Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Alirocumab (rch)

Proprietary Product Name: Praluent (Golyra/Eliriduc)

Sponsor: Sanofi-Aventis Australia Pty Ltd

December 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
Apo A-1	apolipoprotein A-1
Apo B	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AUC	area under the serum concentration versus time curve to time infinity
AUC_{last}	area under the serum concentration versus time curve from time zero to real time T_{last}
AUC_{0-28}	area under the serum concentration versus time curve from time zero to Day 29
AUC_{0-14}	area under the serum concentration versus time curve from time zero to Day 15
BMI	body mass index
C_{D15}	serum concentration observed on Day 15 (14 days post dose)
C_{D29}	serum concentration observed on Day 29(28 days post dose)
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use (EU)
CKD	chronic kidney disease
CL/F	apparent total body clearance of drug from serum
C_{max}	maximum serum concentration observed
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DMC	data monitoring committee
EOS	end of study

Abbreviation	Meaning
EOT	end of treatment
FAS	full analysis set
GCP	Good Clinical Practice
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
heFH	heterozygous familial hypercholesterolemia
HLT	high level term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
IMP	investigational medicinal product
ITT	intention-to-treat
LC-MSMS	liquid chromatography with tandem mass spectrometry
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LLOQ	lower limit of quantification
LMT	lipid-modifying therapy
Lp(a)	lipoprotein (a)
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MMRM	mixed-effect model with repeated measures
MRT	mean residence time (mean time molecule resides in body)
NMAR	not-missing-at-random
non-FH	non-familial hypercholesterolemia
non-HDL-C	non-high-density lipoprotein cholesterol

Abbreviation	Meaning
PCSK 9	proprotein convertase subtilisin kexin type 9
PD	pharmacodynamics
PFP	pre-filled pen
PFS	pre-filled syringe
PK	pharmacokinetics
POP PK	population pharmacokinetic
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SC	subcutaneous
SE	standard error
SMQ	standardised MedDRA query
SOC	system organ class
SREBP-2	sterol regulatory element-binding-protein-2
TEAE	treatment emergent adverse event
TGs	triglycerides
T_{last}	time corresponding to the last concentration above the limit of quantification
T½z	terminal half life
Total-C	total-cholesterol
Vss/F	distribution volume at steady state
Vz/F	distribution volume in the terminal phase

I. Introduction to product submission

Submission details

Type of submission:	New biological entity.
Decision:	Approved
Date of decision:	13 May 2106
Date of entry onto ARTG	17 May 2016
Active ingredient(s):	Alirocumab
Product name(s):	Praluent/Golyra/Eliriduc
Sponsor's name and address:	Sanofi Aventis Australia Pty Ltd 12-24 Talavera Road Macquarie Park NSW 2113
Dose form(s):	Solution for injection
Strength(s):	75 mg/mL and 150 mg/mL
Container(s):	Pre-filled syringe, pre-filled pen
Pack size(s):	1 (starter pack), 1, 2 or 6
Approved therapeutic use:	*Praluent / Golyra /Eliriduc is indicated as an adjunct to diet and exercise in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease:* *-in combination with a statin, or statin with other lipid-lowering therapies or,* *-in combination with other lipid-lowering therapies in patients who are statin-intolerant.* *The effect of Praluent / Golyra /Eliriduc on cardiovascular morbidity and mortality has not yet been determined (see CLINICAL TRIALS).'*
Route(s) of administration:	Subcutaneous (SC)
Dosage:	Dependent on indication. See Product Information (Attachment 1) for details
ARTG numbers:	AUST R 238285, AUST R 238299 to AUST R 238306, AUST R 238308238300 to AUST R 238310

Product background

This AusPAR describes the application by the sponsor to register Praluent/Golyra/Eliriduc for the following indication:

> *Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:*
>
> - *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
> - *alone or in combination with other lipid-lowering therapies in patients who have documented atherosclerotic cardiovascular disease and are statin-intolerant, or for whom a statin is contraindicated*
>
> *The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.*

Praluent has been clinically developed for the treatment of hypercholesterolemia (presence of high concentrations of low-density lipoprotein cholesterol (LDL-C) or high total cholesterol) and mixed dyslipidemia (presence of high concentrations of LDL-C and triglycerides) and for the reduction of cardiovascular (CV) events.

In 2009 about one third of deaths in Australia were the result of cardiovascular disease and 2,027 per 100,000 people were hospitalised with cardiovascular disease as a principal diagnosis in 2009-2010(AIHW). Although a number of therapeutic options are registered for use in patients with hypercholesterolaemia, they do not universally result in the achievement of target serum lipid levels and have adverse effects that the population for which they are suitable. A reduction in serum lipids as measured by low density lipoprotein cholesterol (LDL-C) has been associated with a reduction in the risk of cardiovascular events and serum lipid reduction is advocated in international guidelines for managing cardiovascular risk.

Familial hypercholesterolaemia is generally thought to occur in about 1:500 people in the population, however the prevalence may be higher in certain populations such as Afrikaners in South Africa (1:70). Heterozygous familial hypercholesterolaemia (HeFH) is caused by heterozygous loss of function mutations in low density lipoprotein receptor (LDLR) ApoB affecting the LDLR-binding domain of apolipoprotein B (ApoB), or heterozygous gain-of-function mutations in pro-protein convertase subtilisin kexin type 9 (PCSK9). There are over 1200 mutations, mostly for LDLR. Familial hypercholesterolaemia, untreated, is associated with a high risk of atherosclerotic coronary arterial disease in young adult-hood.

Human PCSK9 is synthesised mainly in the liver, kidney and small intestine under the regulation of the sterol regulatory element-binding protein 2 (SREPB-2), a transcription factor that is activated in response to cellular cholesterol depletion. In some animal species, for examplefor example, zebrafish, there are neurological consequences for the absence of PCSK9. Although first discovered in neural tissue the role of PCSK9 in non-hepatic tissues such as the for example, brain is not well understood.

The LDLR on the surface of the hepatocyte is the primary receptor that clears circulating LDL-C. PCSK9, upon binding to the LDLR, initiates internalisation and lysosomal degradation of the LDLR-PCSK9 complex. By inactivating PCSK9, PCSK9 inhibitors upregulate LDLR, especially on the surface of hepatocytes, leading to increased uptake of circulating LDL-C and the consequent reduction of the plasma LDL-C concentration. The

expression of hepatic LDLR and its function in removing LDL-C from circulation is dependent on intracellular cholesterol levels and serum PCSK9 concentrations.

Alirocumab is a fully human immunoglobulin type G1 (IgG1) directed against human PCSK9. It binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to the LDL receptor on the surface of the hepatocyte. By binding to PCSK9 it increases the concentration of LDLR on hepatic cells by inhibiting LDLR degradation and promoting recycling of the receptor. The inhibition also increases LDLR expression. It differs from statins in its mode of action although the action of statins leads to an increase in LDLR on the hepatocyte cell surface by increasing LDLR expression. The alirocumab-PCSK9 complex is internalised in the hepatocyte and degraded in lysosomes, thereby removing PCSK9 from circulation.

Current pharmacotherapy for hypercholesterolaemia includes HMG Co-A reductase inhibitors (statins), ezetimibe, bile acid binding resins and lipoprotein apheresis.

Regulatory status

Praluent was not registered in any country at the time of this submission in Australia. It is a new biological entity for Australian regulatory purposes.

During the evaluation Praluent was approved by the FDA (on 24 July 2015; FDA website). The approved indication in the USA is:

> *'PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C).*
>
> *Limitations of Use: The effect of PRALUENT on cardiovascular morbidity and mortality has not been determined.'*

The Committee for Medicinal Products for Human Use CHMP also recommended approval of Praluent in July 2015 (24 July 2015 Press Release) for the following indication:

- *'Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:*
  - *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
  - *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated*
- *The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.'*

Similar applications are under review in Canada and New Zealand.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction (if applicable)

Alirocumab is a fully human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

Drug substance (active ingredient)

Alirocumab is a covalent heterotetramer consisting of two disulphide-linked human heavy chains, each covalently linked through a disulphide bond to a fully human kappa light chain (see Figure 1). The alirocumab heavy chain has an IgG1 isotype constant region. There is a single N-linked glycosylation site (Asn^{298}) in each heavy chain, located within the CH2 domain of the Fc constant region in the molecule. The antibody, based on the primary sequence (in the absence of N-linked glycosylation), has a molecular weight of 145,983.8 Da, taking into account the formation of 16 disulphide bonds and removal of Lys^{448} from each heavy chain C-terminus. The variable domains of the heavy and light chains combine to form complementarity-determining regions (CDRs) for the binding of alirocumab to its target, proprotein convertase subtilisin/kexin type 9 (PCSK9).

Manufacture

Alirocumab is produced by expression in Chinese Hamster Ovary cells using proprietary cell expression technologies.

The purification and formulation of alirocumab consists of a series of steps including particulate filtration, impurity removal, chromatography steps, reduction of potential viral contaminants, and the addition of excipients to the sucrose-adjusted concentrated/diafiltered pool to produce the drug substance. This material is dispensed and stored frozen and transported to the drug manufacturing site for filling into pre-filled syringes.

Alirocumab is manufactured without the direct use of animal-derived raw materials.

Physical and chemical properties and specifications

Alirocumab solution for injection is a clear, colourless to pale yellow solution with a nominal pH of 6.0. The formulation was developed to be close to iso-osmolarAs it is intended for subcutaneous injection, the drug product must be sterile and have low endotoxin levels.

Table 2: Physical and chemical properties of Praluent

Characteristic	Data
Description	Alirocumab is a recombinant human IgG1 isotype monoclonal antibody that specifically binds to proprotein convertase subtilisin kexin type 9 (PCSK9).
Quaternary structure	Covalent heterotetramer consisting of two heavy chains and two light chains

Characteristic	Data
Molecular weight based on primary sequence (without heavy chain C-terminal Lys^{448})[a]	145,983.8 Da (in the absence of N-linked glycosylation)
Number of N-glycosylation sites/molecule	2 glycosylation sites (1 glycosylation site per heavy chain (Asn^{298}) No glycosylation sites within light chain primary sequence
Number of disulphide bonds/molecule	16 intra- and inter-chain disulphide bonds
Ligand binding specificity	Human, monkey, murine, hamster and rat mature PCSK9
Appearance of solution	Colourless to pale yellow liquid

Drug product

Praluent (alirocumab) is an aqueous buffered solution for injection, pH 6.0 in a pre-filled 1 mL injection pen and pre-filled 1 mL syringe, containing 75 mg/mL and 150 mg/mL of purified alirocumab protein, 6 mM histidine, 10% (w/w) sucrose, and 0.01% polysorbate 20. Other tradenames include Golyra and Eliriduc.

Solution for injection in pre-filled pen, 75 and 150 mg/mL

The DP primary container is a siliconized 1 mL long, clear, glass syringe, equipped with a siliconized staked stainless steel needle. A coated bromobutyl rubber plunger stopper and a styrene-butadiene rubber needle shield form the closure system. This bulk pre-filled syringe is the same as the bulk pre-filled syringe used for the pre-filled syringe presentation.

Solution for injection in pre-filled syringe, 75 and 150 mg/mL

Alirocumab drug products are packaged in a 1 mL Type I clear glass single use pre-filled syringe with coated bromobutyl rubber plunger stopper. A styrene-butadiene rubber soft needle shield covers the needle.

Praluent contains alirocumab as well as histidine, sucrose, polysorbate 20 and Water for injection.

Stability

- Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data - the product is not photostable.
- The proposed shelf life is 14 months when stored at 2-8^{o}C.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Praluent, Golyra and Eliriduc (alirocumab) 75 mg/mL and 150 mg/mL solution for injection, pre-filled pen.

III. Nonclinical findings

Introduction

An adequate dossier of good quality studies was submitted. The package of studies was appropriate for the drug. Relevant studies were conducted in accordance with Good Laboratory practice (GLP), although in all studies, there were some components that were not in full compliance with GLP. It is unlikely that these deviations from full GLP compliance impacted significantly on data integrity or interpretation. The repeat-dose toxicity studies and the reproductive and developmental studies included toxicokinetic components.

Pharmacology

Primary pharmacology

Alirocumab bound with high affinity to PCSK9 from all species tested (humans, cynomolgus monkeys, rats, mice and hamsters) under neutral and acidic conditions (K_D at pH 7.4 ranged from 0.52 nM (monkey) to 14.5 nM (rat)). K_D values for human (0.52 nM) and monkey were similar. Alirocumab blocked the binding of PCSK9 (from all above-mentioned species) to human LDLR, and also the binding of the human gain-of-function mutant (D374Y) PCSK9 which is associated with some forms of familial hypercholesterolaemia[1]. Further, alirocumab reversed PCSK9-mediated inhibition of uptake of fluorescent-labelled LDL-C into HepG2 cells (all above-mentioned species).

Alirocumab did not induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) in any of 4 different cell lines when tested using a validated in vitro assay, and did not form soluble immune complexes with recombinant human PCSK9 that are capable of binding to C1q, the first step in the complement cascade.

The ability of alirocumab to lower circulating LDL-C and total-C was demonstrated in various murine models. A challenge in studying the role of PCSK9 in rodents is that the majority of cholesterol circulates within HDL-C particles, with smaller amounts in the form of LDL-C, making it difficult to assess drugs designed to lower LDL-C. Strategies used to increase serum LDL-C levels in mice in the primary pharmacology studies were: (i) use of mouse strains with higher than normal levels of LDL-C (ii) administration of hPCSK9 to mice and (iii) dietary manipulation.

Although the binding affinity of alirocumab to mouse PCSK9 is 4.5 times lower than its affinity to hPCSK9 as indicated by K_D (human 0.58 nM versus mouse 2.61 nM), a single SC dose of 5 mg/kg alirocumab resulted in a substantial (although non-significant) decrease in serum LDL-C in apoE knockout mice. Moreover, single intraperitoneal (IP) doses of 5, 10 and 30 mg/kg significantly reduced serum LDL-C levels in C57.085 mice given hPCSK9, and 3 and 10 mg/kg/week SC alirocumab for 18 weeks significantly decreased plasma total-C and LDL-C in APOE*3Leiden.CETP mice.

In $PCSK9^{hum/hum}$ mice which express human PCSK9 rather than mouse PCSK9, pre-treatment with a single dose of alirocumab (5 mg/kg IP) nearly fully blocked the approximately 2 fold increase in serum LDL-C concentrations caused by hPCSK9 injection. Single doses of 1, 5 or 10 mg/kg SC alirocumab dose-dependently reduced serum LDL-C in

[1] Horton *et al*. Molecular Biology of PCSK9: Its role in metabolism. *Trends Biochem Sci*. 2007;32:71-77.

PCSK9$^{hum/hum}$ mice given a high carbohydrate diet, and a single dose of 10 mg/kg SC reduced serum LDL-C in *Pcsk9*$^{hum/hum}$*Ldlr*$^{+/-}$ mice which have impaired LDL-C uptake.

Administration of hPCSK9 to mice leads to a decrease in hepatic LDLR protein levels. In PCSK9$^{hum/hum}$ mice, pre-treatment with alirocumab (single dose of 5 mg/kg IP) was shown not only to fully prevent the reduction in liver LDLR level caused by hPCSK9 injection, but to raise liver LDLR to levels above those in the PBS control. In C57.085 mice given hPCSK9, alirocumab (30 mg/kg IP) also significantly increased liver LDLR levels.

In APOE*3Leiden.CETP mice, alirocumab at 3 and 10 mg/kg/week SC for 18 weeks decreased atherosclerotic lesion area and severity, increased the percentage of segments without disease? and resulted in improvements in atherosclerotic lesion composition.

Broadly dose-dependent LDL-C lowering effects were also demonstrated following single doses in hamsters and in cynomolgus monkeys (in a pharmacokinetic study), with the effects being long lasting. In hamsters fed a normal diet, after a single dose of 10 mg/kg, serum LDL-C did not return to baseline levels until 28 days after dosing and significant reductions in total-C were still observed on Day 21. In monkeys, after single doses of 1 and 15 mg/kg SC and 1, 3 and 15 mg/kg IV, decreases in serum LDL-C and total-C were detected at the first measurement time (48 h post dose), and were still observed at 10, 16 and 30 days at the respective IV dose levels. Consistent with the high bioavailability of alirocumab (see below), effects were of comparable magnitude following SC and IV administration.

Reductions in serum LDL-C and total-C were also consistently observed in the repeat-dose studies in rats and cynomolgus monkeys, with some significant reductions (mainly in LDL-C) being observed in some studies in both of the species at 0.5 mg/kg/week SC or IV. Animal: human exposure ratios were below 1 at this dose level. Effects of alirocumab on other circulating lipids (HDL-C, very low density lipoprotein cholesterol (VLDL)-C and triglycerides) were not extensively examined in the primary pharmacology studies, but such data were available from the repeat-dose toxicity studies, and are discussed below.

Combination treatment with alirocumab and atorvastatin (a primary pharmacology study in APOE*3Leiden.CETP mice and repeat-dose studies in monkeys) resulted in greater reductions in LDL-C, total C and atherosclerotic lesion area than treatment with either drug alone. The ability of alirocumab to elicit a further reduction in LDL-C when combined with statins (compared to when given alone) may be due to an increase in PCSK9 levels induced by statins (Dubuc *et al*., 2004).

Secondary pharmacology and safety pharmacology

No secondary pharmacology studies were submitted but such studies are not considered necessary. PCSK9 acts mainly on hepatic LDLR and the action of alirocumab in blocking the activity of PCSK9 does not have any anticipated secondary pharmacological effects. There were no findings in either the primary pharmacology or repeat-dose toxicity studies that were suggestive of secondary pharmacological effects.

No specialised safety pharmacology studies were submitted, but a number of safety pharmacology endpoints were incorporated into the repeat-dose toxicity studies, an acceptable approach for a monoclonal antibody. Thus, cardiovascular endpoints (blood pressure and electrocardiogram (ECGs), including heart rate) and body temperature was assessed in all of the repeat-dose toxicity studies in monkeys except for the exploratory study and the higher dose 13 week combination study. There were no clinical signs or pathological changes seen in the repeat-dose toxicity studies that would suggest any effect of alirocumab on the central nervous, respiratory or renal systems. Findings of urinalysis in the repeat-dose toxicity studies were also negative.

A study by Labonte et al. (2009) indicated a functional relationship between PCSK9 expression and cell surface levels of CD81, a major component of the HVC entry complex, and the addition of large quantities of purified soluble PCSK9 to cell culture supernatant impeded hepatitis C virus (HCV) infection. Several in vitro and in vivo experiments were conducted to address the associated speculation that reducing PCSK9 could result in an increase in HCV infection. Physiological concentrations of soluble hPCSK9 were not found to alter cell surface or total levels of CD81 in Huh-7 cells and the blocking of PCSK9 by alirocumab had no effect on CD18 levels. Neither the addition of hPCSK9 or treatment with alirocumab had any effect on the propagation of HCV. It seems appropriate to conclude that a reduction in PCSK9 levels by alirocumab is unlikely to increase in HCV infection.

Pharmacokinetics

The proposed clinical route is SC and the pharmacokinetic profile of total alirocumab was determined following single doses by this route and the IV route to rats and cynomolgus monkeys, the species used in the repeat-dose and reproductive toxicity studies. Additional single dose studies compared the pharmacokinetic profiles of alirocumab produced by different processes or using different cell lines (initial cell line and proposed commercial cell line) and investigated the effect of test article concentration (and hence dose volume) on pharmacokinetic profile. There were no substantial differences between the pharmacokinetic profiles in rats given the different process lots of alirocumab or in monkeys given the lots produced using different cell lines, and no apparent effect of dose volume on the pharmacokinetics of alirocumab.

After SC administration, absorption was slow (time to peak plasma concentration (T_{max}) was approximatelyapproximately 70 h (3 days) in both rats and monkeys, and 3-7 days in humans). Clearance was slow (approximately 0.5 and 0.35 mL/h/kg in rats and monkeys, respectively), and volume of distribution was small (approximately 80 and 45 mL/kg in rats and monkeys, respectively, and 40-50 mL/kg in humans) reflecting distribution primarily in the circulatory system, as is typical for monoclonal antibodies. The half-life ($t_{1/2}$) was correspondingly long (approximately 120 h in rats, approximately 150 h in monkeys and 17-20 days in humans). In monkeys (Studies REGN727-PK-09019 and REGN727/728-PK-09003) and humans, clearance was clearly biphasic. In monkeys, above a concentration threshold, $t_{1/2}$ was longer (approximately 150 h) than below the threshold (approximately 60 h), but the majority of exposure was above the threshold (>90% in Study REGN727-PK-09019). The biphasic clearance of alirocumab is typical of the pharmacokinetic behaviour of monoclonal antibodies and reflects saturable target-mediated clearance. At low concentrations, elimination is presumably predominantly through saturable binding to target (PCSK9) and endocytosis, while at higher concentrations, elimination is largely through a non-saturable proteolytic pathway, for example, through a reticuloendothelial-mediated process.

Bioavailability was moderate to high (44-68% in rats, 72-77% in monkeys and 85% in humans). Exposure (peak plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC)) was broadly dose-proportional in both rats and monkeys, while in humans, C_{max} was dose proportional but AUC was slightly supra-proportional. No consistent gender differences in the pharmacokinetics of total alirocumab were observed in rats, monkeys or humans. Accumulation was observed in the rat and monkey following repeated IV or SC administration. In rats, steady state concentrations were generally reached after 4-5 weeks/doses and accumulation was in the order of 2 fold. In monkeys, the plateau tended to be reached later (about 8-12 weeks/doses) and at doses of ≥5 mg/kg/week, accumulation was in the order of 3 fold. In humans, steady state concentrations were reached after 2 to 3 SC doses, and accumulation was about 2 fold

Distribution, metabolism and excretion studies were not conducted and are not required. Monoclonal antibodies are largely distributed in the circulatory system, and since they are proteins, they are known to be metabolised to amino acids or small peptides.

Anti-alirocumab antibody responses were not frequently observed in either rats or monkeys, but were somewhat more prevalent in the former than the latter. The positive antibody responses that were observed were often transient (for example when a positive response was observed in an individual animal, that animal often did not show a positive response at subsequent sampling times) and this was also the case clinically. In rats, positive responses were more frequently observed following SC than IV administration. The occurrence of positive responses was not related to the dose of alirocumab. The occurrence of anti-alirocumab antibodies in monkeys generally did not reduce serum total alirocumab concentrations (relative to antibody-negative animals), and this was also the case clinically. In rats, the occurrence of anti-alirocumab antibodies was usually associated with a small to moderate reduction in systemic concentrations of total alirocumab. Despite the occasional occurrence of anti-alirocumab antibody responses, continuous and substantial exposure to alirocumab was maintained throughout the dosing phase in all toxicology studies in both species.

Conclusion: the pharmacokinetic characteristics of total alirocumab in the species used in the pivotal repeat-dose toxicity studies (rats and monkeys) were sufficiently similar to those in humans to allow these species to serve as appropriate models for the assessment of drug toxicity.

Pharmacokinetic drug interactions

Toxicokinetic data from the repeat-dose combination studies (alirocumab IV weekly + atorvastatin PO daily) in cynomolgus monkeys did not reveal any consistent effect of alirocumab (15 or 75 mg/kg/week) on the pharmacokinetics of atorvastatin (10, 25 to 40 mg/kg/day) or its active *o*-hydroxy and *p*-hydroxy metabolites. However, serum total alirocumab concentrations tended to be reduced with increasing atorvastatin doses. This would be consistent with the statins increasing production of PCSK9 and thus increasing the target-mediated clearance of alirocumab.

Toxicology

Acute toxicity

No standard single dose toxicity studies were submitted and such studies are not considered essential for a monoclonal antibody. Toxicity findings following single doses of monoclonal antibodies are not common. The high exposure ratios for alirocumab achieved in the repeat-dose studies (10 in rats and >100 in monkeys) and the lack of toxicity in these studies suggests that this would be the case for alirocumab.

Repeat-dose toxicity

Repeat-dose toxicology studies of up to 26 weeks duration were conducted in rats and cynomolgus monkeys. Alirocumab was pharmacologically active in these species. Thus, it bound with high affinity to PCSK9 from these species, and it lowered serum LDL-C in these species, despite differences in cholesterol metabolism between rodents and other species (see below). The pharmacokinetic characteristics of alirocumab in rats and monkeys were similar to those in humans. Although some species differences were observed in the tissue cross-reactivity studies, overall, these species are considered appropriate models.

The toxicology studies were conducted using weekly SC injections (the clinical route) or weekly 30 min IV infusions (to maximise systemic exposure and support a possible alternate route of administration). A weekly dosing regimen was used to achieve continuous exposure to alirocumab in rats and monkeys. The dosing frequency was higher than that proposed clinically (once fortnightly), consistent with the shorter half-life of alirocumab in the laboratory animal species compared to humans. The repeat-dose toxicity studies were adequately conducted and consistent with guidelines (with respect to species, duration, group sizes, both genders, toxicity end-points assessed and so on).

Significant, broadly dose-dependent reductions in LDL-C and total-C concentrations were observed in all the repeat-dose toxicity studies, consistent with the primary pharmacological activity of alirocumab. Decreases in serum HDL-C were observed in all the repeat-dose rat studies, but not in the monkey studies, nor clinically. The changes in HDL-C seen in rats may reflect inter-species differences in the proportion of serum total-C that is present as HDL-C versus LDL-C. The ratio of (LDL + VLDL)/HDL in rats (0.41) and mice (0.25), as well as dogs (0.26), is lower than in humans (1.92) and monkeys (0.91).[2]

There were no consistent changes in VLDL-C or triglycerides in the repeat-dose studies in either species, although occasional increases were seen in triglycerides in the rat studies.

The effects of alirocumab on serum LDL-C and total-C were long lasting, reflecting the long half-life of the drug. Serum LDL-C and total-C had reversed to baseline and/or control levels by the end of the recovery period in most studies, although, in some studies, mainly at the higher doses, full reversal was not observed. No compensatory increases above baseline and/or control levels were observed.

No target organ toxicity was observed. Sinusoidal cell hyperplasia/hypertrophy was observed in the liver in the 16 day IV and 5 week SC rat studies, and extramedullary haematopoiesis in the spleen in the former study, but neither of these changes was seen in the longer-term studies in this species at comparable dose levels. This is probably a reflection of the interpretation of histological sections by the study pathologists, as these two studies were conducted by Covance Laboratories, whereas the other rat studies were conducted by WIL Research Laboratories. This gave rise to the unusual finding of lower No observable adverse effect levels (NOAELs) in the short-term compared to the longer-term rat studies. Given the lack of consistent findings across studies and the lack of any findings in these organs in the monkey studies, these observations are not considered to indicate target organ toxicity.

Increased adrenal gland weight was observed in the 13 and 26 week rat studies (at 75 mg/kg/week IV (both sexes) and 50 mg/kg/week SC (females) in the 13-week study and in females at 50 mg/kg/week SC (NS) and 30 mg/kg/week IV in the 26-week study). This change was moderate in magnitude and was not seen in monkeys.

No adverse effects of treatment with alirocumab were observed in any of the repeat-dose studies in monkeys, so the NOAEL was the highest dose tested in each study. In the pivotal 26 week study, NOAEL values were 75 mg/kg/week SC and 50 mg/kg/week IV. In rats, the NOAEL was the highest dose tested in the pivotal 26-week study (50 mg/kg/week SC and 30 mg/kg/week IV).

Given the expected clinical use of alirocumab together with statins, combination toxicity studies of up to 13 weeks duration with alirocumab (at IV doses of up to 75 mg/kg/week) and atorvastatin (at oral doses of up to 40 mg/kg/day) were conducted in cynomolgus monkeys to investigate any potential pharmacological, toxicological and toxicokinetic

[2] Greeve *et al*. Apolipoprotein B mRNA editing in 12 different mammalian species: hepatic expression is reflected in low concentrations of apoB-containing plasma lipoproteins. *Journal of Lipid Research*. 1993;34:1367-1383.

interactions between the two drugs. No toxicologically significant interactions were observed.

Decreased vacuolation of adrenal gland cortical cells was observed with both alirocumab alone (75 mg/kg/week IV) and atorvastatin alone (25 and 40 mg/kg/day PO) in the higher dose 13 week combination study, and was observed at higher incidence when the two drugs were given in combination. Adrenal cortical vacuoles often represent accumulations of various lipids or cholesterol. Thus, a decrease in adrenal cortical vacuolation might not be unexpected in the presence markedly reduced serum cholesterol concentrations due to alirocumab, together with the inhibition of intracellular cholesterol synthesis due to atorvastatin. Some effects on liver histopathology were observed with atorvastatin in the same study, but these did not appear to be consistently exacerbated by alirocumab. Zymogen granules were observed in the pancreas of females given atorvastatin, alirocumab and the combinations in the lower dose 13-week combination study. They had resolved by the end of the recovery period, were not observed in the higher dose study or in males, and are not considered toxicologically significant.

In the combination studies, serum total-C was reduced by both alirocumab and atorvastatin, with the most marked effects observed with the combination. There were similar findings for LDL-C, although, as expected, this parameter was affected more by alirocumab than by atorvastatin. HDL-C was reduced by atorvastatin and the combinations, with the effect tending to be slightly more marked in the combination groups. Reductions in VLDL-C, significant in some instances, were generally observed in the combination groups. In the higher dose 13 month study, triglycerides were reduced in the high dose (HD) atorvastatin group and the combination groups. In summary, the effects on serum lipids were more marked for the combinations that for either drug alone.

Relative exposure

Exposure ratios have been calculated based on animal: human serum AUC (Table 4). The human reference value is from Clinical Study POH0377 (population pharmacokinetics study).

Exposure ratios were moderate (rat) to high (monkey).

Table 4. Relative exposure in repeat-dose toxicity studies

Species	Study duration; route	Dose (mg/kg/day)	AUC^ (ng·h/mL)	Exposure ratio (ER)#
Rat (SD)	5 weeks; SC	0.5	532	0.2
		5	6,161	2.4
		15	13,005	5
		75	55,895	22
	13 weeks; IV	5	10,969	4.3
		15	33,906	13
		75	168,700	66
	13 weeks; SC	50	167,673	66

Species	Study duration; route	Dose (mg/kg/day)	AUC^ (ng·h/mL)	Exposure ratio (ER)#
	26 weeks; SC	5	2,579	1.0
		15	8,494	3.3
		50	27,943	11
	26 weeks; IV	30	62,159	25
Cynomolgus monkey	13 weeks; IV	0.5	926	0.4
		5	23,372	9
		15	99,404	39
		75	479,110	189
	26 weeks; SC	5	16,563	7
		15	55,735	22
		75	259,834	102
	26 weeks; IV	50	280,667	111
Human (Phase III studies)	steady state	[150 mg]	2537*	–

^AUC units varied for the different studies (AUC_{all} for the 5-week rat study, $AUC_{0.538\ h\text{-}168\ h}$ for the IV doses and $AUC_{24\ h\text{-}168\ h}$ for the SC dose in the 13-week rat study, $AUC_{0\text{-}\infty}$ for the 26-week rat study, AUC_{all} for the 13-week monkey study and $AUC_{0\text{-}168\ h}$ for the 26-week monkey study and for the clinical value); # animal:human serum AUC; * extrapolated from $AUC_{0\text{-}336\ h}$ data for by dividing by 2 ($AUC_{0\text{-}336\ h}$ data for patients using both the prefilled syringe and prefilled pen ((5030 x 1437 + 5390 x 203)/1640)); ER at the NOAEL is in bold

Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity studies were not submitted. Monoclonal antibodies are not expected to enter the cell and interact with DNA and there is no specific genotoxicity concern for alirocumab, so genotoxicity studies are not required. Standard carcinogenicity studies are generally inappropriate for monoclonal antibodies. Unless the mechanism of action of the drug or findings from other studies (such as proliferative findings in the repeat-dose toxicity studies) suggest concern regarding potential carcinogenicity, no assessment of carcinogenic potential is required.

Reproductive toxicity

An embryofetal development study was conducted in rats at SC doses of 0, 5, 15 and 75 mg/kg given on gestational day (GD) 6 and GD12 (termination on GD21). The study was adequately conducted and dose selection was appropriate. No rabbit embryofetal development study was conducted but this is acceptable for a monoclonal antibody.

A pre-/postnatal study was conducted in cynomolgus monkeys at SC doses of 15 and 75 mg/kg/week SC given from GD20 through to parturition (approximately GD160). The study was adequately conducted and the dose levels were appropriate. It should be noted that females were dosed only during gestation and not during lactation. Although there were only 2 dose levels, this was adequate in light of the lack of any major adverse findings at the HD and the high exposure ratio achieved at the NOAEL (see Table 5). Growth and development of the infants was comprehensively assessed over the first 6 months of life.

No fertility and early embryonic developmental study was conducted but surrogate fertility endpoints were investigated in the 26 week repeat-dose toxicity study in monkeys. Menstrual cycling, testicular volume and semen parameters (sperm motility, ejaculation volume, sperm concentration and total sperm count per ejaculation) were assessed. No adverse effects of alirocumab were seen in this assessment. The standard determination of organ weights, and macroscopic and microscopic examination of reproductive organs, in both males and females, did not reveal any effects of alirocumab in any of the repeat-dose studies in rats or monkeys. This is considered an adequate assessment of the effects of alirocumab on fertility.

Table 5. Relative exposure

Species	Study	Dose (mg/kg/day)	AUC^ (ng·h/mL)	Exposure ratio#
Rat (SD)*	Embryofetal development	5	6,161	2.4
		15	13,005	5
		75	55,895	22
Cynomolgus monkey	Pre-/postnatal development	15	33,612	13
		75	203,908	80
Human (Phase 3 studies)	steady state	[150 mg]	2537	–

^ AUC_{all} for rats and AUC_{0-168} for monkeys and humans; * data from the 5-week SC toxicity study in rats as sampling in the embryofetal development study was only conducted pre-dose and 24 h post dose on the days of dosing (GD6 and GD12) and at study termination (GD21 (9 days after the final dose)) – serum concentrations of alirocumab at 24 h post the GD12 dose in this study were comparable to those measured in the 5 week SC toxicity study at 24 h post dose on day 30; # = animal AUC:human serum AUC; ER at the NOAEL is in bold

High exposure ratios were achieved in both the embryofetal development and pre-/postnatal development studies (up to 22 in the rat study and 80 in the monkey study).

Placental transfer was demonstrated in rats, based on the measurement of alirocumab in serum samples taken from fetuses at termination (GD21, 9 days post the final dose). At this time point, serum alirocumab concentrations were higher in fetuses than in dams at all dose levels, with fetal: maternal serum alirocumab ratios ranging from 1.02 to 3.45. Placental transfer of alirocumab was an expected finding as IgG antibodies are known to cross the placenta. In the pre-/postnatal development study, alirocumab was readily detectable in the serum of 7 and 30 day old infants at both dose levels, but was either not detected or was detected at low concentrations when the infants were 90 and 178 days old. Given that females were only dosed until the end of gestation, placental transfer was

probably the main contributor to alirocumab in the infants, although milk may also have contributed, given the long half-life of the drug and the known excretion of monoclonal antibodies in milk.

No teratogenic or other adverse effects on embryofetal development were observed in the rat study, so the NOAEL was the HD (75 mg/kg/administration SC) at which the exposure ratio was 22.

In the pre-/postnatal development study, the incidence of stillbirth in the HD group, although higher than the concurrent control value (25% compared to 12.5%) was within historical control values reported for the laboratory (mean 14.4%, range 0-33.3%). Surviving infants at 7 days after birth were 14/20 (70%), 14/20 (70%) and 12/20 (60%). These values also lie just within the anticipated distribution of live infant numbers.[3] The only observed effect of treatment in this study was a slight attenuation of secondary anti-KLH IgG antibody response in infants of the HD group. This finding was considered of minimal toxicological significance as there was no evidence of an effect of alirocumab on the immune system in other relevant measures (clinical, histopathology or immunophenotyping) in either the pre-/postnatal study or any other study in which such testing was conducted. Overall, alirocumab was considered to be without significant toxicological effect in the pre/-postnatal study and the NOAEL was therefore the HD of 75 mg/kg/week SC, at which the exposure ratio was 80.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[4] which is considered appropriate.

Tissue Cross-reactivity

A tissue-cross reactivity study in which biotinylated alirocumab was tested for binding to cryosections of human, cynomolgus monkey and rat tissues revealed some similarities, but also a considerable number of differences, between species with respect to the staining of the various tissue elements. Results for the monkey were more similar to results for humans than were the results for the rat. The reasons for the interspecies differences are not clear, but the differences are not considered to invalidate the animal models used in the toxicity studies.

Local tolerance

No specific local tolerance studies were conducted. This is acceptable. The proposed clinical route is SC and there was no evidence of irritation at the SC injection sites (or at the IV infusion sites) in any of the repeat-dose toxicity studies (visual, macroscopic and microscopic observations).

Immunotoxicity

A specific immunotoxicity study was not conducted but 3 studies in monkeys contained an immunotoxicological assessment (the 26 week repeat-dose study, the higher dose 13 week combination study and the pre/-postnatal study). This assessment included immunophenotyping of peripheral blood lymphocytes (T lymphocytes and/or lymphocyte

[3] Jarvis *et al*. The cynomolgus monkey as a model for developmental toxicity studies: variability of pregnancy losses, statistical power estimates, and group size considerations. *Birth Defect Res (Part B).* 2010;89:175-187.
[4] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

subsets, B lymphocytes and NK cells) by flow cytometry (testing of both maternal animals and infants in the pre/-postnatal study) which did not reveal an effect of treatment, except in the13 week combination study in which a decrease in NK cells was observed in the alirocumab-treated groups, although this was not significant at the end of the study. NK cells can be detected by the CD16 marker (used in the 13 week combination study) or by the CD159a marker (used in the other two studies). NK cell cytotoxicity was unaffected in the13 week study, and since NK cell numbers and cytotoxicity are theoretically proportional, this suggested a possible interference in the detection of NK cells in this study. Study DIV1640 was therefore conducted to evaluate the potential affinity of alirocumab for CD16 (FcγRIIIA receptor) and it revealed an interaction between alirocumab and CD16 which would explain the apparent decrease in the number of NK cells in the 13-week study.

In the combination study (higher dose, 13 week), the immunotoxicity assessment also included evaluation of T cell dependent antibody response (TDAR), NK cell activity and cytotoxic T cell activity, while TDAR was evaluated in infants in the pre/-postnatal study. There were no effects of alirocumab on any of these parameters, with the exception of part of the TDAR response in infant cynomolgus monkeys in the pre/-postnatal study (discussed above). The immunotoxicological potential of alirocumab is considered to have been adequately investigated by these studies which used doses of up to 75 mg/kg/week SC and 50 mg/kg/week IV. No toxic effects of alirocumab were observed on organs of the immune system in any of the repeat-dose studies, in either rats or monkeys and there was no increase in the incidence of infection in treated animals in any of the studies. The weight of evidence suggests that alirocumab lacks immunotoxic potential.

Impurities

The company established an overall process control strategy to validate the ability of the manufacturing process to remove impurities from sources such as the expression system, leachates and media, and to remove endotoxins, bioburden and adventitious agents.

Paediatric use

Alirocumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

Nonclinical summary

- Primary pharmacology studies adequately demonstrated the mechanism of action of alirocumab (blocking the binding of PCSK9 to the LDLR and reversing PCSK9-mediated inhibition of LDL-C uptake). Alirocumab was shown to be effective in lowering serum LDL-C and total-C levels in various animal models, including rats and cynomolgus monkeys in the repeat-dose toxicity studies. Other serum lipid fractions were not consistently altered by alirocumab.
- Alirocumab did not induce ADCC or CDC, and did not form soluble immune complexes with recombinant human PCSK9 that are capable of binding to C1q.
- No secondary pharmacology or safety pharmacology studies were submitted for alirocumab but some safety pharmacology end-points (blood pressure, body temperature and ECG, including heart rate) were included in the repeat-dose toxicity studies in cynomolgus monkeys, with no significant effects noted.

- Alirocumab was cleared slowly, its volume of distribution was consistent with blood volume and its half-life was long. Bioavailability of alirocumab after SC administration was moderate to high. The pharmacokinetic profiles of alirocumab in rats and cynomolgus monkeys (the species used in the toxicity studies) were similar to that in humans.
- No single dose toxicity studies were conducted.
- Repeat-dose toxicity studies by the IV (30 minute infusion) and SC routes were conducted in rats and cynomolgus monkeys. Pivotal studies were 26 weeks duration in both species, with once weekly dosing, and used the SC route with an IV single dose level also tested. There were no toxic effects that were clearly associated with treatment. Exposure ratios at the HD were 11 in rats and approximately 100 in monkeys. The development of anti-alirocumab antibodies was not common, particularly in monkeys, and the impact of antibodies on serum alirocumab concentrations was not marked.
- Combination studies of alirocumab with atorvastatin showed more marked effects on serum lipids than with either drug given alone. Alirocumab did not exacerbate the adverse effects of atorvastatin.
- Genotoxicity and carcinogenicity studies are not normally required for monoclonal antibodies and were not conducted.
- Placental transfer of alirocumab was demonstrated in rats. An embryofetal development study in rats with SC dosing on GD6 and GD12 did not reveal any embryofetotoxic effects (exposure ratio up to 22). Alirocumab was also without effect on the offspring (observed for 6 months after birth) of cynomolgus monkeys given weekly SC doses from GD20 until parturition (exposure ratio up to 80).
- Alirocumab showed no evidence of immunotoxic potential in assessments conducted as part of three repeat-dose/reproductive toxicity studies in cynomolgus monkeys which included immunophenotyping (lymphocyte subsets, B cells and NK cells) and measurements of T-cell dependent antibody responses.
- A tissue-cross reactivity study in which biotinylated alirocumab was tested for binding to cryosections of human, cynomolgus monkey and rat tissues revealed some similarities, but also some differences, between species with respect to the staining of the various tissue elements. Results for the monkey were more similar to results for humans than were those for the rat.
- Local tolerance was not investigated in specific studies but no injection site irritation was observed in the repeat-dose toxicity studies following either SC or IV administration.

Conclusions

- The nonclinical data provided were satisfactory.
- Primary pharmacology studies adequately demonstrated the mechanism of action, and alirocumab was shown to be effective in lowering serum LDL-C and total-C levels in various animal models and in rats and cynomolgus monkeys in the repeat-dose toxicity studies.
- Secondary and safety pharmacology studies were not conducted but measurements of ECG, blood pressure and body temperature in the repeat-dose toxicity studies in monkeys revealed no effect of alirocumab.

- Adequate repeat-dose toxicity studies in rats and monkeys did not identify any target organs. Adequate to high exposure ratios were achieved (up to 11 in rats and approximately 100 in cynomolgus monkeys).
- Alirocumab did not exacerbate the adverse effects of atorvastatin when administered in combination with atorvastatin in repeat-dose toxicity studies in cynomolgus monkeys. Effects on serum LDL-C and total-C were greater than for either drug given alone.
- Genotoxicity and carcinogenicity studies were not conducted and are not required.
- An embryofetal development study in rats and a pre-/postnatal study (dosing until parturition) in cynomolgus monkeys did not reveal any adverse effects (exposure ratios achieved were 22 and 80, respectively). The sponsor has proposed Pregnancy Category B1 which is considered appropriate.
- Alirocumab showed no evidence of immunotoxic potential in assessments conducted as part of repeat-dose toxicity/reproductive toxicity studies.
- There are no nonclinical objections to registration.
- Amendments to the draft PI were recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the Western world, and an increasing burden in developing countries and in Asia. Hypercholesterolaemia, particularly increased LDL-C, constitutes a major risk factor for the development of atherosclerosis and consequently ASCVD, especially coronary heart disease (CHD). LDL-C is identified as the primary target of lipid lowering and has been accepted as a valid surrogate endpoint for CHD risk. Numerous studies have demonstrated that reducing LDL-C levels, mainly via 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibition with statins, reduces the risk of CHD, with a strong direct relationship between LDL-C levels and incidence of CHD events. A large meta-analysis (*Cholesterol Treatment Trialists' Collaborators, 2005*) of 14 randomised trials including 90,056 individuals found that for every 1.0 mmol/L reduction in LDL-C, major vascular events were reduced by about 20%. An update of this meta-analysis (*Cholesterol Treatment Trialists' Collaboration, 2010*) on nearly 170,000 individuals noted that more significant LDL-C reductions provided further CV risk reduction. The authors postulated that a 2-3 mmol/L (77-116 mg/dL) reduction in LDL-C would result in a 40-50% reduction in major vascular events.

Guidelines for the management of dyslipidaemias have evolved over time in light of evidence from statin trials, and recommend a strategy of treating to specific LDL-C goals based on patients' CV risk level. European and US guidelines both recommend high intensity treatment in patients at very high CV risk:

Europe: in patients at high cardiovascular disease (CVD) risk, an LDL-C goal< 2.6 mmol/L (< 100 mg/dL) should be considered, and in patients at very high CVD risk, the recommended

LDL-C target is < 1.8 mmol/L (< 70 mg/dL) or a ≥ 50% LDL-C reduction when the target level cannot be reached.[5,6]

USA: in the most recent guidelines, the use of high intensity statins is recommended in all high CV risk patients rather than specific LDL-C targets, to achieve a ≥ 50% LDL-C reduction, regardless of the LDL-C level.[7]

Despite the use of statins, the LDL-C targets suggested in guidelines are often not achieved and additional lipid-modifying therapies (LMTs) are needed. These are most needed for patients requiring substantial reductions in their LDL-C level, such as patients with familial hypercholesterolemia, or individuals at the highest risk of ASCVD. In addition, some patients suffer from statin side effects that limit their ability to take a statin or a high enough dose of statin to reach their LDL-C goal. Non-statin therapies include ezetimibe, nicotinic acid, bile acid sequestrants, fibrates, and high-dose omega-3 fatty acids. These medications have less LDL-C lowering efficacy compared to statins (typically provide only about a 15 to 20% reduction in LDL-C) and their actions on cardiovascular outcomes have not yet been convincingly demonstrated. There is a need for additional therapies that can have more profound effects on LDL-C, and provide corresponding CV benefit, particularly for patients who do not meet their LDL-C goals even on the highest tolerated doses of statins

Contents of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies.

The submission contained the following clinical information:

- 13 clinical pharmacology studies, including 10 that provided pharmacokinetic data and 3 that provided pharmacodynamic data.
- 3 population pharmacokinetic analyses (POH400, POH377, POH394)
- 3 dose-finding studies (DFI11565, R727-CL-1003)
- 10 pivotal efficacy/safety studies (EFC12492, R727-CL-1112, EFC12732, EFC11568, EFC11569, EFC11716, R727-CL-1118, R727-CL-1119, LTS11717)
- 3 other efficacy/safety studies (DFI11566, R727-CL-1032, DFI12361)
- 1 Integrated Summary of Efficacy and Integrated Summary of Safety (tables only)
- 6 efficacy/safety studies of which only the protocol was submitted. These studies are stated to be ongoing or planned. As there were no study reports, these protocols were not evaluated (EFC13786, R727-CL-1308, PDY13670, LTS13463, EFC13672, and EFC11570).

[5] Reiner et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European Heart Journal*. 2011;32(14):1769-1818.
[6] Perk et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *European Heart Journal.* 2012;33:1635-1701.
[7] Stone et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to reduce Atherosclerotic Cardiovascular risk in Adults. *Journal of the American College of Cardiology.* 2014;63(25):2889-2934

Paediatric data

The submission did not include paediatric data. Paediatric development programs are ongoing for Praluent and plans have been agreed with both the FDA (PSP) and the EMA (PIP).

Good clinical practice

The submission states that all studies were conducted in compliance with Good Clinical Practice (GCP), the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the sponsor, all applicable international laws and regulations as well as national laws and regulations of the country(ies) in which the studies were performed. Clinical study protocols and amendments were subject to Health Authority and Ethics Committee approvals prior to initiation as applicable and adverse events (AEs) were reported according to local laws.

Non-compliance with GCP was identified at 3 sites (2 in USA and 1 in Russia) which affected three of the pivotal studies. The sites were terminated and health authorities notified. The patients were discontinued from the study and sensitivity analysis was conducted to test for effect on the results. The non-compliance and analyses are detailed and discussed in each study.

Pharmacokinetics

Studies providing pharmacokinetic data

The following table shows the studies relating to each pharmacokinetic topic:

Table 6. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK - Single dose	PKD12010	Tolerability
		PKD12011	Tolerability
		PKD12275	Injection site tolerability
		R727-CL-0902	Tolerability IV
		R727-CL-0904	Safety
		TDU12190	Safety in Japanese
	Bioavailability - sites	BDR13362	BA
		PKD12010	Tolerability
		PKD12011	Tolerability
		PKD12275	Injection site tolerability
PK in special populations	Target population[1] - Multi-dose	R727-CL-1001 PKD12910	Safety PD/PK

PK topic	Subtopic	Study ID	Primary aim
	Hepatic impairment	POP12671	PK
	Dose finding	R727-CL-1003 DFI11565 DFI12361	Dose finding Dose finding Efficacy/Safety
PK Interactions	Atorvastatin	R727-CL-1001	Interaction
	Ezetimibe and fenofibrate	PKD12910	PD/PK
Population PK analyses	Healthy subjects and Target population	POH400 POH377 POH394	PD PK PK/PD

[1] Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

There were 3 studies conducted to investigate the bioequivalence of the formulations used in the clinical development program. None of the studies were powered to demonstrate bioequivalence and no explanation for this is provided. The studies showed only that the PK of alirocumab was similar between the 2 alirocumab cell lines, and process lots:

- between 2 different formulations 175 mg/mL and 150 mg/mL drug product forms, both produced using the C1 cell line; (Study PKD12010)
- between investigational medicinal product batches produced using 2 different cell lines (C1 and C2; Study PKD12011) and
- between the administration of the same dose with different injection volumes or number of injections: 1 injection of 2 mL of 150 mg/mL, 1 injection of 1.71 mL of 175 mg/mL or two injections of 1 mL of 150 mg/mL, each produced using the C2 cell line (Study PKD12275).

The PK profile was described by non-linear target mediated clearance and at low concentrations of alirocumab exposure increased in a greater than dose proportional manner. Upon achieving target saturation, exposure continued to increase in a linear and dose proportional manner. The concentration-time profiles of alirocumab following SC administration are characterised by an initial absorption phase followed by a bi-phasic elimination phase consisting of a linear beta elimination, followed by a terminal target mediated elimination phase.

When alirocumab is administered in combination with other LMTs known to increase the production of the target (PCSK9), an enhanced target mediated elimination phase is observed, with a more rapid clearance, compared to alirocumab administered alone. When administered using an every 2 weeks (Q2W) dosing regimen, alone or in combination with other LMTs, steady state concentrations of total alirocumab were achieved within 2 or 3 SC administrations.

The main intrinsic sources of PK variability identified in patients are age, body weight and free PCSK9, but they have a moderate effect (less than 1.6 fold). As expected for a mAb,

race, gender, and mild or moderate hepatic or renal impairment did not impact the PK of alirocumab. Because patients with severe hepatic or renal impairment were excluded from the studies, there is no data on alirocumab exposure in such patients. Patients with severe hepatic impairment were not included in the POP12671 study, justified by the observation that most of these patients have decreased lipid levels, and hypercholesterolemia is rarely observed.

The proposed Product Information (PI) is consistent with the data from the PK clinical studies conducted.

Pharmacodynamics

Studies providing pharmacodynamic data

The table below shows the studies relating to each PD topic and the location of each study summary.

Table 7. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary aim
Primary Pharmacology	Effect on LDL-C	R727-CL-1018i	PD
		PKD12910	PD
Population PD and PK-PD analyses	Healthy subjects and Target population	POH0394	PK/PD

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The clinical pharmacology data demonstrated that alirocumab decreases LDL-C, through binding and inhibition of PCSK9, which regulates LDLR. When free PCSK9 was completely bound, maximal LDL-C reductions of 55 to 70%, were observed. Higher concentrations of alirocumab did not result in further reduction of LDL-C, but resulted in a prolongation of the maximal binding of free PCSK9 and a corresponding prolongation of LDL-C reduction.

Alirocumab was designed to bind and inhibit PCSK9, a negative regulator of LDLR. This inhibition of PCSK9 by complex formation with alirocumab resulted indirectly in the increase in LDLR and a corresponding decrease in LDL-C. When PCSK9 was maximally bound, higher concentrations of alirocumab did not result in further reduction of LDL-C through this mechanism. However, increasing the dose of alirocumab prolonged the time of maximal binding of free PCSK9 with a corresponding prolongation of LDL-C reduction. With restoration of detectable concentrations of free PCSK9 and with continued increases in PCSK9 concentrations, LDL-C concentrations increase with both parameters returning to pre-treatment concentrations once alirocumab is no longer present.

As a negative regulator of LDL-R, the increase in PCSK9 induced by statins appears to limit their maximal efficacy (reduction in LDL-C). When used in combination with statins, the ability of alirocumab to inhibit PCSK9 suppresses this negative regulatory effect of statins, resulting in a further reduction of circulating LDL-C. However, the increase in PCSK9

concentrations induced by statins and other LMTs also shortened the duration of alirocumab effect through enhanced target mediated clearance. These effects were less pronounced when alirocumab was combined with other LMTs such as ezetimibe and fenofibrate.

Dosage selection for the pivotal studies

The doses and dose regimens of alirocumab tested in two Phase II dose finding studies (DFI11565 and CL-1003): 50, 100, and 150 mg Q2W, and 200 and 300 mg Q4W were selected based on the observation of dose-dependent reductions in LDL-C concentrations seen in the Study CL-1001, as well as the absence of dose-related adverse events (AEs) in Phase I studies. The dose range included doses expected to maintain maximum LDL-C lowering efficacy, based on the observed reduction of free PCSK9 concentrations in the Phase I studies.

The 150 mg Q2W dose demonstrated safety and biological activity in Phase I and Phase II studies. In the 2 dose-finding studies of 12 week treatment duration (DFI11565 and CL-1003) in patients who were also administered statins, statistically significant decreases in the percent change from baseline in LDL-C were observed in all of the alirocumab groups investigated (50 mg, 100 mg, and 150 mg Q2W; 150 mg, 200 mg, and 300 mg Q4W) compared with the placebo group; the largest decrease was seen in the 150 mg Q2W group. The 300 mg alirocumab Q4W dose also showed significant decrease in LDL-C, but the maximum treatment effect was not fully maintained over the 4 week inter-dosing interval in all of the statin-treated patients. The Q2W regimen maintained constant LDL-C lowering throughout the inter-dosing interval in all patients, regardless of the background therapy. Although found to be safe and biologically active throughout the dosing interval, the full LDL-C lowering effect of the 150 mg Q2W dose may be more than is needed to achieve individual target LDL-C in some patients, and therefore a lower initiation dose was considered using a dose-response model. Through this model, the dose of 75 mg Q2W was predicted to provide an approximately 50% decrease in LDL-C from baseline.

Efficacy

Studies providing efficacy data

The sponsor provided ten pivotal efficacy studies for each indication and they are summarised in Table 8.

Table 8. Submitted pivotal efficacy studies

Indication	Pivotal Studies
Heterozygous Familial Hypercholesterolaemia, not adequately controlled by current lipid modifying therapy	Study EFC12492 - (FH I) Study R727-CL-1112 - (FH II) Study EFC12732 (High FH)
Patients with high cardiovascular risk and hypercholesterolaemia not adequately controlled by statins and other LMT.	Study EFC11568 - (Combo I) Study EFC11569 – (Combo II) Study LTS11717 (Long Term)
Monotherapy in patients with hypercholesterolaemia and moderate	Study EFC11716 – (Mono)

Indication	Pivotal Studies
cardiovascular risk.	
Mixed hyperlipidaemia or variations of therapy	Study R727-CL-1110 – (Options I) Study R727-CL-1118 – (Options II) Study R727-CL-1119 – (Alternative)

Evaluator's conclusions on efficacy

In 8 of 10 Phase III studies described in the CTD, the dose of 75 mg Q2W was used as the initiation dose with up-titration to 150 mg Q2W after 12 weeks of treatment in patients not achieving their individual LDL-C target by Week 8, leading to 1560 patients randomised and treated with this dosing regimen. In the 2 remaining Phase III studies, the 150 mg Q2W dose was used as the initiation dose with 1,622 patients randomised and treated with this dose. This approach applied in Phase III was aiming to provide data supporting the initiation of treatment with either alirocumab 75 mg or 150 mg Q2W based on the clinical situation.

There were variable percentages of patients in each trial who up-titrated the dose from 75 mg to 150 mg Q2W (from approximately 14% to approximately 44%). The trend is for patients with higher starting LDL-C to be more likely to need up titration but this is not clear and although the sponsor suggests starting at the higher dose based on the 'individual patient characteristics and goal of therapy', it is unclear what is intended by 'patient characteristics' and it would therefore seem more prudent to start all patients at the lower dose and only increase the dose after 12 weeks if the response (to a target) is less than required. This matches what was done in the majority of trials.

The efficacy studies all had similar design and the same primary endpoint and all demonstrated reduction in the LDL-C, either as add-on to statin or as monotherapy that was superior to placebo and to ezetimibe. The 75 mg dose was associated with a mean reduction in LDL-C of approximately 45 to 50% and the 150 mg dose of approximately 60% which was sustained for 52 weeks. Long term efficacy of greater than 52 weeks is still awaiting the completion of many of the studies, including the long term safety study.

Consistent reduction in LDL-C was observed with alirocumab across age, BMI, race, baseline LDL-C levels, and patients with diabetes. LDL_C reduction was consistent regardless of which statin was concomitantly used as well as statin dose.

The effect of praluent was not as consistent on the other lipid parameters, especially triglycerides which were reduced in the comparison to placebo studies but not significantly different in the comparison to ezetimibe studies.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- 10 pivotal Phase III studies: 5 are completed (EFC11568 [COMBO I], EFC11716 [MONO], CL-1110 [OPTIONS I], CL-1118 [OPTIONS II], and the double-blind treatment period of CL-1119 [ALTERNATIVE]). The other 5 studies have completed the prespecified primary assessment period (first step analysis) but are ongoing, in order to obtain additional long-term safety information; the prespecified primary

assessment period corresponds to the individual study's cut-off date defined as the last Week 52 visit for EFC11569 (COMBO II), EFC12492 (FH I), CL-1112 (FH II), and EFC12732 (HIGH FH) and as the date when approximately 600 patients had completed the 18 month double-blind treatment period for LTS11717 (LONG TERM).

- Four completed Phase II clinical studies: 3 dose-finding studies (DFI11565, CL-1003, and DFI12361) and 2 exploratory study (DFI11566).

Patient exposure

Patient exposure in the studies submitted are summarised in the tables below.

Table 9. Number of patients in pivotal studies included in the integrated safety database

Phase	Study	Treatment group		
		Placebo	Alirocumab	Ezetimibe
Phase II				
Placebo-controlled	CL-1003	15	16[a]	
	DFI11565	31	31[a]	
	DFI11566	31	61	
	DFI12361	25	50[b]	
Total		102	158	
Phase III				
Placebo-controlled	EFC12492 (FH I)	163	322	
	CL-1112 (FH II)	81	167	
	EFC12732 (HIGH FH)	35	72	
	EFC11568 (COMBO I)	107	207	
	LTS11717 (LONG TERM)	788	1550	
Total		1174	2318	
Ezetimibe-controlled	EFC11569 (COMBO II)		479	241

Phase	Study	Treatment group		
		Placebo	Alirocumab	Ezetimibe
	CL-1110 (OPTIONS I)		104	101
	CL-1118 (OPTIONS II)		103	101
	CL-1119 (ALTERNATIVE)		126	124
	EFC11716 (MONO)		52	51
Total			864	618
Grand total		1276	3340	618

[a] Number of patients included in the alirocumab150 mg Q2W group only. [b] Number of patients included in the alirocumab 75 mg and 150 mg Q2W group.

Table 10. Exposure to investigational medicinal product - Pool of placebo-controlled studies and Pool of ezetimibe-controlled studies - (Safety population)

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Cumulative injection exposure (patient-years)	1407.6	2758.5	419.4	692.2
Duration of IMP injection exposure (weeks)				
Number	1275	2470	617	861
Mean (SD)	57.60 (22.39)	58.27 (21.86)	35.47 (21.96)	41.94 (23.09)
Median	65.10	65.10	24.00	27.30
Min : Max	2.0 : 84.9	2.0 : 84.0	2.0 : 94.1	2.0 : 93.4
Duration of IMP injection exposure by category [n (%)]				
Number	1275	2470	617	861

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
≥ 1 day to < 4 weeks	13 (1.0%)	24 (1.0%)	15 (2.4%)	21 (2.4%)
≥ 4 weeks to < 8 weeks	20 (1.6%)	54 (2.2%)	26 (4.2%)	27 (3.1%)
≥ 8 weeks to < 12 weeks	47 (3.7%)	105 (4.3%)	18 (2.9%)	15 (1.7%)
≥ 12 weeks to < 16 weeks	93 (7.3%)	111 (4.5%)	18 (2.9%)	18 (2.1%)
≥ 16 weeks to < 24 weeks	20 (1.6%)	41 (1.7%)	53 (8.6%)	59 (6.9%)
≥ 24 weeks to < 36 weeks	35 (2.7%)	66 (2.7%)	277 (44.9%)	297 (34.5%)
≥ 36 weeks to < 52 weeks	37 (2.9%)	70 (2.8%)	1 (0.2%)	15 (1.7%)
≥ 52 weeks to < 64 weeks	277 (21.7%)	576 (23.3%)	132 (21.4%)	250 (29.0%)
≥ 64 weeks to < 76 weeks	444 (34.8%)	848 (34.3%)	47 (7.6%)	95 (11.0%)
≥ 76 weeks	289 (22.7%)	575 (23.3%)	30 (4.9%)	64 (7.4%)

Placebo-controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I), Phase II (DFI11565, DFI11566, CL-1003, DFI12361). Ezetimibe-controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). The duration of IMP injection exposure in weeks is defined as: (last IMP injection date + 14 days - first IMP injection date)/7, regardless of intermittent discontinuations.

Table 11. Patient disposition (randomised population) - pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1277 N (%)	Alirocumab N=2482N (%)	Ezetimibe N=620 N (%)	Alirocumab N=864N (%)
Randomised but not treated	1 (<0.1)	6 (0.2)	2 (0.3)	0
Randomised and treated	1276 (>99.9)	2476 (99.8)	618 (99.7)	864 (100)

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1277 N (%)	Alirocumab N=2482N (%)	Ezetimibe N=620 N (%)	Alirocumab N=864N (%)
Did not complete the study treatment period (as per CRF)	214 (16.8)	435 (17.5)	128 (20.6)	155 (17.9)
Treatment ongoing	713 (55.8)	1377 (55.5)	206 (33.2)	406 (47.0)
Reason for not completing the study treatment period (as per CRF)				
Adverse event	66 (5.2)	136 (5.5)	60 (9.7)	76 (8.8)
Poor compliance to protocol	50 (3.9)	79 (3.2)	14 (2.3)	18 (2.1)
Other reasons [a]	97 (7.6)	220 (8.9)	54 (8.7)	61 (7.1)
Missing	1 (<0.1)	0	0	0

OPTIONS II, ALTERNATIVE). Note: Percentages are calculated using the number of patients randomized as denominator. Only the main reason for stopping treatment was entered in e-CRF *a* Includes patients who completed the planned treatment duration (For example patient exposed to IMP for at least 102 weeks in study COMBO II, at least 76 weeks in studies FH I, FH II, HIGH FH, LTS17117, at least 50 weeks in study COMBO I, or at least 22 weeks in studies OPTIONS I, OPTIONS II, ALTERNATIVE and MONO, with associated visit performed, or completed as per CRF in Phase II studies) but who otherwise did not fulfil the strict CRF criteria for study treatment period completion

Safety issues with the potential for major regulatory impact

Cardiovascular safety

Suspected CV events and all deaths that occurred from time of randomisation until the follow-up visit were adjudicated by a data monitoring committee in all the pivotal efficacy studies. Analyses of the adjudicated events were performed on the global pool, placebo controlled pool, and ezetimibe controlled pool. The data from the adjudication are presented below with the primary focus on major adverse cardiovascular events (MACE) coronary heart disease(CHD) death, nonfatal Myocardial Infarction (MI), fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalisation.

MACE Events

The adjudicated MACE events composite endpoint occurred in 52 (1.6%) patients in the alirocumab group and in 33 (1.8%) patients in the control group. The incidence rate (per 100 patient-years) was 1.5 and 1.8 in the alirocumab and control groups, respectively, with HR (95% CI): 0.81 (0.52 to 1.25).

Table 12. Positively adjudicated cardiovascular TEAEs: MACE EVENT - global pool of Phase III studies- safety population

Category of adjudication	Control N=1792 N (%)	Alirocumab N=3182 N (%)
Any patients with treatment emergent MACE event		
N (%)	33 (1.8)	52 (1.6%)
95% mid-p CI	1.3 to 2.5	1.2 to 2.1
Number of patients with an event per 100 patient year a	1.8	1.5
95% CI	1.2 to 2.5	1.1 to 1.9
Hazard ratio versus control (95% CI) b		0.81 (0.52 - 1.25)
CHD death (including undetermined cause)	9 (0.5)	8 (0.3)
Non-fatal MI	23 (1.3)	30 (0.9)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	3 (0.2)	12 (0.4)
Unstable angina requiring hospitalisation	1 (<0.1)	2 (<0.1)

Placebo controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). n (%) = number and percentage of patients with at least one event. [a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period. [b] calculated using a Cox model stratified on the study.

No significant study-by-treatment interaction was identified in the global pool.

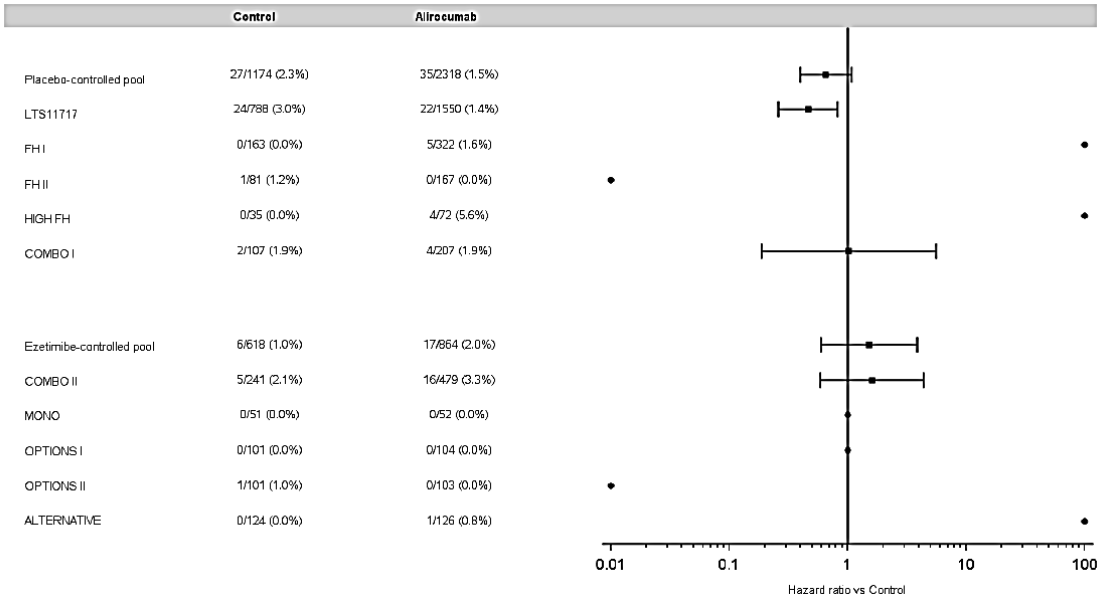
Table 13. Positively adjudicated cardiovascular TEAEs: MACE EVENT - summary table according to adjudication (safety population) - pool of Phase III placebo controlled studies and pool of ezetimibe controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
Category of adjudication	Placebo N=1174 N (%)	Alirocumab N=2318 N (%)	Ezetimibe N=618 N (%)	Alirocumab N=864N (%)
Any patients with treatment emergent MACE event				

	Placebo-controlled pool		Ezetimibe-controlled pool	
Category of adjudication	Placebo N=1174 N (%)	Alirocumab N=2318 N (%)	Ezetimibe N=618 N (%)	Alirocumab N=864N (%)
n(%)	27 (2.3)	35 (1.5)	6 (1.0)	17 (2.0)
95% mid-p CI	1.6 to 3.3	1.1 to 2.1	0.4 to 2.0	1.2 to 3.1
Number of patients with an event per 100 patient year [a]	1.9	1.3	1.3	2.3
95% CI	1.3 to 2.8	0.9 to 1.7	0.5 to 2.8	1.4 to 3.7
Hazard ratio versus control (95% CI) [b]		0.65 (0.40 to 1.08)		1.51 (0.59 to 3.85)
CHD death (including undetermined cause)	7 (0.6)	6 (0.3)	2 (0.3)	2 (0.2)
Non-fatal MI	19 (1.6)	17 (0.7)	4 (0.6)	13 (1.5)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	2 (0.2)	11 (0.5)	1 (0.2)	1 (0.1)
Unstable angina requiring hospitalisation	1 (<0.1)	1 (<0.1)	0	1 (0.1)

Placebo-controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe-controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). N (%) = number and percentage of patients with at least one event. a Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period. b calculated using a Cox model stratified on the study.

Figure 2. Positively adjudicated cardiovascular TEAEs: MACE EVENT - Forest plot of hazard ratio versus control by study (safety population) - pool of Phase III placebo controlled studies and pool of ezetimibe controlled studies



Placebo controlled studies: Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe controlled studies: Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). Studies with no event in at least one treatment group are conventionally displayed as follows: dot at HR=1 in case of no event in both groups, dot at right extremity in case of 0 event in control arm, dot at left extremity in case of 0 event in alirocumab arm.

The sponsor conclusion on this data is as follows:

'*Firm conclusions on the effect of alirocumab on CV morbidity and mortality cannot be drawn from these data. This effect on cardiovascular morbidity and mortality is being further evaluated in the ongoing OUTCOMES study. The primary endpoint of this study is adjudicated MACE events.*'

Immunogenicity

Serum samples for immunogenicity assessment were collected in all studies. The anti-Drug antibody (ADA) response was generally assessed at baseline, during the treatment, and after the last alirocumab administration.

In the clinical pharmacology studies, including healthy subjects and subjects with hypercholesterolaemia, positive low titre responses in the ADA assay were observed in a few subjects at baseline, suggesting a pre-existing reactivity. At the 75 mg dose and 150 mg dose, 22.4% and 16.7% of the subjects were positive in the ADA assay, respectively. Most of the ADA positive samples exhibited a low titre response (≤ 240), except for a few subjects who presented titres up to 1,920. However, titres diminished over time and were not associated with any specific safety findings.

Across all pivotal efficacy studies, pre-existing reactivity was observed in 1.1% of patients from the control group and 1.4% of patients from the alirocumab group. Treatment emergent positive ADA responses were observed in 4.8% of patients in the alirocumab group and in 0.6% of patients in the control group. Most of these treatment emergent ADA responses (63%) in the alirocumab group were classified as transient responses. The median time to the onset of treatment emergent ADA response was 12 weeks (first post-baseline ADA assessment in most studies) in the alirocumab group. The incidence of treatment emergent ADA response was similar according to up-titration status.

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

ADA status was not identified as a significant covariate impacting alirocumab population parameters (Study POH0377). Patients with an ADA positive status did not exhibit any difference in alirocumab exposure compared to patients that were ADA negative.

A few patients (36/3033, 1.2%) exhibited neutralising antibodies (Nab), all of them in the alirocumab group. Most of these patients had only one positive neutralising sample, indicating most patients only exhibited a transient neutralising response. When looking at the durability of this response, only 10 patients (0.3%) had 2 or more NAb positive samples. This does not suggest a correlation between NAb and LDL-C lowering efficacy or safety.

Musculoskeletal related disorders

Musculoskeletal related events have been associated with the use of statins. Musculoskeletal related events were an AE of special interest for a single study (ALTERNATIVE – R727-CL-1119) that specifically enrolled patients with documented statin intolerance. Patients had to have been intolerant based on musculoskeletal AEs to at least 2 statins, including 1 at the lowest starting dose. A control arm of atorvastatin 20 mg was included in the study and this is likely to have limited enrolment to patients willing to accept the possibility of a statin re-challenge, thus excluding patients with a history of severe reactions. It is noted that despite this criteria about 75% of the patients completed the statin arm of the study and approximately80% had not AEs.

Overall in the ALTERNATIVE study, there were fewer patients with skeletal muscle related treatment emergent adverse events (TEAEs) in the alirocumab group than the atorvastatin (Hazard ratio (HR) 0.61 [0.38 to 0.99]) or ezetimibe (HR 0.70 [0.47 to 1.06]) groups. A lower percentage of patients in the alirocumab group (15.9%) discontinued study treatment due to musculoskeletal adverse events as compared to the atorvastatin group (22.2%). Patients in the alirocumab treatment group had a longer time to first occurrence of a skeletal muscle related TEAE than patients in the atorvastatin and ezetimibe groups.

In the other trials, in the placebo-controlled pool, 15.1% patients in the alirocumab group versus 15.4% patients in the placebo group experienced a skeletal muscle related TEAE. The rate of patients who experienced a skeletal muscle related TEAE leading to permanent treatment discontinuation was 0.4% in the alirocumab group and 0.5% in the placebo group.

Safety profile in patients achieving very low LDL-C

In the global pool, a total of 1,371 (41.0%) patients treated with alirocumab had at least 1 value of LDL- C < 25 mg/dL (< 0.65 mmol/L) and 796 (23.8%) patients had 2 consecutive values of LDL-C < 25 mg/dL (< 0.65 mmol/L) or < 15 mg/dL (< 0.39 mmol/L). These mostly occurred in the studies involving only the 150 mg Q2W dose. The overall rate of patients with at least 1 TEAE, treatment emergent SAE, TEAE leading to death, and TEAE leading to treatment discontinuation was comparable between patients with 2 consecutive values of LDL-C < 25 mg/dL and 2 consecutive values of LDL-C < 15 mg/dL (< 0.39 mmol/L) and the overall alirocumab patient population, as well as the control group. No meaningful differences were observed in neurological or neurocognitive AEs between alirocumab-treated patients and alirocumab-treated patients having reached either 2 consecutive values of LDL-C < 25 mg/dL or 2 consecutive values < 15 mg/dL (< 0.39 mmol/L).

Evaluator's conclusions on safety

The safety database for alirocumab is based on a large number of patients (3,340 subjects) but because most of the studies have been reported early, after only 24 to 52 weeks on therapy, there is not a large dataset of subjects who have been treated long term. This is especially true when evaluating the cardiovascular safety and the sponsor's requests for a very broad indication including monotherapy.

No specific safety issues were identified in the clinical trials and the only expected AEs are likely to be injection site reactions, pruritus and influenza. General allergic events were more frequently reported in patients treated with alirocumab compared to the pooled control group and the most common AE was pruritus. Rare and sometimes serious allergic reactions (for example, hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis) were reported in patients taking alirocumab.

The incidence of the skeletal muscle-related AEs was similar between treatment groups (15.1% of the alirocumab group versus 15.4% of the placebo group). Alirocumab may be an option for patients with documented muscle related statin intolerance who are unwilling to attempt another course of statin therapy.

Treatment-emergent neutralising ADA occurred in 36/3,033 (1.2%) alirocumab treated patients and most events of neutralising ADA were transient and did not appear associated with loss of efficacy.

The data suggest that alirocumab is not associated with hepatic effects or muscle related AEs, which are known safety concerns associated with statins. There was no signal for neurocognitive events or worsening diabetes but the studies are not of long enough duration to conclusively exclude.

First round benefit-risk assessment

First round assessment of benefits

The benefits of alirocumab in the proposed usage are:

- Consistent lowering of LDL-C in all the studies
- No serious safety issues identified to date but long term data is limited.

First round assessment of risks

The risks of alirocumab in the proposed usage are:

- No conclusion can be made about cardiovascular benefit as the studies are too short and were not planned to investigate cardiovascular events
- Concern about the long term compliance with an injectable medication intended to be given every 2 weeks for an asymptomatic condition
- AEs of injection site reaction, pruritus and influenza
- Other potential risks of neurocognitive disorders, effects on liver enzymes, glycaemic control and ophthalmic disorders have not been excluded.

First round assessment of benefit-risk balance

The benefit-risk balance of alirocumab, given the proposed usage, is favourable.

Alirocumab has consistently demonstrated that it lowers LDL-C greater than placebo in all the clinical studies and there does not appear to be any serious safety concerns that would preclude approval.

There is however a number of crucial issues to address in considering whether alirocumab can be approved for all the indications requested.

The first issue is the approval of a new product class based solely on the efficacy endpoint of a reduction in LDL-C as the surrogate marker for a reduction in cardiovascular disease. This has generally been the accepted endpoint for cholesterol lowering studies for the lipid lowering agents currently on the market. However the statins and more recently ezetimibe have been found in long term studies after drug approval to lead to a reduction in cardiovascular disease .[8] This then raises the question as to whether a new class of products can be approved based solely on LDL-C without also demonstrating a reduction in CV events. Should a new product be approved which may be used in place of existing therapy without demonstrating the clinical benefit? This question remains controversial.

The adopted EU guideline states: *'Such studies [clinical benefit] are not foreseen for the registration of a new HMG-CoA reductase inhibitor. For other medicinal products acting on LDL-C, at least a detrimental effect on mortality and morbidity should be excluded prior to registration'*. Until clinical trial data are available, it should be specifically mentioned in the SmPC that beneficial effects on mortality and morbidity have not been evaluated.

Alirocumab is a new class of product and most of the clinical studies have not yet been completed and the long term study is only reporting the first 52 weeks of therapy (600 patients have only completed 18 months of treatment). Only the long term study is investigating the overall mortality and morbidity. A specific study is planned /underway to address cardiovascular events.

While the studies have demonstrated a consistent LDL-C lowering effect, a detrimental CV effect has not yet been excluded as the number of events to date is too low to make any firm conclusions (see Safety section). It is therefore not recommended that the product be approved for monotherapy in place of statins. It is also noted that in the statin intolerant study (R727-CL-119 ALTERNATIVE) where the inclusion criteria required patients to have documented statin intolerance to 2 different statin drugs up to approximately70% of patients were able to tolerate 24 weeks of 20 mg atorvastatain.

There has to be a serious concern about abandoning statins for a new drug which has not established long-term safety and CV benefit. The sponsor's conclusion that the data does not allow for firm conclusions means they have not meet the EU Guideline requirement to exclude a detrimental effect on mortality and morbidity.

Until a cardiovascular benefit or lack of a detrimental effect is proved alirocumab should only be recommended for approval for use in combination with 'maximally-tolerated' statin doses.

A further issue, not addressed in the submission, is the question of compliance. Compliance in the 'real world' is very difficult to measure in a clinical trial as compliance is always better in the clinical trial setting. Patients completed a dosing diary to document compliance with self-injection of study drug and generally the results were very good but it is to be expected that this would be much lower when not in a clinical study, especially given the asymptomatic nature of high cholesterol and the only every second week dosing regimen.

[8] Cholesterol Treatment Trialists' Collaboration. *Lancet* 2010;376:1670-81, and Cannon CP, et al. 2015

The warning on the lack of a demonstrated cardiovascular benefit should be included in the indication.

It is noted that this recommendation is in line with that the sponsor agreed in the USA.

First round recommendation regarding authorisation

Based on the clinical data provided in the submission it is recommended that alirocumab be approved but for an amended indication.

Until the CV benefit of alirocumab is proven and given the obvious benefit of the product in reducing LDL-C, it is recommended that alirocumab is approved only for those patients at highest risk, that is, familial hypercholesterolaemia and proven cardiovascular disease on maximal existing statin therapy, and the indication be strictly in line with the conditions of the clinical studies in the submission, that is, that the indication should be:

> '*Alirocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolaemia or documented atherosclerotic cardiovascular disease*.'

Approval of the other indications sought for example dyslipidaemia, combination with non-statins and other lipid lowering therapy should await the completion of the studies to document no detrimental effect and/or to demonstrate a clinical benefit.

Clinical questions

No clinical questions were raised.

The sponsor has provided a number of documents relevant to the clinical evaluation addressing the issues raised in the first round evaluationDetails of sponsor's responses are contained in Attachment 2

Second round benefit-risk assessment

The benefit-risk balance of alirocumab, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Based on the data submitted in response to the first round evaluation report it is recommended that alirocumab be approved for the following indication:

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,

- alone or in combination with other lipid-lowering therapies in patients who have documented atherosclerotic cardiovascular disease and are statin-intolerant, or for whom a statin is contraindicated

The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP (Version: 1.0, dated 31 October 2014) with an Australian Specific Annex (ASA) Version: 1.0, dated 5 May 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 14

Table 14. Summary of safety concerns and missing information for Praluent's risk Management Plan.

Important identified risks	
Important potential risks	Cataract (in context of very low LDL-C*) Neurocognitive disorders
Missing information	Use in children and adolescents Use in pregnant and lactating women Use in patients with severe hepatic impairment Long-term use (>5 years) Clinical impact of very low LDL-C* for extended periods of time Use in chronic hepatitis C virus (HCV) carrier/hepatitis Influence of alicuromab on gonadal steroid hormones and gonadotropins (in men and women)

* For example less than 25mg/dL(0,65 mmol/L).

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information. The ASA states: *'No additional pharmacovigilance activities are proposed in this RMP'.*

In addition, the EMA website provides the following additional information (Table 15) from the EU-RMP (Version: 1.2), which is not captured in Table 2: 'Required additional pharmacovigilance activities (Category 3) - Ongoing studies as of 31-Aug-2014' of the EU-RMP:

Table 15. Required additional pharmacovigilance activities (Category 3) - Ongoing studies as of 31-Aug-2014' of the EU-RMP

Study/activity Type, title and category	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
LTS14580 (post-ODYSSEY OUTCOMES registry study (PASS): prospective registry	Evaluate safety in long term use (> 5 years) Evaluate potential clinical impact of very low LDL-C for extended period of time Include a specific neurocognitive evaluation Evaluate the influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)	Safety in long term use (> 5 years) Clinical impact of very low LDL-C for extended period of time Neurocognitive disorders Circulating gonadal steroid hormones and gonadotropins levels measured in both men and women	planned	Q3 2022 (Final report)
A PASS in patients infected with HIV	Gather relevant safety data in patients infected with HIV	Safety data in patients infected with HIV	planned	Q2 2016 (protocol submission)
A trial with a dedicated prospective assessment of neurocognitive function	Prospective assessment of neurocognitive function using a neurocognitive battery of tests	Evaluate neurocognitive disorders considered as potential risk	planned	Q2 2016 (protocol submission)
Drug utilisation survey	To assess the effectiveness of dosing recommendation as per labelling	Clinical impact of very low LDL-C for extended period of time	planned	Q2 2016 (protocol submission)

*Stands for date of final report, dates updated as of 8 May 2015; ACS: acute coronary syndrome; ADH: autosomal dominant hypercholesterolaemia; CV: cardiovascular; heFH: heterozygous familial hypercholesterolaemia; LDL-C: low density lipoprotein – cholesterol; LMTs: lipid modifying therapy; non-FH: non-familial hypercholesterolaemia; OLE: open label extension; Q2W: once in 2 weeks; Q4W: once in 4 weeks; HIV human immunodeficiency virus; PASS: post-authorisation safety study. Q=quarter

Risk minimisation activities

Routine risk minimisation activities will comprise labelling, including pharmacokinetic information, precautionary statements, instructions for use and/or notification of undesirable effects for all the specified safety concerns and missing information. The ASA states: *'No additional risk minimisation activities are proposed in this RMP'*.

Reconciliation of issues outlined in the RMP report

Table 16 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.

Table 16. Summary of first round evaluation of the RMP

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
It is drawn to the Delegate's attention that the wording of the indications approved by the EMA for Praluent are different to those sought for in Australia. Section 1.2: 'Regulatory History' and Section 1.3: 'Indication' of the ASA should be updated accordingly, including identifying and explaining any differences between the indications in Australia and the EU.	The sponsor has now agreed to revise the proposed indication to somewhat align with the indication approved in EU, which is to some extent consistent with the recommendations of the Autralian Committee on the Safety of Medicines (ACSOM), and has now been reflected in the ASA.	The clinical evaluator has recommended different wording for the Australian indications to include '*patients who have documented atherosclerotic cardiovascular disease*' and to note: '*the effect of Praluent on cardiovascular morbidity and mortality has not yet been determined*'. This is consistent with the recommendations of the ACSOM and is drawn to the Delegate's attention for consideration. If the Delegate decides to amend the approved indications as recommended, then Section 1.3: '*Indication'* of the

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
		ASA should be revised accordingly, preferably before this application is approved, including identifying and explaining any differences between the indications in Australia and the EU.
The sponsor should clarify whether the US FDA required clinical trials have been included in the Pharmacovigilance Plan in the ASA, and if not why not.	The sponsor states: '*The ASA is now aligned to the EU-RMP version 1.3, and adequately reflects the planned Pharmacovigilance Plan, including the 2 above described ongoing or planned clinical trials that also address the FDA PMRs*'. The FDA post-marketing requirements referred to are serious risks of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity and changes in neurocognitive function. In regard to the serious risk of adverse foetal, infant, and childhood outcomes related to humoral immune suppression, the sponsor proposes as a commitment to provide the TGA with the final report of the prospective observational study of pregnant women	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	exposed to alirocumab to evaluate fetal, infant, and childhood outcomes through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-foetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The estimated date for the availability of the final report is December 2030.	
Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor states: '*The sponsor confirms that the Nonclinical and Clinical Evaluation Reports have been reviewed to ensure that any responses provided to issues raised have been considered for relevance to the Risk Management Plan*'.	Section 16.3: 'Second round comments on clinical aspects of the Safety Specification in the draft RMP' of the CER states inter alia: '*The role of the clinical evaluation is to provide advice to the RMP evaluator as to whether the Safety Specification in the proposed RMP matches the risks identified in the clinical studies. For a new product it is important that all risks are identified and accounted for in the RMP until usage data becomes available. The identified risks were all identified in the CSR and Summaries and*

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
		while they may be found in the future to be not significant side effects at this stage of the clinical experience of the product safety has not been proven and it is reasonable to be conservative and identify these additional risks'. Therefore despite the sponsor's justification and based on clinical advice it is reiterated that the important potential risks: '*Effects of liver enzymes*', '*Glycaemic control*' and '*Ophthalmic disorders*' should be included as new safety concerns. Consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for these new safety concerns and the ASA must be revised accordingly before this application is approved.
Consistent with the EU-RMP (Version: 1.2), which has been endorsed by the CHMP, the sponsor should include the important potential risks: '*Cataract (in context of very low LDL-C)*' and '*Neurocognitive*	The sponsor states: '*The ASA has been updated to align with the approved EU-RMP v1.3 and now includes all of the above mentioned risks and missing information and*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
disorders'; and the missing information: '*Long-term use (> 5 years)*', '*Clinical impact of very low LDL-C for extended period of time*', '*Use in chronic hepatitis C virus (HCV) carrier/hepatitis*' & '*Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)*' as new safety concerns. Consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for this new safety concerns and the ASA must be revised accordingly.	*the associated pharmacovigilance plan (see also QUESTION 6) and risk minimisation activities*'.	
Consistent with the US FDA '*Postmarketing Requirements'*, the important potential risks: '*Adverse foetal, infant, and childhood outcomes related to humoral immune suppression'* & '*New-onset diabetes mellitus*' should be included as new safety concerns or compelling justification for such omission should be provided. Consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for these new safety concerns and only the ASA need be revised accordingly.	The sponsor has provided justification for not including the important potential risk: '*Adverse foetal, infant, and childhood outcomes related to humoral immune suppression'* as a new safety concern. Alternatively the sponsor proposes to use a Pregnancy and Neonatal form as routine pharmacovigilance for the missing information: '*Use in pregnant and lactating women*' and has made other commitments as per its response to *Recommendation 2.* The sponsor has provided justification for not including the important potential risk: '*New-onset diabetes mellitus*' as a	This is acceptable. See comments as per *Recommendation 3.*

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	new safety concern.	
As previously stated consideration must be given as to what pharmacovigilance activities will be proposed for the new important potential risks and the missing information alluded to in Section 7. To that end the sponsor should at least include the above additional pharmacovigilance activities observed in the EU-RMP (Version: 1.2) and the US FDA required clinical trials, or provide compelling justification for such omission. The ASA should be revised accordingly and it is expected that at least draft protocols for these planned studies will be attached to the revised ASA. If these protocols are not yet available the sponsor should provide an assurance that they will be submitted to the TGA once they become available.	See response to Recommendations 4 and 5.	See comments as per Recommendation 3 and 4.
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the first sentence under the heading: '*What Praluent is used for*' in the draft consumer medicine information document be revised to: *'Praluent contains the active substance alirocumab, a protein produced in Chinese*	The sponsor states: '*The CMI has been revised to include that alirocumab protein is made using Chinese hamster ovary cells. Please see revised CMI*'.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
hamster ovary cells'. This is consistent with the draft PI and will alert patients who have a known allergy to proteins derived from this source.		

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

It was drawn to the Delegate's attention that the wording of the indications approved by the EMA for Praluent was different to those sought for in Australia. The sponsor has now agreed to revise the proposed indication to somewhat align with the indication approved in EU, which is to some extent consistent with the recommendations of the ACSOM, and has now been reflected in the ASA. Nevertheless the clinical evaluator has recommended different wording for the Australian indications to include '*patients who have documented atherosclerotic cardiovascular disease*' and to note: '*the effect of Praluent on cardiovascular morbidity and mortality has not yet been determined*'. This is consistent with the recommendations of the ACSOM and is drawn to the Delegate's attention for consideration. If the Delegate decides to amend the approved indications as recommended, then Section 1.3: '*Indication*' of the ASA should be revised accordingly, preferably before this application is approved, including identifying and explaining any differences between the indications in Australia and the EU.

The sponsor was asked to respond to safety considerations raised by the nonclinical and clinical evaluators in the context of relevance to the RMP. The sponsor states: '*The sponsor confirms that the Nonclinical and Clinical Evaluation Reports have been reviewed to ensure that any responses provided to issues raised have been considered for relevance to the Risk Management Plan*'. However, Section 16.3: 'Second round comments on clinical aspects of the Safety Specification in the draft RMP' of the CER states: '*The role of the clinical evaluation is to provide advice to the RMP evaluator as to whether the Safety Specification in the proposed RMP matches the risks identified in the clinical studies. For a new product it is important that all risks are identified and accounted for in the RMP until usage data becomes available. The identified risks were all identified in the CSR and Summaries and while they may be found in the future to be not significant side effects at this stage of the clinical experience of the product safety has not been proven and it is reasonable to be conservative and identify these additional risks*' (see below). Therefore despite the sponsor's justification and based on clinical advice it is reiterated that the important potential risks: 'Effects of liver enzymes', 'Glycaemic control' and 'Ophthalmic disorders' should be included as new safety concerns. Consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for these new safety concerns and the ASA must be revised accordingly before this application is approved.

In regard to the proposed routine risk minimisation activities, it was recommended by the ACSOM to the Delegate that the draft product information document be amended as follows:

- Neurocognitive effects should be mentioned in the Product Information (PI), as part of the risk minimisation activities.

- The committee noted the nomination of alirocumab for Category B1 of the Australian categorisation system for prescribing medicines in pregnancy. The justification for this categorisation was unclear: alirocumab is expected to cross the placental barrier; there is no evidence of safety in pregnancy; the results of a US Food and Drug Administration (US FDA) mandated study on the potential safety signals of adverse pregnancy outcomes and embryo-fetal growth and development is outstanding; and, there is some evidence to suggest possible adverse events in pregnancy due to humoral immune suppression.
- Reference in the PI to an outcome based on '*post-hoc interim analysis*' should be removed from the PI. It could be misleading to inform health practitioners of a halved rate of major adverse cardiovascular disease, based on a post-hoc interim analysis, when the European regulator has recently concluded that the effect of alirocumab on cardiovascular morbidity and mortality has not yet been determined.

In regard to the proposed routine risk minimisation activities, it was recommended by the ACSOM to the Delegate that the draft consumer medicine information document be amended as follows:

- The committee noted that no information has been provided in the Consumer Medicine Information (CMI) on self-injection technique. Specific written information should complement training from a healthcare professional, as a one-off training session is not likely to be sufficient to ensure competence and adherence. There are models for providing information for patients who self-administer injectable medicines regularly (For example for diabetes) or rarely (for example, for anaphylaxis). Written information for patients should include:
  - pictorial representation of the procedure for injection
  - specific advice about sites for injection, and potential rotation of sites
  - advice concerning infection control measures - hand washing, skin preparation, disposal of sharps
  - specifics of injection technique
  - recognition of any injection related complications.

Any changes to the proposed routine risk minimisation activities negotiated with the Delegate should be accurately reflected in a revised ASA, preferably before this application is approved.

The sponsor has submitted the document: '*RISK MANAGEMENT PLAN CHANGE HISTORY*' as separate from the ASA. The sponsor should include the information in this document in a revised ASA as per Section1.3: 'History of RMPs submitted in Australia' of the ASA template (as found on the TGA website as of 4 May 2015). It is noted that Part VI.2.7. '*Summary of changes to the Risk Management Plan over time'* of the EU-RMP does not document the changes from Version: 1.0 to Version: 1.3.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

Background

Alirocumab is a fully human monoclonal antibody (IgG1 isotype) that targets pro-protein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the major pathway through which cholesterol-rich low-density lipoprotein (LDL) particles are cleared from circulation and hepatic LDL uptake is a major determinant of circulating low-density lipoproteins cholesterol (LDL-C) levels, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting

the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

The proposed indications for this medicine in Australia are:

> *Praluent is indicated, as adjunct therapy to diet, for long-term use in adult patients with primary hypercholesterolaemia (non-familial and heterozygous familial) or mixed dyslipidaemia, to reduce low-density lipoprotein cholesterol (LDL-C).*
>
> *Praluent also decreases other atherogenic lipid parameters, such as total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), and lipoprotein (a) [Lp(a)]. Praluent also increases high-density lipoprotein cholesterol (HDL-C).*
>
> *Praluent is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT), in patients not appropriately controlled with a statin.*
>
> *Praluent is indicated as monotherapy, or as add-on to other non-statin LMT, in patients who cannot tolerate statins.*

In September 2015 the European Medicines Agency authorised the use of alirocumab for the following indications:

> *Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:*
>
> - *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
> - *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*
>
> *The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.*

The recommended dose for alirocumab is 75 mg or 150 mg administered subcutaneously once every two weeks. The patient may self-inject the medicine after guidance has been provided by a healthcare professional on proper subcutaneous injection technique. Maximum LDL-C reduction is usually achieved after four weeks.

The committee noted the following safety concerns:

- Important identified risks: immunogenicity; systemic hypersensitivity reactions
- Important potential risks: none
- Missing information: use in children and adolescents; use in pregnant and lactating women; use in patients with severe hepatic impairment.
- The committee noted that there are ongoing studies to assess if there is an effect of alirocumab on cardiovascular mortality.

In addition to the information presented in the agenda papers, the committee referred to papers by Robinson et al[9] and Poirier et al[10], and recent professional guidelines.[11]

The committee provided advice on specific questions asked by the TGA relating to the RMP.

Advice

The committee was concerned that the proposed indication is very broad and for high prevalence conditions, while the safety and efficacy of alirocumab is not yet fully characterised.

The safety of use of alirocumab is likely to be improved if its use is restricted to people at high absolute risk of serious cardiovascular disease, rather than for treatment of cholesterol levels as such. The recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that there are no data that support treatment or titration to a specific LDL-C goal for secondary prevention in adults with clinical atherosclerotic cardiovascular disease.

The committee endorsed the wording of the European indication which refers to patients at 'the maximum tolerated dose of a statin' (with respect to both prescribing of the maximum tolerated doses, and adherence to therapy), and that this should be in place prior to the introduction of another agent.

The committee also endorsed the wording of the European indication which states that '*the effect of Praluent on cardiovascular morbidity and mortality has not yet been determined*', as this reflects the current state of knowledge.

1. Does the committee agree that the specified summary of safety concerns and missing information should be amended as follows?

Consistent with the EU-RMP (Version: 1.2), the sponsor should include the important potential risks: '*Cataract (in context of very low LDL-C)*' and '*Neurocognitive disorders'*; and the missing information: '*Long-term use (> 5 years)*', '*Clinical impact of very low LDL-C for extended period of time*', '*Use in chronic hepatitis C virus (HCV) carrier/hepatitis'* and '*Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)*' as new safety concerns.

Consistent with the US FDA '*Postmarketing Requirements'*, the important potential risks: '*Adverse foetal, infant, and childhood outcomes related to humoral immune suppr*ession' and '*New-onset diabetes mellitus'* should be included as new safety concerns or compelling justification for such omission should be provided.

The committee agreed with the proposed amendments to the summary of safety concerns based on updated information from the sponsor and the regulatory approvals of alirocumab in Europe and the United States of America (USA).

The clinical impact of inhibition of PCSK9 for an extended period of time needs to be considered and differentiated from the maintenance of low LDL-C levels for an extended period of time.

[9] Robinson JG, Farnier M, Krempf M, et al. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. *N Engl J Med* 2015; 372:1489-99. doi: 10.1056/NEJMoa1501031
[10] Poirier S, Prat A, Marchinkiewicz E, et al. Implication of the proprotein convertase NARC-1/PCSK9 in the development of the nervous system. *J Neurochem* 2006; 98:838-50.
[11] 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults - A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129: S1-S45 doi: 10.1161/01.cir.0000437738.63853.7a

The committee noted that the 'missing information' does not include numerous population groups or co-morbidities that had been excluded from clinical trials but will not be contraindicated if the product is approved.

2. Can the committee comment on whether any further ongoing safety concerns are considered necessary, and if so what pharmacovigilance and risk minimisation activities may be proposed for these new safety concerns?

Having agreed in Q1 that '*Neurocognitive disorders'* is an important potential risk, the committee highlighted that Robinson et al[12] identified neurocognitive effects in 1.2% of patients taking alirocumab, compared to 0.5% of patients taking placebo, with all patients also receiving statin therapy at the maximum tolerated dose and/or with other lipid modifying therapy. While neurocognitive events, by definition consist of deliria; cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; and mental impairment disorders, Robinson et al specifically identified amnesia, memory impairment and confusional states. The committee noted that it is unknown if these effects are long-term permanent neurocognitive effects, or if the effects are reversible over time or on discontinuation of alirocumab.

The committee also noted work that implicates PCSK9 in the development of the nervous system[13] and that another monoclonal antibody targeting PSCK9, evolocumab, also has concerning signals with regard to neurocognitive events.[14]

Therefore, the committee advised that neurocognitive effects should be addressed by a prospective pharmacovigilance study of sufficient duration, with defined outcomes and formal neurocognitive testing, and be designed to address the possibility that patients with neurocognitive effects will be overrepresented in patients lost to follow-up. A patient survey would be insufficient to address the concern on neurocognitive effects.

Neurocognitive effects should be mentioned in the Product Information (PI), as part of the risk minimisation activities.

The committee noted the nomination of alirocumab for Category B1 of the Australian categorisation system for prescribing medicines in pregnancy. The justification for this categorisation was unclear: alirocumab is expected to cross the placental barrier; there is no evidence of safety in pregnancy; the results of a US Food and Drug Administration (US FDA) mandated study on the potential safety signals of adverse pregnancy outcomes and embryo-fetal growth and development is outstanding; and, there is some evidence to suggest possible adverse events in pregnancy due to humoral immune suppression.

The committee noted that the number of participants in the clinical program to date would only likely have detected adverse events with a frequency of at least 1 in 1000 and more rare adverse effects may be undetected. Given the proposed broad indications and potential for widespread use in the Australian population, the possibility of rare adverse events emerging with time is likely.

The committee noted that no information has been provided in the Consumer Medicine Information (CMI) on self-injection technique. Specific written information should complement training from a healthcare professional, as a one-off training session is not likely to be sufficient to ensure competence and adherence. There are models for

[12] Robinson et al. Efficacy and Safety of Alirocumab in reducing Lipids and Cardiovascular Events. *N Eng J Med.* 2015;372:1489-1499.
[13] Poirier et al. The biology of PCSK9 from the endoplasmic reticulum to lysosomes: new and emerging therapeutics to control low-density lipoprotein cholesterol. *Drug Des Devel Ther*. 2013;7:1135-1148.
[14] Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. *N Engl J Med* 2015;372:1500-9. doi: 10.1056/NEJMoa1500858

providing information for patients who self-administer injectable medicines regularly (for example, for diabetes) or rarely (for example, for anaphylaxis). Written information for patients should include:

- pictorial representation of the procedure for injection
- specific advice about sites for injection, and potential rotation of sites
- advice concerning infection control measures; hand washing, skin preparation, disposal of sharps
- specifics of injection technique
- recognition of any injection related complications.

Other

Reference in the PI to an outcome based on '*post-hoc interim analysis'* should be removed from the PI. It could be misleading to inform health practitioners of a halved rate of major adverse cardiovascular disease, based on a post-hoc interim analysis, when the European regulator has recently concluded that the effect of alirocumab on cardiovascular morbidity and mortality has not yet been determined.

The committee noted the European approval of alirocumab relied on Version 1.2 of the RMP, rather than Version 1.0 as provided in the committee's agenda papers.

Key changes to the updated RMP

In their response to the TGA the sponsor

provided an updated EU-RMP (Version 1.3, dated 23 September 2015) with an updated ASA (Version 1.1, dated 18 December 2015).[15] Key changes from the previous versions evaluated are summarised in Table 17:

Table 17. Key changes to EU-RMP and ASA

Document	Key changes
EU-RMP	Part VI.2.7. 'Summary of changes to the Risk Management Plan over time' does not document the changes from Version: 1.0 to Version: 1.3, but erroneously states: *'Not applicable'.*
ASA	Updated as part of response to TGA recommendations and to align with EU-RMP v1.3 Update to sub-sections 1.2 Regulatory History and 1.3 Indication Section 4 – Risk Management Plan New Important Potential Risks: - Cataract (in the context of very low LDL-C*) - Neurocognitive Disorders New Important Missing Information: - Use in patients with chronic HCV carrier/hepatitis

[15] The sponsor addressed a number of the issues raised by the TGA and ACSOM including the provision of a patient support video based on the instructions for use. The video is designed to be available through a QR code link from the carton or via a patient support website.

Document	Key changes
	- Long-term use (> 5 years) - Clinical impact of very low LDL-C (ie, less than 25mg/dL (0.65mmol/L)) for extended period of time - Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women) Additional Pharmacovigilance Activities included to align with EU-RMP - Four post-authorisation safety studies (PASS) to evaluate safety of long term use of alirocumab prospective registry As part of routine surveillance, a 'specific pregnancy/drug exposure via parent data collection form' is used to document spontaneous or solicited cases of pregnancy exposed to alirocumab. Changes to section summarising ongoing and planned clinical trials Update to Annex 1 - Revised 'Product Information (PI)' Update to Annex 2 - Revised 'Consumer Medicines Information (CMI)'

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator had no objection to the approval of alirocumab. The following was noted during the evaluation of the quality aspects of this submission:

Alirocumab is produced by expression in Chinese Hamster Ovary cells using proprietary cell expression technologies. Purification and formulation of alirocumab consists of a series of steps including particulate filtration, impurity removal, two chromatography steps, reduction of potential viral contaminants, and the addition of excipients to the sucrose-adjusted concentrated/diafiltered pool to product the drug substance. This material is dispensed and stored frozen and transported to the drug manufacturing site for filling into pre-filled syringes.

Alirocumab is manufactured without the direct use of animal-derived raw materials.

Alirocumab is a colourless to pale yellow liquid with a nominal pH of 6.0. The excipients in the formulation are histidine, sucrose polysorbate 20 and water for injection.

The stability data support a shelf-life of 14 months at 2 to 8°C. The formulation is not photostable.

Nonclinical

The nonclinical evaluator had no objection to the approval of alirocumab. A summary of the findings of the nonclinical evaluation is as follows:

- The primary pharmacology studies demonstrated that alirocumab blocks the binding of PCSK9 to the LDL receptor and reverses the PCSK9-mediated inhibition of LDL-C uptake.
- Alirocumab was shown to be effective in lowering serum LDL-C and total cholesterol levels in animal models including rats and monkeys. Other serum lipid fractions were not consistently altered by alirocumab.
- Alirocumab in combination with atorvastatin showed more marked effects on serum lipids than either drug alone. Alirocumab did not exacerbate the adverse effects of atorvastatin.
- Single dose toxicity studies were not conducted but repeat dose toxicity studies did not identify any target organs in rats and monkeys. No specific local tolerance studies were conducted but no injection site irritation was seen in repeat-dose toxicity studies with SC or IV injection.
- Alirocumab did not induce antibody-dependent cell-mediated or complement-dependent cytotoxicity. There was no evidence of immunotoxic potential in monkeys including in B cells and NK cells and measurements of T-cell dependent antibody responses). The development of anti-alirocumab antibodies was not common, particularly in monkeys, and antibodies had no marked impact on serum alirocumab concentrations.
- Genotoxicity and carcinogenicity studies were not conducted but adequate justification was provided for this approach.
- Alirocumab crossed the placenta in rats. No embryo-foetal toxicity was demonstrated in rat offspring, or in cynomolgus monkey offspring exposed to alirocumab from gestational day 20 until birth and observed for the first 6 months of infancy. The evaluator supported the sponsor's proposed Pregnancy Category B1.

Clinical

The clinical evaluator recommended approval for the following indication:

> *Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non- familial) or mixed dyslipidaemia, as an adjunct to diet:*
>
> - *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
> - *alone or in combination with other lipid-lowering therapies in patients who have documented atherosclerotic cardiovascular disease and are statin-intolerant, or for whom a statin is contraindicated*

The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.

The clinical dossier comprised:

- 13 clinical pharmacology studies, including 10 PK studies and 3 PD studies
- 3 population pharmacokinetic analyses (POH400, POH377, POH394)
- 3 dose finding studies (DFI11565, R727-CL-1003 and DF12361)
- 10 Phase III efficacy and safety studies (EFC12492, R727-CL-1112, EFC12732, EFC11568, EFC11569, EFC11716, R727-CL-1118, R727-CL-1119, LTS11717)
- 3 other efficacy/safety studies (DFI11566, R727-CL-1032, DFI12361)
- 1 Integrated Summary of Efficacy and Integrated Summary of Safety
- Protocols for 6 additional efficacy/safety studies underway or planned

Pharmacology

The pharmacology studies noted the following findings:

Pharmacokinetics

- The absolute bioavailability of alirocumab after SC administration was about 85%.
- The site of injection (abdomen, upper arm or thigh) did not substantially affect the PK of a single 75 mg dose of alirocumab.
- Median Tmax was 3 – 7 days
- Cmax, but not AUC increased, in a dose-proportional manner. Alirocumab AUC was slightly more than dose proportional but the deviation from linearity was modest in healthy subjects and in patients a 2.1 to 2.7 fold increase in Cmax and 2.3 to 2.5 fold increase in AUC 0-336 with a 2-fold increase in dose.
- Steady state was reached in 2 – 3 doses. The median accumulation ratio was 1.7 and 1.9 after alirocumab 75 mg and 150 mg Q2W respectively and was similar to that predicted from single-dose healthy volunteer studies. There was no difference between monotherapy and combinations with other lipid modifying therapies.
- The Vd was 0.04 to 0.05 L/kg.
- Metabolism was assumed to be by degradation into small peptides and individual amino acids. Based on the PopPK analysis the elimination of alirocumab was characterised by saturable (non-linear) target mediated clearance at lower concentrations but becomes more linear with increasing dose. Having achieved target saturation, exposure continued to increase in a linear and dose proportional manner.
- In patients receiving statins the apparent half-life over the dosing interval was 12 days, and in monotherapy the median half-life was 17 to 20 days. The co-administration of statins increases production of PCSK9 and thus increasing the target-mediated clearance of alirocumab.
- Single dose alirocumab had similar PK in patients with mild-moderate hepatic impairment and healthy subjects. The absorption kinetics were similar and there was a non-significant shift towards faster elimination in the hepatic impaired groups. The peak percent LDL-C decrease in the hepatic impairment groups (33.2% for mild and 35.8% in moderate hepatic impairment) was slightly less than in healthy subjects (peak decrease 45.4%).

- The large molecular weight of alirocumab impedes glomerular filtration, and it was considered that renal function is unlikely to significantly impact the PK of alirocumab but this was not specifically studied. In the PopPK analysis renal function was not a significant covariate when controlling for body weight and age.
- The main sources of intrinsic variability were age, body weight and free PSCK9 (but the effects of these variables is modest (<1.6 fold).
- The PopPK model showed a first order absorption form the injection site to the central compartment, from which there were two elimination process – 1 linear (representing catabolic clearance) and one non-linear (giving an overall non-linear picture). Clearance was decreased 78% in patients weighing 50 kg and increased in patients weighing 100 kg. In the typical 82.9 kg patient clearance via the linear pathway increased 52% when alirocumab was co-administered with a statin.
- Target mediated drug disposition modelling showed inter-individual variability ranged from 23.7% to 71.5%, depending on the parameter estimated. The central compartment was 1.56 fold larger in patients (mainly on statins) compared with healthy volunteers (mainly no statins).
- Baseline total PCSK9 (1.77 fold increase in EC50) and baseline high impact statin (20.6% increase versus no statin) were important for the modelled effective concentration of alirocumab.
- Use of the prefilled syringe or the autoinjector pen resulted in comparable steady state Cmax and AUCs

Pharmacodynamics:

- The PD of alirocumab is governed by saturable PCSK9 (target) binding.
- Alirocumab reduced free PCSK9 concentrations in a dose-dependent manner. When alirocumab is in excess and free PCSK9 is depleted any newly formed PCSK9 is immediately complexed. With the elimination of PCSK9-alirocumab complex being relatively slow compared to formation further increases in dose result in a plateau of total PCSK9 concentration.
- Q2W and Q4w dosage regimens result in the reduction in free PCSK9. The 75 mg Q2W dose approached target saturation and there was a marginal increase in total PCSK9 resulting from up titration to 150 mg Q2W.
- By binding with PCSK9 alirocumab with the subsequent increase in LDLR indirectly reduces LDL-C. In single dose studies LDL-C was consistently reduced in doses ranging from 50 mg to 300 mg maximum mean percent reductions of 40 to 50% occurred between Days 15 and 22. At the highest doses the maximum reduction occurred earlier and was sustained for longer.
- The PK/PD relationships between alirocumab and LDL-C can results in a clockwise hysteresis loop. By augmenting PCSK9 production statins resulted in a horizontal compression of the relationship possibly because the decrease of maximal systemic concentrations of alirocumab from statin-induced increases in PCSK9 production and the resulting downstream increase in alirocumab clearance suggested in consistent with the PopPK finding that statins, but not ezetimibe or fenofibrate, are an important factor in the clearance of alirocumab. The net effect with statins is a further reduction of circulating LDL-C, although the duration of effect was reduced because of enhanced target-mediated clearance.
- The dose selection studies tested 50, 100, and 150 mg Q2W and 200 mg and 400 mg Q4W dosing. Although the 300 mg Q4W dose showed significant LDL-C reduction the effect was not sustained over the 4 week interval. The largest sustained reduction

occurred in the 150 mg Q2W dosing but this exceeded the target saturation in some individuals. A dose-response model predicted 75 mg Q2W would provide an LDL-C reduction of about 50% from baseline.

Efficacy

Ten Phase III studies were provided in the submission to support the proposed indication. Because the study designs were similar for each of the proposed patient groups included in the indication, the studies will be briefly described The CER should be referred to for the key secondary endpoints and additional details regarding the baseline characteristics of patients in each of the studies.

Study EFC12492- (FH I)– A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 [Alirocumab] in Patients with Heterozygous Familial Hypercholesterolaemia Not Adequately Controlled With Their Lipid Modifying Therapy.

This was an interim analysis to Week 52 of this multinational, multicentre study conducted over 3 periods for a total duration of 89 weeks (3 week screening, 78 week double-blind, 8 weeks follow-up). The study included 486 patients aged ≥ 18 years with HeFH not adequately controlled on maximally tolerated statin (atorvastatin, rosuvastatin or simvastatin) and/or other LMT. It excluded patients with a LDL-C < 1.81 mmol/L; on fibrates other than fenofibrate within 6 weeks of enrolment; using a nutraceutical that may affect lipids within 4 weeks of enrolment; patients with unstable cardiovascular disease or requiring interventions (for example, PCI or CABG) and newly diagnosed or unstable diabetics (HbA1C > 9%). There was a 2:1 randomisation to alirocumab SC by auto-injector to the abdomen, thigh or outer upper arm (n=323) or placebo (n=163). All alirocumab patients commenced with 75 mg SC Q2W from week 0 to 12, then were up-titrated to 150 mg SC Q2W if the Week 8 LDL-C was ≥ 1.81 mmol/L up, but otherwise continued on 75 mg Q2W. The Week 12 dose was continued up to the last dose at Week 76. An interim analysis of this study was provided to include data to Week 52. Premature discontinuations occurred in about 11% of each treatment arm, with discontinuations due to AEs in 4.9% of the placebo arm and 3.7% of the alirocumab arm. Baseline characteristics were similar between the two patient groups: patients had a mean (SD) age of 52 years (13), were mostly male (56%), and White (91%), and 83% were taking statins. The mean baseline LDL-C was 3.711 (1.3) mmol/L. While all had high or very high CV risk, 46% had coronary heart disease. The study had a > 95% power to detect a difference in mean percent change in LDL-C of 30% with a 0.05 two-sided significant assuming a standard deviation of 25%. To allow for drop-outs over the duration of the study and regulatory considerations the sample size was 471.

The primary endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population (mixed effects model with repeat measures analysis):

- Week 24 Least squares mean (SE)% change from baseline in alirocumab group: -48.8 (1.6)%
- Week 24 Least squares mean % change from baseline versus placebo: -57.9% (95% CI: -63.3 to -52.6) p<0.0001

The key secondary endpoints were numerous and included reductions in LDL-C at Week 12 and Week 52, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details.

Up-titration occurred in 135 patients, with the following results:

Table 18 Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patients alirocumab group Study FH I

n up-titrated	% change from baseline LDL-C Week 12 up-titrated mean (SD)	% change from baseline LDL-C Week 24 up-titrated mean(SD)	% change from baseline LDL-C Week 12 non up-titrated mean (SD)	% change from baseline LDL-C Week 24 Non up-titrated mean(SD)
135	-34.9% (25.9)	-51.5% (27.1)	-51.5% (27.1%)	-48.9 (26.1%)

Reductions in LDL-C at Week 24 were maintained at Week 52.

R727-CL-1112-(FH II)- A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolaemia Not Adequately Controlled with Their Lipid Modifying Therapy.

This was an interim analysis to Week 52 of this multicentre, multinational (European) study in 249 adult patients conducted over 3 periods for a total duration of 88 weeks (2 week screening, 78 week double-blind, 8 weeks follow-up). At the end of the study participants will be eligible to transition to a long term extension study (LTS13463, not included in the submission).The inclusion and exclusion criteria, efficacy variables and analysis populations were the same as study EF12492. There was a 2:1 randomisation to alirocumab SC by auto-injector to the abdomen, thigh or outer upper arm (n=167), or placebo (n=81). All alirocumab patients commenced with 75 mg SC Q2W from Week 0 to 12, then were up-titrated to 150 mg SC Q2W if the Week 8 LDL-C was ≥ 1.81 mmol/L up, but otherwise continued on 75 mg Q2W. The Week 12 dose was continued up to the last dose at Week 76. Baseline characteristics were similar between the groups. The mean age (SD) was 52(13) years, most were male (53%), and White (98%). The mean baseline calculated LDL-C was 3.5 (1.1) mmol/L and 88% were taking statins. Premature discontinuations occurred in 3.7% and 6.6% of the placebo and alirocumab groups, respectively, with 1.2% and 3.0% of the discontinuations of the placebo and control groups due to AEs. The power of the study was similar to study FH I and the calculation was based on the same assumptions.

The primary endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population (mixed effects model with repeat measures analysis):

- Week 24 Least squares mean (SE)% change from baseline in alirocumab group: -48.7 (1.9)%
- Week 24 Least squares mean % change from baseline versus placebo: -51.4% (95% CI: -58.1 to -44.8) p<0.0001

The key secondary endpoints were numerous and included reductions in LDL-C at Week 12 and Week 52, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details.

Up-titration occurred in 61 patients, with the following results:

Table 19. Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patients alirocumab group Study FH II

N up-titrated	% change from baseline LDL-C Week 12 up-titrated mean (SD)	% change from baseline LDL-C Week 24 up-titrated mean(SD)	% change from baseline LDL-C Week 12 non up-titrated mean(SD)	% change from baseline LDL-C Week 24 Non up-titrated mean(SD)
61	-37.4% (25.5%)	-54.1% (28.4%)	-49.3%(17.7%)	-46.1% (26.9%)

Reductions in LDL-C at Week 24 were maintained at Week 52.

EFC12732 (High FH)- A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 in Patients with Heterozygous Familial Hypercholesterolaemia and LDL-C Higher or Equal to 160 Mg/Dl with Their Lipid Modifying Therapy.

This was an interim analysis to Week 52 of this multinational, multicentre study conducted over 3 periods for a total duration of 89 weeks (3 week screening, 78 week double-blind, 8 weeks follow-up). The inclusion criteria were the same as studies EFC12492 and R7272-CL-1112 but exclusion criteria limited the study to patients with a baseline LDL-C ≥ 4.14 mmol/L. The study design and randomisation was the same as Studies EFC12492 and R7272-CL-1112, but the study treatment was 150 mg alirocumab (n= 72) or placebo SC Q2W (N=35) by auto-injector pen. The background LMT was managed similarly to the previous studies until Week 24 when therapy could be modified if TG or LDL-C reached threshold levels. The efficacy variables and analysis populations were the same as the previous studies (FH I and FH II). Baseline characteristics were similar at baseline although more alirocumab patients had CHD risk equivalents (9.0% alirocumab and 4.9% placebo). The mean patient age was 51 (13) years, 53% were male and 88% were White. The mean baseline LDL-C was 5.1 (1.4) mmol/L and 79% were taking statins. The sample size was based on the rationale for study FH I. Premature discontinuations occurred in 17.1% of the placebo group (2.9% due to AEs) and 20.8% of the alirocumab group (4.2% due to AEs). Protocol violations caused the closure of 2 sites, and major protocol deviations were reported for 13.9% of the alirocumab group and 5.7% of the placebo group.

The primary endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population (mixed effects model with repeat measures analysis):

- Week 24 Least squares mean (SE)% change from baseline in alirocumab group: -45.7 (3.5)%
- Week 24 Least squares mean % change from baseline versus placebo: -39.4% (95% CI: -51.1 to -27.1), p<0.0001

The key secondary endpoints were numerous and included reductions in LDL-C at Week 12 and Week 52, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details. Triglycerides, HDL-C and Apo-A1 were not statistically significantly different from placebo.

Reductions in LDL-C at Week 24 were maintained at Week 52.

EFCI1568 – (Combo I) A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Lipid Modifying Therapy.

This multicentre, study was conducted over 3 periods for a total duration of 62 weeks (2 week screening, 52 week double-blind, 8 weeks follow-up) in the US. The study included 316 patients aged ≥ 18 years with hypercholesterolaemia and established coronary heart disease (CHD) or CHD risk equivalents not adequately controlled on maximally tolerated statin ± LMT, but excluded patients with known homozygous or heterozygous familial hypercholesterolaemia, those not on a stable dose of LMT for at least 4 weeks and/or fenofibrate for at least 6 weeks, those taking a statin other than simvastatin, atorvastatin or rosuvastatin; recent (within 3 months) MI, unstable angina leading to hospitalisation, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularisation, endovascular procedure or surgical intervention for peripheral vascular disease; newly diagnosed (within 3 months) or poorly controlled diabetes (HbA1c >8.5%). There was a 2:1 randomisation to alirocumab SC by auto-injector to the abdomen, thigh or outer upper arm (n=209), or placebo (n=107). All alirocumab patients commenced with 75 mg SC Q2W from Week 0 to 12, then were up-titrated to 150 mg SC Q2W if the Week 8 LDL-C was ≥ 1.81 mmol/L but otherwise continued on 75 mg Q2W. The Week 12 dose was continued up to the last dose at Week 50. Baseline characteristics were similar between the groups, the mean age was 63 years, 66% were male and 82% were White. About 99% had at least one cardiovascular risk factor or history (all categorised as very high CV risk). The mean calculated LDL-C was 2.6(0.8) mmol/L and 63% were taking statins. A sample size of 45 patients had a 95% power to detect a difference in mean percent change in LDL-C of 30% with a 0.05 two-sided significant assuming a standard deviation of 25%. To allow for drop-outs over the duration of the study and to increase the safety set the sample size was increased to 306. Premature discontinuations occurred in 29.9% of the placebo group (7.5% due to AEs) and 24.4% of the alirocumab group (6.2% due to AEs). Major protocol deviations occurred in 17.7% of the alirocumab group and 16.8% of the placebo group (mostly missing assessment values). Of those 1.9% of the alirocumab group and 0.9% of the placebo group had no LDL-C value in the Week 24 window and were excluded from the intention-to-treat (ITT) population. The remainder were included.

The primary endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population (mixed effects model with repeat measures analysis):

- Week 24 Least squares mean (SE)% change from baseline in alirocumab group: - 48.2 (1.9)%
- Week 24 Least squares mean % change from baseline versus placebo: -45.9% (95% CI: -52.5 to 39.3) p<0.0001

The key secondary endpoints were numerous and included reductions in LDL-C at Week 12 and Week 52, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details. Triglycerides were not statistically significantly different from placebo.

Up-titration occurred in 32 patients, with the following results:

Table 20. Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patients alirocumab group Study Combo I

N up-titrated	% change from baseline Week 12 up-titrated mean (SD)	% change from baseline Week 24 up-titrated	% change from baseline Week 12 non up-titrated mean (SD)	% change from baseline Week 24 Non up-titrated
32	-25.3(26.6)	-50.2 (32.5)	-52.2 (22.0)	-49.5 (26.3)

Reductions in LDL-C at Week 24 were similar at Week 52.

EFC11569 – (Combo II) A Randomised, Double Blind, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Versus Ezetimibe in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Statin Therapy.

This was an interim analysis to Week 52 of this multinational, multicentre study conducted over 3 periods for a total duration of 112 weeks (3 week screening, 104 week double-blind, 8 weeks follow-up). The study included 720 patients aged ≥ 18 years with hypercholesterolaemia and established coronary heart disease (CHD) or CHD risk equivalents not adequately controlled on maximally tolerated statin ± LMT. The exclusion criteria were the same as the Combo I study. There was a 2:1 randomisation to alirocumab SC Q2W by auto-injector to the abdomen, thigh or outer upper arm (n=479), or ezetimibe 10 mg daily (n=241). Randomisation was stratified according to prior history of MI or ischaemic stroke (Yes/No), statin treatment (high intensity statin, as defined by atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily; versus simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily) and geographic region. All alirocumab patients commenced with 75 mg SC Q2W from Week 0 to 12, then were up-titrated to 150 mg SC Q2W if the Week 8 LDL-C was ≥ 1.81 mmol/L but otherwise continued on 75 mg Q2W. The Week 12 dose was continued up to the last dose at Week 102. Baseline characteristics were similar between the groups. The mean age was 62 years, most (74%) were male, 85% were White and 90% had CHD. Baseline calculated LDL-C was 2.8 (0.9) mmol/L and 69% were taking statins. A sample size of 96 patients had a 95% power to detect a difference in mean percent change in LDL-C of 20% with a 0.05 two-sided significant assuming a standard deviation of 25%. To allow for drop-outs over the duration of the study and to increase the safety set the sample size was 660. Premature discontinuations occurred in 14.5% of the ezetimibe group (5.4% due to AEs) and 15.2% of the alirocumab groups (7.5% due to AEs). Major protocol deviations occurred in 14.8% of the alirocumab group and 13.3% of the placebo group (mostly missing assessment values). Of those 2.5% of the alirocumab group and 0.4% of the placebo group had no LDL-C value in the Week 24 window and were excluded from the ITT population. The remainder were included.

The primary endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population (mixed effects model with repeat measures analysis):

- Week 24 Least squares mean (SE)% change from baseline in alirocumab group: -50.6(1.4)%
- Week 24 Least squares mean % change from baseline versus ezetimibe: -29.8% (95% CI: -34.4 to -25.3) p<0.0001

The key secondary endpoints were numerous and included reductions in LDL-C at Week 12 and Week 52, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C,

lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details. Triglycerides were not statistically significantly different from ezetimibe.

Up-titration occurred in 82 patients, with the following results:

Table 21. Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patients alirocumab group Study Combo II

N up-titrated	% change from baseline Week 12 up-titrated mean (SD)	% change from baseline Week 24 up-titrated	% change from baseline Week 12 non up-titrated mean (SD)	% change from baseline Week 24 Non up-titrated
82	-30.1 (33.5)	-42.5(33.7)	-57.6 (19.9)	-54.7 (24.3)

Reductions in LDL-C at Week 24 were similar at Week 52.

LTS11717 - (Long Term) A Randomised, Double Blind, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Versus Ezetimibe in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Statin Therapy.

This was a primary safety study and the efficacy variables were secondary endpoints. This was an interim analysis of this multinational, multicentre, study conducted over 3 periods for a total duration of 86 weeks (3 week screening, 78 week double-blind, 8 weeks follow-up). The study included 2343 patients aged ≥ 18 years with HeFH with or without established CHD or CHD risk equivalents, or patients with hypercholesterolaemia with established CHD or CHD risk equivalents not adequately controlled on maximally tolerated statin for at least 4 weeks prior to screening ± LMT. There was a 2:1 randomisation to alirocumab SC Q2W by pre-filled syringe to the abdomen, thigh or outer upper arm (n=1553), or placebo (n=788). Randomisation was stratified by HeFH, prior history of acute or silent MI or ischemic stroke, statin treatment (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily, versus simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily) and geographic region. All alirocumab patients received with 150 mg SC Q2W. Baseline characteristics were well matched between the groups. The mean age was 61 years, most were male (62%), and White (93%). The majority (69%) had a history of CHD, and 46% had coronary revascularisation procedures. The mean calculated LDL-C was 3.2 (1.1) mmol/L and 47% were taking statins. The sample size was based on safety. A sample size of 1400 alirocumab treated allows detecting AEs with a rate ≥0.002 with 95% confidence. An alirocumab ophthalmology substudy of 270 patients with 25% discontinuation in 1 year had 95% confidence to detected ophthalmological events with a true occurrence of 0.021 and 0.024. Premature discontinuations occurred in 18.5% of the placebo patients (5.6% due to AEs) and 20% of the alirocumab patients (6.3% due to AEs). Major protocol deviations occurred in 15.3% of the alirocumab group and 15.6% of the placebo group (mostly missing assessment values). Of those 1.5% of the alirocumab group and 1% of the placebo group had no LDL-C value in the Week 24 window and were excluded from the ITT population. The remainder were included.

The primary efficacy outcome was the percent change from baseline in LDL-C at Week 24 in the ITT population.

- Week 24 Least squares mean (SE)% change from baseline in alirocumab group: -61.0(0.7)%
- Week 24 Least squares mean % change from baseline versus ezetimibe: -61.9% (95% CI: -64.3 to -59.4) p<0.0001

For the key secondary endpoints were numerous and included reductions in LDL-C at Week 12 and Week 52, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details. Triglycerides, and HDL-C were not statistically significantly different from placebo.

Reductions in LDL-C at Week 24 were similar at Week 52.

EFC11716 – (Mono) A Randomised, Double Blind, Active Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Over 24 Weeks in Patients with Hypercholesterolaemia

This multicentre, multinational study was conducted over 3 periods for a total duration of 22 weeks (2 week screening, 24 week double-blind, 8 weeks follow-up). The study included 103 patients aged ≥ 18 years with LDL-C 2.59 to 4.91 mmol/L and moderate CV risk (10 year risk of fatal CV disease ≥ 1% and <5%) but excluded patients with established CHD or CHD risk equivalents transient ischaemic attacks (TIAs) or ischaemic stroke or significant carotid artery disease; patients with diabetes mellitus (DM) associated with a risk SCORE ≥5% or with any additional risk factor. Use of other LMT was not permitted during the study. Baseline characteristics were similar between the groups, and the mean age was 60 years, 53% were male and 90% were White. None had a history of CHD. The mean (SD) calculated baseline LDL-C was 3.7 (0.7) mmol/L and 10% had previously taken statins). There was a 1:1 randomisation to alirocumab SC by auto-injector to the abdomen, thigh or outer upper arm (n=52), or ezetimibe 10 mg daily (n=51). All alirocumab patients commenced with 75 mg SC Q2W from Week 0 to 12, then were up-titrated to 150 mg SC Q2W if the week 8 LDL-C was ≥ 2.59 mmol/L but otherwise continued on 75 mg Q2W, however there was a serious error and patients were up-titrated with a LDL-C of ≥ 1.8 mmol/L. The Week 12 dose was continued up to the last dose at Week 24. A sample size of 45 patients per arm had a 95% power to detect a difference in mean percent change in LDL-C of 20% compared with ezetimibe with a 0.05 two-sided significant assuming a standard deviation of 25%. To allow for drop-outs over the duration of the study, 5% exclusions from the mITT the total sample size of 50 per arm. Premature discontinuations occurred in 13.7% of the ezetimibe group (7.8% due to AES) and 15.4% of the alirocumab group (9.6% due to AEs). Major protocol deviations occurred in 28.8% of the alirocumab group and 17.6% of the placebo group (mostly missing assessment values). No patients were excluded from the ITT population but 5.8% of the alirocumab group and 9.8% of the ezetimibe group had no LDL-C value in the Week 24 window.

The primary efficacy outcome was the percent change from baseline in LDL-C at Week 24 in the ITT population.

- Week 24 LS Mean change from baseline (SE)%: -47.2 (3.0)%
- Week 24 LS Mean change difference from ezetimibe: -31.6 (95% CI: -40.2 to -23.0), p<0.0001

The key secondary endpoints were numerous and included reductions in LDL-C at Week 12, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in

subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details. Results for lipoprotein (a), fasting triglycerides and HDL-C did not reach statistical significance.

Up-titration occurred in 14 patients, with the following results:

Table 22. Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patients alirocumab group Study Mono

N up-titrated	% change from baseline Week 12 up-titrated mean (SD)	% change from baseline Week 24 up-titrated	% change from baseline Week 12 non up-titrated mean (SD)	% change from baseline Week 24 Non up-titrated
14	-49.2 (10.1)	-50.6 (11.7)	-54.9 (14.7)	-55.5 (15.1)

R727-CL-1110 – (Options I) A Randomised, Double Blind Study of the Efficacy and Safety of Alirocumab Added to Atorvastatin Versus Ezetimibe Added on to Atorvastatin Versus Atorvastatin Dose Increase Versus Switch to Rosuvastatin in Patients who are Not Controlled on Atorvastatin.

This multicentre, multinational study in to evaluate the reduction of LDL-C by alirocumab as add-on therapy to atorvastatin in comparison with ezetimibe as add-on therapy to atorvastatin, in comparison with doubling the atorvastatin dose, or in comparison with a therapy switch from atorvastatin to rosuvastatin. The study was conducted over 3 periods for a total duration of 32 weeks (option 4 week single-blind run in atorvastatin 20 or 40 mg period for patient not established on atorvastatin, 24 week double-blind, 8 weeks follow-up). Baseline characteristics were similar across all the groups. The mean age was 63 years, most were male (66%) and white (82%). The mean calculated LDL-C was 2.7(0.9) mmol/L. The study randomised 355 patients aged ≥ 18 years with a LDL-C≥ 1.81 mmol/L, documented CHD, non-CHD CVD or diabetes with target organ damage, OR LDL-C ≥ 2.59 mmol/L without documented CHD or non-CHD CVD but with other risk factors; and established CHD or non-CHD CVD but a calculated 10 year fatal CVD risk SCORE ≥ 5% or moderate CKD or diabetes but no target organ damage, AND inadequate LDL-C control on stable doses of atorvastatin (20 or 40 mg daily) ± LMT (not ezetimibe). Exclusion criteria included Homozygous FH, taking a statin other than atorvastatin 20 mg or 40 mg; taking ezetimibe within 4 weeks of screening; not on a stable dose of allowable LMT (excluding ezetimibe) for at least 4 weeks and/or fenofibrate for at least 6 weeks prior to the screening.

Randomisation was to 1 of 7 treatment arms to the following groups, according to their baseline atorvastatin dose:

1. Patients on atorvastatin 20 mg baseline regimen
   a. Alirocumab + atorvastatin 20 mg + placebo for ezetimibe (n=57)
   b. Atorvastatin 40 mg + placebos for alirocumab and ezetimibe(n=57)
   c. Atorvastatin 20 mg + ezetimibe 10 mg + placebo for alirocumab 75 mg Q2W (n=55)
2. Patients on atorvastatin 40 mg baseline regimen
   a. Alirocumab + atorvastatin 40 mg + placebo for ezetimibe (n=47)

b. Atorvastatin 80 mg + placebos for alirocumab and ezetimibe (n=46)

c. Rosuvastatin 40 mg + placebos for alirocumab and ezetimibe (n=45)

d. Atorvastatin 40 mg + ezetimibe 10 mg + placebo for alirocumab 75 mg Q2W (n=47)

Randomisation in equal proportions ratio was to 1 of the above treatment groups. At Week 12 up titration to alirocumab 150 mg Q2W was based on the Week 8 LDL-C and baseline CV risk (up titration threshold ≥ 1.8 mmol/L for high risk group and ≥ 2.59 mmol/L for lower risk group.The Week 12 dose was continued up to the last dose at Week 22.

Five pairwise comparisons of alirocumab benefit to multiple control groups were hypothesised for the primary efficacy analysis: a sample size of 50 patients per group would have 90% power to detect a difference in means of at least 20% in any 1 pairwise comparison (that is, alirocumab mean = 50% and control mean = 30%), assuming that the common SD was 25% using an independent group t-test. The alpha level for each of the 5 pairwise comparisons was adjusted to a 2-sided alpha level of 0.01, thereby maintaining an overall study alpha level of 0.05. Premature discontinuations in 22.8%/27.3%/19.3% of the atorvastatin 40 mg/ atorvastatin 20 mg + ezetimibe 10 mg/ alirocumab+atorvastatin 20 mg patients on the atorvastatin 20 mg baseline regimen, and in 17%/13.3%/12.8%/19.1% of the atorvastatin 80 mg/rosuvastatin 40mg/ezetimibe 10 mg+ atorvastatin 40mg/alirocumab +atorvastatin 40 mg groups on the atorvastatin 40 mg baseline regimen. Of these 7.0%/5.5%/8.8% the atorvastatin 40 mg/ atorvastatin 20 mg + ezetimibe 10 mg/alirocumab+atorvastatin 20 mg patients on the atorvastatin 20 mg baseline regimen and 6.4%/2.2%/2.1%4.3% atorvastatin 80 mg/rosuvastatin 40mg/ezetimibe 10 mg+ atorvastatin 40mg/alirocumab +atorvastatin 40 mg groups on the atorvastatin 40 mg baseline regimen were due to AEs. Major protocol deviations occurred in 18.0% that resulted in exclusion of 2.8% from the ITT population, and 4.2% from the on-treatment analysis.

The primary endpoint was the LS mean (SE) LDL-C from baseline to week 24 (ITT analysis) were as follows:

1. Atorvastatin 20 mg baseline group

   d. alirocumab + atorvastatin 20 mg group: -44.1 (4.5)%

   e. atorvastatin 40 mg: -5.0 (4.6)%

   f. atorvastatin 20 mg + ezetimibe 10 mg: -20.5(4.7)%

   g. LS mean change differences:

      i. alirocumab + atorvastatin 20 mg versus atorvastatin 40 mg

      ii. -39.1%; 99% CI [-55.9 to -22.2]; p<0.0001

      iii. alirocumab + atorvastatin 20 mg versus atorvastatin 20 mg + ezetimibe 10 mg

      -23.6%; 99% CI [-40.7 to -6.5]; p=0.0004)

2. Atorvastatin 40 mg baseline group

   h. Atorvastatin 80 mg: -4.8 (4.2)%

   i. Rosuvastatin 40 mg: -21.4 (4.2)%

   j. Ezetimibe 10 mg + atorvastatin 40 mg: -22.6 (4.3)%

   k. Alirocumab + atorvastatin 40 mg: -54 (4.3)%

l. LS mean change differences:

iv. alirocumab + atorvastatin 40 mg versus atorvastatin 80 mg

v. -49.2 %, 99% CI [-65.0 to-33.5]; p<0.0001

vi. alirocumab + atorvastatin 40 mg versus rosuvastatin 40 mg

vii. -32.6 %, 99% CI [-48.4to -16.9]; p<0.0001

viii. alirocumab + atorvastatin 40 mg versus atorvastatin 40 mg + ezetimibe 10mg

-31.4%, 99% CI [-47.4to -15.4]; p<0.0001

Key secondary endpoints were numerous and included reductions in LDL-C at Week 12 and Week 52, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details.

13 patients had their dose up-titrated and the results are as follows:

Table 23. Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patients alirocumab group Study Options I

Study arm	N up-titrated	% change from baseline Week 12 up-titrated mean (SD)	% change from baseline Week 24 up-titrated	% change from baseline Week 12 non up-titrated mean (SD)	% change from baseline Week 24 Non up-titrated
Atorvastatin 20 mg	4	-41.3(38.3)	-9.9 (112.8)	-55.2 (21.5)	-54.7(21.9)
Atorvastatin 40 mg	9	-25.4 (41.1)	-32.1 (65.2)	-58.8 (18.1)	-60.0 (23.1)

R727-CL-1118 – (Options II) A Randomised, Double Blind, Study of the Efficacy and Safety of REGN727 Added-on to Rosuvastatin Versus Ezetimibe Added-on to Rosuvastatin Versus Rosuvastatin Dose Increase in Patients who are Not Controlled on Rosuvastatin.

This multinational, multicentre, study was conducted over 3 periods for a total duration of 36 weeks (4 week single-blind run in placebo-only period, 24 week double-blind, 8 weeks follow-up). The study randomised 305 patients aged ≥ 18 years with hypercholesterolaemia (HeFH and non-FH) and who had established CHD or non CHD CVD or who were at high risk for CVD due to other risk factors, with LDL-C levels that were not adequately controlled with a 10 mg or 20 mg daily dose of rosuvastatin, with or without other LMT, except ezetimibe. Exclusion criteria included LDL-C < 1.8 mmol/L and with documented CHD or non-CHD CVD, or LDL-C <2.59 mmol/L with documented CHD or non-CHD CVD but other risk factors, homozygous FH, currently taking a statin other than rosuvastatin 10 mg or 20 mg daily.

Randomisation was to 1 of 6 treatment regimens.

1. Rosuvastatin 10 mg baseline regimen:
   a. Alirocumab 75 mg SC Q2W, rosuvastatin 10 mg QD, and placebo ezetimibe QD
   b. Placebo alirocumab SC Q2W, rosuvastatin 20 mg QD, and placebo ezetimibe QD
   c. Placebo alirocumab SC Q2W, rosuvastatin 10 mg QD, and ezetimibe 10 mg QD
2. Rosuvastatin 20 mg baseline regimen:
   a. Alirocumab 75 mg SC Q2W, rosuvastatin 20 mg QD, and placebo ezetimibe QD
   b. Placebo alirocumab SC Q2W, rosuvastatin 40 mg QD, and placebo ezetimibe QD
   c. Placebo for alirocumab SC Q2W, rosuvastatin 20 mg QD, and ezetimibe 10 mg QD

All alirocumab patients commenced with 75 mg SC Q2W from week 0 to 12, then were up-titrated to 150 mg SC Q2W if the week 8 LDL-C was ≥ 1.81 mmol/L patients with heFH or non-FH, and a history of documented CHD or CVD, or other risk factors, OR if LDL-C > 2.59 mmol/L if HeFH or non-FH, but with other risk factors and who had LDL-C ≥100 mg/dL (2.59 mmol/L) but otherwise continued on 75 mg Q2W. The Week 12 dose was continued up to the last dose at Week 22. Baseline demographics were comparable. The mean age was 61 years and the mean (SD) calculated LDL-C was 2.9 (1.) mmol/L; most were male (61%) and White (84%).

A sample size of 47 patients per arm had a 90% power to detect a difference in means of 20% in any of the four pair-wise comparisons with a 0.05 two-sided significant assuming a standard deviation of 25%. The α was adjusted to 0.0125 to maintain the overall α of 0.05. Premature discontinuations occurred in 10.4%/29.2%/22.4% of the rosuvastatin 20 mg/ rosuvastatin 10 mg + ezetimibe 10 mg/ alirocumab+ rosuvastatin 10 mg patients on the rosuvastatin 10 mg baseline regimen, and in 15.1%/17.0%24.1% of the rosuvastatin 40mg/ezetimibe 10 mg+ rosuvastatin 20 mg /alirocumab + rosuvastatin 20 mg groups on the rosuvastatin 20 mg baseline regimen patients. Of those 4.2%/12.5%/6.1% rosuvastatin 20 mg/ rosuvastatin 10 mg + ezetimibe 10 mg/ alirocumab+ rosuvastatin 10 mg patients on the rosuvastatin 10 mg baseline regimen, and 5.7%/3.8%/3.7% rosuvastatin 40mg/ezetimibe 10 mg+ rosuvastatin 20 mg /alirocumab + rosuvastatin 20 mg groups on the rosuvastatin 20 mg baseline regimen were due to AEs. Major protocol deviations occurred in 26.2% % of the alirocumab group, 12.9% of the double-dose rosuvastatin group and 21.8% of the ezetimibe group (mostly missing assessment values). None were excluded from the ITT population.

The primary endpoint was the LS mean (SE) LDL-C from baseline to week 24 (ITT analysis) were as follows:

- Rosuvastatin 10 mg baseline group
  - alirocumab + rosuvastatin 10 mg group: -50.6(4.2)%
  - rosuvastatin 20 mg: -16.3 (4.1)%
  - rosuvastatin 10 mg + ezetimibe 10 mg: -14.4(4.4)%
  - LS mean differences from baseline :
    - alirocumab + rosuvastatin 10 mg versus rosuvastatin 20 mg
    - -34.2%, 99% CI [-49.2 to -19.3]; p<0.0001
    - alirocumab + rosuvastatin 10 mg versus ezetimibe 10 mg + rosuvastatin 10 mg

- -36.1%, 99% CI [-51.5 to -20.7]; p<0.0001

- Rosuvastatin 20 mg baseline group
  - Rosuvastatin 40 mg: -15.9 (7.1)%
  - Ezetimibe 10 mg + rosuvastatin 20 mg: -11.0 (7.2)%
  - Alirocumab + rosuvastatin 20 mg: -36.3 (47.1)%
  - LS mean differences:
    - alirocumab + rosuvastatin 20 mg versus rosuvastatin 40 mg
    - -20.3%, 99% CI [-45.8 to 5.1]; p=0.045
    - alirocumab + rosuvastatin 20 mg versus ezetimibe 10 mg + rosuvastatin 20 mg
    - -25.3%, 99% CI [-50.9 to 0.3]; p=0.014 (not significant at 0.0125 level)

Key secondary endpoints were numerous and included reductions in LDL-C at Week 12, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details. Results for Apolipoprotein- A, fasting triglycerides and HDL-C did not reach statistical significance.

Seventeen patients had their alirocumab dose up-titrated and the results are as follows:

Table 24. Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patient alirocumab group Study Options II

Study arm	N up-titrated	% change from baseline Week 12 up-titrated mean (SD)	% change from baseline Week 24 up-titrated	% change from baseline Week 12 non up-titrated mean (SD)	% change from baseline Week 24 Non up-titrated
Rosuvastatin 10 mg	7	-38.5 (13.4)	-51.9 (12.2)	-56. (17.8)	-53.1 (26.9)
Rosuvastatin 20 mg	10	-7.7 (26.9)	-20.8 (64.6)	-44.7(28.8)	-45.8(26.6)

R727-CL-1119 – (Alternative) A Randomised, Double Blind, Double Dummy, Active Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients with Primary Hypercholesterolaemia who are Intolerant to Statins.

An analysis to Week 24 of the double-blind period of this multinational, multicentre study that was conducted over 3 periods for a total duration of 32 weeks (4 week single-blind run in placebo-only period, 22 week double-blind, 8 weeks follow-up) was included in the submission. An open-label period is to follow the double-blind period. The study

randomised 314 patients aged ≥ 18 years with hypercholesterolaemia (HeFH and non-FH) and moderate, high or very high CV risk, either statin intolerant (see Appendix 1 for definition) or not able to tolerate a weekly statin dose of 7 times the lowest approved table size. Exclusion criteria included LDL-C < 1.8 mmol/L and very high CV risk, LDL-C < 2.59 mmol/L and high or moderate CV risk, 10 year fatal CVD risk score < 1%, a skeletal muscle-related AE (not strain/trauma) prior to randomisation. Baseline characteristics were similar across the groups. The mean age was 63 years, with patients mostly male (55%) and White (94%). Across the study 56% patients had a cardiovascular history or risk factors and 51% of the alirocumab group had CHD. The mean (SD) calculated LDL-C was 5.0 (1.8) mmol/L, and 43% were taking background LMT other than statins and none were taking ezetimibe.

Randomisation in a 2:2:1 ratio was to 1 of 3 treatment groups (alirocumab SC Q2W (n=126), ezetimibe 10 mg daily (125) or atorvastatin 20 mg daily (n=63)). All alirocumab patients commenced with 75 mg SC Q2W from Week 0 to 12, then were up-titrated to 150 mg SC Q2W if the week 8 LDL-C was ≥ 1.81 mmol/L but otherwise continued on 75 mg Q2W. The Week 12 dose was continued up to the last dose at Week 22. A sample size of 84 patients had a 95% power to detect a difference in mean percent change in LDL-C of 20% with a 0.05 two-sided significant assuming a standard deviation of 25%. To allow for drop-outs over the duration of the study and to increase the safety set the sample size was increased to 250. Major protocol deviations occurred in 18.3% of the alirocumab group, 17.5% of the atorvastatin group and 20% of the ezetimibe group (mostly missing assessment values). Of those 1.6% of the atorvastatin group and 2.4% of the ezetimibe group had no LDL-C value in one of the analysis windows up to Week 24 window and were excluded from the ITT population, and 2.4%/5.6%/4.8% of the alirocumab/ezetimibe/atorvastatin groups were excluded from the modified intention-to-treat (mITT) population because of no LDL-C value in the efficacy period and within one of the analysis windows up to Week 24 window. Premature discontinuations occurred frequently in this study: 33.3%/33.6%/23.8% of the atorvastatin/ezetimibe/alirocumab groups discontinued prematurely, 25.4%/24.8%/18.3% because of AEs.

The primary analysis was of alirocumab versus ezetimibe. The sponsor did not plan formal statistical analyses from the alirocumab versus atorvastatin and ezetimibe versus atorvastatin citing expected high rates of discontinuation (introduced bias). The atorvastatin arm was a re-challenge arm.

The primary endpoint was the LS mean (SE) LDL-C from baseline to week 24 (ITT analysis) were as follows:

- Ezetimibe 10 mg -14.6 (2.2)%
- Alirocumab + rosuvastatin 20 mg: -45.0(2.2)%
- LS mean differences:
  - alirocumab versus ezetimibe 10 mg
    - -30.4 %, 95% CI [-36.6 to -24.2]; p<0.0001

Key secondary endpoints were numerous and included reductions in LDL-C at Week 12, Week 24 results for total cholesterol, apolipoprotein B, non-HDL-C, lipoprotein (a), fasting triglycerides, HDL-C, and Apolipoprotein- A1. Analyses were also conducted in subpopulations reaching an LDL-C target of < 1.8 mmol/L. See CER for details. Results for Apolipoprotein- A1, fasting triglycerides and HDL-C did not reach statistical significance.

Fifty-four patients had their alirocumab dose up-titrated and the results are as follows:

Table 25. Week 12 and Week 24 percent change from baseline up-titrated and non up-titrated patient alirocumab group Study Alternative

N up-titrated	% change from baseline Week 12 up-titrated n, mean (SD)	% change from baseline Week 24 up-titrated	% change from baseline Week 12 non up-titrated n, mean (SD)	% change from baseline Week 24 Non up-titrated
54	-46.3%	-52.6%	-57.2%	-54.1%

Phase II studies

The following is a tabulated summary of the Phase II efficacy studies.

Table 26. Summary of Phase II efficacy studies

Study DFI11565 A Randomised, Double-Blind, Parallel Group, Placebo-controlled, Fixed Dose Regimen, Multicentre /study Evaluating the efficacy and Safety of SAR236553 when Co-Administered with 80 mg atorvastatin over 8 weeks in patients with primary hypercholesterolaemia and LDL cholesterol ≥100 mg/dL (≥ 2.59 mmol/L) on atorvastatin 10 mg.	
n	92 enrolled, 80 completed (6 discontinued because of AEs), 88 analysed for efficacy
Treatment groups	Atorvastatin 80 mg + placebo Alirocumab 150 mg Q2W + atorvastatin 80 mg daily Alirocumab 150 mg Q2W + atorvastatin 10 mg daily
Eligible patients	Adults, primary hypercholesterolaemia on stable dose of 10 mg atorvastatin or other LMT, OR, not on a stable dose of atorvastatin or treatment naïve and likely to have LDL-C >= 2.59 mmol/L at screening
Primary endpoint	Week 8 LSM (SE) LDL-C percent change from baseline: Atorvastatin 80 mg + placebo - 17.3 (3.5)% Alirocumab 150 mg Q2W + atorvastatin 80 mg - 73.2 (3.5)% Alirocumab 150 mg Q2W + atorvastatin 10 mg - 66.2 (3.5)% Alirocumab 150 mg Q2W + atorvastatin 80 mg v atorvastatin 80 -55.8% (95% CI: -65.6 to 46), p<0.0001 Alirocumab 150 mg Q2W + atorvastatin 80 mg v Alirocumab 150 mg Q2W + atorvastatin 10 mg -7% (95% CI: -16.8 to 2.81)
Key secondary	Total cholesterol, ApoB, Non-HDL-C, and ApoB/ApoA-1 ratio were consistent with the primary endpoint results. HDL-C increased

Study DFI11565 A Randomised, Double-Blind, Parallel Group, Placebo-controlled, Fixed Dose Regimen, Multicentre /study Evaluating the efficacy and Safety of SAR236553 when Co-Administered with 80 mg atorvastatin over 8 weeks in patients with primary hypercholesterolaemia and LDL cholesterol ≥100 mg/dL (≥ 2.59 mmol/L) on atorvastatin 10 mg.	
endpoints	2.6% in the alirocumab 150 + atorvastatin 10 and 5.8% for Alirocumab 150 mg Q2W + atorvastatin 80 mg. TG outcomes were variable.

Study DFI12361 a Multicentre, Randomised, Double-Blind Parallel-Group, Placebo controlled Study evaluating the efficacy and safety of three doses of alirocumab (ARE236553/REGN727) over 12 weeks in patients with primary hypercholesterolaemia and LDL-C ≥ 100 mg/dL (≥ 2.59 mmol/L)	
n	100, 95 completed
Treatment groups	Alirocumab 50 mg Q2W Alirocumab 75 mg Q2W Alirocumab 150 mg Q2W Placebo
Eligible patients	Aged ≥ 20 and ≤ 75 years primary hypercholesterolaemia treated with a stable dose (5 – 20 mg) at least 6 weeks prior to enrolment, or receiving a LMT (not atorvastatin), or drug naïve and BMI ≥ 18 or ≤ 40 kg/m^2
Exclusion	Type 1 diabetes, unstable type 2 diabetes
Primary endpoint	Week 12 Alirocumab 50 mg Q2W v placebo LSM% difference -52.2% (95% CI: -60.73 to 40 43.6) Alirocumab 75 mg Q2W v placebo LSM% difference -59.4% (95% CI: -68.2 to 51) Alirocumab 150 mg Q2W v placebo LSM% difference -69.1% (95% CI:-77.6 to-60.5)
Key secondary endpoints	Large dose-dependent reductions in total cholesterol, non-HDL-C, ApoB and ApoB/ApoA-1 ratio. Small increases in HDL-C, TG and ApoA-1 in all doses.

Study R727-CL-1932 a Phase 2, Open Label Extension Study of the dose-finding study R727-CL-1003 to Evaluate the Long Term Safety and Efficacy of REGN727 administered by Subcutaneous Injection in patients with Heterozygous Familial Hypercholesterolaemia, conducted in Canada and the US, planned to run for 4 years. The data-lock point was May 2014.	
N	58, 12 from the placebo group in the parent study, 46 from the alirocumab group in the parent study. 4 patients from the parent alirocumab group discontinued, 1 due to AE.
Treatment groups	Alirocumab 150 mg Q2W pre-filled syringe (n=58) Stable dose of statin for the first two years
Eligible patients	Patients with HeFH on a stable daily statin regimen with or without LMT who had completed study R7272-CL-1003 without AE or major protocol violation
Primary efficacy endpoint	Safety was the primary endpoint Mean (SD) baseline LDL-C was 3.9 (1.0) mmol/L Mean (SD) percent change from baseline: Week 12 -62.2% Week 24 -63.5% Week 52 -55.43% (week 52 mean LDL-C 1.72 (1.3) mmol/L Week 76 -60.5%
Other secondary endpoints	Decreases in ApoB, non-HDL-C, total cholesterol, Lp(a), fasting TG and ApoB/ApoA-1 Increases in HDL-C and ApoA-1

Safety

Safety information is derived from the primary outcome of Study LTS11717 (below) and an integrated safety analysis across the Phase II and III studies. A summary is presented here. Please see the CER for additional details.

LTS11717 - (Long Term) A Randomised, Double Blind, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Versus Ezetimibe in High Cardiovascular Risk Patients with Hypercholesterolaemia Not Adequately Controlled with Their Statin Therapy. This was a primary safety study. Safety information was provided for Week 78 of the double-blind period of this multinational, multicentre, study conducted over 3 periods for a total duration of 86 weeks (3 week screening, 78 week double-blind, 8 weeks follow-up). The study design is described in the Efficacy section of this Overview. The safety set of patients exposed for ≥ 52 weeks comprised 1343 alirocumab patients and 677 placebo patients, and 405 alirocumab patients and 202 placebo patients had received ≥ 76 weeks of treatment and had completed their Week 78 visit. In this study 78.6% alirocumab patients and 80.6% placebo patients reported any AE with the most frequent being nasopharyngitis (12.6% versus 12.7%), injection site reaction (5.7% versus 4.3%), influenza (5.5% versus 5.4%), bronchitis (5.2% versus 4.7%), myalgia (4.9% versus 3.0%), muscle spasms (3.7% versus 3.2%), cough (3.2% versus 2.2%), and contusion (2.3% versus 0.8%). Injection site reaction was the most common treatment related

adverse events (TRAE). Other TRAEs (alirocumab versus placebo) included headache (0.8% versus 1.4%), diarrhoea (1.0% versus 0.5%), dizziness (0.6% versus 0.6%), nausea (0.6% versus 0.9%), pruritus (0.5% versus 0.1%), arthralgia (0.5% versus 0.5%), myalgia (1.2% versus 0.4%), muscle spasm (0.6% versus 0.5%), fatigue (0.7% versus 0.5%), and decreased blood cortisol (0.4% versus 0.8%).

Data were collated regarding special interest event. Cardiovascular events occurred in 4.0% of the alirocumab group and 4.4% of the placebo group. Neurocognitive effects were reported in 18 patients (1.2%) of the alirocumab, 3 were SAEs, and 4 patients (0.5%) of the placebo group. Diabetes was reported by 4.3% of the alirocumab group and 3.9% of the placebo group, although there were no meaningful differences between the groups for fasting glucose and HbA1C.

In the Ophthalmologic substudy 139 patients had periodic review of colour vision, intraocular pressure, and structural assessment with slit-lamp ophthalmoscopy, fundoscopy or disc and fundus photography). Ophthalmological TEAEs were reported in 4 patients (1.9%) in the alirocumab group and 2 (0.9%) patients in the placebo group, with no clear pattern of events.

Integrated Safety Analysis

1. The integrated safety database included 5,204 patients exposed to study medication with 3,340 exposed to alirocumab. Of those, approximately 72% of the alirocumab patients were exposed to at least 52 weeks of treatment. The sponsor has pooled the safety information into two sets based on the comparator arm in the relevant clinical trial: the placebo controlled pool of 3,752 patients from the Phase 3 studies Long-Term, FH I, FH II, High FH, Combo I, and the phase 2 studies DFI11565, DFI11566, and CL-1003, and DFI12361 (1276 placebo and 2476 alirocumab) and the ezetimibe-controlled pool of 1,482 patients from the Phase 3 studies Combo II, Mono, Options I, Options II, Alternative (618 ezetimibe and 864 alirocumab). In the placebo-controlled pool almost all patients took the investigational product in addition to concomitant statins, and 75 – 80% took statins in the ezetimibe-controlled pool.
2. TEAEs were reported in 76.4% and 75.8% of the placebo and alirocumab patients, respectively in the placebo-controlled pool. Events more frequent in the alirocumab group compared to placebo (incidence ≥2.0% in the alirocumab group and difference ≥0.5% versus placebo) were injection site reaction, influenza, myalgia, muscle spasms, contusion, and musculoskeletal pain. In the ezetimibe-controlled pool, 68.1% and 70.3% of the ezetimibe and alirocumab patients reported TEAEs. Events more frequent in the alirocumab group compared to placebo (incidence ≥2.0% in the alirocumab group and difference ≥0.5% versus placebo) were accidental overdose, headache, influenza, injection site reaction, fatigue, and constipation.
3. The proportions of TEAEs in patients that had their dose up-titrated from 75 mg Q2W to 150 mg Q2W were similar between those up-titrated and those not in both pools. The types of events that were more frequent in the up-titrated versus the non-titrated patients in the placebo-controlled pool were back pain, diarrhoea, gastroenteritis, abdominal pain muscle spasms peripheral oedema (2.6% v 0.7%), influenza-like illness and blood creatinine, and in the ezetimibe pool bronchitis, myalgia, headache, hypertension (5.0% v 2.0%) and accidental overdose (3.9% v 3.3%). It is noted that upper respiratory tract infection, bronchitis, influenza, dizziness and myalgia were all more common in the non-titrated group than the titrated group across both safety pools. TEAEs leading to discontinuation in the placebo-controlled pool comprised 5.1% and 5.3% of the placebo arm and alirocumab patients, respectively and in the ezetimibe-controlled pool comprised 9.7% and 8.8% of the ezetimibe and alirocumab patients, respectively.
4. Three TRAEs occurred more frequently in alirocumab groups across various analyses:

a. Injection site reactions:

   i. placebo-controlled pool – alirocumab 7.3%, placebo 5.2%

   ii. ezetimibe-controlled pool – alirocumab 3.1%, ezetimibe 2.1%

b. Pruritus:

   i. placebo-controlled pool – alirocumab 1.1%, placebo 0.4%

   ii. ezetimibe-controlled pool – alirocumab 0.8%, ezetimibe 0.5%

c. Influenza

   i. placebo-controlled pool – alirocumab 5.7%, placebo 4.6%

   ii. ezetimibe-controlled pool – alirocumab 3.7%, ezetimibe 2.3%

5. Across the Phase II and III studies 0.6% of alirocumab and 0.9% of control group patients died while on-study (exact odds ratio 0.44 (95% CI: 0.21 to 0.93)). Of those, 0.5 % of alirocumab and 0.6% of control group patients died of cardiovascular causes. Equal numbers of alirocumab and control patients died of a new or worsening malignancy. SAEs were reported for 14.3% and 13.7% of the placebo and alirocumab patients in the placebo-controlled pool and 11.2% and 13.1% of the ezetimibe and alirocumab patients in the ezetimibe-controlled pool. Similar proportions of patients in each set experienced a non-fatal SAE, and no relevant differences between the sets were noted for individual SOCs. The proportions of patients experiencing a SAE were slightly higher (9.5% to 10.6%) in the non-up-titrated than up-titrated groups (8.3%) within each pool.

6. Effects on laboratory tests. Although only measured in one study there was no apparent effect on fat soluble vitamins, cortisol and gonadal hormones. The three SAEs with increased creatine kinase suitable had an alternative explanation for the events.

7. Events of Special Interest

   a. Local injection site reactions were more common in the alirocumab groups than the control groups (6.0 versus 4.2 per 100 patient years, respectively; HR [95% CI]: 1.50 [1.15 – 1.95]), and all but 1 event were transient and mild. Discontinuations due to local injection site reactions occurred in 0.2% and 0.3% of the alirocumab and polled control groups, respectively.

   b. Allergic reactions were more common in the alirocumab groups than the control groups (placebo-controlled pool: 6.0 versus 4.2 per 100 patient years, respectively; HR [95% CI]: 1.50 [1.15 – 1.95], ezetimibe controlled pool: 8.4 (alirocumab) versus 7.3 (ezetimibe) patients per 100 patient years, HR [95%CI]: 1.31 [0.85 – 2.02]) mostly due to local pruritus with alirocumab. Other reactions included nummular eczema, urticaria and hypersensitivity vasculitis.

   c. Neurologic events were reviewed because cholesterol is a major component of myelin and cell membranes. 3.4% to 3.5% of alirocumab patients had neurological events compared to 3.5% of placebo and 2.4% of ezetimibe patients, but the differences were not statistically significant. Isolated rare events of optic neuritis, Miller-Fisher syndrome, demyelination and transverse myelitis were reported for alirocumab.

   d. Neurocognitive disorders: in the placebo controlled study pool 21 (0.8%) patients in the alirocumab group and 9 (0.7%) in the placebo group (HR [95% CI]: 1.18 [0.54 – 2.58] and in the ezetimibe controlled pool: 8 (0.9%) patients in the alirocumab group and 6 (1.0%) in the ezetimibe group, (HR [95% CI: 0.95

[0.32 – 2.74]) reported neurocognitive events. It is noted there was variability in studies: For example the Long-Term study in which 47% of patients were taking statins at baseline, neurocognitive events were reported in 1.2% (18/1550) of alirocumab patients and 0.5% (4/783) of placebo patients.

e. Ophthalmological events were investigated in the specific substudy, as above. In the integrated safety set in the placebo-controlled pool events occurred in 1.8% versus 1.4% in the alirocumab and placebo groups respectively, and in the ezetimibe controlled pool in 0.8% versus 0.5% in the alirocumab and ezetimibe groups, respectively (1.5% alirocumab versus 1.1% any comparator). The most common standardised MedDRA queries (SMQ) was retinal disorders with 1.2% alirocumab patients versus 0.8% with any comparator. The numbers of events are very small in each subgroup and the types of events were consistent with concomitant disease or patient age.

f. Diabetes was reviewed because of the concern that the LDLR upregulation of pancreatic beta cell function may be impacted by PCSK9, however there was no clear evidence of an increased risk of diabetic AEs compared to placebo or ezetimibe.

g. Hepatic safety was similar between the two groups with a rate per 100 patient-years of 2.2 (95% CI: 1.7 - 2.8) in the alirocumab group and 1.6 (95% CI: 1.0 - 2.4) in the placebo group (HR [95% CI]: 1.36 [0.84 - 2.20] in placebo-controlled pooled studies, and in the ezetimibe controlled pool the incidence rates were 2.2 (95% CI: 1.3 - 3.6) in the alirocumab group and 3.1 (95% CI: 1.7 - 5.1) in the ezetimibe group (HR [95%CI]: 0.69 [0.34 - 1.43]).

h. MACE Adjudicated: MACE events composite endpoint (CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalisation) occurred in 1.6% of alirocumab patients and 1.8% control patients (HR [95%CI]; 0.81 [0.52 to 1.25]). MACE TEAEs were more common with placebo than alirocumab in the pooled placebo-controlled studies (2.3% versus 1.5% for placebo and alirocumab, respectively) but less common than ezetimibe in the pooled ezetimibe-controlled studies (1.0% and 2.0% for ezetimibe and alirocumab, respectively).

i. Musculoskeletal events were of particular interest in patients with statin intolerance, in particular the Alternative study patients. Skeletal muscle-related TEAEs in the alirocumab group were less frequent than the atorvastatin (HR 0.61 [0.38 to 0.99]) or ezetimibe (HR 0.70 [0.47 to 1.06]) groups. In the other studies similar proportions of patients (about 15%) in the alirocumab and placebo groups experienced musculoskeletal TEAEs and (0.4 – 0.5%) led to discontinuation.

j. Safety of very low LDL-C: A total of 1371 (41.0%) patients treated with alirocumab had at least 1 LDL-C of <0.65 mmol/L and 796 (23.8%) patients had 2 LDL-C measure of <0.65 mmol/L or <0.39 mmol/L. The safety profiles of these patients were similar to patients on active treatment with higher LDL-C, including neurological or neurocognitive outcomes.

k. Immunogenicity: The ADA response was measured in the clinical pharmacology and pivotal efficacy studies. In the clinical pharmacology studies about 22% and 17% of the 75 mg and 150 mg dosage groups, respectively were ADA positive. About 1% of patients across the studies had baseline ADA. TEAE ADA responses occurred in 4.8% and 0.6% of the alirocumab and control groups, respectively, and had a median time to onset of 12 weeks. Up-titration patients had similar proportions of ADA responses. Most trial participants had low titres (0.7% had titres above 240), but most were transient or reduced with subsequent testing.

ADA status did not impact alirocumab exposure and was not a covariate impacting population parameters. About 1.2% (36/3033) of patients, all from the alirocumab group had neutralising antibodies (NAb) and only 10 of those had ≥ 2 Nab+ samples. There was no apparent correlation between NAb and alirocumab efficacy or safety.

l. Device-related adverse events among patients using the pre-filled pen in the placebo-controlled pool 9.1% and 6.0% in the placebo and alirocumab groups, respectively reported device-related events.

8. At the time of submission there were no post-market data.

Risk management plan

The TGA has considered the EU-RMP (Version 1.3, dated 23 September 2015) with an updated ASA (Version 1.1, dated 18 December 2015) but has noted outstanding issues relating to the RMP that the sponsor should address.

Risk-benefit analysis

Efficacy

Alirocumab is a fully humanised antibody of PCSK9 the circulating negative regulator of LDLR. Alirocumab was administered by subcutaneous injection by patients or carers at home mostly in fortnightly treatment regimens. Alirocumab is intended as second-line therapy.

The sponsor has provided evidence of the efficacy of alirocumab to reduce LDL-C in 10 similarly designed Phase III studies in which assessed LDL-C reduction at 24 weeks as the primary endpoint in 9 studies and a secondary endpoint in the tenth. LDL-C is a PD endpoint that has been accepted in the past by the TGA and is described in TGA adopted EU guidelines as a surrogate marker for cardiovascular risk reduction and suitable endpoint in lipid lower therapies. The effects on cardiovascular mortality and morbidity have not been established for alirocumab, and the sponsor plans to state this in the Indication. Although it is unusual to include an efficacy disclaimer in the Indication it is consistent with the position in the EU and the US and with the Indication for the PCSK9 inhibitor, evolocumab, currently registered in Australia. The statement itself is accurate at this time.

In general the populations were adequately defined. Five of the 10 Phase III studies included data from 52 weeks of treatment (FH I, FH II, High FH, Combo I, Long Term). The duration of the studies is adequate to support the indications although it is noted that there are ongoing and planned studies. The efficacy of alirocumab was studied comparing placebo or ezetimibe in the larger studies and in two smaller studies alirocumab was compared with statins, and statin-ezetimibe combinations. The combination doses reasonably reflect patterns of use and the statin doses included the maximum recommended for either rosuvastatin or atorvastatin. The proportions of patients not completing the treatment period in the studies range from 11 to 33%, which is of concern, although the proportion discontinuing because of adverse events (1.2% to 18.3%) was lower. Eight of the 10 studies included patients at very high or high cardiovascular risk. The two studies with monotherapy patients had patients at lowest risk (Mono and Alternative). Nine of the 10 studies had a statistically significant improvement in LDL-C versus the comparator. LDL-C reduction of about 30 – 60% was observed in the studies. Statin intolerant patients and those with HeFH at highest risk had the greatest LDL-C reduction. Between 14 and 50% of alirocumab patients (n= 408) up-titrated after not

reaching a LDL-C target of <1.8 mmol/L in the studies allowing up-titration. Alirocumab patients that had their dose up-titrated went on to have similar results to the non-up-titrated patients.

Two delivery systems were used although 9 of the 10 studies used the pre-filled pen auto-injector device, and the Long-Term study used a pre-filled syringe. A direct comparison of the two dosage forms was not located in the submission although the sponsor has requested the registration of both.

Sufficient evidence has been provided for use in patients with HeFH, with three dedicated studies and HeFH patients included in the study populations of 4 others.

The Combo studies and the Mono study included only non-FH patients but there was a preponderance of non HeFH patients in Long-Term, Options I and II and Alternative. The majority of the patients in each of these studies had either CHD or CHD risk equivalents. The Combo patients were also at high risk of cardiovascular disease and 78% of Combo I and 90% of Combo II had coronary heart disease. The primary endpoint for most of the comparisons in these studies was met as were many of the key secondary endpoints however the rosuvastatin 20 mg baseline group in Combo II did not the primary endpoint.

Monotherapy is requested in statin intolerant/contraindicated patients. In the submission the Mono study did not include statin intolerant patients. The Alternative study included 126 patient in the alirocumab group of which 23.8% did not complete study treatment (to 24 weeks). The numbers are insufficient to support this component of the Indication as the sponsor proposes that it should apply to HeFH, non-FH and mixed dyslipidaemia subpopulations.

Mixed dyslipidaemia patients have elevated triglycerides. Alirocumab did not achieve statistically significant improvements in triglycerides in the studies in patients with mixed dyslipidaemia. Alirocumab has not been demonstrated to reduce the all lipid abnormalities in this group and is not supported.

Safety

In the Phase II/III studies 3340 study participants were exposed to alirocumab and 2408 had ≥ 52 weeks of treatment. The numbers are sufficient according to the guidelines.

Safety information from 75 mg q2W and 150 mg Q2W doses was included. Concomitant lipid lowering therapies were used in almost all the studies and confound the safety findings. Nevertheless, alirocumab was generally well tolerated. Adverse events were similar in patients up-titrated and those not. There was a relatively low rate of SAEs and no clear pattern was seen. No evidence of an increased risk of cardiovascular disease was demonstrated. In the studies alirocumab had a weak immunogenicity profile. There was no apparent increase in AEs with up-titrations with similar proportions of patients having SAEs and TEAEs and injection site reactions. There were higher rates of adverse events in the alirocumab groups in studies with only 150 mg doses although this may reflect the higher risk in the study populations.

There are a number of safety areas of special interest. Low and very low LDL-C levels are of concern because of the possible risks of cancer, haemorrhagic stroke and neurocognitive events, and potentially steroid and vitamin production. Most low and very low LDL-C levels were seen in patients taking 150 mg Q2W, although one low level was seen in 41% alirocumab patients overall. Although there was no specific signal for neurocognitive events when taking into account the whole exposed population, however in the safety study, a more than 2 fold difference was seen in the numbers of patients reporting neurocognitive events compared to placebo. When studied there was no impact on steroid synthesis or vitamin production with alirocumab. There are uncertainties about

the long-term safety of alirocumab and the long-term consequences of the inhibition of PCSK9 in other tissues, including brain.

A higher incidence of device related adverse events were reported in the auto-injector studies (9.1%) than the pre-filled syringe study (the sponsor will be asked for comment).

Indication

Having taken into account the efficacy and the safety findings the balance of the benefits is weighted against the concern about the possible long term effects. A large population of patients may be exposed to alirocumab for long durations of treatment so the uncertainties about long-term safety outcomes are weighted heavily in this consideration. The benefit – risk is considered positive in patients with HeFH and clinical evidence of atherosclerotic disease and this is reflected in the proposed indication. The balance of the benefits and risks/uncertainties is less clear for patients with non-FH without demonstrated/clinical cardiovascular disease. The sponsor is requested to address this question and the ACPM is requested to comment. At this time, the following Indication is supported:

> *Praluent is indicated in adults with heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease:*
>
> - *In combination with a statin or statin with other lipid lowering therapies, or*
> - *In combination with other lipid-lowering therapies in patients who are statin-intolerant.*
>
> *The effect of Praluent on cardiovascular morbidity and mortality has not been determined.*

Dose

The proposed doses are 75 mg SC Q2W and 150 mg Q2W. The 75 mg SC Q2W is supported as a general starting dose across the indication. The dose can be up-titrated after 12 weeks. From a PD viewpoint there was a small incremental benefit in up-titration. The comparative long-term consequences of the higher dose is unknown, however it is noted that the very low LDL-C levels occurred in patients persisting on 150 mg Q2W.

Data deficiencies

There are no data in patients with severe hepatic impairment. Patients with Homozygous Familial Hypercholesterolaemia were excluded from the Phase III trial. It is noted that the sponsor has not applied for use in this population but there may be off-label use. There are no data in children but the sponsor has not requested a paediatric indication. There are no data in patients requiring plasma apheresis that may be considered in HeFH patients that are compound heterozygotes with severe disease. There is limited long-term safety data, although many of the studies are ongoing.

Conditions of registration

The following is an outline of the conditions of registration

1. There will be a condition to include an EU-RMP and Australian Specific Annex.
2. The final studies/reports for the ongoing studies [EFC12492 (FH I), R727-CL-1112 (FH II), EFC12732 (High FH), LTS11717 (Long Term), Phase II OLE) must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission.

3. There will be a batch release condition (as outlined in the Quality evaluation reports).

Questions for the sponsor

1. Please comment on any common factors among non-responders to alirocumab.
2. Please provide an overview of the efficacy data to support the use of alirocumab:
    a. In patients with primary (non-familial) hypercholesterolaemia that do not have clinical atherosclerotic cardiovascular disease
    b. In patients with mixed dyslipidaemia that do not have clinical atherosclerotic cardiovascular disease
    c. In monotherapy (that is, with no other LMT) in primary hypercholesterolaemia

    In the response please include the numbers of patients assigned the therapy
3. The PK/PD of alirocumab delivered by prefilled syringe and by autoinjector pen does not appear to have been directly compared (for example, a bioequivalence study), although there was a comparison made in a population pharmacokinetic study. Please justify.
4. Using the most recently available safety data please provide an overview of the adverse events in the following patient groups:
    a. 2 consecutive calculated LDL-C values of <0.65 mmol/L
    b. 2 consecutive calculated LDL-C values of <0.39 mmol/L
5. Using the most recently available safety information please provide an account of the following types of adverse effects in patients taking alirocumab:
    a. Neurocognitive events
    b. Ophthalmic events
    c. Hypersensitivity events
    d. Malignancy
    e. Reactivation of Hepatitis C
    f. Device-related events
6. How were neurological and neurocognitive outcomes measured during the studies? How will the sponsor continue to investigate this potential safety concern?
7. What was the risk of haemorrhagic stroke with alirocumab compared with placebo or ezetimibe?
8. Please comment on the possible role for decreased expression of PCSK9 in hepatocellular carcinoma. Has alirocumab been given to patients with HCC, and is there evidence of acceleration of HCC with PCSK9 inhibitor use?
9. Device related AEs occurred in about 9% of patients in the clinical programme presented. What were these events? What strategies does the sponsor propose to mitigate the risk of device-related events.
10. Please provide an updated list of the recently completed and ongoing clinical trials with estimates of when interim and final clinical study reports will be available.

Summary of issues

- The submission relies on the surrogate endpoint of LDL-C reduction to demonstrated efficacy. The impact on cardiovascular outcomes has not been established.

- Whether sufficient evidence has been provided to support the efficacy of alirocumab in monotherapy
- Whether there is sufficient safety information to support groups other than those with heterozygous familial hypercholesterolaemia and clinical coronary atherosclerotic disease in the indication
- Whether the potential safety concerns such as neurocognitive events and ophthalmological events have been sufficiently well characterised

Proposed action

The Delegate had no reason to say that the application for alirocumab should not be approved for registration for the amended indication:

Praluent is indicated as an adjunct to diet and exercise in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease:

- *in combination with a statin or statin with other lipid lowering therapies or,*
- *in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated*

The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.

Request for ACPM advice

The committee was requested to provide advice on the following specific issues:

1. The sponsor has proposed that alirocumab should be indicated in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia and mixed dyslipidaemia. Please comment on whether the safety and efficacy of alirocumab has been sufficiently established for each of these subpopulations of patients with hypercholesterolaemia.
2. The sponsor has proposed that alirocumab should be indicated as monotherapy or with another lipid-lowering agent in patients with documented atherosclerotic cardiovascular disease who are statin intolerant or in whom statins are contraindicated. Please comment on whether the safety and efficacy of alirocumab, particularly as monotherapy, has been sufficiently established for each of the subpopulations of patients with hypercholesterolaemia.
3. Please comment on the adequacy of the clinical trial program to characterise the safety issues of interest with this class of medicines such as neurocognitive effects.
4. Should alirocumab dosing commence with 75 mg Q2W in all patients, or is there a subgroup in which the dosage should commence at 150 mg Q2W?

The committee was also requested to provide advice on any other issues that it thought may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor's comments on the issues for which the advice of the ACPM is sought, as outlined in the Delegate's Overview of 2 March 2016, are presented below.[16] The sponsor is proposing alignment of the Australian indication with that approved in the EU

[16] The sponsor also provided the requested data to address the Delegate's questions.

recognising the similarity in patient populations, clinical practice and lipid treatment guidelines between the EU and Australia; the common risk management approach to effectively mitigate the potential safety concerns and the adoption of the same CHMP clinical guidelines as the basis of the Australian regulatory assessment framework. The indication wording is as follows:

> *Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet:*
>
> - *In combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
> - *alone or in combination with other lipid lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated*
>
> *The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.*

Advice from ACSOM supported adoption of the EU indication and the clinical evaluator proposed a modified EU indication which recommended monotherapy for statin intolerant patients be limited to those at greatest risk of cardiovascular events. The Delegate has recommended a more conservative approach to align the indication to that for Repatha the only currently approved PCSK9 inhibitor in Australia.

The sponsor considers that differences in the design of the clinical program and the available evidence to support a favorable benefit/risk profile for alirocumab in all the populations included in the indication, justify the proposed alignment of the Australian indication for Praluent with that approved in the EU based on the following:

- Comprehensive assessment of safety and efficacy from 10 phase 3 studies, with a total of 5296 patients (3182 patients on alirocumab for 3420 patient-years of exposure) including clinical study sites in Australia
  - 2408 patients treated with alirocumab for at least 52 weeks
  - 639 patients treated with alirocumab for at least 76 weeks
- Studies designed for long-term double-blind assessment of safety and efficacy based on primary efficacy analysis at 24 weeks, with data provided based on a double-blind treatment period of at least 52 weeks in 5 studies (up to 76 weeks in the LONG TERM study)
  - For comparison the Repatha trial program included 7 trials with a double blind assessment period of 12 weeks duration and 1 trial with a 52 week duration
- Benefits in terms of LDL-C lowering and efficacy on other lipid parameters in all populations studied (heterozygous familial and non-familial hypercholesterolaemia; mixed dyslipidaemia) are greater than the risks associated with alirocumab treatment as an add-on to statins, with or without other LMTs, or as monotherapy or add-on to non-statin LMT in patients with statin intolerance.
- Patients with a history of documented statin intolerance in the ALTERNATIVE study were less likely to have musculoskeletal TEAEs in the alirocumab arm than in the statin re-challenge and had significantly better LDL-C lowering in the alirocumab arm than in the ezetimibe arm.
  - These data indicate that alirocumab is a valuable alternative in patients who are unable or unwilling to take a statin
- The option of two doses 75 mg/mL and 150 mg/mL offers the convenience of flexibility to allow prescribers to tailor therapy to meet individual patient needs to

achieve LDL-C goals, particularly in those patients who are not well controlled despite their current therapies, including a maximally tolerated dose of statin.

- Adverse reactions (injection site reaction, pruritus and upper respiratory tract signs and symptoms) were generally mild, transient and manageable; more significant serious allergic reactions were very rare.
- Although the studies were not powered to provide CV outcomes evidence, CV events were adjudicated and a decrease in CV events (MACE) was observed in the alirocumab-treated patients. With long-term double-blind studies and large proportion of high CV risk patients in the ODSYSSEY program, the MACE event rate provided reassurance of a lack of detrimental effect on CV outcome
    - These results are consistent with the expected benefit of the large additional LDL-C reduction achieved by alirocumab treatment beyond that achieved with treatment with a statin ± ezetimibe , that is being evaluated in the ongoing OUTCOMES trial in 18,000 patients
- Adoption of the EU RMP in Australia based on comparable patient populations and clinical practice provides an equal level of reassurance that any potential risks in all the sub-populations proposed are effectively managed in clinical practice. Of note, no risk evaluation and mitigation strategy (REMS) was required in the USA.
    - Real world experience following launch of Praluent in the EU, which has a significantly larger population base compared to Australia, will inform the ongoing benefit/risk assessment with the first periodic benefit-risk evaluation report (PBRER) data lock point planned for March 2016

In summary Praluent provides an important treatment option that addresses an unmet medical need for those patients where existing therapies are unable to provide the desired reduction in LDL-C. The sponsor considers Australian patients should have access to the same innovative therapies as available in the EU and approval of Praluent for the same indication is supported by the available evidence.

1. The sponsor has proposed that alirocumab should be indicated in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia and mixed dyslipidaemia.Please comment on whether the safety and efficacy of alirocumab has been sufficiently established for each of these subpopulations of patients with hypercholesterolaemia.

Praluent is targeting patients who cannot reach LDL-C goals with the best standard of care for example, maximum tolerated dose of a statin. All the populations included in the indication have an unmet medical need to achieve further reductions in LDL-C as a primary lipid treatment goal. In the Australian guidelines, high intensity treatment is recommended for high CV risk patients with established CHD with a goal of 1.8 mmol/L (70 mg/dL) or for those without established ASCVD, including diabetes with additional risk factors, LDL-C goal is <2 mmol/L (<77.3 mg/dL).[17][18]

Based on the favourable CV effects of LDL-C lowering for both statins and ezetimibe, the sponsor considers that where patients are unable to reach recommended LDL-C levels on established LMT, irrespective of their genetic predisposition, additional therapy is warranted.

[17] National Heart Foundation and Cardiac Society of Australia and New Zealand. Reducing risk in heart disease an expert guide to clinical practice for secondary prevention of coronary heart disease. 2012
[18] National Vascular Disease Prevention Alliance Guidelines for the management of absolute cardiovascular disease risk. 2012

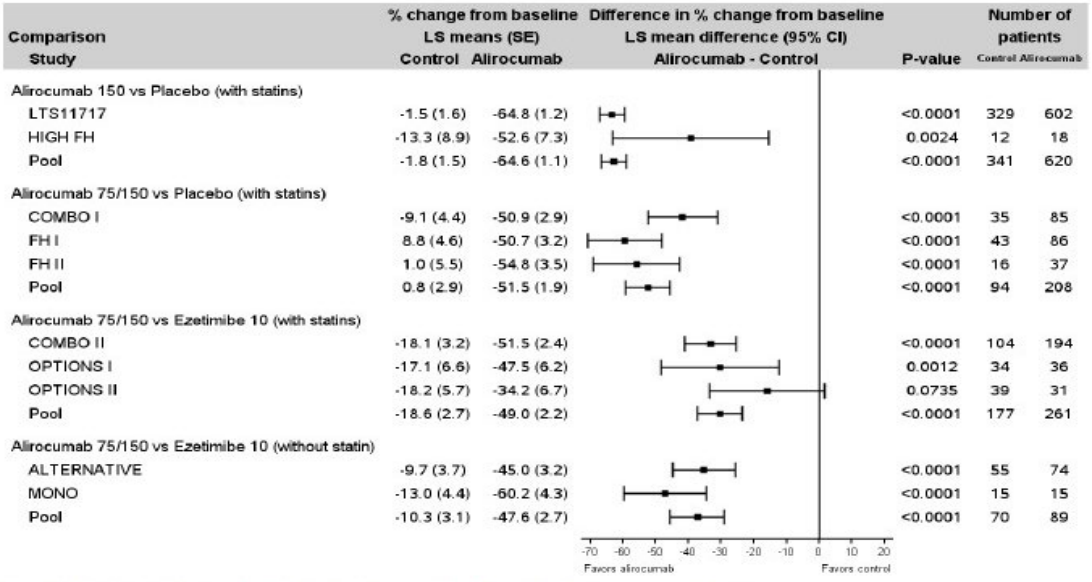
The sponsor considers that all three populations were adequately represented in the clinical program to justify the same indication as approved in the EU where post marketing experience continues to confirm the favourable benefit/risk profile.

Patients with heFH represented approximately 25% of the global phase 3 population (N=1257 in specific studies, N= 1377 overall), and non-FH approximately 75%. The common primary time point for primary efficacy analysis was at 24 weeks, but the double-blind treatment period was of at least 52 weeks in 6 studies to assess long-term efficacy, and for safety evaluation. Overall, this includes 2408 patients treated with alirocumab for at least 52 weeks (12 months), and 639 for at least 76 weeks (18 months), to assess long-term efficacy, and for safety evaluation.

Besides the pooled data, specific studies provide efficacy and safety data in specific populations (FH studies in heFH, COMBO studies in patients at very high CV risk , which also represent the largest stratum in the LONG TERM study).

There were 2025 patients with mixed dyslipidemia (1199 on alirocumab). Although no specific study was carried out in this population, pre-specified efficacy and safety analyses were carried out in this patient population. The effect on LDL-C was very similar in patients with mixed dyslipidemia to that observed in the overall population. Clinically meaningful decreases from baseline in fasting triglycerides (TG) were also consistently seen, although at individual study level, interpretation is more limited, due to small number of patients with mixed dyslipidemia in some studies and the high variability inherent to fasting TGs. It is to be noted that the Phase III studies were not powered to demonstrate a statistically significant difference in fasting TGs in patients with mixed dyslipidemia. Given the high variability of this parameter, a minimal sample size of 128 patients with mixed dyslipidemia (64 per treatment arm) would be necessary to demonstrate a 20% difference versus placebo with 80% power (assuming a SD of 40% as observed in the Phase III studies). This minimal sample size was only achieved in study LONG TERM, and a statistically significant difference was observed in this study.

Figure 3. Percent change from baseline in calculated LDL-C at Week 24: MMRM (ITT analysis in patients with mixed dyslipidaemia) – Phase 3 studies



The review of TEAEs did not indicate any specific pattern in this mixed dyslipidaemia population.

Of note, alirocumab is presented as 2 doses, 75 and 150 mg Q2W, which will offer the option of individualizing therapy to achieve treatment goals through appropriate dose selection.

2. The sponsor has proposed that alirocumab should be indicated as monotherapy or with another lipid lowering agent in patients with documented atherosclerotic cardiovascular disease who are statin intolerant or in whom statins are contraindicated. Please comment on whether the safety and efficacy of alirocumab, particularly as monotherapy, has been sufficiently established for each of the subpopulations of patients with hypercholesterolaemia.

As outlined above, the sponsor is proposing alignment with the EU indication wording that does not include reference to atherosclerotic cardiovascular disease.

In Australia standard clinical practice is to aggressively treat lipids, resulting in higher intensity treatment with statins than in other countries to achieve the desired clinical outcome. However, there are patients who are truly statin intolerant and represent a therapeutic challenge, as they can present with sustained elevated serum cholesterol levels that in turn significantly increases their risk of a CV event (ALTERNATIVE study in statin intolerant patients, baseline LDL-C was 4.95 mmol/L). Non-statin LMTs are generally prescribed, but given that these non-statin LMTs, including the most effective of these agents (ezetimibe), provide no more than 20 to 25% reduction in LDL-C, these patients have great difficulty reaching the currently recommended LDL-C targets for high or very high risk patients.

Additional patient populations with an unmet medical need for LDL-C management, and in whom alirocumab might serve as an alternative treatment due to its different pharmacological mechanisms and drug properties as compared to statins, are those with muscle related, liver related events or hypersensitivity to statins or possible drug interactions.

The efficacy and safety of alirocumab as a monotherapy (without statins, and without ezetimibe which was the active comparator) was evaluated in two clinical trials (N=417):

- ALTERNATIVE, a 6 month study that included 314 patients with statin intolerance, with 82.5% patients at high/very CV risk, and 47.8% patients with prior CVD, compared alirocumab and ezetimibe in addition with non-statin lipid-lowering therapies, or diet alone.
- MONO (N=103), a 6 month monotherapy study in patients at moderate CV risk, provided complementary information to ALTERNATIVE in patients who were not receiving any statin or non-statin LMT.

In both studies alirocumab demonstrated clinically meaningful and statistically significant reduction in LDL-C levels, with no particular safety observations. Efficacy when used as a monotherapy is comparable when used with concomitant statins. In the overall safety analysis, alirocumab displayed similar safety profiles in patients defined with 'No background statin therapy' and in patients receiving statins. The only difference was Musculoskeletal and connective tissue disorders TEAEs, specifically myalgia, that were reported at higher rates in the ALTERNATIVE study, not unexpected in a trial carried out in patients with statin intolerance. The sponsor thus considers that there is sufficient clinical evidence to justify inclusion of the monotherapy sub-populations in the indication considering the favorable benefit/risk, the lack of other treatment options and the limited number of patients that will be considered for monotherapy based on the vast majority being treated with a maximum tolerated dose of a statin or other LMT.

3. Please comment on the adequacy of the clinical trial program to characterise the safety issues of interest with this class of medicines such as neurocognitive effects.

The design of the Phase III program was adequate to characterize the safety issues of interest, including the risk of neurocognitive events. The large clinical program allowed for the safety evaluation in 5234 patients, whom 3340 patients were exposed to alirocumab, 1276 to a placebo and 618 to ezetimibe.

Overall, the majority of patients were at high/very high CV risk, with most of them having a history of CVD, and receiving maximally tolerated doses of statin (see Question 1). The safety database included a significant number of elderly patients: 1799 patients (34.4%) were ≥65 years of age or older, including 375 patients (7.2%) ≥75 years, and mean age in non-FH patients was 60-63 years. The double-blind treatment duration up to 18 months resulted in an overall exposure of 3451 patient-years in the alirocumab group.

A number of safety areas of special interest potentially related to low LDL-C levels were prospectively analysed during the clinical program, including neurocognitive events. These were analysed using 2 different groupings of MedDRA terms based on a broad company MedDRA query (CMQ) and a more focused set of terms that the FDA proposed.

- In the placebo- and ezetimibe-controlled pools, neurocognitive events were reported overall at a low incidence and were similar between the alirocumab and control groups using both FDA's and sponsor's CMQ.
- In the placebo-controlled pool, neurocognitive events were reported in 0.8% and 0.7% of patients in the alirocumab and placebo groups, respectively (HR: 1.18; 95% CI: 0.54 to 2.58) using the Sponsor's CMQ and in 0.8% and 0.9% of patients in the alirocumab and placebo groups, respectively (HR: 0.96; 95% CI: 0.46 to 2.00) using the FDA's query.
- In the ezetimibe-controlled pool, the HR was <1.0 in both the analyses.

Thus, these analyses suggest that the incidence of neurocognitive events with alirocumab use is similar to control. Further robust analyses of neurocognitive events and rare events are anticipated to be provided by the ongoing ODYSSEY OUTCOMES study, which has estimated exposure of 60,000 patient-years at trial completion. In this study, neurocognitive events are considered adverse events of special interest and a group of outside experts, blinded to treatment and LDL-C level, are regularly reviewing all these events and providing advice on the collection of data. The expert group issues quarterly reports for the Data Monitoring Committee and will provide their assessment on the potential risk of neurocognitive events associated with alirocumab, after the data are unblinded. Finally, a specific large post-marketing clinical study will be conducted to evaluate the effect of alirocumab on neurocognitive function in patients with heterozygous familial hypercholesterolemia or with non-familial hypercholesterolemia at high and very high cardiovascular risk.

4. Should alirocumab dosing commence with 75 mg Q2W in all patients, or is there a subgroup in which the dosage should commence at 150 mg Q2W?

During the course of developing alirocumab, the paucity of data surrounding the safety, efficacy profile and utilisation of PCSK9 mAbs led to 75 mg Q2W as the usual starting dose with the potential for dose adjustment to 150 mg. This was the basis for eight of the ten Phase III trials. However, based on the extensive clinical experience and current information regarding the PK, PD, efficacy and safety profile of alirocumab, the sponsor believes that the starting dose should be selected by the prescriber, based on the patient's LDL-C level, medical history and individual target LDL-C. Physicians may want to start patients at the highest CV risk on the 150 mg Q2W dose particularly if they believe that the patient requires the lower LDL-C targets suggested by IMPROVE-IT study with ezetimibe, or other recent studies. These lower targets are anticipated to be reflected in the revised Australian clinical guidance that is currently being developed.

The 150 mg starting dose may be more likely to be selected for those patients that need a larger reduction in LDL-C. The sponsor used 60% as a threshold in two separate analyses of our Phase 3 data:

As shown in Figure 4, 36% of patients started on the 75 mg dose achieved a 60% or greater reduction in LDL-C. By contrast, nearly 70% of patients started on the 150 mg Q2W can achieve a 60% or greater reduction in LDL-C.

Nearly 800 patients in the alirocumab Phase III program achieved 2 consecutive LDL-C levels <25 mg/dL (0.65 mmol/L). The majority of these (562) were observed in patients from the ODYSSEY LONG TERM study, where patients with LDL-C >70 mg/dL (1.8 mmol/L) were started and maintained up to 78 weeks on the 150 mg Q2W dose. As shown in Figure 5, patients with lower baseline LDL-C are more likely to achieve LDL-C levels <25 mg/dL (0.65 mmol/L).

No adverse effects were identified in patients who achieved the lower levels of LDL-C (extensive examinations in the Phase III program plus a similar number of patients from a parallel PCSK9 mAb development program). As demonstrated in the early phase studies, there is a dose-dependent increase in efficacy up until the point that saturation in target binding has been achieved. At that point, any further increase in dose merely increases the reservoir of available antibody and extends the period of maximal efficacy. Based on the Phase I and II studies alirocumab dosing was designed in the following fashion:

- 150 mg Q2W represents a dose where vast majority of patients are achieving saturation binding and maximal efficacy. This is demonstrated by the fact that studies that have included higher doses than 150 mg Q2W have not demonstrated incremental increases in LDL-C efficacy.
- 75 mg Q2W represents a dose where a greater proportion of patients achieve less than saturation dosing (though some proportion of patients can achieve saturation and maximal efficacy).

Although some patients achieve saturation of PCSK9 binding and thus the same degree of LDL-C lowering with 75 mg Q2W as with 150 mg Q2W, there is no way to identify these patients a priori. In the absence of a class safety concern related to PCSK9 inhibitors or to low-LDL-C, it would be optimal to allow physicians/patients to have the choice of the most clinically appropriate dose at the initiation of therapy. For all of the above reasons the sponsor does not consider that any change to the proposed Dosage and administration Section in the PI is warranted.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Praluent / Golyra / Eliriduc solution for injection containing 75 mg/mL and 150 mg/mL of alirocumab to have an overall positive benefit–risk profile for the amended indication;

> *Praluent is indicated as an adjunct to diet and exercise in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease:*
>
> - *in combination with a statin or statin with other lipid lowering therapies or,*
> - *in combination with other lipid-lowering therapies in patients who are statin-intolerant*
>
> *The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.*

In making this recommendation the ACPM noted the submission relies on the surrogate endpoint of LDL-C reduction to demonstrate efficacy. The impact on cardiovascular

outcomes has not been established: This is considered acceptable with guidelines, in the absence of any evidence of increased cardiovascular risk.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate's proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement should be included to define statin intolerance, at least as in trial
- in the Pharmacodynamic section, the first paragraph on other lipid sub-fractions should either be removed or, if thought relevant, moved to be the last paragraph. This medicine is to be prescribed for the effect on LDL and the paragraph in question is confusing in this context
- the PI Figure 3 graph showing LDL-C levels over time may imply that the treatment effect is maximal (the y axis should extend to below drug effect at least as much as it extends above it. As it stands it is visually misleading, although it is consistent with other graphs in PI
- a table of adverse events similar to that from the US Package Insert, Very common and common AEs (Table 1 [in US Package insert]), would be appropriate to add to the Australian PI
- noted that there are no data in humans on safety in pregnancy and the Use in Pregnancy Category proposed was B1, based on studies in animals. Relevant patients should be provided with this information.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

> 1. *The sponsor has proposed that alirocumab should be indicated in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia and mixed dyslipidaemia. Please comment on whether the safety and efficacy of alirocumab has been sufficiently established for each of these subpopulations of patients with hypercholesterolaemia.*

The ACPM advised that in the absence of outcome data in the populations specified and to be consistent within the class, the indications should be limited to heterozygous familial hypercholesterolaemia or clinical atherosclerotic disease.

> 2. *The Sponsor has proposed that alirocumab should be indicated as monotherapy or with another lipid-lowering agent in patients with documented atherosclerotic cardiovascular disease who are statin intolerant or in whom statins are contraindicated. Please comment on whether the safety and efficacy of alirocumab, particularly as monotherapy, has been sufficiently established for each of the subpopulations of patients with hypercholesterolaemia.*

The ACPM advised that, given excellent data for statins, and in the absence of outcome data in the populations specified, and taking into consideration there are still outstanding uncertaintites over safety, use as monotherapy is not supported. The ACPM was of the view that use without a statin in statin intolerant patients is supported and covered by the amended indication.

3. *Please comment on the adequacy of the clinical trial program to characterise the safety issues of interest with this class of medicines such as neurocognitive effects.*

The ACPM, agreed with ASCOM advice that data on adverse neurological events and cataracts should be highlighted in the RMP should include them as '*important potential risks – cataracts, neurocognitive events* ' and mentioned in the PI. These events would be better characterised in dedicated post-market studies. Specific analyses of these events should be conducted in studies that are already underway.

4. *Should alirocumab dosing commence with 75 mg Q2W in all patients, or is there a subgroup in which the dosage should commence at 150 mg Q2W?*

The ACPM advised that all patients should commence on 75 mg Q2W and should the effect be insufficient dose escalation is available.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Praluent, Golyra and Eliriduc containing alirocumab (rch) 75mg/mL and 150mg/mL, indicated for:

Praluent / Golyra /Eliriduc is indicated as an adjunct to diet and exercise in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease:

- *in combination with a statin, or statin with other lipid-lowering therapies or,*
- *in combination with other lipid-lowering therapies in patients who are statin-intolerant.*

The effect of Praluent / Golyra /Eliriduc on cardiovascular morbidity and mortality has not yet been determined (see CLINICAL TRIALS).

Specific conditions of registration applying to these goods

- The alirocumab European Risk Management Plan (EU-RMP), version 1.3, 13 September 2015, data lock point of 31 August 2014), with Australian Specific Annex (version 1.2, 15 March 2016), included with submission (PM-2015-00764-1-3), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The sponsor is required to provide the final clinical study reports for following studies to the TGA for evaluation as a Category 1 application, when the study reports become available:
  - Study LTS11717 (LONG TERM)
  - Study EFC12492 (FH I)
  - Study CL-112 (FH II)
  - EFC12732 (HIGH FH)
  - CL-1308 (CHOICE I)
  - EFC11569 (COMBO II)
  - EFC13786 (CHOICE II)

  - EFC11570 (OUTCOMES)

- All batches of Praluent, Golyra and Eliriduc (alirocumab) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- Each batch of Praluent, Golyra and Eliriduc (alirocumab) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. The sponsor must supply:
  - Certificates of Analysis of all active ingredient (drug substance) and final product.
  - Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
  - Evidence of the maintenance of registered storage conditions during transport to Australia.
  - Five (5) Prefilled Pens and five (5) Prefilled syringes of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

The PI for Praluent approved with the submission which is described in this AusPAR is at Attachment 1. The PIs for Golyra and Eliriduc are identical except for the product name. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

Attachment 2. Extract from the Clinical Evaluation Report

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