumab is associated with a full therapeutic effect on PCSK9 suppression, considering that the average (\pm SD) IC_{50} value in the LDLR:PCSK9 binding assay for evolocumab is 0.25 ± 0.16 nM.

In summary, it appears that with the 420 mg Q2W dose aligned with biweekly apheresis, there is negligible evolocumab loss after apheresis, and trough levels are associated with sufficient post-apheresis concentrations to maintain PCSK9 suppression.

The mean evolocumab serum concentrations pre- and post-apheresis by visit from week 2 through week 12 are shown in [Table 23](#).

Table 23 Mean Pre- and Post-Apheresis Unbound Evolocumab Concentrations in HoFH Subjects Through Week 12 Receiving Evolocumab 420 mg SC Q2W (Post-Apheresis) in Study 20110271

Study Week	Pre-Apheresis		Post-Apheresis		Concentration Difference (µg/mL)	Estimated Drug Loss ^a (mg)	Estimated Dose Lost (%)
	N	Unbound Evolocumab Concentration (µg/mL)	N	Unbound Evolocumab Concentration (µg/mL)			
2	29	31.1	27	21.5	9.6	32	8
4	27	49.5	25	34.4	15.1	50	12
6	27	61.9	24	43.6	18.3	61	15
8	25	63.4	21	45.8	17.6	59	14
10	24	69.0	20	49.7	19.3	64	15
12	22	77.0	16	61.3	15.7	52	12

⁰¹ April 2014 data cutoff date

^aEstimated using volume of distribution from Phase 1 IV 420 mg dose = 3.34 L

(source: RTQ 09-12Feb Clinical Information Request_Response 2 - SN 0026, page 35)

2.7.4 Can different injection sites be used to deliver evolocumab subcutaneously?

Evolocumab was administered via subcutaneous injection in the abdomen in all Phase 1 studies. The clinical trial instructions to the investigators for Phase 2 and Phase 3 studies indicated that evolocumab doses may be administered in the upper arm, thigh, or abdomen. Injection sites were to be rotated and injections not be given into areas where the skin is tender, bruised, red, or hard. Trial specific instructions could not be located in the BLA submission, presumably these instructions delivered to trial sites, were followed in the clinical trials. It is not clear if there are PK/PD differences between the different sites of administration since a dedicated Phase 1 study evaluating the PK and PD differences of evolocumab following administration in the upper arm, thigh, or abdomen was not conducted.

2.8 Analytical

2.8.1 Are the analytical methods for Evolocumab, LDL-C and PCSK9 appropriately validated?

Over the course of the development of Evolocumab, three assays were used for the determination of evolocumab and PCSK9. The assays were validated for analyzing the moieties of interest in plasma samples in terms of recovery, linearity, accuracy, precision and sensitivity.

Evolocumab:

The method is briefly described as follows:

PCSK-9:

The method is briefly described as follows:

LDL-C:

LDL-C serum concentrations and other lipid parameters were determined using calculated and preparative ultracentrifugation (UC) laboratory measurements.

Calculated LDL-C: LDL-C was calculated using the Friedewald equation⁵, where LDL-C equals total cholesterol minus (very low density lipoprotein cholesterol [VLDL-C] plus high density lipoprotein cholesterol [HDL-C]), and VLDL-C is estimated by the concentration of triglycerides divided by a correction factor⁶ (5 when using conventional mass based units). Calculated measurement introduces error in estimates of LDL-C when VLDL-C composition is altered. Calculated LDL-C also returns low

⁵ Schechtman G, Patsches M, Sasse EA. Variability in cholesterol measurements: comparison of calculated and direct LDL cholesterol determinations. Clin Chem. 1996;42:732-737.

⁶ Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.

values when LDL-C concentrations are < 40 mg/dL or triglycerides are high, thereby resulting in a larger estimated treatment difference in LDL-C percent reduction.

UC LDL-C: The most accurate LDL-C concentrations are obtained by direct measurement after UC, with removal of the upper VLDL-C layer prior to measuring LDL-C. LDL-C is determined by measuring the cholesterol in the bottom fraction and subtracting HDL-C from this value. The UC method eliminates the inaccuracies introduced using the Friedewald equation.

Across the evolocumab clinical development program, LDL-C serum concentrations were determined using both UC and the Friedewald equation. According to the sponsor, in phase 1 studies, the primary pharmacodynamic analysis used UC LDL-C. In Phase 2 studies of subjects with primary hyperlipidemia or mixed dyslipidemia, the primary efficacy endpoint was also based on UC LDL-C. In phase 3 studies of subjects with primary hyperlipidemia or mixed dyslipidemia, the primary efficacy analysis used an LDL-C reflexive approach, where the UC LDL-C value was determined and reported for LDL-C whenever calculated LDL-C was < 40 mg/dL (1.0 mmol/L) or triglycerides were > 400 mg/dL (4.5 mmol/L).

A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in [Table 24](#).

Table 24 Summary of key descriptive parameters for Evolocumab and PCSK9 bioanalytical assays used in clinical studies

Study #	Sample Type	PCSK9		Evolocumab	
		Accuracy (%Bias)	Precision (%CV)	Accuracy (%Bias)	Precision (%CV)
CLINICAL PHARMACOLOGY STUDIES					
Healthy Subject Pharmacokinetics/Pharmacodynamics & Initial Tolerability					
20080397	Standards	-2 to 2	1 to 3	-1 to 1	1 to 3
	Quality Controls	-7 to -2	4 to 8	-3 to -2	4 to 6
20110121	Standards	0	1 to 5	-1 to 1	2 to 4
	Quality Controls	-2 to 5	8 to 11	7 to 10	4 to 7
20120136	Standards	-3 to 1	1 to 4	-3 to 2	2 to 4
	Quality Controls	5 to 6	7 to 13	-3 to 1	5 to 13
Patient Pharmacokinetics/Pharmacodynamics and Initial Tolerability					
20080398	Standards	-1 to 1	0 to 3	-1 to 1	1 to 2
	Quality Controls	1 to 5	6 to 10	6 to 9	3 to 6
Intrinsic Factors					
20120341	Standards	-1 to 2	1 to 3	-4 to 2	1 to 4
	Quality Controls	2 to 3	6 to 9	-3 to -1	5 to 6
BIOPHARMACEUTIC STUDIES					
Comparative Bioavailability and Bioequivalence					
20110168	Standards	0 to 1	1 to 4	-4 to 3	2 to 5
	Quality Controls	4 to 7	5 to 9	-3 to 1	6 to 16
20120133	Standards	-1 to 1	1 to 3	-4 to 3	2 to 4
	Quality Controls	3 to 3	5 to 7	1 to 6	4 to 11

Study #	Sample Type	PCSK9		Evolocumab	
		Accuracy (%Bias)	Precision (%CV)	Accuracy (%Bias)	Precision (%CV)
EFFICACY AND SAFETY STUDIES – PRIMARY HYPERLIPIDEMIA AND MIXED DYSLIPIDEMIA					
Controlled Studies					
20101154	Standards	0 to 1	1 to 4	-2 to 1	1 to 4
	Quality Controls	0 to 4	9 to 12	6 to 11	4 to 5
20101155	Standards	0	1 to 4	-1 to 1	1 to 4
	Quality Controls	4 to 7	9 to 10	5 to 11	5
20090158	Standards	-1 to 1	1 to 4	-1 to 1	1 to 3
	Quality Controls	7 to 9	8 to 11	6 to 10	4 to 6
20090159	Standards	0 to 1	1 to 4	-1 to 1	1 to 3
	Quality Controls	4 to 8	8 to 11	6 to 10	4 to 6
20110114	Standards	-1 to 1	1 to 3	-1 to 2	1 to 3
	Quality Controls	-2 to 1	6 to 8	1 to 5	4 to 5
20110115	Standards	0 to 1	0 to 3	-1 to 2	1 to 4
	Quality Controls	-1 to 2	6 to 9	1 to 4	4 to 9
20110116	Standards	0 to 1	0 to 2	-1 to 2	1 to 3
	Quality Controls	-3 to -1	6 to 8	3 to 4	4 to 5
20110117	Standards	0	1 to 3	-1 to 1	1 to 3
	Quality Controls	-1 to 1	8 to 13	1 to 4	3 to 4
Supportive Studies					
20110231	Standards	-1 to 2	1 to 5	-3 to 2	2 to 4
	Quality Controls	1 to 1	9 to 11	-2 to 1	4 to 7
Pivotal Studies: Long-term Efficacy and Safety					
20110109	Standards	0 to 1	1 to 4	-4 to 2	2 to 4
	Quality Controls	2 to 3	10 to 12	-1 to 2	6 to 7
20110110	Standards	-1 to 1	1 to 4	-4 to 2	2 to 4
	Quality Controls	2 to 3	9 to 15	0 to 3	6 to 8

Study #	Sample Type	PCSK9		Evolocumab	
		Accuracy (%Bias)	Precision (%CV)	Accuracy (%Bias)	Precision (%CV)
EFFICACY AND SAFETY STUDIES – HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA					
Controlled Studies					
20110233	Standards	0 to 1	1 to 4	-4 to 2	2 to 4
	Quality Controls	-1 to 3	9 to 13	1 to 3	6 to 7
Uncontrolled Studies					
20110271	Standards	-1 to 1	1 to 4	-4 to 2	2 to 4
	Quality Controls	1 to 2	8 to 11	0 to 3	5 to 10
OTHER STUDIES - DEVICE USE					
20120348	Standards	-2 to 0	1 to 3	-3 to 3	1 to 4
	Quality Controls	-1 to 1	5 to 9	1 to 5	4 to 5
20120356	Standards	-1 to 1	0 to 3	-1 to 1	1 to 5
	Quality Controls	-7 to 0	6 to 13	1 to 6	4 to 8

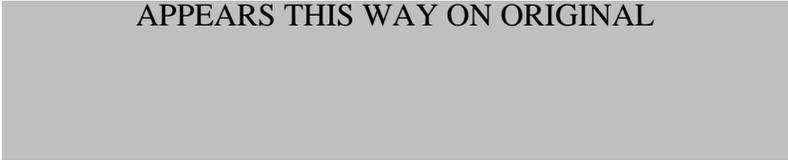
CV = coefficient of variation; PCSK9 = proprotein convertase subtilisin/kexin type 9.

(source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Table 38, page 156-158)

3 *Labeling Comments (Preliminary)*

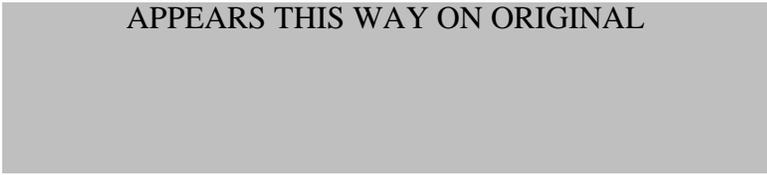
Labeling comments will be addressed in a separate addendum.

APPEARS THIS WAY ON ORIGINAL



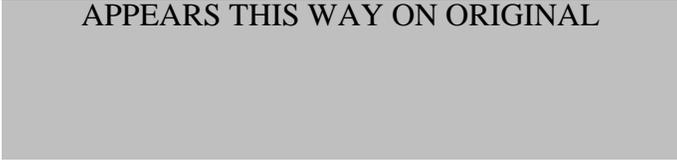
4 APPENDIX

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4.1 Pharmacometric Review

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OFFICE OF CLINICAL PHARMACOLOGY

Pharmacometric Review

A1 Summary of Findings

A1.1 Key Review Questions

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

A1.1.1 The proposed dosing does not discriminate between Q2W and QM dosing for patients with primary hypercholesterolemia, are there patient characteristics that inform when Q2W vs QM dosing should be used?

As the responses appeared to be similar between regimens and no baseline demographic factors were identified that might inform which dosing regimen to give. The applicant's proposed dosing of either 140 mg Q2W or 420 mg QM in patients with HeFH appears reasonable. A univariate exposure-response analysis was performed using data from patients with primary hyperlipidemia and mixed dyslipidemia to ascertain the relationship between evolocumab concentrations and LDL-C lowering in order to evaluate the appropriateness of the dosing regimen.

The mean change from baseline LDL-C for each of 10 exposure bins were plotted against the median evolocumab trough concentration for the respective exposure bin in studies 20110114 (Figure 43, left panel) and 20110115 (Figure 43, right panel). The shape of the curves between the two studies appears similar with the nadirs occurring close to 5 µg/mL.

This univariate analysis would suggest that increasing the exposures may not decrease LDL-C concentrations further. The Q2W and QM regimens produce concentrations that fall near the nadir of these exposure response relationships, as seen by comparing the peaks of the orange density plots for each dosing regimen in Figure 43. This was consistent with the applicant's findings.

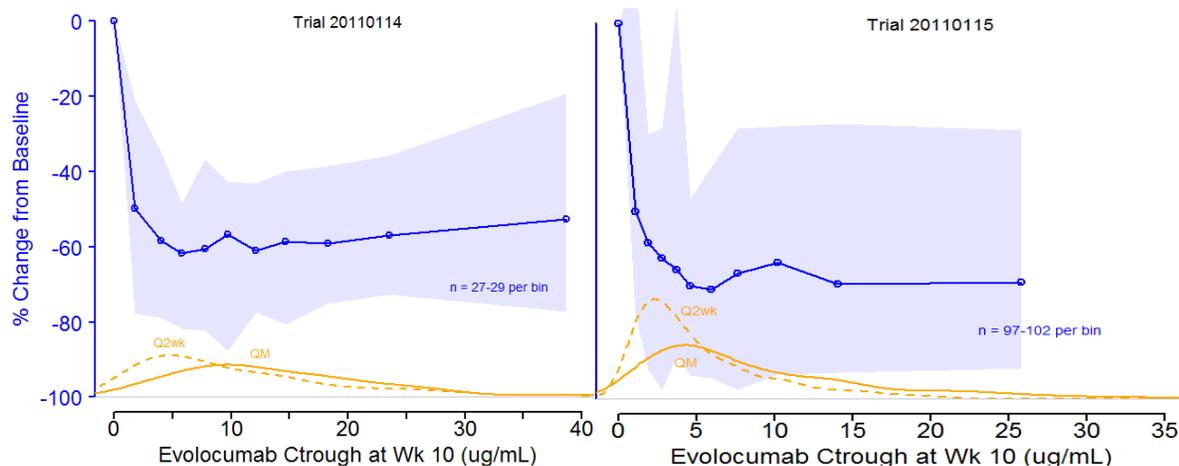


Figure 43. Exposure-response relationships for evolocumab trough concentrations at week 10 and LDL-C change from baseline in studies 20110114 (left panel) and 20110115 (right panel). Mean LDL-C and the range of 5th – 95th percentiles at the corresponding median C_{trough} are shown for each of 10 exposure bins in Trial 20110114 and Trial 20110115 by the blue solid lines and shaded region. Solid orange lines depict the distribution of evolocumab C_{trough} with each respective dosing regimen.

Additionally, the LDL-C change from baseline and percent change from baseline at weeks 10 and 12 were evaluated against different baseline demographic factors. No clinically meaningful correlations

between baseline PCSK9, baseline LDL-C, age, sex, race, weight, and statin use were found to influence LDL-C for either evolocumab dosing regimen.

Results from study 114 for baseline LDL-C, baseline PCSK9, BMI, and gender are shown in (Figure 44 - Error! Reference source not found.). Results for study 115 were similar to that of 114 for the mentioned demographics and are shown in Section 4. LDL-C by statin intensity and dose group for study 115 is shown in Figure 48. Baseline demographic factors evaluated as continuous variables (PCSK9, LDL-C, age, and weight) were divided into four quartiles by dosing regimen and the mean LDL-C and 95% CI was determined. It was observed that there was a numerical trend towards greater LDL-C lowering with the Q2W regimen compared to the Q4 regimen. However, the difference was sufficiently small that it was not considered important given the large extent of LDL-C reduction in both regimens.

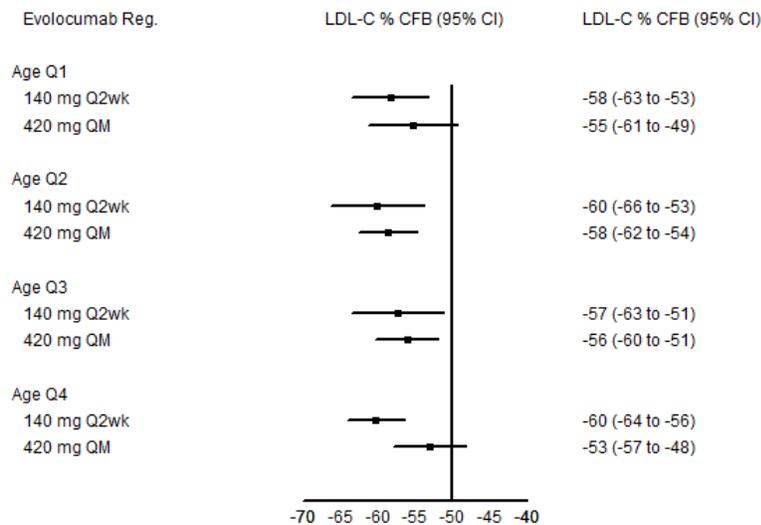


Figure 44. Percent Change from Baseline in LDL-C by Baseline Age Quartile for Trial 20110114. Q1, Q2, Q3, and Q4 refer to the lowest through highest quartiles. Minimum = 20 yr, 25% = 44 yr, Median = 55 yr, 75% = 63, Maximum = 80 yr.

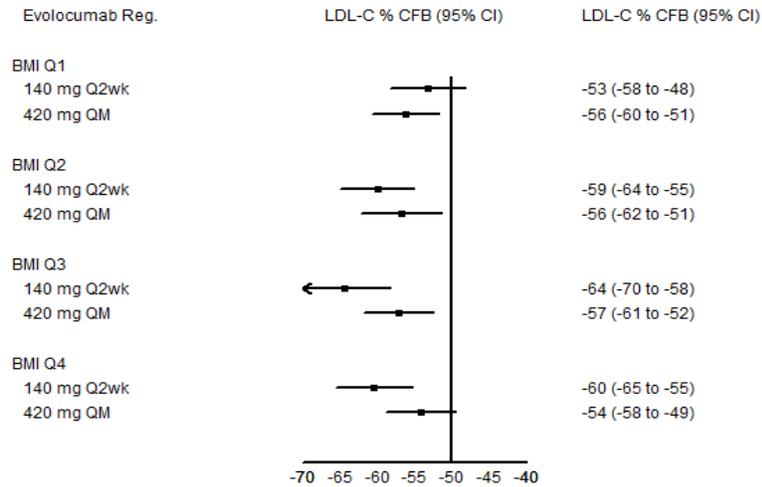


Figure 45. Percent Change from Baseline in LDL-C by Baseline BMI Quartile for Trial 20110114. Q1, Q2, Q3, and Q4 refer to the lowest through highest quartiles. Minimum = 16.7, 25% = 24.1 yr, Median = 27.1 yr, 75% = 32.7, Maximum = 64.3.

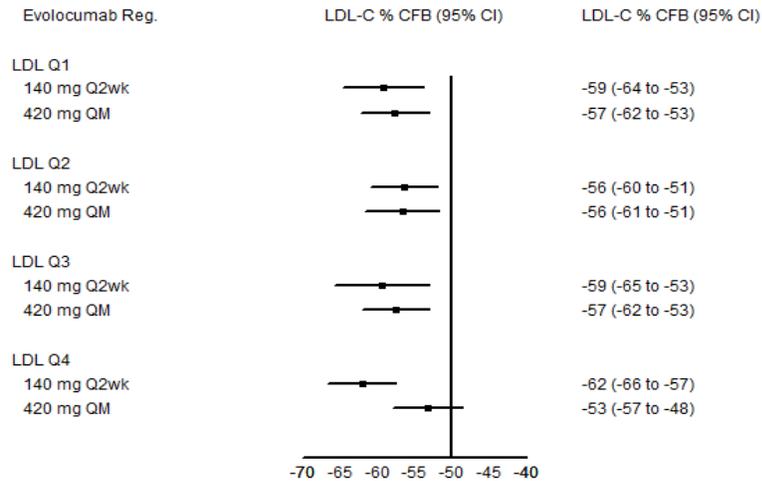


Figure 46. Percent Change from Baseline in LDL-C by Baseline LDL-C Quartile for Trial 20110114. Q1, Q2, Q3, and Q4 refer to the lowest through highest quartiles. Minimum = 81.2 mg/dL, 25% = 124 mg/dL, Median = 140 mg/dL, 75% = 161 mg/dL, Maximum = 236 mg/dL.

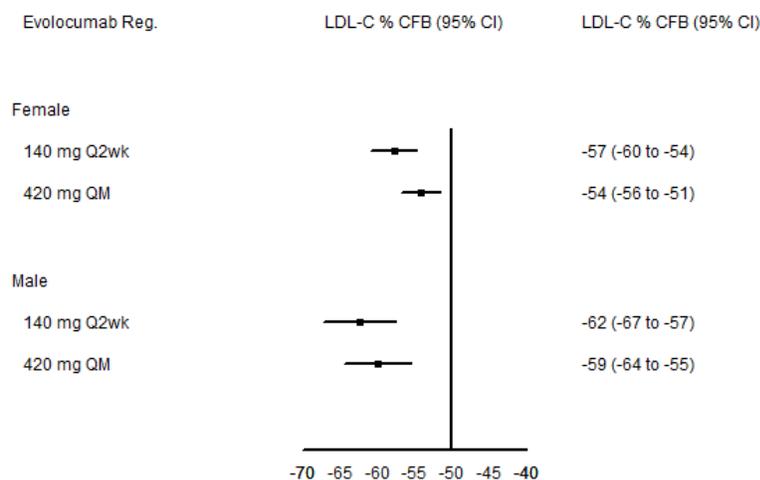


Figure 47. Percent Change from Baseline in LDL-C by Gender for Trial 20110114.

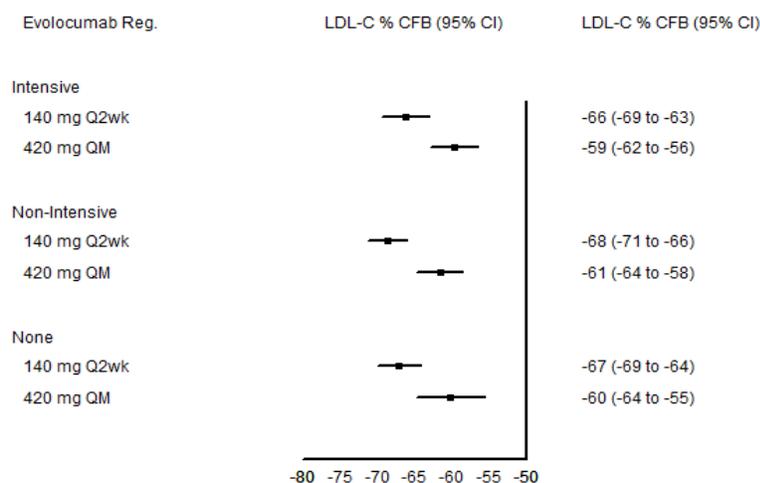


Figure 48. Percent Change from Baseline in LDL-C by Concomitant Statin Intensity for Trial 20110115.

A1.1.2 Does the 420 mg Q2W regimen provide additional benefit to patients who started with 420 mg evolocumab?

The 420 mg Q2W regimen appears to offer little additional benefit (~6% additional reduction in LDL-C) to HoFH patients. The intent of the reviewer's analysis in patients with HoFH was to determine whether switching from 420 mg once-monthly to 420 mg biweekly dosing in HoFH patients provided additional LDL-C lowering value. The applicant conducted a similar analysis and while they achieved similar numerical results, proposed the Q2W regimen.

Open Label Trial 271 was utilized as part of the reviewer's analysis to evaluate the effect of switching from QM to Q2W and vice versa on LDL-C lowering. This was a phase 2/3 open-label extension trial designed to evaluate the long-term safety and efficacy of evolocumab in patients with HoFH and severe FH. The trial design is laid out in [Figure 49](#). Subjects receiving apheresis started the trial with 420 mg Q2W dosing, whereas patients not receiving apheresis started with 420 mg QM dosing. For the purposes of clarity in the text it should be assumed that all patients in Trial 271 received 420 mg and the distinction

in dosing frequency will be made in the text for whether the dosing was every two weeks (Q2W) or once-monthly (QM). This was the only trial where patients switched between dosage strengths during the trial treatment period based on response and PCSK9 criteria.

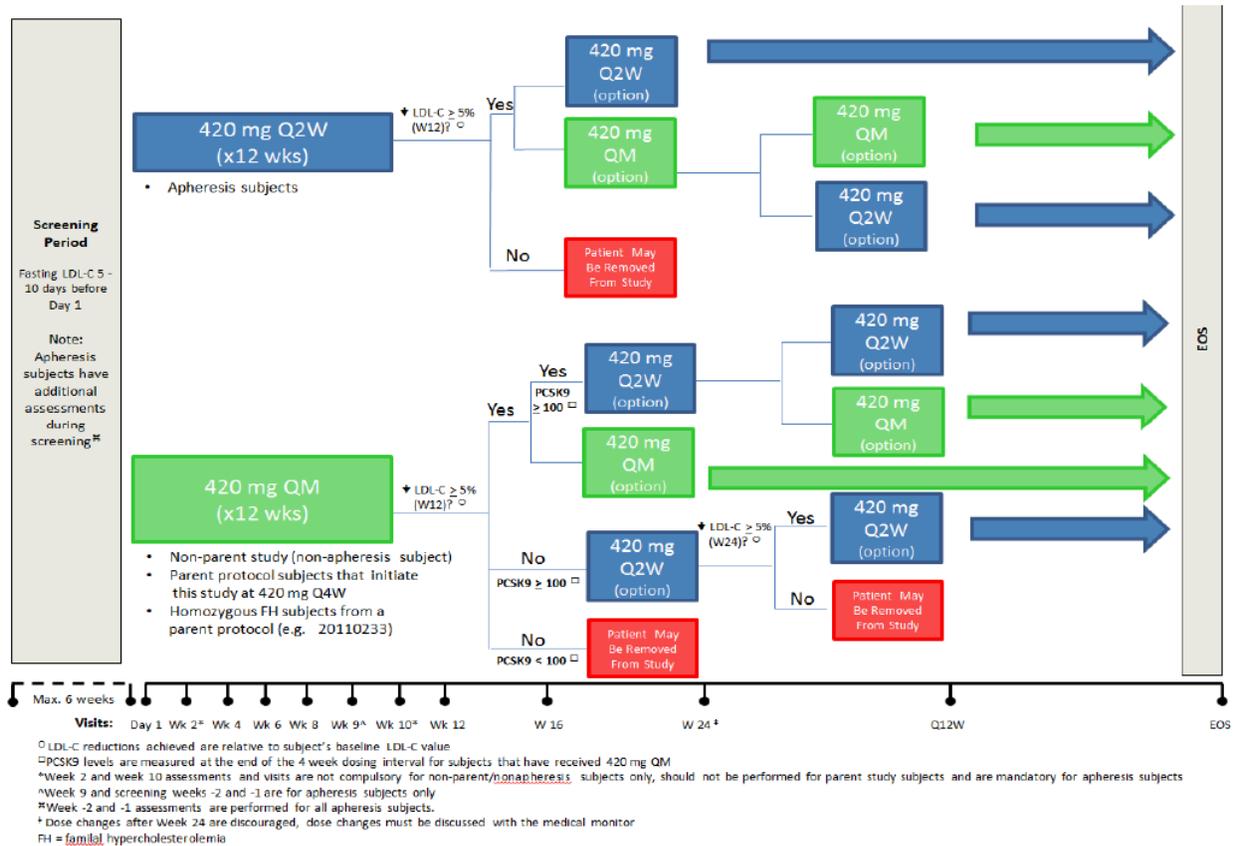


Figure 49. Trial 20110271 – Open Label, Long-Term Safety and Efficacy in HoFH and severe HeFH patients.

(Source: eCTD module 5.3.5.2, Applicant's Clinical Study Report 20110271, Figure 8-1, page 57)

Figure 50 and Figure 51 show the distribution of the average LDL-C concentrations over the duration of the treatment for 1) those patients that did not switch, 2) before the switch and 3) after the switch for those patients that changed their dosing frequency. Two things are readily apparent in Figure 50: 1) The patients that did not up-titrate (Figure 50, left box and whisker plot) were responding better than those that required titration. 2) There was a mild numerical lowering (6%) in the mean LDL-C concentrations in patients who up-titrated (Figure 50, center and right box and whisker plots). At the individual level there was a sustaining of effect, but not much improvement. Further, exposure-response data were not available in the HoFH populations. However, the relationship in the HeFH population suggests that the exposures from the QM dose are already in the plateau of the response curve and that dosing higher amounts will not likely provide additional benefit.

From an efficacy perspective, the 420 mg Q2W regimen does not appear to offer much additional benefit. From safety perspective, there may be an insufficient amount of data in patients who received 420 mg Q2W (see the clinical review by Dr. Eileen Craig for further details).

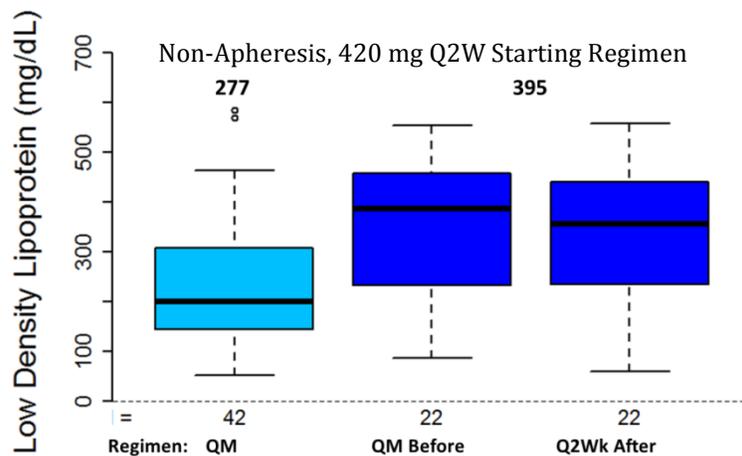


Figure 50. Patients who switched from 420 mg QM to 420 mg Q2W exhibited a 6% reduction in the mean LDL-C lowering. The left box and whisker plot depicts the average LDL-C during the treatment period for patients who did not up-titrate to 420 mg Q2W. The right two plots depict the average LDL-C concentrations before and after the up-titration occurred for those patients who did increase their dosing frequency to Q2W. The numbers above each plot indicate the baseline LDL-C level for each group.

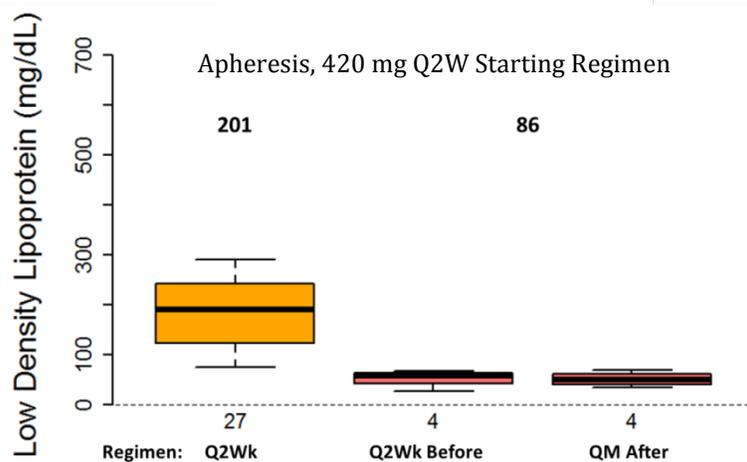


Figure 51. Patients who switched from 420 mg Q2W to 420 mg QM appeared to retain low LDL-C concentrations. The left box and whisker plot depicts the average LDL-C during the treatment period for patients who did not down-titrate to 420 mg QM. The right two plots depict the average LDL-C concentrations before and after the down-titration occurred for those patients who did decrease their dosing frequency to QM. The numbers above each plot indicate the baseline LDL-C level for each group.

A1.1.3 Should patients with lower body-weight receive a lower evolocumab dose?

No, there is no need for dose adjustment in patients with lower body weight. There does not appear to be any safety reason that would suggest patients with lower body weight receive a lower dose of evolocumab. [Figure 52](#) suggests approximately a three-fold increase in the AUC of someone who is 40 kg compared to an 80 kg individual (~median weight for studies 20110114, 20110115, 20110116, 20110117) and a two-fold decrease in AUC when comparing 140 kg individual to an 80 kg individual. 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).

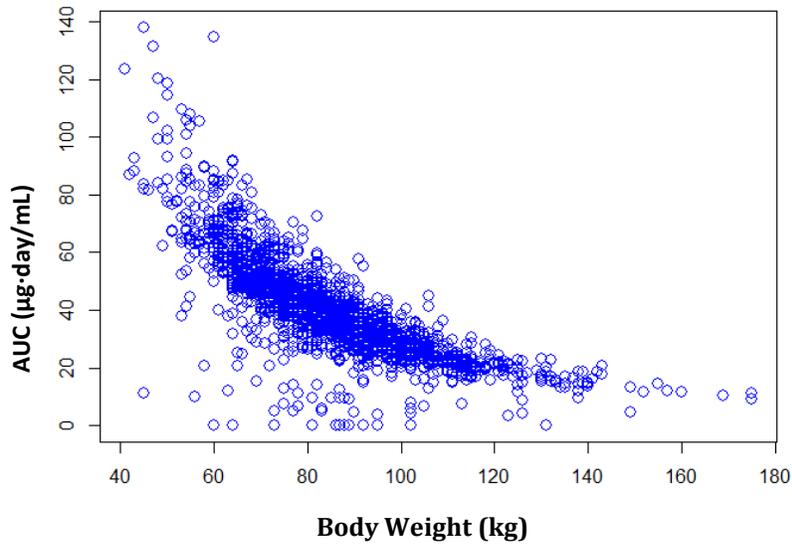


Figure 52. Dose-Normalized AUC correlates with Body Weight (kg) (studies 20110114, 20110115, 20110116, 20110117). AUC was determined from the applicants population PK model using the Bayesian post hoc parameters for each individual at steady-state.

***A1.2* Recommendations**

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

***A1.3* 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



(b) (4)

A2 Pertinent regulatory background

Evolocumab is a new molecular entity NDA being submitted for the treatment of primary hyperlipidemia or mixed dyslipidemia as well as homozygous familial hypercholesterolemia. Evolocumab 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.

A3 Results of Applicant's Analysis

A3.1 Clinical Trials:

A3.1.1 Primary Hyperlipidemia and Mixed Dyslipidemia

The analysis to focus on dosing of evolocumab considered data from a number of the applicants phase 3 trials. Their phase 2/3 program relevant to dose selection and efficacy and safety is laid out in [Figure 53](#) and [Table 25](#).

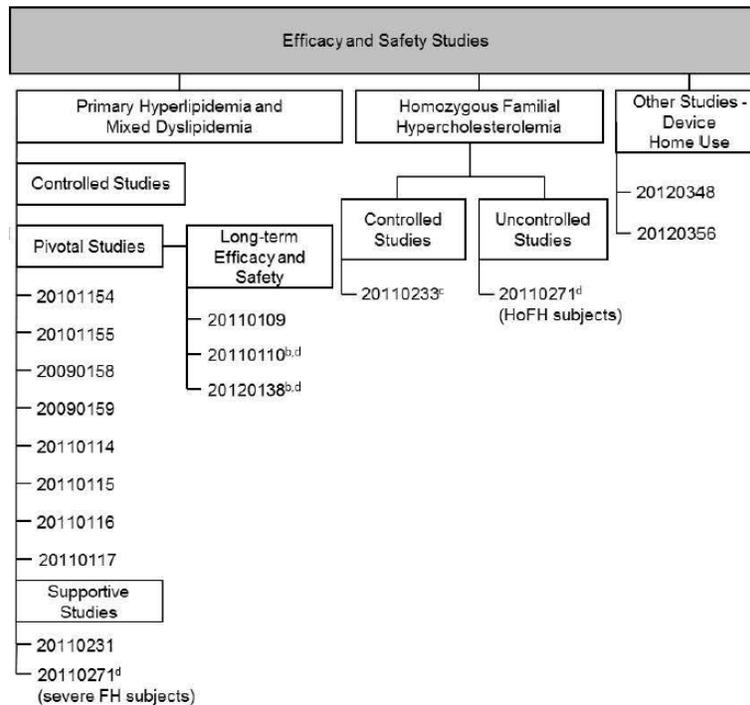


Figure 53. Organization of the evolocumab efficacy and safety studies in the submission

(Source: Applicants Clinical Overview, Figure 1)

Table 25 Tabular Listing of Clinical Phase 2 and 3 Studies Related to Safety and Efficacy

Type of Study	Study Identifier Protocol No.	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	No. Subjects Enrolled/ Analyzed	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Duration of Study ^a	Study Status; Type of Report/ Location
Primary Hyperlipidemia and Mixed Dyslipidemia in Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication)								
Efficacy/ Safety	20101154	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 2, randomized, PBO and Eze-controlled, dose-ranging, monotherapy	PBO SC Q2W or QM EvoMab 70, 105, or 140 mg SC Q2W; 280, 350, or 420 mg SC QM via vial and syringe Eze 10 mg PO QD	411/406	Subjects with hypercholesterolemia LDL-C \geq 100 (2.6 mmol/L) and < 190 mg/dL (4.9 mmol/L) NCEP ATP III Framingham risk score of \leq 10% No lipid-lowering agents up to 3 months prior Age 18 to 75 years	12 or 14 weeks	Complete; full CSR/ 5.3.5.1 (20101154)

Efficacy/ Safety	20101155	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 2, double-blind, randomized, PBO-controlled, dose-ranging, combination therapy	PBO SC Q2W or QM EvoMab 70, 105, or 140 mg SC Q2W; 280, 350, or 420 mg SC QM Via vial and syringe	631/629	Subjects with hypercholesterolemia LDL-C \geq 85 mg/dL (2.2 mmol/L) Stable dose of statin with/without Eze Age 18 to 80 years	12 or 14 weeks	Complete; full CSR/ 5.3.5.1 (20101155)
Efficacy/ Safety	20090158	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 2, double-blind, randomized, PBO- controlled, combination therapy	PBO SC QM or EvoMab 350 or 420 mg SC QM Via vial and syringe	168/167	Subjects with HeFH (but not with HoFH) LDL-C \geq 100 mg/dL (2.6 mmol/L) On stable dose of a statin with/without Eze for at least 4 weeks prior Age 18 to 75 years	12 weeks	Complete; full CSR/ 5.3.5.1 (20090158)
Efficacy/ Safety	20090159	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 2, randomized, parallel group, double-blind, PBO and Eze-controlled, dose-ranging	EvoMab 280, 350, or 420 mg SC QM Eze 10 mg PO QD + EvoMab 420 mg SC QM Eze 10 mg PO QD + PBO SC QM Via vial and syringe	160/157	Subjects with hypercholesterolemia and documented statin intolerance LDL-C \geq 100 mg/dL (2.6 mmol/L) with diagnosed CHD or CHD risk equivalent LDL-C \geq 130 mg/dL (3.4 mmol/L) without diagnosed CHD or risk equivalent and 2 or more risk factors LDL-C \geq 160 mg/dL (4.1 mmol/L) without diagnosed CHD or risk equivalent and with 1 or no risk factors Age 18 to 75 years	12 weeks	Complete; full CSR/ 5.3.5.1 (20090159)
Efficacy/ Safety	20110114	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 3, double-blind, randomized, parallel group, PBO and Eze- controlled, monotherapy	PBO SC Q2W or QM EvoMab 140 mg SC Q2W or 420 mg SC QM Via Al/pen Eze 10 mg PO QD	615/614	Subjects with NCEP ATP III Framingham risk score of \leq 10% LDL-C \geq 100 (2.6 mmol/L) and < 190 mg/dL (4.9 mmol/L) No lipid-lowering agents 3 months prior Age 18 to 80 years	12 or 14 weeks	Complete; full CSR/ 5.3.5.1 (20110114)
Efficacy/ Safety	20110115	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 3, double-blind, randomized, PBO and Eze-controlled, combination therapy	PBO SC Q2W or QM EvoMab 140 mg SC Q2W or 420 mg SC QM Via Al/pen Eze 10 mg PO QD	1899/1896 ^b	Subjects with primary hypercholesterolemia and mixed dyslipidemia LDL-C \geq 80 mg/dL (2.1 mmol/L) if already on an intensive statin LDL-C \geq 100 mg/dL (2.6 mmol/L) if on a non-intensive statin LDL-C \geq 150 mg/dL (3.9 mmol/L) if not on a statin No previous intolerance to rosuvastatin, atorvastatin, or simvastatin Age 18 to 80 years	12 or 14 weeks	Complete; full CSR/ 5.3.5.1 (20110115)
Type of Study	Study Identifier Protocol No.	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	No. Subjects Enrolled/ Analyzed	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Duration of Study^a	Study Status; Type of Report/ Location
Efficacy/ Safety	20110116	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 3, double-blind, randomized, PBO and Eze-controlled	PBO SC Q2W or QM EvoMab 140 mg SC Q2W or 420 mg SC QM Via Al/ pen Eze 10 mg PO QD	307/307	Subjects with hypercholesterolemia and documented statin intolerance LDL-C \geq 100 mg/dL (2.6 mmol/L) with CHD or CHD risk equivalent LDL-C \geq 130 mg/dL (3.4 mmol/L) without diagnosed CHD or risk equivalent and \geq 2 risk factors LDL-C \geq 160 mg/dL (4.1 mmol/L) without diagnosed CHD or risk equivalent and with 1 risk factor LDL-C \geq 190 mg/dL (4.9 mmol/L) without diagnosed CHD or risk equivalent and with no risk factors Age 18 to 80 years	12 or 14 weeks	Complete; full CSR/ 5.3.5.1 (20110116)
Efficacy/ Safety	20110117	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 3, double-blind, randomized, PBO- controlled, combination therapy	PBO SC Q2W or QM EvoMab 140 mg SC Q2W or 420 mg SC QM Via Al/pen	331/329	Subjects with HeFH LDL-C \geq 100 mg/dL (2.6 mmol/L) Age 18 to 80 years On stable dose of a statin with or without eze for 4 weeks	12 or 14 weeks	Complete; full CSR/ 5.3.5.1 (20110117)
Efficacy/ Safety	20110109	Efficacy (LDL-C and other lipid parameters), safety, and tolerability	Phase 3, double-blind, randomized, PBO- controlled, long-term	PBO or EvoMab 420 mg SC QM Via val and syringe	905/901	Subjects with hypercholesterolemia LDL-C \geq 75 mg/dL (1.9 mmol/L) CHD or CHD risk equivalent and not receiving statin therapy with LDL-C < 99 mg/dL (2.6 mmol/L) not eligible Age 18 to 75 years	52 weeks	Complete; full CSR/ 5.3.5.1 (20110109)

Efficacy/ Safety	20110231	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 2, double-blind, randomized, PBO- controlled, combination therapy	PBO SC Q2W or QM EvoMab 70 or 140 mg Q2W SC; 280 or 420 mg SC QM Via vial and syringe	310/307	Japanese subjects with high risk for CV events LDL-C \geq 115 mg/dL (3.0 mmol/L) Age 20 to 80 years	12 or 14 weeks	Complete; full CSR/ 5.3.5.1 (20110231)
Efficacy/ Safety	20110110	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Phase 2 long-term extension Year 1 controlled (vs SoC) Year 2+ open-label EvoMab ^c	Year 1: EvoMab 420 mg SC QM + SoC or SoC alone Years 2 to 5: EvoMab 420 mg SC QM + SoC Via vial and syringe or Al/pen	1324/1324	Completion of a qualifying EvoMab protocol without treatment related SAE that led to IP discontinuation	~ 5 years	Ongoing; interim full CSR/ 5.3.5.1 (20110110)
Efficacy/ Safety	20120138	Efficacy (LDL-C and other lipid parameters), safety, and tolerability	Phase 3, long-term extension. Year 1 controlled (vs SoC) Year 2+ open-label EvoMab ^c	Year 1: EvoMab 140 mg SC Q2W or 420 mg SC QM + SoC or SoC alone Year 2: EvoMab 140 mg SC Q2W or 420 mg SC QM + SoC	3121/2928 ^d	Completion of a qualifying EvoMab protocol without discontinuation of IP for any reason	~2 years	Ongoing; interim full CSR/ 5.3.5.1 (20120138)
Homozygous Familial Hypercholesterolemia in Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication)								
Efficacy/ Safety	20110233	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Part A: phase 2, open-label, single-arm, pilot Part B: phase 3, double-blind, randomized, PBO- controlled	Part A: EvoMab 420 mg SC QM Part B: PBO or EvoMab 420 mg SC QM Via vial and syringe or Al/pen	Part A: 8/8 Part B: 50/49	Subjects with HoFH On a stable low-fat diet and pre-existing, lipid-lowering therapies at least 4 weeks prior with LDL-C \geq 130 mg/dL (3.4 mmol/L) Age 12 to 80 years	Part A: 12 weeks Part B: 12 weeks	Complete; full CSR/ 5.3.5.1 (20110233)
Homozygous Familial Hypercholesterolemia in Module 5.3.5.2 (Study Reports of Uncontrolled Clinical Studies)								
Efficacy/ Safety	20110271	Efficacy (LDL-C and other lipid parameters), safety, and tolerability	Phase 2/3, open-label, long-term	EvoMab 420 mg SC QM or SC Q2W (if eligible) Via vial and syringe, Al/pen, or AMD	238/198 (of the 198 subjects, 96 were HoFH)	Completion of a qualifying EvoMab protocol without treatment related SAE that led to IP discontinuation and have a diagnosis of severe FH If de-novo subject then must have severe FH and be on background lipid-lowering therapy for \geq 4 weeks prior LDL-C \geq 100 mg/dL (2.6 mmol/L) (with CHD or CHD risk equivalent) or \geq 130 mg/dL (3.4 mmol/L) (no CHD or CHD risk equivalent) Age 12 to 80 years	~ 5 years	Ongoing; interim full CSR/ 5.3.5.2 (20110271)

(Source: Applicant's Tabular Listing of Clinical Studies)

The reviewer's analysis focused on the results from trials 20110114 and 20110115 and more detailed schematics of these trial designs are shown in [Figure 54](#) and [Figure 55](#).

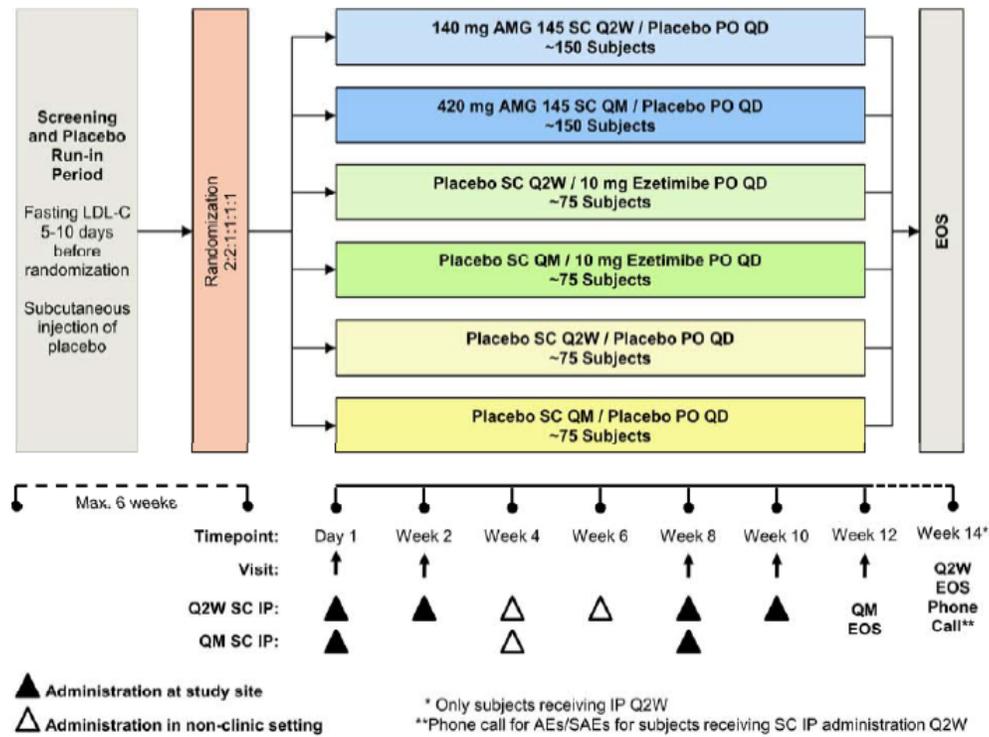


Figure 54. Study 20110114 – Placebo and Ezetimibe Controlled Trial

(Source: Applicant's Clinical Study Report, Study 20110114, Figure 8-1)

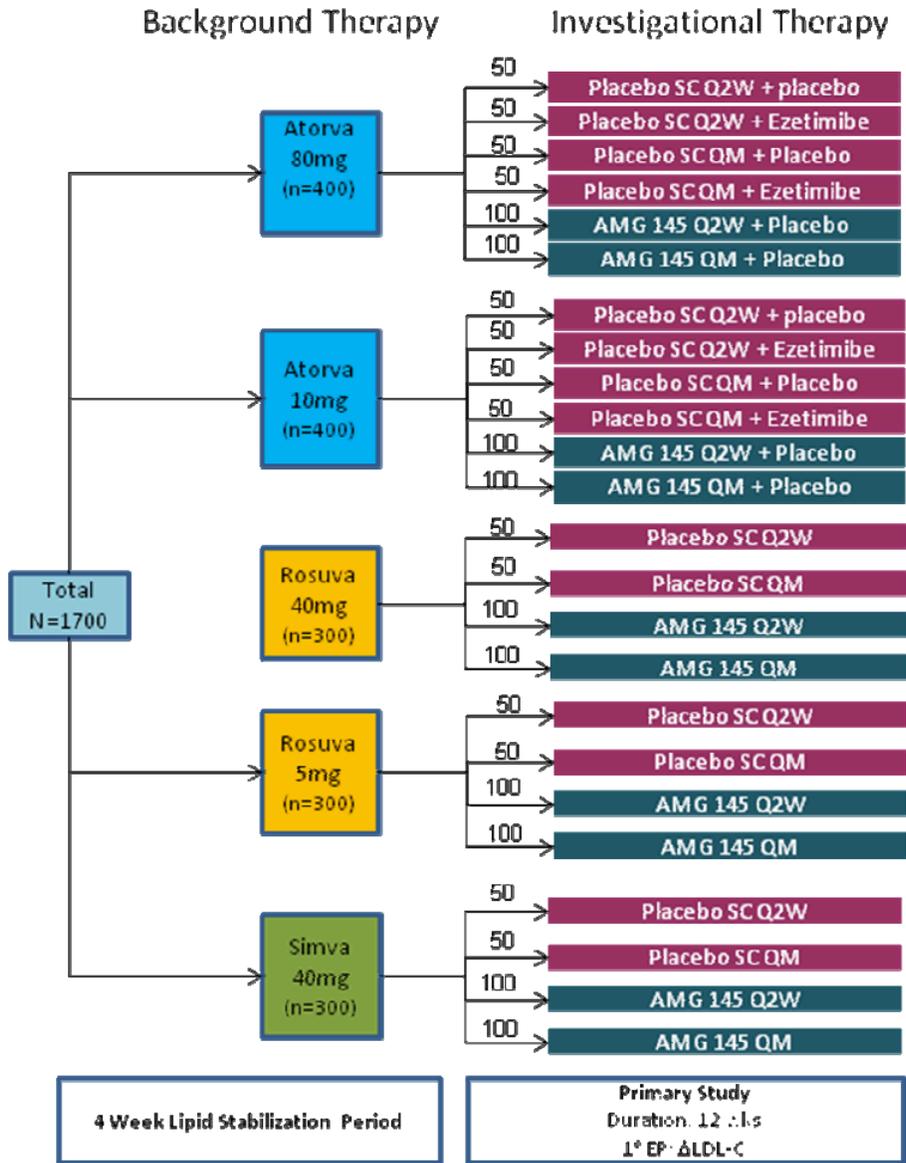


Figure 55. Study 20110115 – Concomitant Statin Therapy

(Source: Applicant's Clinical Study Report, Study 20110115, Figure 8-1)

Figure 56 summarizes the primary efficacy findings from the phase 3 trials 20110114, 20110115, 20110116, 20110117, and 20110109.

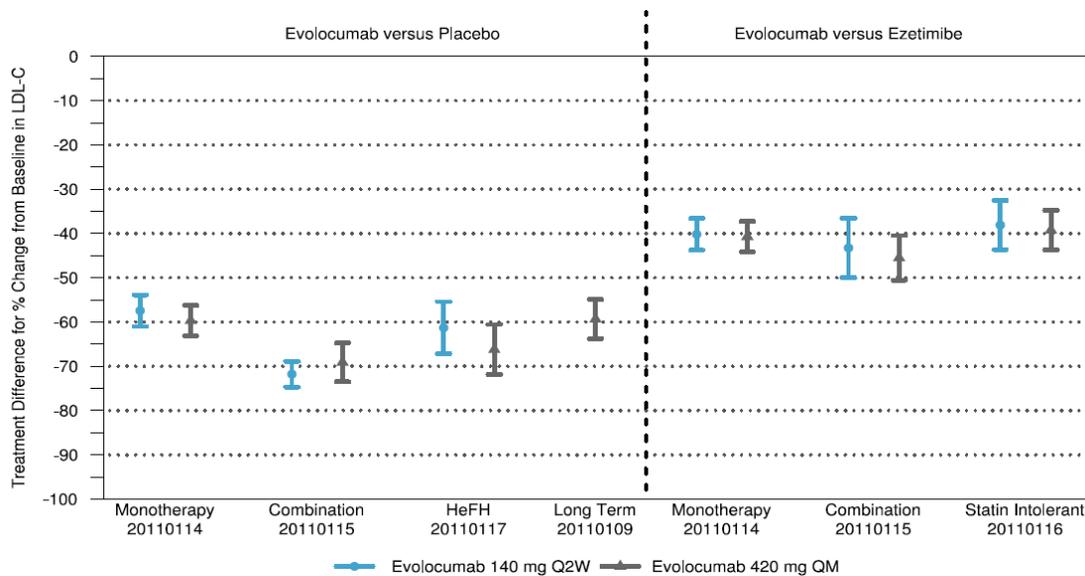


Figure 56. Treatment differences for % change from baseline in calculated LDL-C in the phase 3 evolocumab program.

(Source: Applicants Clinical Overview, Figure 2)

Dose selection for the phase 3 studies was supported by results from the phase 2 single-dose and multiple dose studies (Studies 20090158, 20090159, 20101154, and 20101155). The dose-ranging studies in phase 2 evaluated evolocumab dosed as 70 mg, 105 mg, and 140 mg Q2W and 280 mg, 350 mg, and 420 mg. In all cases, the efficacy was the highest with the highest doses (i.e. 140 mg Q2W and 420 mg QM). The applicant noted that increased adverse events were not associated with increased evolocumab dose. These doses were carried forward into the phase 3 program and tested in a randomized parallel comparison with placebo and ezetimibe. In general the applicant assessed the treatment difference in percent change from baseline from placebo or active control for both the 140 mg Q2W and 420 mg QM regimens to be sufficiently similar (Figure 56). Thus their draft label proposes either regimen in without specific recommendations as to who should start with which dosing regimen. The purpose of the reviewer’s analysis was to evaluate the appropriateness of the dose regimen and whether these two regimens were distinguishable in different patient populations.

A3.1.2 Homozygous Familial Hyperlipidemia

Open Label Study 271 was utilized as part of the reviewer’s analysis to evaluate the effect of switching from 420 mg Q2W to 420 mg QM and vice versa on LDL-C concentrations. This was the only study where patients switched between dosage strengths during the study treatment period. This was a phase 2/3 open-label extension trial designed to evaluate the long-term safety and efficacy of evolocumab in patients with HoFH and severe FH. The trial design is laid out in Figure 57 and Table 25 and an overview of the efficacy results from study 20110271 are shown in Table 26 and Table 27.

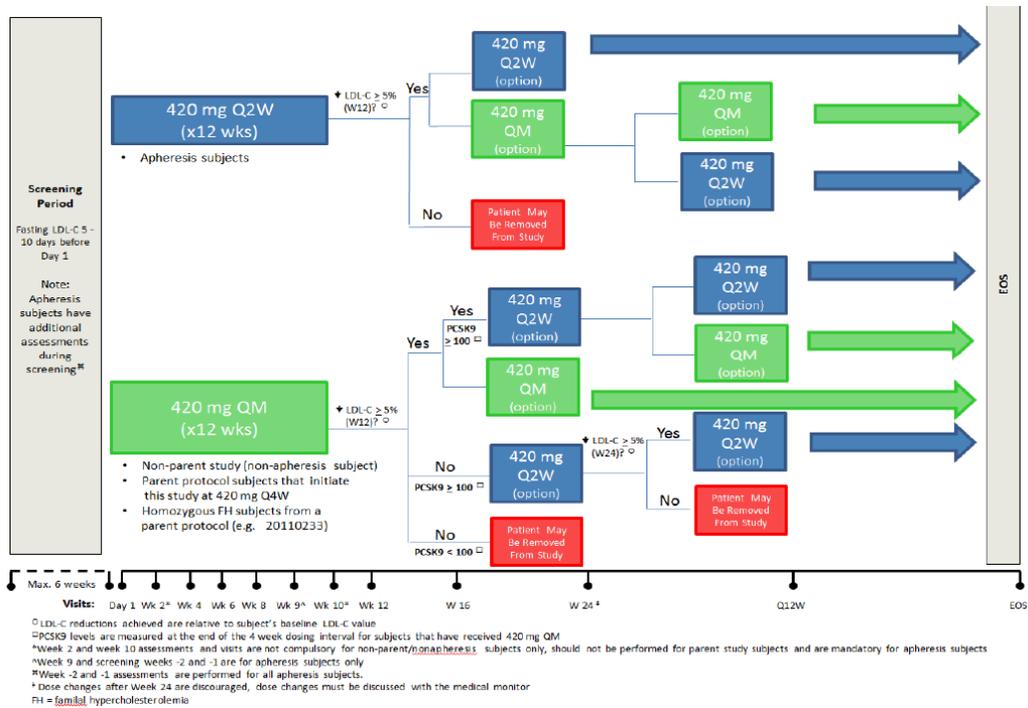


Figure 57. Study 20110271 – Open Label, Long-Term Safety and Efficacy in HoFH

Table 26. Percent change from baseline in UC LDL-C by study visit (HoFH interim analysis set, Study 20110271)

Analysis Set	Summary Statistic	OLE Week 12	OLE Week 24	OLE Week 36
HoFH Interim Analysis Set (N = 96)	n	68	45	29
	Mean (SE)	-19.03 (3.04)	-23.06 (3.62)	-26.19 (4.51)
	Median	-15.61	-24.14	-27.84
	Range	-89.1, 47.3	-67.8, 43.1	-72.4, 44.9
Non-apheresis subjects (N = 65)	n	44	32	26
	Mean (SE)	-20.37 (3.33)	-24.50 (4.20)	-27.17 (4.62)
	Median	-18.24	-23.07	-28.92
	Range	-80.4, 23.9	-67.8, 39.9	-72.4, 44.9
Apheresis subjects (N = 31)	n	24	13	3
	Mean (SE)	-16.59 (6.14)	-19.51 (7.30)	-17.66 (19.91)
	Median	-14.89	-24.14	-12.13
	Range	-89.1, 47.3	-59.5, 43.1	-54.6, 13.7

FH = familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; OLE = open-label extension; SE = standard error; UC = ultracentrifugation.

N/n = number of evaluable subjects (N) and subjects with observed LDL values at specific visit (n).

(Source: Applicant's Clinical Study Report Synopsis, Trial 20110271, page 6)

Table 27. Percent change from baseline in UC LDL-C by study visit (Severe FH interim analysis set, Study 20110271)

Analysis Set	Summary Statistic	OLE Week 12	OLE Week 24	OLE Week 36
Severe FH Interim Analysis Set (N = 102)	n	(b) (4)		
	Mean (SE)			
	Median			
	Range			

^a Of these 8 subjects, 1 subject made changes to background lipid lowering therapy and 1 subject had a late assessment performed at OLE week 24.

FH = familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; OLE = open-label extension; SE = standard error; UC = ultracentrifugation.

N/n = number of evaluable subjects (N) and subjects with observed LDL values at specific visit (n).

(Source: Applicant's Clinical Study Report Synopsis, Trial 20110271, page 6)

A3.2 Population PK:

The applicant's population PK analysis was performed in two parts. In the first step, data from the phase 1 and 2 studies were utilized to develop the structural model and covariate model. In the second step, the model developed in part one was reevaluated with all the data from the phase 1, 2, and three studies listed in [Table 28](#).

Table 28. Summary of studies included in the population PK analysis.

Study	Evolocumab Dosing	Study Population	Pharmacokinetic Sampling	No. of Subjects
Phase 1a 20080397	Single Dose: IV: 21, 420 mg; SC: 7, 21, 70, 210, 420 mg	Healthy subjects	Intensive	56
Phase 1b 20080398	Multiple Dose: Q1Wx6 SC: 14, 35 mg; Q2Wx3 SC: 140, 280 mg; QMx3 SC: 420 mg	Hypercholesterolemia patients treated with a statin	Intensive	57
Phase 2 20090158	QMx3 SC: 350, 420 mg	Combination therapy in HeFH patients	Trough and PK substudy	167
Phase 2 20090159	QMx3 SC: 280, 350, 420 mg	Combination therapy in statin intolerant patients	Trough and PK substudy	157
Phase 2 20101154	Q2Wx6 SC: 70, 105, 140 mg; QMx3 SC: 280, 350, 420 mg	Monotherapy in hypercholesterolemia patients	Trough and PK substudy	361
Phase 2 20101155	Q2Wx6 SC: 70, 105, 140 mg; QMx3 SC: 280, 350, 420 mg	Combination therapy in hypercholesterolemia patients	Trough and PK substudy	629
Phase 3 20110109	QMx12 SC: 420 mg	Effect durability in hypercholesterolemia patients: monotherapy or combination therapy	Sparse	901
Phase 3 20110114	Q2Wx6 SC: 140 mg; QMx3 SC: 420 mg	Monotherapy in hypercholesterolemia patients	Sparse	614
Phase 3 20110115	Q2Wx6 SC: 140 mg; QMx3 SC: 420 mg	Combination therapy in hypercholesterolemia patients	Sparse	1896
Phase 3 20110116	Q2Wx6 SC: 140 mg; QMx3 SC: 420 mg	Combination therapy in statin intolerant patients	Sparse	307
Phase 3 20110117	Q2Wx6 SC: 140 mg; QMx3 SC: 420 mg	Combination therapy in HeFH patients	Sparse	329

Q1W, every week; Q2W, every 2 weeks; QM, every 4 weeks.

The final structural model (Figure 58) is a one-compartment linear model with nonlinear Michaelis-Menten clearance in addition to a linear clearance pathway.

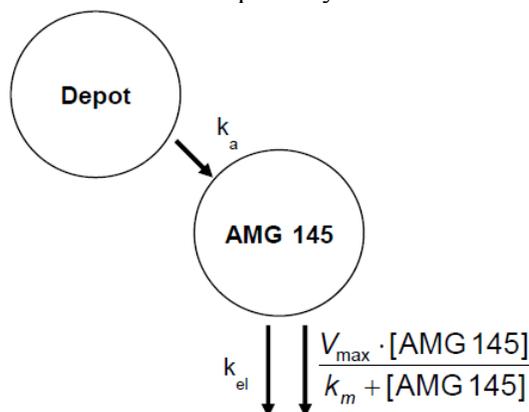


Figure 58. Schematic of the final Pharmacokinetic Structural Model.

(Source: Applicant's Population PK Report 116744, Figure 5-3)

The final model parameters are shown in [Table 29](#). Continuous covariates were modeled using Equation 1.

Equation 1

$$P_j = TVP \cdot \left(\frac{COV_j}{COV} \right)^\Theta \cdot \exp(\eta_j)$$

Binary covariates were modeled using Equation 2.

Equation 2

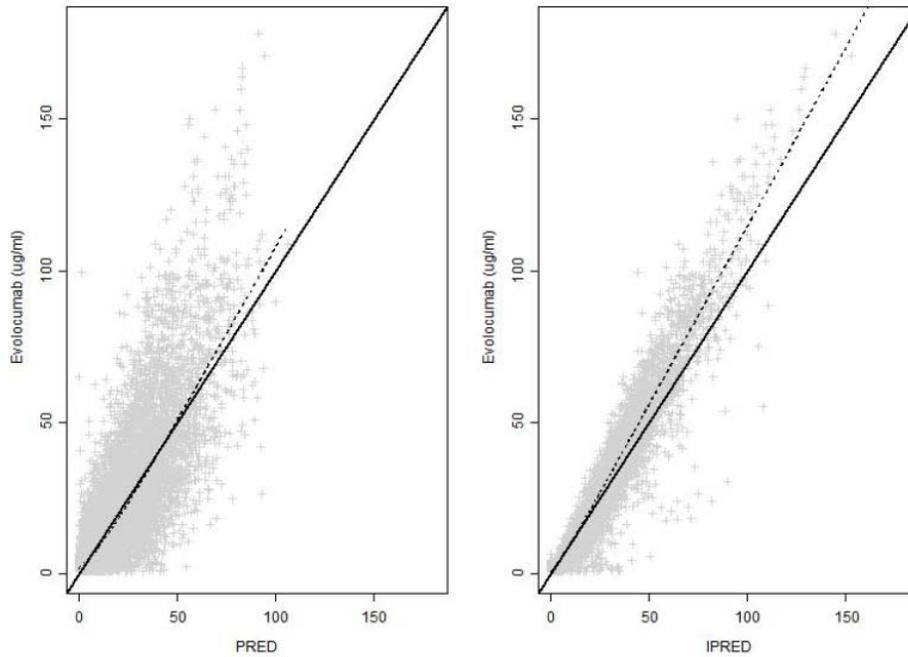
$$P_j = TVP \cdot \Theta^{COV_j} \cdot \exp(\eta_j)$$

P_j is the individual model parameter for the j^{th} subject.

Table 29. Final population PK model parameters. Note the parameters that were fixed were evaluated in the original analysis with the phase 1 and 2 data only.

Parameter	Units	Estimate (RSE)	BSV (RSE)	Shrinkage
F	%	0.72 (FIXED)	0%	-
k_a	day ⁻¹	0.319 (FIXED)	74.6% (FIXED)	48.4%
CL	L/day	0.105 (2.18%)	54.3 % (3.20%)	47.6%
BW exponent		0.276 (30.4%)		
V	L	5.18 (1.15%)	28.3% (3.27%)	25.2%
BW exponent		1.04 (4.05%)		
Female exponent		1.11 (1.42%)		
V_{max}	nM/day	9.85 (FIXED)	31.1% (3.54%)	43.8%
BW exponent		0.145 (33.0%)		
Statin exponent		1.13 (1.02%)		
Statin+ezetimibe exponent		1.20 (1.59%)		
PCSK9 BL exponent		0.194 (7.47%)		
k_m	nM	27.3 (FIXED)	0% (FIXED)	-
Residual proportional error	%	0.282 (1.12%)	-	
Residual additive error	nM	5.41 (2.50%)	-	

PCSK9 BL: PCSK9 baseline; BSV: Between-Subject Variability; F: Subcutaneous bioavailability; k_a : absorption rate constant; CL: linear clearance; V: volume of distribution; V_{max} : nonlinear clearance capacity; k_m : concentration of half maximal nonlinear clearance; %RSE: Relative Standard Error, determined by NONMEM standard error after Importance Sampling.



PRED: Population Predicted Concentration; IPRED: Individual Predicted Concentration; Solid Line: Line of Unity; Dashed Line: Lowess Smooth.

Figure 59. Model Diagnostic Plots for Observations vs Predictions.

(Source: Applicant's Population PK Report 119663, Figure 6-3)

Two forest plots shown in [Figure 60](#) depict the expected range of covariate effects, in the studied population, on the PK of evolocumab.

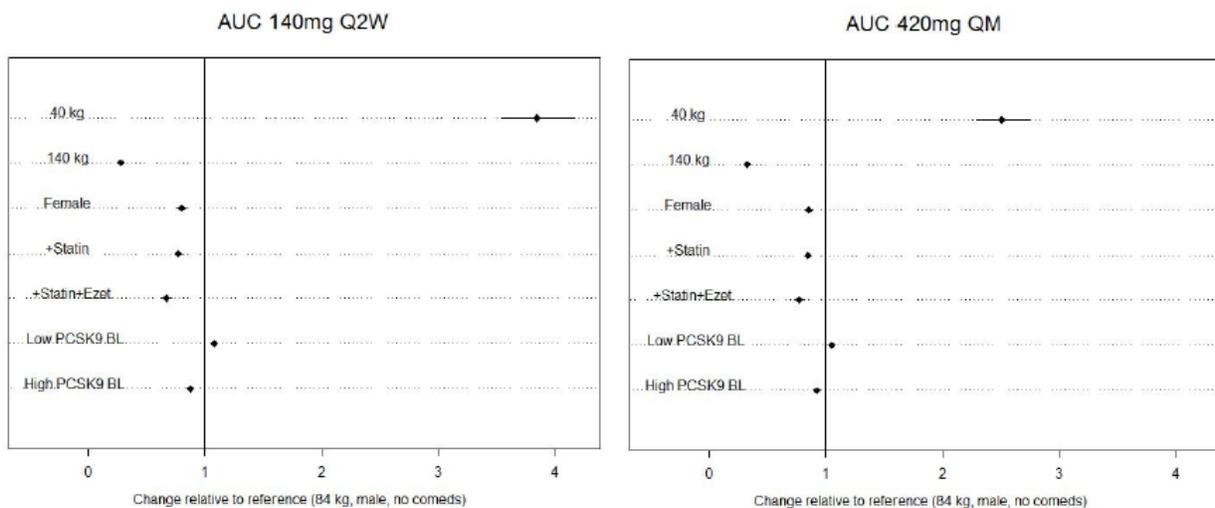


Figure 60. Forest plots of covariate effects with 95% confidence interval for evolocumab AUC at week 8-12 for 140 mg Q2W (left panel) and 420 mg QM (right panel).

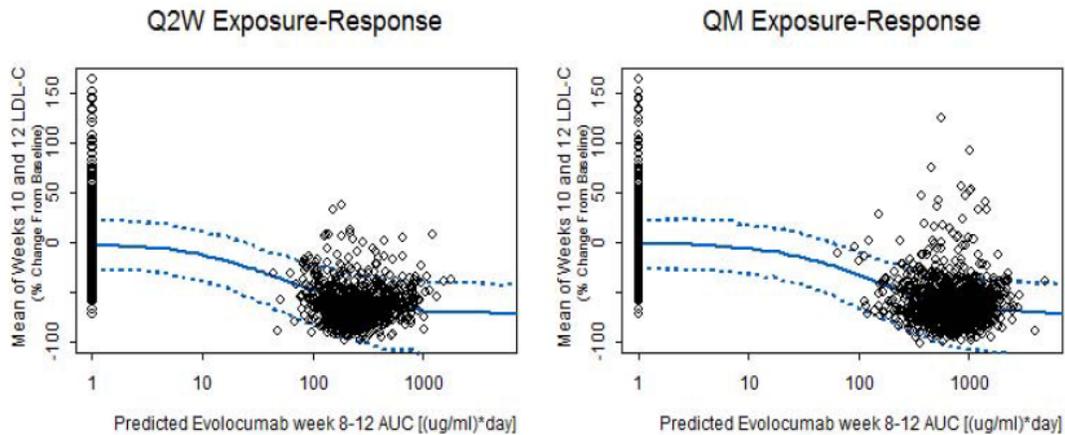
(Source: Applicant's Population PK Report 119663, Figure 6-6)

Reviewer's Comments: The sponsor's population PK model appears reasonable for labeling the PK properties of evolocumab. Regarding the claim of (b) (4) this is reasonable given the large number of patients with PK both taking statins as part of a trial regimen and patients not taking statins, the duration during which statin use occurred (>12 weeks), and the nature of the interaction being due to increased PCSK9 expression. The mechanism of drug-interaction is induction of an enzyme that should reach a new steady-state over several weeks unlike competitive

inhibition which may be contained in a much shorter time frame and can possibly be missed by sparse sampling. Regarding special populations, the conclusion that no dose adjustments are needed for age, race, gender, and body weight is reasonable. Any effects of these population characteristics were minor compared to the extent of LDL-C reduction achieved at the population level for each dose.

A3.3 Exposure-Response:

The exposure-response model was developed from the phase 1 and 2 data. With regards to the phase three data the updated PK model was used to predict the phase 3 data and compare against the observations.



Prediction of the mean of weeks 10 and 12 calculated LDL-C in percent change from baseline, 50th (solid line) and 5th and 95th (dashed lines) percentiles. Simulations were formed for n = 2000 patients. Points: observed individual mean of weeks 10 and 12 calculated LDL-C measurements from subjects in phase 3 studies (Studies 20110109, 20110114, 20110115, 20110116, and 20110117), individual predicted evolocumab AUC_{wk8-12} from the updated PK model. For Study 20110109, the week 12 LDL-C values were included because LDL-C was not evaluated at week 10.

Figure 61. Phase 3 observed and phase 1+2 model-predicted mean of calculated LDL-C at weeks 10 and 12 by the population predicted AUC over weeks 8 – 12.

(Source: Applicant's Population PK Report 119663, Figure 6-8)

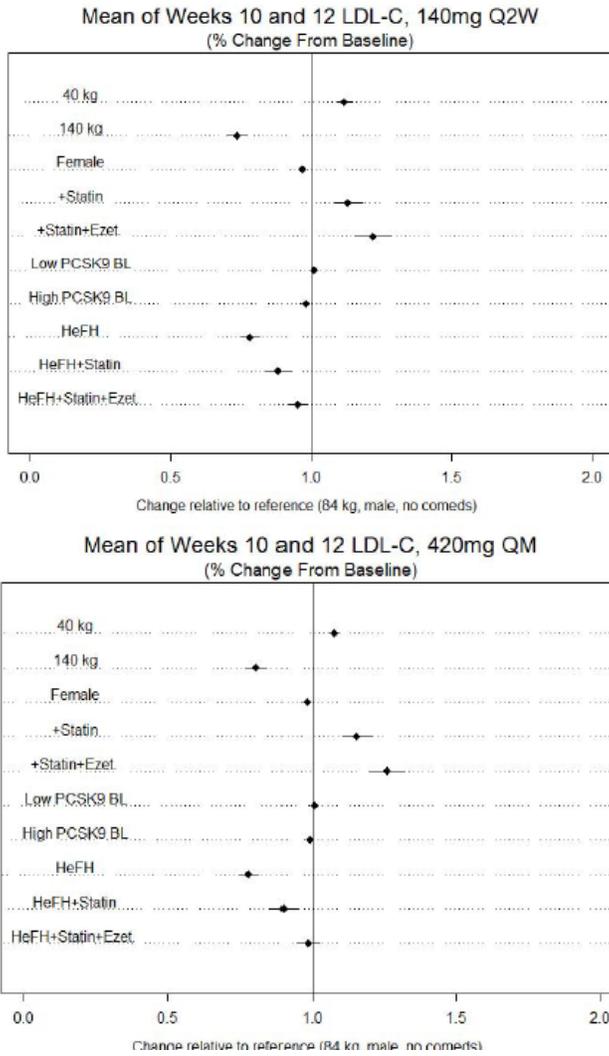


Figure 62. Forest plots of covariate effects with 95% confidence interval for calculated LDL-C at weeks 10 and 12 following 140 mg Q2W (left panel) and 420 mg QM (right panel) evolocumab.

(Source: Applicant's Population PK Report 119663, Figure 6-9)

Table 30. Predicted mean calculated LDL-C lowering (mg/dL, and 95% confidence interval), mean of weeks 10 and 12 for reference and covariate conditions.

	140 mg Q2W	420 mg QM
Reference	63.8 (60.4-67.2)	61.3 (58.2-64.5)
40 kg	53.9 (49.6-58.2)	54.8 (50.9-58.7)
140 kg	86.4 (82.2-90.6)	78.5 (74.6-82.3)
Female	66.6 (62.7-70.4)	63.0 (59.7-66.3)
+Statin	42.0 (38.7-45.3)	38.2 (35.0-41.4)
+Statin+Ezet.	34.7 (29.0-40.3)	29.6 (24.1-35.0)
Low PCSK9 BL	62.9 (59.4-66.3)	60.9 (57.6-64.1)
High PCSK9 BL	65.4 (62.1-68.8)	62.2 (59.1-65.3)
HeFH	105.9 (96.3-115.5)	103.4 (94-112.9)
HeFH+Statin	75.6 (68.7-82.4)	71.7 (64.9-78.5)
HeFH+Statin+Ezet.	67.0 (61.4-72.6)	61.9 (56.3-67.4)

The statin covariate represents patients only on a statin and no other comedication. Ezet.: Ezetimibe; PCSK9 BL: PCSK9 baseline (Low = 355 ng/ml; High = 599 ng/ml)

(Source: Applicant's Population PK Report 119663, Table 6-7)

Reviewer's Comments:

It is unclear why dose frequency was modeled as a covariate on the EC50 parameter. This unconventional use of dosing regimen as a covariate may reduce the ability to test the effect of other covariates shown in Figure 20 using post hoc Bayesian estimates. The reviewer's analysis did not reveal any additional baseline factors linked to response, thus we did not critique the model further. This was in part driven by the observation that the overall response tended to be much greater than differences due to baseline patient characteristics.

A4 Reviewer's Analysis

A4.1 Introduction

The intent of the reviewer's exposure-response analysis was to evaluate whether 140 mg QW and 420 mg QM evolocumab give similar responses in patients with primary dyslipidemia. Additionally the analysis was also conducted to determine if any benefit was observed in patients with HoFH receiving 420 mg QM vs 420 mg Q2W. Additionally, a safety analysis was conducted with body weight and LDL-C levels to determine if exposure or response to evolocumab correlated with particular adverse event classifications.

A4.2 Objectives

Analysis objectives are:

- Determine whether biweekly dosing versus once-monthly administration offered a therapeutic benefit to specific HeFH patient demographics.
- Determine whether switching from 420 mg once-monthly to 420 mg biweekly dosing in HoFH patients provided additional LDL-C lowering value.

A4.3 Methods

A4.3.1 Data Sets

Data sets used are summarized in [Table 31](#).

Table 31. Analysis Data Sets

Study Number	Name	Link to EDR
ISS	adsl.xpt	\\cdsesub1\evsprod\BLA125522\0000\m5\datasets\iss\analysis\adam\datasets\adsl.xpt
ISS	adae.xpt	\\cdsesub1\evsprod\BLA125522\0000\m5\datasets\iss\analysis\adam\datasets\adae.xpt
ISS	adlb03.xpt	\\cdsesub1\evsprod\BLA125522\0000\m5\datasets\iss\analysis\adam\datasets\adlb03.xpt
114	dm.xpt, ex.xpt, pc.xpt, lb.xpt, vs.xpt	\\Cdsesub1\evsprod\BLA125522\0000\m5\datasets\20110114\tabulations\sdtm\dm.xpt
115	dm.xpt, ex.xpt, pc.xpt, lb.xpt, vs.xpt	\\Cdsesub1\evsprod\BLA125522\0000\m5\datasets\20110115\tabulations\sdtm\dm.xpt
Pop PK	ph3input.xpt	\\cdsesub1\evsprod\BLA125522\0000\m5\datasets\119663\analysis\legacy\datasets\ph3input.xpt

A4.3.2 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.

A4.3.3 Models

No original modeling was performed by the FDA.

A4.4 Results

A4.4.1 Covariate analysis of the HoFH Population:

Covariate analysis of the response to each dosing regimen (Q2W and QM) by baseline demographic included data from both phase-3 trials 20110114 and 20110115. Covariate plots were shown in section 1. From Trial 20110114 and did not include baseline weight or baseline PCSK9. These plots along with the potential covariate plots for trial 20110115 are shown in [Figure 63](#) through [Figure 68](#). In consideration of the magnitude of response when compared to baseline neither age, bmi, ldl-c, pcsk9, gender, or wt appeared to impact the response to Q2W vs QM to a clinically meaningful extent.

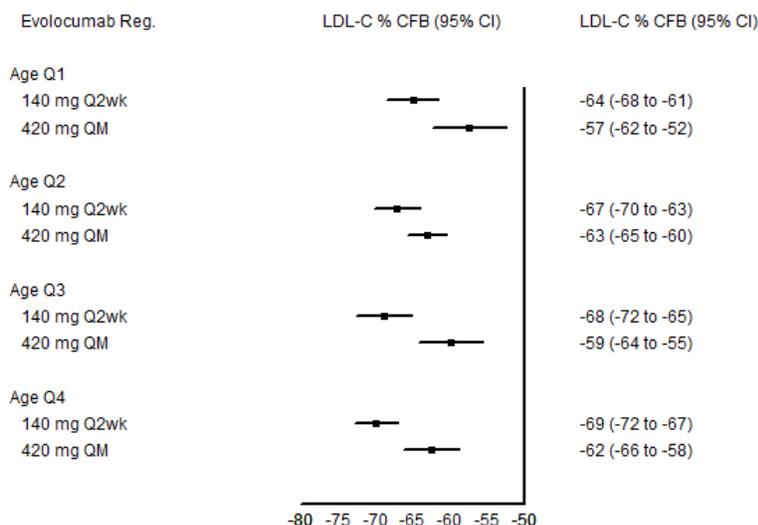


Figure 63. Percent Change from Baseline in LDL-C by Age at Baseline (Study 20110115).

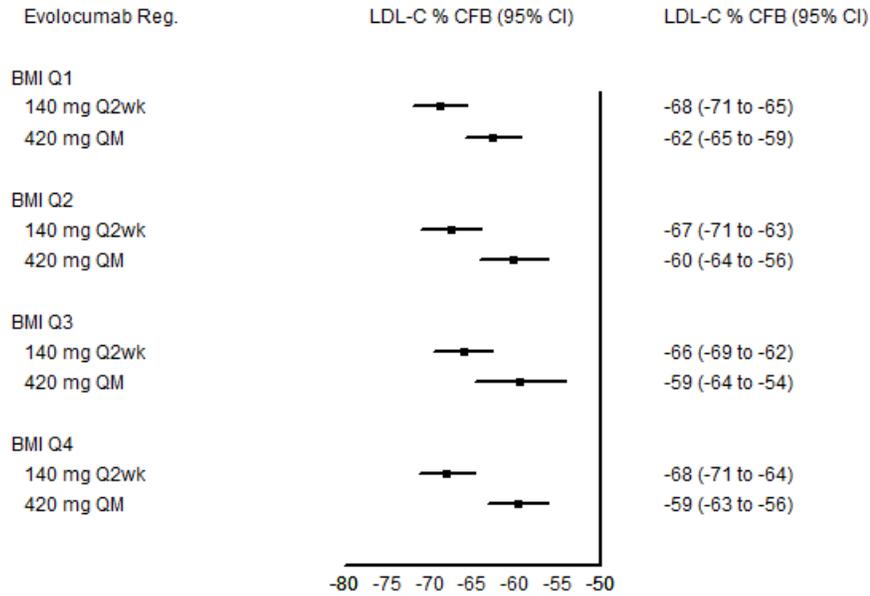


Figure 64. Percent Change from Baseline in LDL-C by BMI at Baseline (Study 20110115).

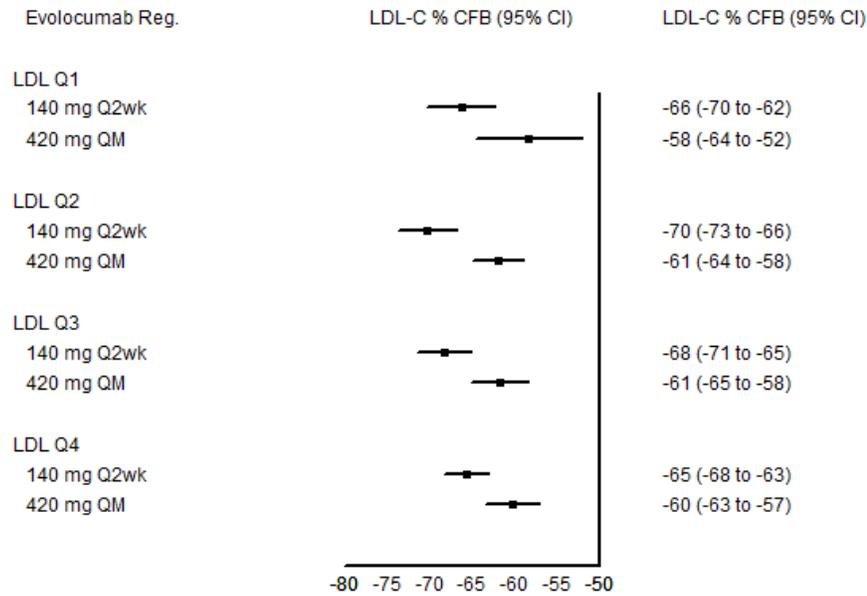


Figure 65. Percent Change from Baseline in LDL-C by Baseline LDL-C (Study 20110115).

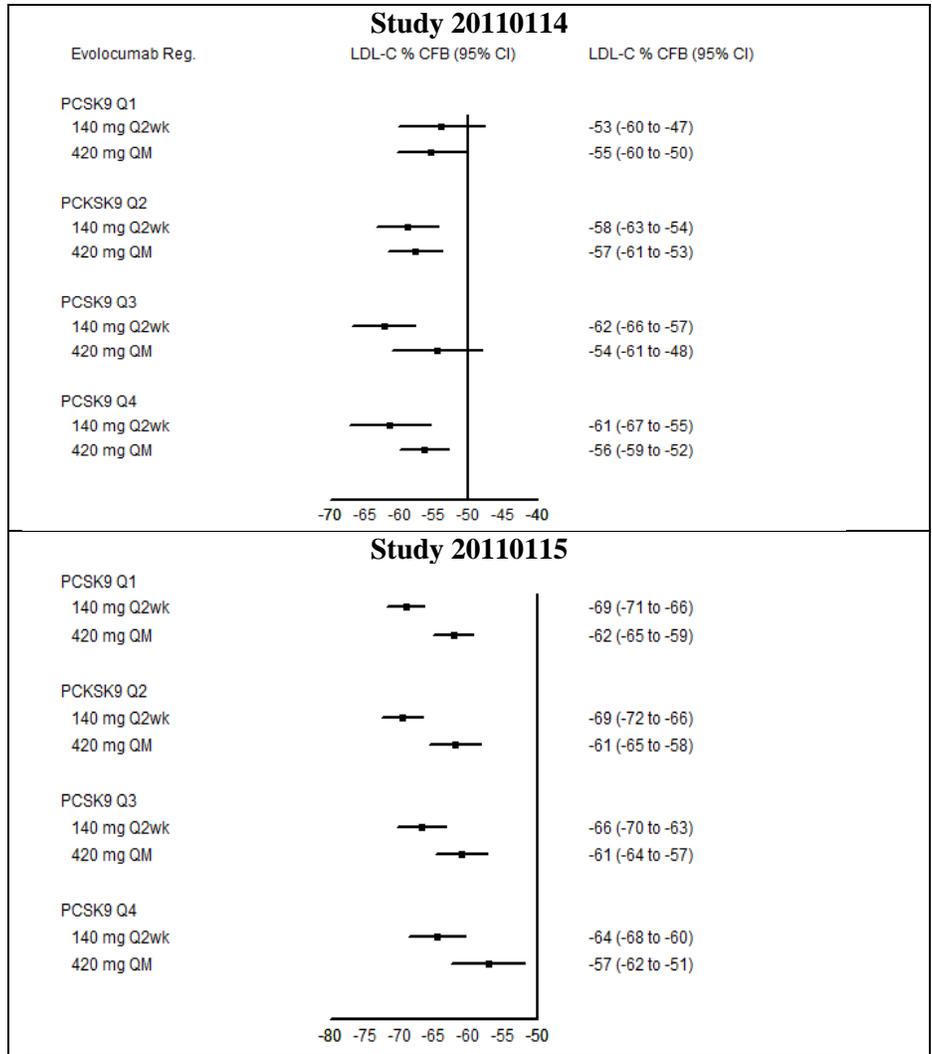


Figure 66. Percent Change from Baseline in LDL-C by PCSK9 at Baseline. Results from study 20110114 and 20110115 are shown in the top and bottom panels respectively.

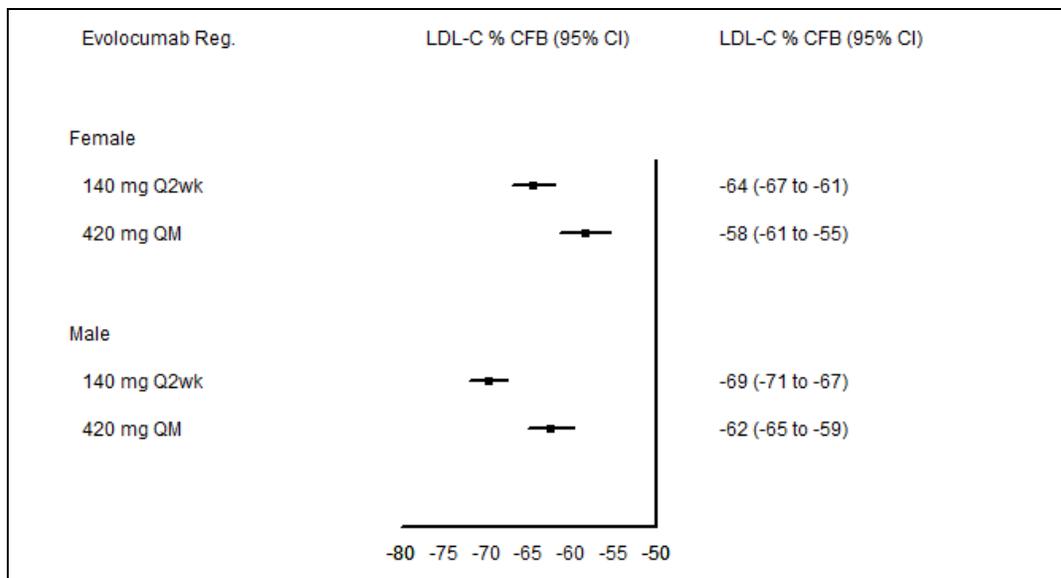


Figure 67. Percent Change from Baseline in LDL-C by Gender (Study 20110115).

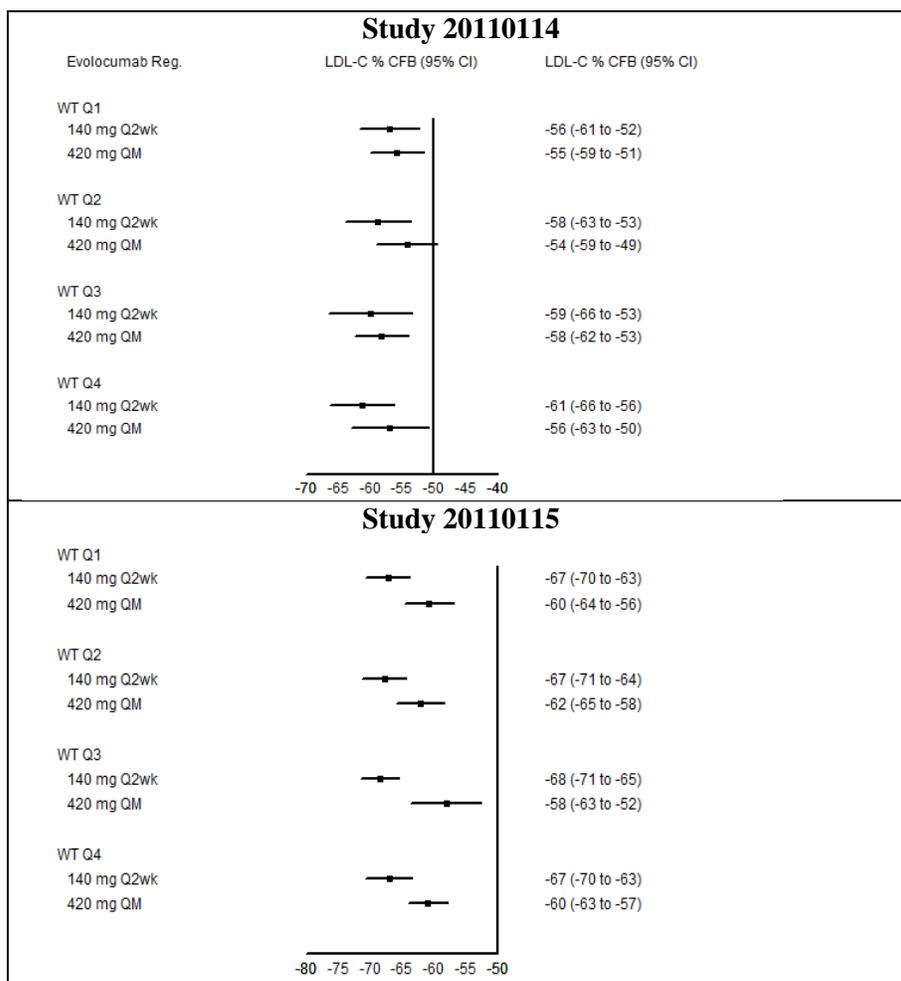


Figure 68. Percent Change from Baseline in LDL-C does by Weight. Results from study 20110114 and 20110115 are shown in the top and bottom panels respectively.

A4.4.2 Individual Timecourses of LDL-C Response for HoFH Patients that Up-Titrated:

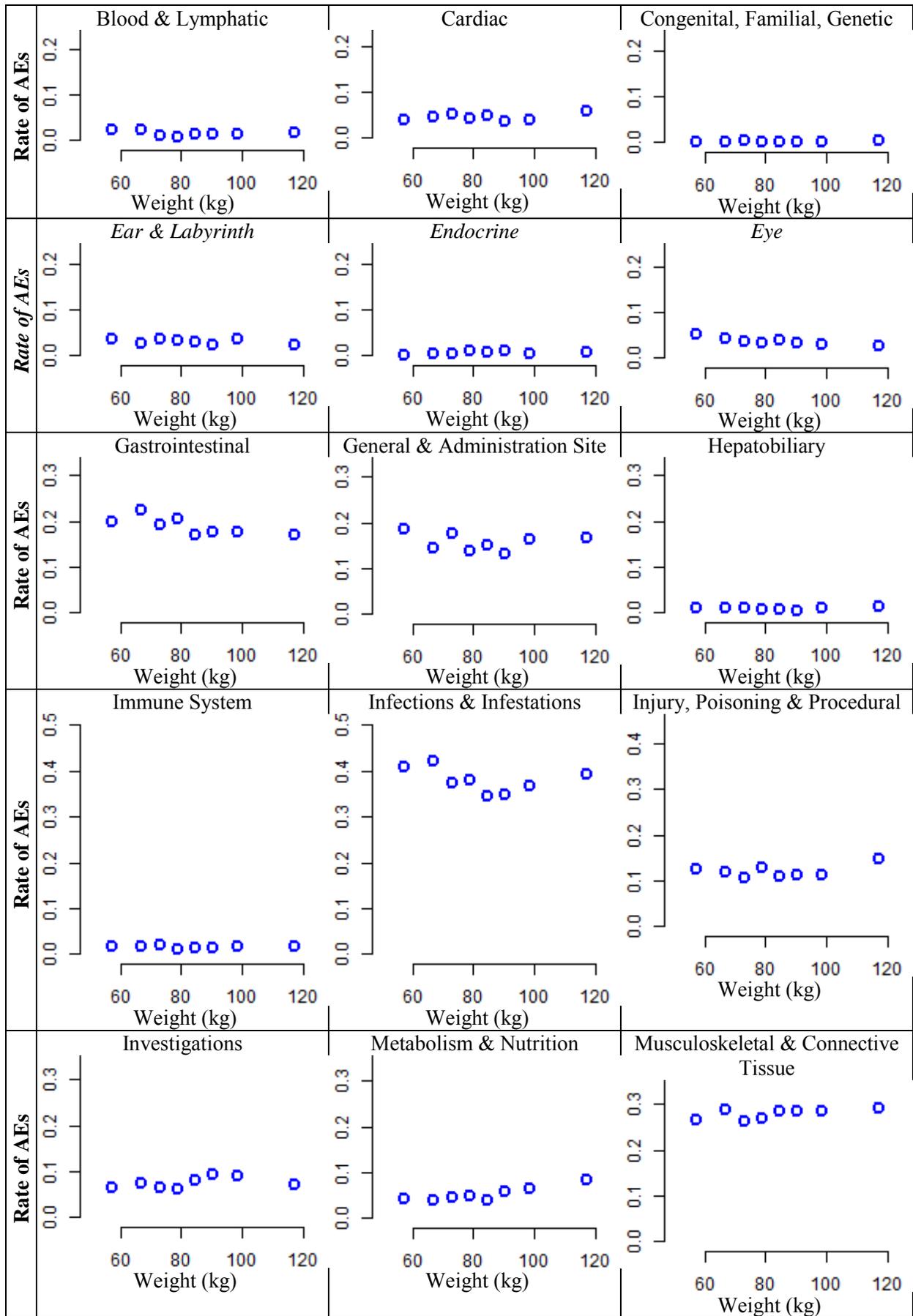
As part of the analysis for HoFH patients who up-titrated their dose from 420 mg QM to Q2W, individual LDL-C levels were plotted over time ([Figure 69](#)). This up-titration occurred at week 12 for patients in Study 20110271. It is apparent that for some patients there was a mild lowering of LDL-C while for others there was no change. This is summarized at a population level in Section 1 by a 6% decrease in the mean LDL-C after up-titration to 420 mg Q2W in HoFH patients.



Figure 69. Individual timecourses of LDL-C for patients who up-titrated their 420 mg evolocumab QM dose to Q2W maintained their LDL-C levels (Study 20110271).

A4.4.3 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 as the AUC of evolocumab changed as much as 7-fold over the range of body weights. This latter point had raised concern that adolescents may require a lower dose if there was a concern with higher exposures and adverse events. [Figure 70](#) 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 and pharm-tox reviewer's (Dr. Eileen Craig and Dr. Calvin Elmore) suggest 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.



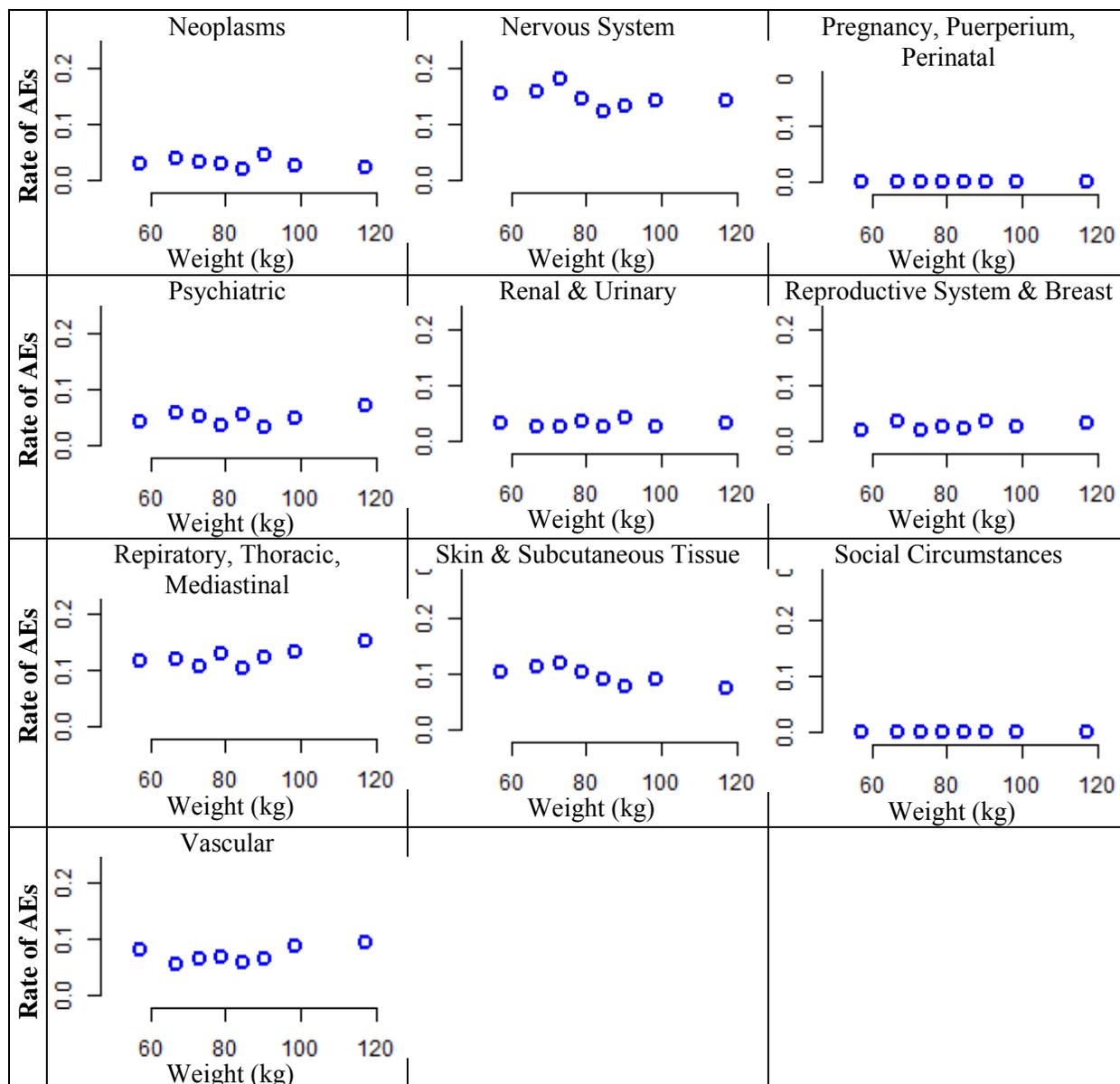
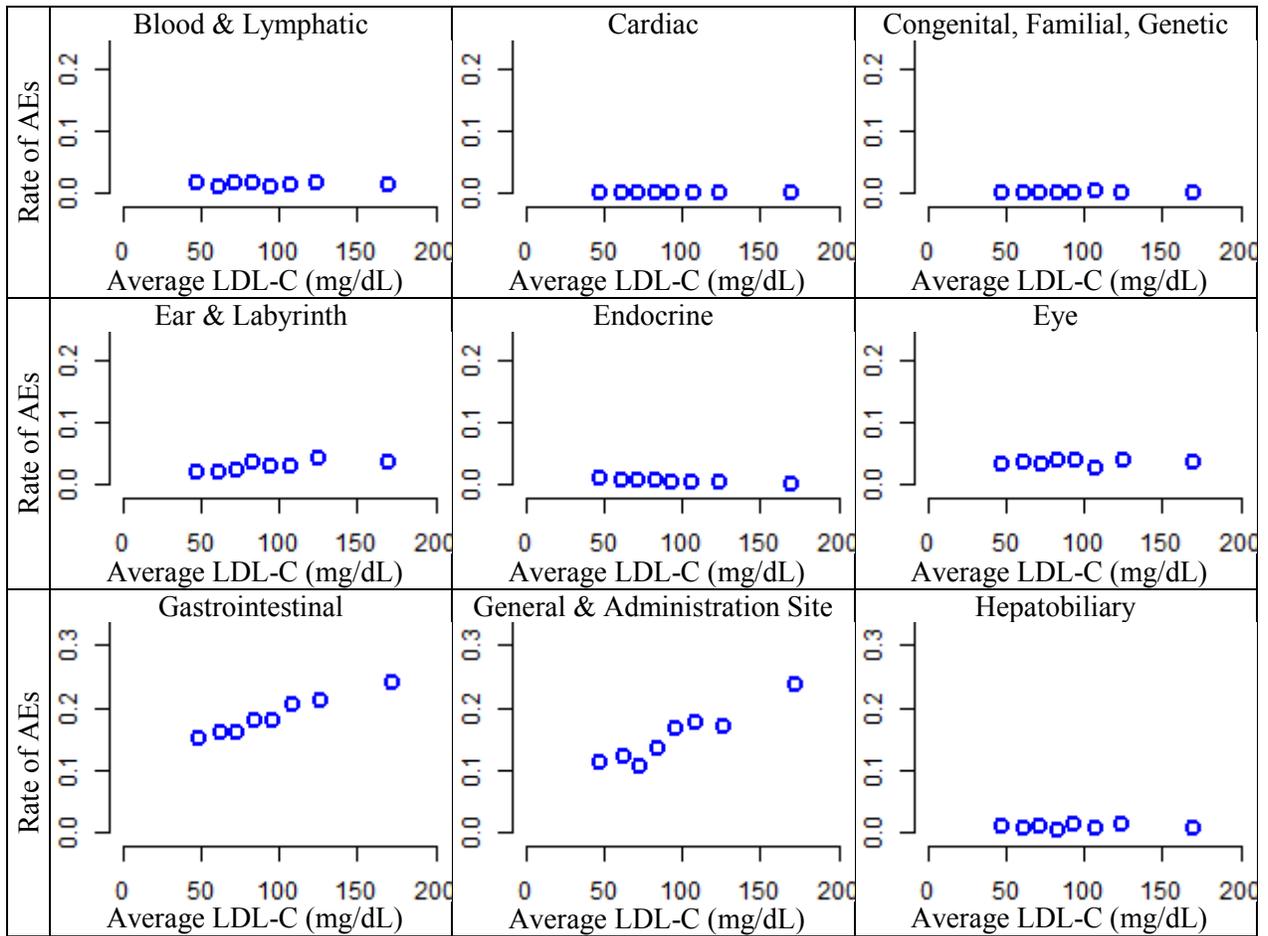
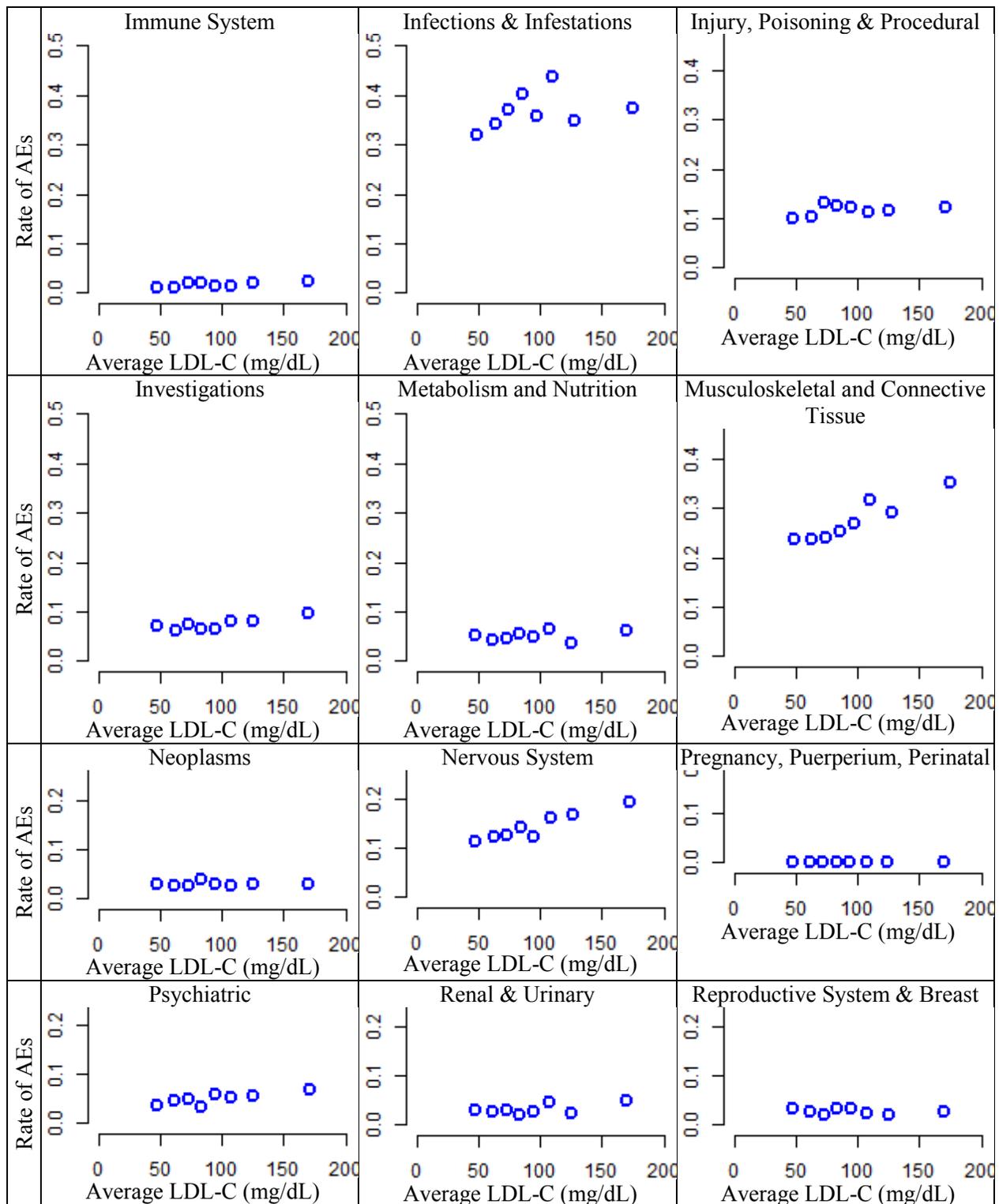


Figure 70. There does not appear to be an increase in any grade adverse events and low body weight by system organ class disorder type. The y-axis is the event rate in the integrated summary of safety population. The x-axis is body weight (kg). The proportion of those in the ISS database with an adverse event are shown for each of 8 octiles of body weight.

A4.4.4 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 metric for each individual. The adverse event rate was then determined for each low LDL-C octile and is shown in [Figure 71](#). 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.





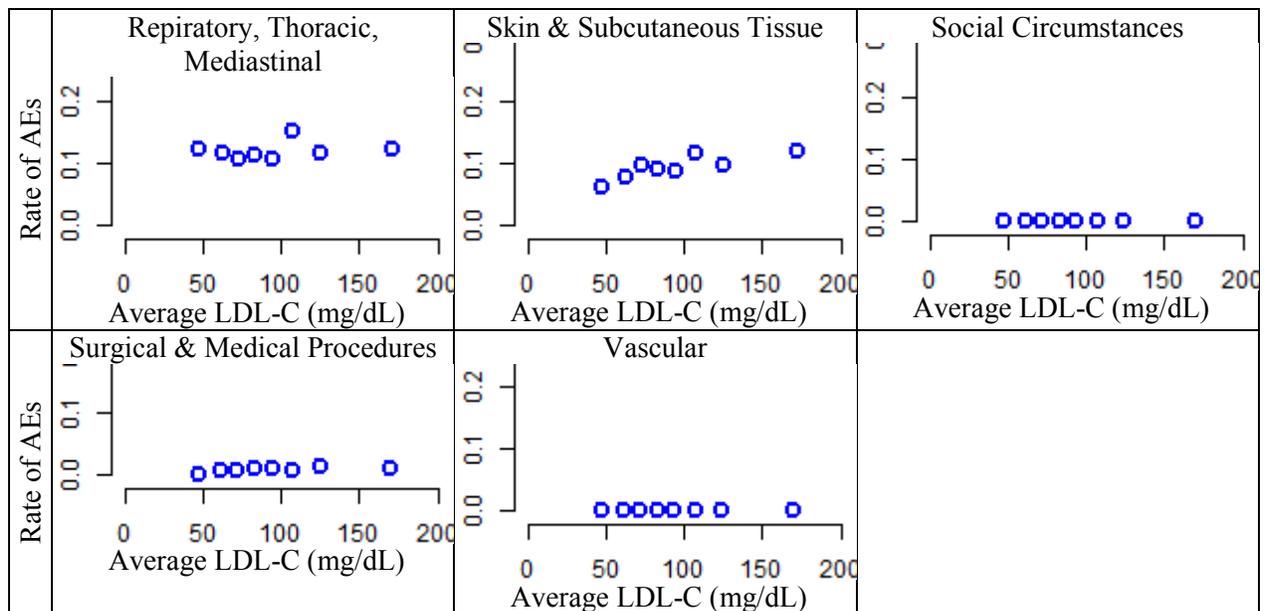


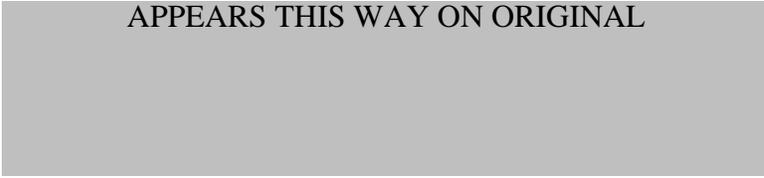
Figure 71. Low LDL-C does not appear to be correlated with any grade adverse events by system organ class. The y-axis is the event rate in the integrated summary of safety population. The x-axis is the average of the LDL-C values prior to the adverse event. The proportion of those in the ISS database 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.

A5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
ISS_*.R	BW and LDL Safety analysis files	..\Reviews\PM Review Archive\Evolocumab_BLA125522_JCE\ER Analyses
*.tif	Output plots	..\Reviews\PM Review Archive\Evolocumab_BLA125522_JCE\ER Analyses\
HeFH_Study11*.R	Exposure-Response files for studies 114 and 115	..\Reviews\PM Review Archive\Evolocumab_BLA125522_JCE\ER Analyses\

4.2 OCP Filing Memo

APPEARS THIS WAY ON ORIGINAL



Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	125522	Brand Name	REPATHA (Proposed)
OCP Division (I, II, III, IV, V)	II	Generic Name	Evolocumab
Medical Division	DMEP	Drug Class	PCSK9 inhibitor
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	<ul style="list-style-type: none"> • Treatment of primary hyperlipidemia and mixed dyslipidemia • Treatment of homozygous familial hypercholesterolemia (HoFH)
OCP Team Leader	Immo Zadezensky, Ph.D.	Dosage Form	injection
Pharmacometrics Reviewer		Dosing Regimen	see below ^a
Date of Submission	08/27/2014	Route of Administration	sub-cutaneous
Estimated Due Date of OCP Review	05/01/2015	Sponsor	Amgen
Medical Division Due Date		Priority Classification	351(a) - Standard
PDUFA Due Date	8/25/2015		

^a Primary hyperlipidemia or mixed dyslipidemia: Administer 140 mg every 2 weeks or 420 mg once monthly in the upper arm, thigh, or the abdomen
Homozygous familial hypercholesterolemia: Administer 420 mg either once monthly or every 2 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	30	26	Module 5.3.1.2: 20110168, 20120133 Module 5.3.3.1: 20120101, 20110234, 20120135, 20120136 Module 5.3.3.3: 20120341 Module 5.3.4.1: 20080397, 20110121 Module 5.3.4.2: 20080398 Module 5.3.5.1: 20110110, 20101154, 20101155, 20090158, 20090159, 20110114, 20110155, 20110116, 20110117, 20110109, 20110231, 20110233, 2012138, 20110233 Module 5.3.5.2: 20110271 Module 5.3.5.4: 20120348, 20120356
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	11	11	Module 5.3.1.4: 112602, 112777, 113215, 113216, 117093, 117094, GCL-277, MET-002439, MET-002468, MET-00349, MVR-000352
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA, BLA or Supplement

Reference ID: 3644721

Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
Pharmacokinetics (e.g., Phase I)	X	22	22	Rich Data: 20080397, 20110121, 20120136, 20080398, 20120341, 20110168, 20120133 Limited Data: 20101154, 20101155, 20090158, 20090159, 20110231, 20110233 Sparse Data: 20110114, 20110115, 20110116, 20110117, 20110109, 20110110, 20110271, 20120348, 20120356
Healthy Volunteers-				
single dose:	X	3	3	20080397, 20110121, 20120136,
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1	1	20080398
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:				
<i>in-vitro</i> :				
Subpopulation studies -				
ethnicity:	X	1	1	20110121
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1	1	20120341
PD -				
Phase 1:	X	2	2	20080397, 20110121
Phase 2:				
Phase 3:	X	1		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				Module 5.3.3.5: 116744, 119663
Data rich:	X	2	2	20080397, 20080398
Data limited:	X	4	4	20090158, 20090159, 20101154, 20101155
Data sparse:	X	5	5	20110109, 20110114, 20110115, 20110116, 20110117
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		20110168, 20120133
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			Waiver request for specific age groups submitted
Literature References	X			
Total Number of Studies		321	26	

Several Studies have been counted more than once since they fall into multiple categories

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA, BLA or Supplement

Reference ID: 3644721

Brief summary about the submission:

Amgen are seeking US marketing approval for Evolocumab (Trade Name: Repatha) under the provisions of Section 351(a) of the Public Health Service (PHS) Act. The proposed indication of Repatha subcutaneous injection is “

- Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia.
 - in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
 - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
 - alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.
- Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia ”.

This BLA is supported by data from 26 clinical studies with evolocumab, of which 8 studies were primarily clinical pharmacology studies and included healthy volunteers, subjects with primary hyperlipidemia or mixed dyslipidemia, and subjects with mild to moderate hepatic impairment. Two studies evaluated the bioequivalence of evolocumab from different presentations (pre-filled syringe (PFS), automated mini-doser (AMD) and auto-injector/pen (AI/Pen)). The remaining sixteen global studies directly supported efficacy in the 2 proposed indications. Fifteen studies, which included 9 phase 3 studies and 6 phase 2 studies conducted at durations ranging from 8 weeks to ≥ 2 years, supported the indication in primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. Two phase 2/3 studies conducted at durations of 12 weeks to ≥ 84 weeks supported the indication in HoFH. These 16 studies also provided supportive data on the pharmacokinetic and pharmacodynamic properties of evolocumab.

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
Healthy Subject Pharmacokinetics and Initial Tolerability Studies			
1.	Phase I PK study (20080397) [Module 5.3.4.1]	To assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of evolocumab at 5 ascending SC doses and 2 ascending IV doses	Double-blind, randomized, placebo- controlled (ascending single dose)
2.	Phase I PK study (20110121) [Module 5.3.4.1]	To assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of evolocumab at 3 ascending SC doses in Japanese subjects; and to compare the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles between Japanese and white subjects	Double-blind, randomized, placebo- controlled (ascending single dose)
3.	Phase I PK study (20120136) [Module 5.3.3.1]	To determine intra-subject variability in the pharmacokinetic and pharmacodynamic profiles of evolocumab following 140 mg SC dose administration in healthy adult subjects; and to evaluate safety, tolerability, and immunogenicity of evolocumab	Open-label, crossover (intra-subject variability)
4.	Phase 0 Safety/Tolerability study (20110234) [Module 5.3.3.1]	(b) (4)	Randomized, crossover (tolerability of placebo SC at various infusion rates)
5.	Phase 0 Safety/Tolerability study (20120101) [Module 5.3.3.1]		Randomized, crossover (tolerability of placebo SC bolus injections with different viscosities)
6.	Phase 0 Safety/Tolerability study (20120135) [Module 5.3.3.1]	To assess (b) (4) (b) (4) tolerability (b) (4)	Single-arm (b) (4) (b) (4)
Patient Pharmacokinetics and Initial Tolerability			
7.	Phase I PK study (20080398) [Module 5.3.4.2]	To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of multiple SC doses of	Double-blind, randomized, placebo-controlled (ascending multiple dose)

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA, BLA or Supplement

Reference ID: 3644721

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
		evolocumab	
Intrinsic Factor PK			
8.	Phase I PK study (20120341) [Module 5.3.3.3]	To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of a single SC dose of evolocumab in subjects with mild or moderate hepatic impairment	open-label (hepatic impairment)
Biopharmaceutic Studies			
9.	Phase I PK study (20110168) [Module 5.3.1.2]	To demonstrate PK equivalence of the AMD to the prefilled AI/pen	Randomized, open-label, single- dose study
10.	Phase I PK study (20120133) [Module 5.3.1.2]	To demonstrate PK equivalence of PFS to AI/pen	Randomized, open-label, crossover study
Phase 2 Studies of Primary Hyperlipidemia and Mixed Dyslipidemia			
11.	Phase 2 Safety and Efficacy study (20101154) [Module 5.3.5.1]	To evaluate the efficacy, safety, tolerability, and PK of EvoMab administered SC as monotherapy every 2 weeks (Q2W) or every 4 weeks (QM) for 12 weeks in subjects with low risk hypercholesterolemia	Randomized, placebo- and ezetimibe-controlled, dose-ranging study
12.	Phase 2 Safety and Efficacy study (20101155) [Module 5.3.5.1]	To evaluate the safety, tolerability, and efficacy of EvoMab administered SC once Q2W or once QM in combination with statin therapy over a 12-week period in subjects with hypercholesterolemia.	Double-blind, randomized, placebo-controlled, dose-ranging study
13.	Phase 2 Safety and Efficacy study (20090158) [Module 5.3.5.1]	To evaluate the safety and efficacy of 12 weeks of EvoMab SC, compared with placebo, on the percent change from baseline in LDL-C in subjects with heterozygous familial hypercholesterolemia (HeFH).	Double-blind, randomized, placebo-controlled, study
14.	Phase 2 Safety and Efficacy study (20090159) [Module 5.3.5.1]	To evaluate the efficacy, safety, and tolerability of 12 weeks of EvoMab SC compared with ezetimibe in subjects with hypercholesterolemia who are unable to tolerate an effective dose of a statin	Randomized, study
15.	Phase 2 Safety and Efficacy study (20110231) [Module 5.3.5.1]	To evaluate tolerability and efficacy of EvoMab on LDL-C in combination with stable statin therapy in Japanese subjects with hypercholesterolemia and high cardiovascular risk	Double-blind, randomized, placebo- controlled, multicenter study

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA, BLA or Supplement

Reference ID: 3644721

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
16.	Phase 2 Safety and Efficacy study (20110110) [Module 5.3.5.1]	To assess the long-term safety and efficacy of evolocumab (interim analysis)	Multicenter, controlled, open-label extension study
Phase 2/3 Studies of Homozygous Familial Hypercholesterolemia			
17.	Phase 2/3 Safety and Efficacy study (20110233) [Module 5.3.5.1]	To assess the safety, tolerability and efficacy of EvoMab in subjects with HoFH	Part A – open-label, single-arm, multicenter pilot study; Part B – double-blind, randomized, placebo-controlled, multicenter study
18.	Phase 2/3 Safety and Efficacy study (20110271) [Module 5.3.5.2]	To assess the long-term safety, tolerability, and efficacy of EvoMab on LDL-C in subjects with severe familial hypercholesterolemia	Multicenter, open-label study
Phase 3 Studies of Primary Hyperlipidemia and Mixed Dyslipidemia			
19.	Phase 3 Safety and Efficacy study (20110114) [Module 5.3.5.1]	To evaluate the efficacy, safety, tolerability, and PK of EvoMab administered SC as monotherapy Q2W or QM for 12 weeks in subjects with primary hyperlipidemia and mixed dyslipidemia and a 10-year Framingham Risk score of 10% or less.	Double-blind, randomized, double-dummy, placebo- and ezetimibe- controlled, parallel-group study
20.	Phase 3 Safety and Efficacy study (20110115) [Module 5.3.5.1]	To evaluate safety, tolerability and efficacy of EvoMab on LDL-C in combination with statin therapy in subjects with primary hypercholesterolemia and mixed dyslipidemia	Double-blind, randomized, placebo and ezetimibe controlled, multicenter study
21.	Phase 3 Safety and Efficacy study (20110116) [Module 5.3.5.1]	To evaluate safety and efficacy of EvoMab, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor (statin)	Double-blind, randomized, multicenter study
22.	Phase 3 Safety and Efficacy study (20110117) [Module 5.3.5.1]	To evaluate safety, tolerability and efficacy of EvoMab on LDL-C in subjects with HeFH	Double-blind, randomized, placebo- controlled, multicenter study
23.	Phase 3 Safety and Efficacy study (20110109) [Module 5.3.5.1]	To evaluate long-term tolerability and durable efficacy of EvoMab on LDL-C in subjects with primary hyperlipidemia and mixed dyslipidemia	Double-blind, randomized, placebo-controlled, multicenter study
24.	Phase 3 Safety and Efficacy study (20120138) [Module 5.3.5.1]	To assess the long-term safety and efficacy of evolocumab (interim analysis)	Multicenter, controlled, open-label extension study
25.	Phase 3 Safety and Efficacy study	To Assess Subjects' Ability to Administer a Full Dose of	Multi-center, Randomized Study in Subjects With

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Reference ID: 3644721

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
	(20120348) [Module 5.3.5.4]	Evolocumab in Home-use, Using Either a Prefilled Syringe or a Prefilled Autoinjector/pen	Primary Hypercholesterolemia and Mixed Dyslipidemia
26.	Phase 3 Safety and Efficacy study (20120356) [Module 5.3.5.4]	To Assess Subjects' Ability to Administer a Full Dose of Evolocumab in Home-use, Using Either a 3.5 mL Personal Injector or a Prefilled Autoinjector/Pen.	Multi-Center, Randomized Study in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia

PFS: pre-filled syringe
AMD: automated mini-doser
AI/Pen: auto-injector/pen

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Drug Substance used in Clinical Studies

- Drug substance for phase 1 and phase 2 clinical studies was manufactured using a different process (Process 1) than that employed in a majority of phase 3 studies (Process 2 –proposed commercial drug substance). – Was an adequate bridge established between Process 1 and Process 2 drug substance?
- To bridge the phase 2 and phase 3 programs for the evaluation of clinical safety, the Sponsor has provided the following in the BLA:
 - A comprehensive analytic comparability assessment (Module 3 summary)
 - PK/PD dataset and analyses from 23 clinical studies (Module 5 & Module 2 summaries)
 - Individual and integrated clinical efficacy and safety data from 23 clinical studies (Module 5 & Module 2 summaries)

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Overview of Clinical Study Results

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PK of Evolocumab

SD PK in Healthy Volunteers

Figure 2. Mean (SD) Evolocumab Serum Concentration-Time Profiles (Meaning: Single-Dose Evolocumab IV or SC in Healthy Subjects (Study 20090701))

Comparative PK in Japanese and Caucasian Population

Figure 3. Mean (SD) Serum Concentration-Time Profiles for Evolocumab in Japanese and Caucasian Populations

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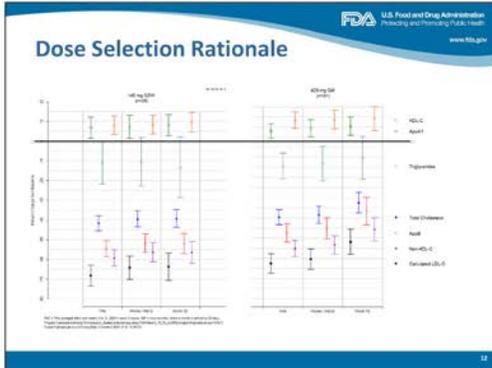
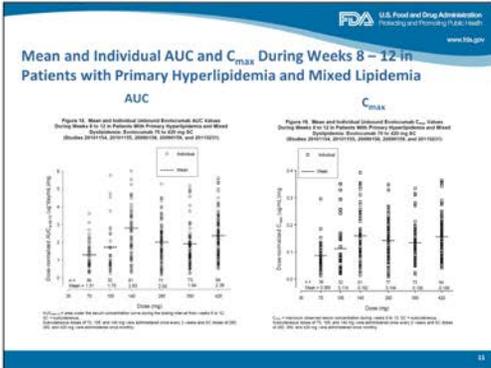
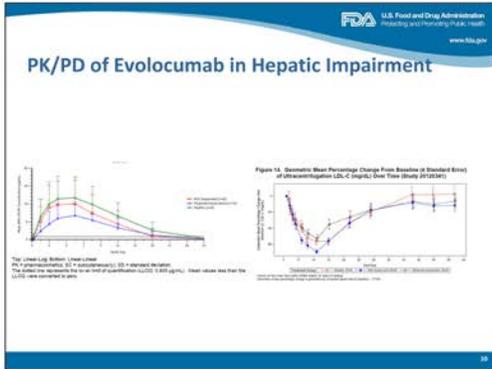
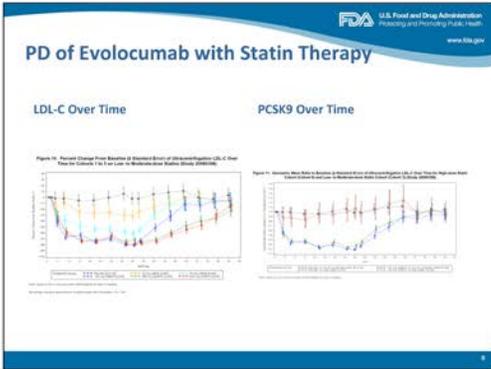
PD of Evolocumab

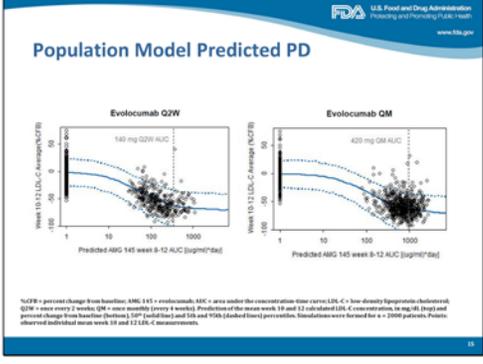
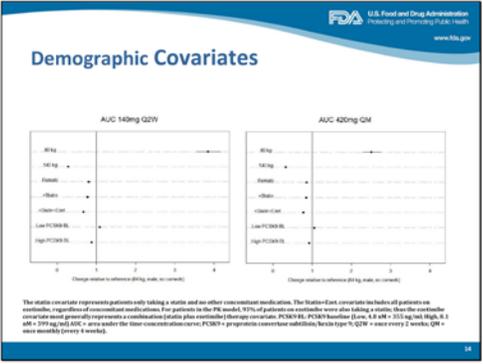
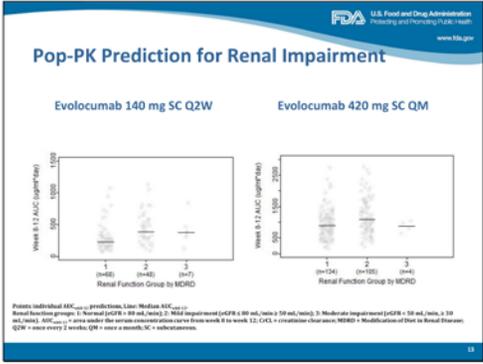
LDL-C Over Time

Figure 4. Mean (SD) LDL-C (mg/dL) Over Time (Actual Values)

PCSK9 Over Time

Figure 5. Mean (SD) PCSK9 (ng/mL) Over Time (Actual Values)





Sponsor's Label Claim

- Primary Hyperlipidemia and Mixed Dyslipidemia:** The recommended dose for [TRADENAME] is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.
- Homozygous Familial Hypercholesterolemia:** The recommended dose for [TRADENAME] is 420 mg either once monthly or every 2 weeks.
- Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.
- No dosage adjustment is necessary in patients with mild to moderate renal impairment.
- No dose adjustment is necessary in patients with mild to moderate hepatic impairment.
- No dosage adjustment is necessary in geriatric patients.
- No formal drug-drug interaction studies have been conducted for [TRADENAME].


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Pediatric Waiver Request

Indication: Primary Hyperlipidemia	(b) (4)
Population	Pediatric Waivers (b) (4)

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Potential Filing Issues/Checklist

- Was BE established between the presentations in pre-filled syringe (PFS), automated mini-doser (AMD) and auto-injector/pen (AI/Pen)?
- Is there a PK or PK/PD bridge between Process 1 and Process 2 drug substance?
- Is there a need for dose adjustment in Specific Population?

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Application Fileability and Consults

- Yes, this application is fileable from a Clinical Pharmacology perspective
- OSI consults – None
- Request for Sponsor - None

CDER, Office of Clinical Pharmacology
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BACKUP SLIDES

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Anti-drug Antibody

- Overall, less than 1% of evolocumab-treated subjects in the safety and efficacy studies included in this marketing application were positive for the development of binding antibodies. In addition, neutralizing antibodies have not been detected in any subject. Therefore, the incidence of anti-evolocumab binding antibodies is low.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		To bridge data from Process 1 material (used in Phase 1, Phase 2 and long-term efficacy study) and Process 2 material (used in Phase 3 trials), the sponsor provided (b) (4) [REDACTED]
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Since evolocumab is a monoclonal antibody, the sponsor did not conduct any <i>in vitro</i> permeability, <i>in vitro</i> metabolism, or <i>in vitro</i> metabolic drug-drug interaction studies that used human biomaterials.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	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)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	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?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for	X			

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA, BLA or Supplement

Reference ID: 3644721

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA, BLA or Supplement

Reference ID: 3772601

	approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor:

None.

Suryanarayana M. Sista	09 Oct, 2014
Reviewing Clinical Pharmacologist	Date
Immo Zadezensky	09 Oct, 2014
Team Leader	Date

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/s/

SURYANARAYANA M SISTA
10/17/2014

IMMO ZADEZENSKY
10/17/2014

Reference ID: 3644721

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/s/

SURYNARAYANA M SISTA
06/01/2015

JUSTIN C EARP
06/01/2015

NITIN MEHROTRA
06/01/2015

JAYABHARATHI VAIDYANATHAN
06/01/2015

CLINICAL PHARMACOLOGY MEMORANDUM

BLA	125522
Submission Date	Aug 27, 2014
Brand Name	Repatha
Generic Name	Evolocumab
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader	Immo Zadezensky, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Amgen
Formulation; Strength	Subcutaneous injection; 140 mg; 420 mg
Indication	<ul style="list-style-type: none">• Treatment of primary hyperlipidemia and mixed dyslipidemia• Treatment of homozygous familial hypercholesterolemia (HoFH)

Background

A review of BLA 125522 Evolocumab (Amgen) indicated that the investigational product (IP) was manufactured using two processes (Process 1 and Process 2) for the clinical trials. Process 1 material was used in all Phase 1 and Phase 2 studies. There are differences in

between the two processes as shown in the table below:

Parameter	Phase 1 Phase 2 Phase 3 (Limited)	Phase 3	
Primary container	Glass vial	Glass PFS	
Clinical administration	Syringe	PFS or prefilled AI/Pen	
Dose	70 to 420 mg	140 mg	420 mg
Injections	Up to three 2.0 mL injections	One 1.0 mL injection	Three 1.0 mL injections
Protein concentration	70 mg/mL	140 mg/mL	
(b) (4)	(b) (4)	20 mM acetate	
pH	(b) (4)	5.0	
(b) (4)	(b) (4)	220 mM proline	
(b) (4)	(b) (4)	0.01% (w/v) polysorbate 80	
Recommended storage temperature	(b) (4)	2°C to 8°C	

(Source: BLA 12552, Module 2.3.P Drug Product, Table 3, page 13)

Additionally, the long term efficacy and safety study (Study 20110109) started initially as a Phase 2 study with Process 1 material, and was later re-classified by the sponsor as a Phase

3 study in the EOP2 meeting held on 10 July 2012 (See IND 105188, module 1.6.3, AMG 145 EOP2 Meeting Minutes). The sponsor confirmed at this meeting that the phase 3 trials will be performed with the formulation of AMG 145 intended for the market. However, it appeared that the study was conducted with Process 1 material only, a formulation which was not intended to be marketed.

Phase	Protocol Number	Type of Study	Brief Descriptor	70 mg/mL Vial	140 mg/mL PFS	140 mg/mL AI/Pen	120 mg/mL AMD
3	20110109	LDL-C lowering	Long-term efficacy and safety	X			

(excerpted from Source: BLA 12552, Module 3.2.P.2.3. Investigational Formulations, Table 1, page 25)

Since Study 20110109 was the only long-term efficacy and safety study (see table below), there was a concern that long-term safety data was unavailable for Process 2 material.

Table 1. Identification of Product Presentations Used in Clinical Studies From Phase 1 Through Phase 3 Supporting the Initial Marketing Application

Phase	Protocol Number	Type of Study	Brief Descriptor	70 mg/mL Vial	140 mg/mL PFS	140 mg/mL AI/Pen	120 mg/mL AMD
1	20080397	Clinical pharmacology	Healthy subject PK/PD & initial tolerability	X			
1	20080398	Clinical pharmacology	Patient PK/PD & initial tolerability	X			
1	20110121	Clinical pharmacology	Healthy subject PK/PD & initial tolerability	X			
1	20110168	Clinical pharmacology	Healthy subject PK AI/Pen to AMD			X	X
1	20120133	Clinical pharmacology	Healthy subject PK AI/Pen to PFS		X	X	
1	20120136	Clinical pharmacology	Healthy subject PK/PD & initial tolerability	X			
1	20120341	Clinical pharmacology	Intrinsic factors			X	
2	20090158	LDL-C lowering	HeFH	X			
2	20090159	LDL-C lowering	Statin intolerant	X			
2	20101154	LDL-C lowering	Monotherapy	X			
2	20101155	LDL-C lowering	Combination therapy	X			
2	20110110	LDL-C lowering	Long-term efficacy and safety (OLE)	X		X	
2	20110231	LDL-C lowering	Japanese population	X			
2/3	20110233	LDL-C lowering	HoFH	X		X	
2/3	20110271	LDL-C lowering	Severe familial hypercholesterolaemia	X		X	
3	20110109	LDL-C lowering	Long-term efficacy and safety	X			
3	20110114	LDL-C lowering	Monotherapy			X	

Page 1 of 2

PFS = prefilled syringe; AI/pen = autoinjector/pen; AMD = automated mini-doser; PK/PD = pharmacokinetics/pharmacodynamics; HeFH = heterozygous familial hypercholesterolaemia; OLE = open-label extension; HoFH = homozygous familial hypercholesterolaemia.

(Source: BLA 12552, Module 3.2.P.2.3. Investigational Formulations, Table 1, page 25)

At the 10 April 2014 Type B Pre-BLA meeting, the Agency made the following request to the sponsor:

“Additional Request: As noted above, you anticipate that (b) (4) % (b) (4) of the subjects with ≥361 days of evolocumab exposure will come from your phase 2 program and its open-label extension studies. We note that you administered evolocumab differently in phase 2 (total volume per administration drawn from six sterile vials) with a formulation (70 mg/mL) that you do not intend to market and that you did not use in phase 3. Please explain how you plan to bridge your phase 2 and phase 3 programs for the evaluation of clinical safety”.

The sponsor's proposal for bridging Process 1 and Process 2 material was as follows:

(b) (4)

Early cursory review of the data to demonstrate the similarity between Process 1 drug substance and Process 2 drug substance showed that the bridging data appeared weak, and the proposed bridging strategy was found to be inadequate. This information and the current policy recommendations for biologic products were presented to the Biologics Oversight Board (BOB) on Oct 30, 2014. Slides and background materials presented to BOB are at the following location:

<http://sharepoint.fda.gov/orgs/CDER-OCP/WorkingGroups/BOB/SitePages/Home.aspx>

At the BOB meeting, the review division (DCP2) proposed that the sponsor conduct a single dose PK study comparing Process 1 and Process 2 material to provide sufficient bridging information. In the ensuing discussion, the consensus from BOB was that the study could be conducted as a parallel study design (b) (4).

. While there was discussion within BOB whether a PK study would at all be needed, or, if Population PK assessment would suffice, in the end BOB did not object to the requirement for a bridging PK study.

In conclusion, the review division believes that this proposed single-dose parallel design study would be a pivotal bridging study for IP made from Process 1 and Process 2 material.

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/s/

SURYNARAYANA M SISTA
01/15/2015

IMMO ZADEZENSKY
01/15/2015

CLINICAL PHARMACOLOGY MEMORANDUM

BLA	125522
Submission Dates	05 Nov 2014
Brand Name	Repatha (Proposed)
Generic Name	Evolocumab
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader (Acting)	Immo Zadezensky, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Amgen, Inc.
Formulation; Strength	140 mg Repatha™ Single-Use pre-filled syringe (PFS); supplied as a 1-pack One ml of a 140 mg/mL solution of evolocumab 140 mg Single-Use Prefilled Repatha™ SureClick® Autoinjector; supplied as a 1 pack, 2-pack, and 3-pack One ml of a 140 mg/mL solution of evolocumab
Indication	Repatha™ is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein (a) [Lp(a)], and to increase HDL-C and ApoA1: <ul style="list-style-type: none">• in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or• alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or• alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate. Repatha™ is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

Background

During the pre-BLA meeting held on 10 April 2014, the Agency informed the sponsor that the bulk of the long-term safety database relied heavily on the phase 2 studies of the evolocumab clinical program, which did not use the drug substance formulation intended to be marketed (Process 1); that this was a concern since the efficacy data were generated with the to-be marketed (Process 2) material, and that there was no bridge between the two processes. The Agency re-iterated this concern in the meeting minutes from the Pre-BLA meeting (dated 07 May 2014), and asked the sponsor to provide their plan to bridge the phase 2 and phase 3 programs for the evaluation of clinical safety. [REDACTED] provided a [REDACTED] (b) (4)

The sponsor submitted the biologics license application (BLA) for evolocumab (BL 125522; Sequence No. 0000) on 27 August 2014. Initial filing review of the BLA revealed that the sponsor had not provided adequate bridging information between Process 1 and Process 2 drug substance. The Agency initiated a teleconference on 24 October 2014 to relay this concern to the sponsor. During the teleconference, the Agency informed the sponsor that the bridging information was weak, and that a potential head-to-head PK/PD study might be required, only if after thoroughly reviewing the BLA, a determination was made that the data supporting the Process 1-Process 2 bridge was insufficient. The Agency strongly recommended that if the sponsor chose to conduct the study, that the protocol be submitted for comments to make sure that there is concurrence on the study design, if needed. The sponsor informed the Agency that they would initiate a PK/PD study immediately. On 30 October 2014, the Agency asked the sponsor to provide a brief synopsis or study summary of the formulation-bridging PK/PD bioequivalence study, if feasible. The current submission is the synopsis of the formulation-bridging PK/PD bioequivalence study.

The synopsis was reviewed and the sponsor was informed that the proposed study design was reasonable. Comments were provided on the inclusion of AUC_{inf} parameter as a primary endpoint, and that Process 1 and Process 2 material should be administered in the same manner in the study as they were in Phase 2 and 3 registration studies.

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/s/

SURYANARAYANA M SISTA
11/25/2014

IMMO ZADEZENSKY
12/02/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	125522	Brand Name	REPATHA (Proposed)
OCP Division (I, II, III, IV, V)	II	Generic Name	Evolocumab
Medical Division	DMEP	Drug Class	PCSK9 inhibitor
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	<ul style="list-style-type: none"> • Treatment of primary hyperlipidemia and mixed dyslipidemia • Treatment of homozygous familial hypercholesterolemia (HoFH)
OCP Team Leader	Immo Zadezensky, Ph.D.	Dosage Form	injection
Pharmacometrics Reviewer		Dosing Regimen	see below ^a
Date of Submission	08/27/2014	Route of Administration	sub-cutaneous
Estimated Due Date of OCP Review	05/01/2015	Sponsor	Amgen
Medical Division Due Date		Priority Classification	351(a) - Standard
PDUFA Due Date	8/25/2015		

- ^a
- Primary hyperlipidemia or mixed dyslipidemia: Administer 140 mg every 2 weeks or 420 mg once monthly in the upper arm, thigh, or the abdomen
 - Homozygous familial hypercholesterolemia: Administer 420 mg either once monthly or every 2 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	30	26	Module 5.3.1.2: 20110168, 20120133 Module 5.3.3.1: 20120101, 20110234, 20120135, 20120136 Module 5.3.3.3: 20120341 Module 5.3.4.1: 20080397, 20110121 Module 5.3.4.2: 20080398 Module 5.3.5.1: 20110110, 20101154, 20101155, 20090158, 20090159, 20110114, 20110155, 20110116, 20110117, 20110109, 20110231, 20110233, 2012138, 20110233 Module 5.3.5.2: 20110271 Module 5.3.5.4: 20120348, 20120356
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	11	11	Module 5.3.1.4: 112602, 112777, 113215, 113216, 117093, 117094, GCL-277, MET-002439, MET-002468, MET-00349, MVR-000352
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
Pharmacokinetics (e.g., Phase I)	X	22	22	Rich Data: 20080397, 20110121, 20120136, 20080398, 20120341, 20110168, 20120133 Limited Data: 20101154, 20101155, 20090158, 20090159, 20110231, 20110233 Sparse Data: 20110114, 20110115, 20110116, 20110117, 20110109, 20110110, 20110271, 20120348, 20120356
Healthy Volunteers-				
single dose:	X	3	3	20080397, 20110121, 20120136,
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1	1	20080398
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:				
<i>in-vitro</i> :				
Subpopulation studies -				
ethnicity:	X	1	1	20110121
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1	1	20120341
PD -				
Phase 1:	X	2	2	20080397, 20110121
Phase 2:				
Phase 3:	X	1		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				Module 5.3.3.5:
Data rich:	X	2	2	116744, 119663 20080397, 20080398
Data limited:	X	4	4	20090158, 20090159, 20101154, 20101155
Data sparse:	X	5	5	20110109, 20110114, 20110115, 20110116, 20110117
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		20110168, 20120133
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			Waiver request for specific age groups submitted
Literature References	X	321		
Total Number of Studies		26		

Several Studies have been counted more than once since they fall into multiple categories

Brief summary about the submission:

Amgen are seeking US marketing approval for Evolocumab (Trade Name: Repatha) under the provisions of Section 351(a) of the Public Health Service (PHS) Act. The proposed indication of Repatha subcutaneous injection is “

- Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia.
 - in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
 - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
 - alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.
- Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia ”.

This BLA is supported by data from 26 clinical studies with evolocumab, of which 8 studies were primarily clinical pharmacology studies and included healthy volunteers, subjects with primary hyperlipidemia or mixed dyslipidemia, and subjects with mild to moderate hepatic impairment. Two studies evaluated the bioequivalence of evolocumab from different presentations (pre-filled syringe (PFS), automated mini-doser (AMD) and auto-injector/pen (AI/Pen)). The remaining sixteen global studies directly supported efficacy in the 2 proposed indications. Fifteen studies, which included 9 phase 3 studies and 6 phase 2 studies conducted at durations ranging from 8 weeks to ≥ 2 years, supported the indication in primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. Two phase 2/3 studies conducted at durations of 12 weeks to ≥ 84 weeks supported the indication in HoFH. These 16 studies also provided supportive data on the pharmacokinetic and pharmacodynamic properties of evolocumab.

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
Healthy Subject Pharmacokinetics and Initial Tolerability Studies			
1.	Phase I PK study (20080397) [Module 5.3.4.1]	To assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of evolocumab at 5 ascending SC doses and 2 ascending IV doses	Double-blind, randomized, placebo- controlled (ascending single dose)
2.	Phase I PK study (20110121) [Module 5.3.4.1]	To assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of evolocumab at 3 ascending SC doses in Japanese subjects; and to compare the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles between Japanese and white subjects	Double-blind, randomized, placebo- controlled (ascending single dose)
3.	Phase I PK study (20120136) [Module 5.3.3.1]	To determine intra-subject variability in the pharmacokinetic and pharmacodynamic profiles of evolocumab following 140 mg SC dose administration in healthy adult subjects; and to evaluate safety, tolerability, and immunogenicity of	Open-label, crossover (intra-subject variability)
4.	Phase 0 Safety/Tolerability study (20110234) [Module 5.3.3.1]	(b) (4)	Randomized, crossover (tolerability of placebo SC at various infusion rates)
5.	Phase 0 Safety/Tolerability study (20120101) [Module 5.3.3.1]	(b) (4)	Randomized, crossover (tolerability of placebo SC bolus injections with different viscosities)
6.	Phase 0 Safety/Tolerability study (20120135) [Module 5.3.3.1]	(b) (4) tolerabilit (b) (4)	(b) (4)
Patient Pharmacokinetics and Initial Tolerability			
7.	Phase I PK study (20080398) [Module 5.3.4.2]	To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of multiple SC doses of	Double-blind, randomized, placebo-controlled (ascending multiple dose)

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
		evolocumab	
Intrinsic Factor PK			
8.	Phase I PK study (20120341) [Module 5.3.3.3]	To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of a single SC dose of evolocumab in subjects with mild or moderate hepatic impairment	open-label (hepatic impairment)
Biopharmaceutic Studies			
9.	Phase I PK study (20110168) [Module 5.3.1.2]	To demonstrate PK equivalence of the AMD to the prefilled AI/pen	Randomized, open-label, single- dose study
10.	Phase I PK study (20120133) [Module 5.3.1.2]	To demonstrate PK equivalence of PFS to AI/pen	Randomized, open-label, crossover study
Phase 2 Studies of Primary Hyperlipidemia and Mixed Dyslipidemia			
11.	Phase 2 Safety and Efficacy study (20101154) [Module 5.3.5.1]	To evaluate the efficacy, safety, tolerability, and PK of EvoMab administered SC as monotherapy every 2 weeks (Q2W) or every 4 weeks (QM) for 12 weeks in subjects with low risk hypercholesterolemia	Randomized, placebo- and ezetimibe-controlled, dose-ranging study
12.	Phase 2 Safety and Efficacy study (20101155) [Module 5.3.5.1]	To evaluate the safety, tolerability, and efficacy of EvoMab administered SC once Q2W or once QM in combination with statin therapy over a 12-week period in subjects with hypercholesterolemia.	Double-blind, randomized, placebo-controlled, dose-ranging study
13.	Phase 2 Safety and Efficacy study (20090158) [Module 5.3.5.1]	To evaluate the safety and efficacy of 12 weeks of EvoMab SC, compared with placebo, on the percent change from baseline in LDL-C in subjects with heterozygous familial hypercholesterolemia (HeFH).	Double-blind, randomized, placebo-controlled, study
14.	Phase 2 Safety and Efficacy study (20090159) [Module 5.3.5.1]	To evaluate the efficacy, safety, and tolerability of 12 weeks of EvoMab SC compared with ezetimibe in subjects with hypercholesterolemia who are unable to tolerate an effective dose of a statin	Randomized, study
15.	Phase 2 Safety and Efficacy study (20110231) [Module 5.3.5.1]	To evaluate tolerability and efficacy of EvoMab on LDL-C in combination with stable statin therapy in Japanese subjects with hypercholesterolemia and high cardiovascular risk	Double-blind, randomized, placebo- controlled, multicenter study

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
16.	Phase 2 Safety and Efficacy study (20110110) [Module 5.3.5.1]	To assess the long-term safety and efficacy of evolocumab (interim analysis)	Multicenter, controlled, open-label extension study
Phase 2/3 Studies of Homozygous Familial Hypercholesterolemia			
17.	Phase 2/3 Safety and Efficacy study (20110233) [Module 5.3.5.1]	To assess the safety, tolerability and efficacy of EvoMab in subjects with HoFH	Part A – open-label, single-arm, multicenter pilot study; Part B – double-blind, randomized, placebo-controlled, multicenter study
18.	Phase 2/3 Safety and Efficacy study (20110271) [Module 5.3.5.2]	To assess the long-term safety, tolerability, and efficacy of EvoMab on LDL-C in subjects with severe familial hypercholesterolemia	Multicenter, open-label study
Phase 3 Studies of Primary Hyperlipidemia and Mixed Dyslipidemia			
19.	Phase 3 Safety and Efficacy study (20110114) [Module 5.3.5.1]	To evaluate the efficacy, safety, tolerability, and PK of EvoMab administered SC as monotherapy Q2W or QM for 12 weeks in subjects with primary hyperlipidemia and mixed dyslipidemia and a 10-year Framingham Risk score of 10% or less.	Double-blind, randomized, double-dummy, placebo- and ezetimibe- controlled, parallel-group study
20.	Phase 3 Safety and Efficacy study (20110115) [Module 5.3.5.1]	To evaluate safety, tolerability and efficacy of EvoMab on LDL-C in combination with statin therapy in subjects with primary hypercholesterolemia and mixed dyslipidemia	Double-blind, randomized, placebo and ezetimibe controlled, multicenter study
21.	Phase 3 Safety and Efficacy study (20110116) [Module 5.3.5.1]	To evaluate safety and efficacy of EvoMab, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor (statin)	Double-blind, randomized, multicenter study
22.	Phase 3 Safety and Efficacy study (20110117) [Module 5.3.5.1]	To evaluate safety, tolerability and efficacy of EvoMab on LDL-C in subjects with HeFH	Double-blind, randomized, placebo- controlled, multicenter study
23.	Phase 3 Safety and Efficacy study (20110109) [Module 5.3.5.1]	To evaluate long-term tolerability and durable efficacy of EvoMab on LDL-C in subjects with primary hyperlipidemia and mixed dyslipidemia	Double-blind, randomized, placebo-controlled, multicenter study
24.	Phase 3 Safety and Efficacy study (20120138) [Module 5.3.5.1]	To assess the long-term safety and efficacy of evolocumab (interim analysis)	Multicenter, controlled, open-label extension study
25.	Phase 3 Safety and Efficacy study	To Assess Subjects' Ability to Administer a Full Dose of	Multi-center, Randomized Study in Subjects With

No.	Type of Study (Study Identifier) [Location of Study Report]	Objective(s) of the Study	Study Design
	(20120348) [Module 5.3.5.4]	Evolocumab in Home-use, Using Either a Prefilled Syringe or a Prefilled Autoinjector/pen	Primary Hypercholesterolemia and Mixed Dyslipidemia
26.	Phase 3 Safety and Efficacy study (20120356) [Module 5.3.5.4]	To Assess Subjects' Ability to Administer a Full Dose of Evolocumab in Home-use, Using Either a 3.5 mL Personal Injector or a Prefilled Autoinjector/Pen.	Multi-Center, Randomized Study in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia

PFS: pre-filled syringe
AMD: automated mini-doser
AI/Pen: auto-injector/pen

BLA 125522 Filing Meeting

Evolocumab

Sponsor: Amgen

Submitted: 08/27/2014

Submitted under section 351(a) of the Public Health Service (PHS) Act

OCP Review Team:

Clin Pharm Reviewer:

Sury Sista, PhD

Clin Pharm Team Leader:

Immo Zadezensky, PhD

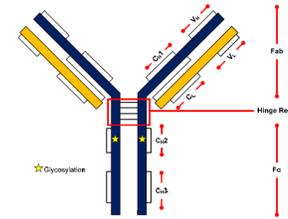
Pharmacometrics Reviewer:

Justin Earp, PhD

Pharmacometrics Team Leader:

Nitin Mehrotra, PhD

Evolocumab is a new molecular entity



Heavy chains are shown in blue and light chains are shown in orange
V_H is the variable domain of the heavy chain
C_H1, C_H2, and C_H3 are the constant domains of the heavy chain
V_L is the variable domain of the light chain
C_L is the constant domain of the light chain

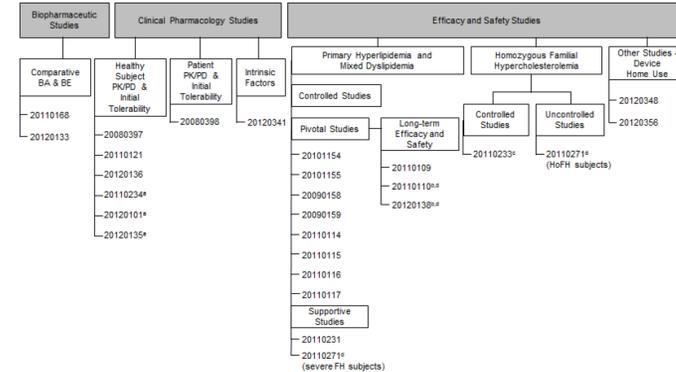
Class	Anti human proprotein convertase subtilisin/kexin type 9 (PCSK9) fully human monoclonal immunoglobulin G2
Proposed Indication	<ul style="list-style-type: none"> indicated as an adjunct therapy to diet to: <ul style="list-style-type: none"> Reduce LDL-C, TC, ApoB, non-HDL-C, TG/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia
Formulation	<ul style="list-style-type: none"> sub-cutaneous (SC) injection Presentations: (vial and syringe, prefilled syringe (PFS), prefilled autoinjector/pen (AI/pen), and automated mini-doser (AMD)) <ul style="list-style-type: none"> 140 mg single-use prefilled syringe; supplied as a 1-pack <ul style="list-style-type: none"> 1 mL of a 140 mg/mL solution of evolocumab 140 mg single-use prefilled SureClick® Autoinjector; supplied as a 1-pack, 2-pack, and 3-pack <ul style="list-style-type: none"> 1 mL of a 140 mg/mL solution of evolocumab
Proposed Dose	<ul style="list-style-type: none"> Primary hyperlipidemia or mixed dyslipidemia: 140 mg every 2 weeks or 420 mg once monthly in the upper arm, thigh, or the Abdomen Homozygous familial hypercholesterolemia: Administer 420 mg either once monthly or every 2 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule

Mechanism of Action

(b) (4)

Evolocumab is a human monoclonal IgG2 that specifically binds to PCSK9 and inhibits the interaction of PCSK9 with the low-density lipoprotein receptor (LDLR), resulting in increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

List of Studies to Support the Clinical Program



BA = bioanalytical, BE = bioequivalence, FH = familial hypercholesterolemia, HoFH = homozygous familial hypercholesterolemia, PK/PD = pharmacokinetics/pharmacodynamics, SC = subcutaneous
* Placebo-only, phase 0 studies in healthy subjects to assess tolerability of SC administration of formulations of various viscosities and tolerability of various SC infusion rates.
* These long-term, open-label studies were controlled in year 1 (evolocumab plus standard of care versus standard of care alone).
* Two-part study: part A is a phase 2, open-label, pilot study, and part B is a phase 3, double-blind, placebo-controlled study.
* Interim data for this study are included in the submission. Study 20110271* enrolled subjects with homozygous familial hypercholesterolemia and severe familial hypercholesterolemia. Subsets of this study support each indication.

Drug Substance used in Clinical Studies

- Drug substance for phase 1 and phase 2 clinical studies was manufactured using a different process (Process 1) than that employed in a majority of phase 3 studies (Process 2 –proposed commercial drug substance). – Was an adequate bridge established between Process 1 and Process 2 drug substance?
- To bridge the phase 2 and phase 3 programs for the evaluation of clinical safety, the Sponsor has provided the following in the BLA:
 - A comprehensive analytic comparability assessment (Module 3 summary)
 - PK/PD dataset and analyses from 23 clinical studies (Module 5 & Module 2 summaries)
 - Individual and integrated clinical efficacy and safety data from 23 clinical studies (Module 5 & Module 2 summaries)

5

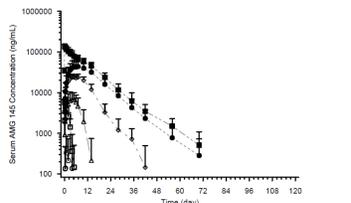
Overview of Clinical Study Results

6

PK of Evolocumab

SD PK in Healthy Volunteers

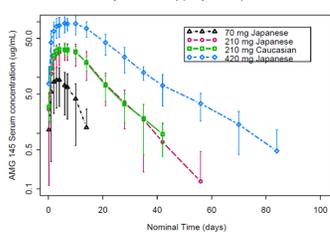
Figure 2. Mean (SD) Unbound Evolocumab Serum Concentration-time Profiles (Semilog): Single-dose Evolocumab IV or SC in Healthy Subjects (Study 20080397)



Legend for Figure 2:
 □ Treatment: AMG 145 21 mg IV (n=54) ◆ Treatment: AMG 145 210 mg SC (n=6)
 ○ Treatment: AMG 145 21 mg SC (n=4) ■ Treatment: AMG 145 420 mg IV (n=6)
 ▲ Treatment: AMG 145 70 mg SC (n=55) ● Treatment: AMG 145 420 mg SC (n=6)

Comparative PK in Japanese and Caucasian Population

Figure 5. Mean (SD) Serum Concentration-time Profile for Unbound Evolocumab by Treatment Group (Study 20110121)



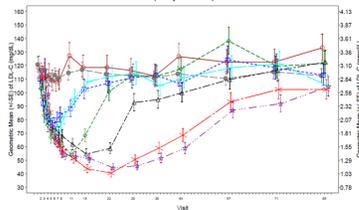
AMG 145 = evolocumab; Caucasian = white; SD = standard deviation.

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PD of Evolocumab

LDL-C Over Time

Figure 3. Geometric Mean (SE) of Ultracentrifugation LDL-C Over Time (Study 20080397)

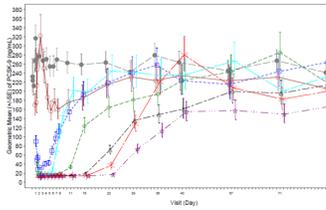


Legend for Figure 3:
 Treatment Group: ●●● AMG 145 21 mg SC, ●●● AMG 145 70 mg SC, ●●● AMG 145 210 mg SC, ●●● AMG 145 420 mg SC, ●●● AMG 145 21 mg IV, ●●● AMG 145 70 mg IV, ●●● AMG 145 210 mg IV, ●●● AMG 145 420 mg IV

Note: Values on the x-axis have been shifted slightly for ease of reading and 0 indicates Day.

PCSK9 Over Time

Figure 4. Geometric Mean (SE) of Unbound PCSK9 (ng/mL) Over Time (Actual Scale) (Study 20080397)



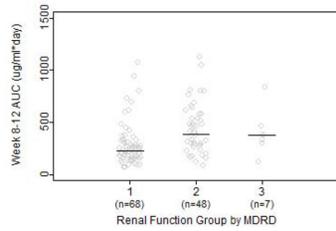
Legend for Figure 4:
 Treatment Group: ●●● AMG 145 21 mg SC, ●●● AMG 145 70 mg SC, ●●● AMG 145 210 mg SC, ●●● AMG 145 420 mg SC, ●●● AMG 145 21 mg IV, ●●● AMG 145 70 mg IV, ●●● AMG 145 210 mg IV, ●●● AMG 145 420 mg IV

Note: Values on the x-axis have been shifted slightly for ease of reading and 0 indicates Day.
 IV = intravenous; SC = subcutaneous; SE = standard error.

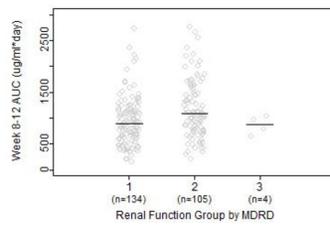
8

Pop-PK Prediction for Renal Impairment

Evolocumab 140 mg SC Q2W



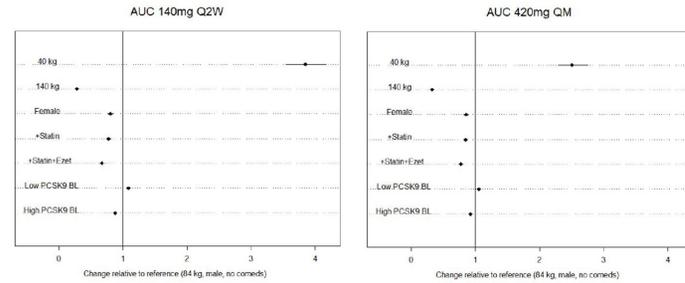
Evolocumab 420 mg SC QM



Points: individual AUC_{0-12} predictions; Line: Median AUC_{0-12}
Renal function groups: 1: Normal (eGFR > 80 mL/min); 2: Mild impairment (eGFR ≤ 80 mL/min ≥ 50 mL/min); 3: Moderate impairment (eGFR < 50 mL/min, ≥ 30 mL/min). AUC_{0-12} = area under the serum concentration curve from week 8 to week 12; CrCl = creatinine clearance; MDRD = Modification of Diet in Renal Disease; Q2W = once every 2 weeks; QM = once a month; SC = subcutaneous.

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Demographic Covariates

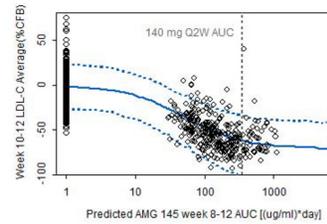


The statin covariate represents patients only taking a statin and no other concomitant medication. The Statin+Ezet. covariate includes all patients on ezetimibe, regardless of concomitant medications. For patients in the PK model, 93% of patients on ezetimibe were also taking a statin; thus the ezetimibe covariate most generally represents a combination (statin plus ezetimibe) therapy covariate. PCSK9 BL: PCSK9 baseline (Low: 4.8 nM = 335 ng/mL; High: 8.1 nM = 599 ng/mL) AUC = area under the time-concentration curve; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q2W = once every 2 weeks; QM = once monthly (every 4 weeks).

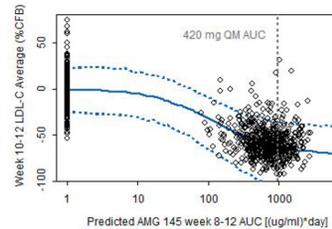
14

Population Model Predicted PD

Evolocumab Q2W



Evolocumab QM



%CFB = percent change from baseline; AMG 145 = evolocumab; AUC = area under the concentration-time curve; LDL-C = low-density lipoprotein cholesterol; Q2W = once every 2 weeks; QM = once monthly (every 4 weeks). Prediction of the mean week 10 and 12 calculated LDL-C concentration, in mg/dL (top) and percent change from baseline (bottom), 50th (solid line) and 5th and 95th (dashed lines) percentiles. Simulations were formed for n = 2000 patients. Points: observed individual mean week 10 and 12 LDL-C measurements.

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Sponsor's Label Claim

- **Primary Hyperlipidemia and Mixed Dyslipidemia:** The recommended dose for [TRADENAME] is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.
- **Homozygous Familial Hypercholesterolemia:** The recommended dose for [TRADENAME] is 420 mg either once monthly or every 2 weeks.
- Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.
- No dosage adjustment is necessary in patients with mild to moderate renal impairment.
- No dose adjustment is necessary in patients with mild to moderate hepatic impairment.
- No dosage adjustment is necessary in geriatric patients.
- No formal drug-drug interaction studies have been conducted for [TRADENAME].

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Pediatric Waiver Request

Indication: Primary Hyperlipidemia	(b) (4)
Population	Pediatric Waivers
(b) (4)	

Potential Filing Issues/Checklist

- Was BE established between the presentations in pre-filled syringe (PFS), automated mini-doser (AMD) and auto-injector/pen (AI/Pen)?
- Is there a PK or PK/PD bridge between Process 1 and Process 2 drug substance?
- Is there a need for dose adjustment in Specific Population?

Application Fileability and Consults

- Yes, this application is fileable from a Clinical Pharmacology perspective
- OSI consults – None
- Request for Sponsor - None

BACKUP SLIDES

Anti-drug Antibody

- Overall, less than 1% of evolocumab-treated subjects in the safety and efficacy studies included in this marketing application were positive for the development of binding antibodies. In addition, neutralizing antibodies have not been detected in any subject. Therefore, the incidence of anti-evolocumab binding antibodies is low.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		To bridge data from Process 1 material (used in Phase 1, Phase 2 and long-term efficacy study) and Process 2 material (used in Phase 3 trials), the sponsor provided (b) (4) 
2	Has the applicant provided metabolism and drug-drug interaction information?			X	ocumab is a monoclonal antibody, the sponsor did not conduct any <i>in vitro</i> permeability, <i>in vitro</i> metabolism, or <i>in vitro</i> metabolic drug-drug interaction studies that used human biomaterials.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	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)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	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?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for	X			

	approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor:

None.

Suryanarayana M. Sista

09 Oct, 2014

Reviewing Clinical Pharmacologist

Date

Immo Zadezensky

09 Oct, 2014

Team Leader

Date

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

/s/

SURYNARAYANA M SISTA
10/17/2014

IMMO ZADEZENSKY
10/17/2014