NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Praluent 75 mg solution for injection in pre-filled pen

Praluent 150 mg solution for injection in pre-filled pen

Praluent 75 mg solution for injection in pre-filled syringe

Praluent 150 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

75 mg/ml solution for injection

Each single-use pre-filled pen contains 75 mg alirocumab in 1 ml solution. Each single-use pre-filled syringe contains 75 mg alirocumab in 1 ml solution.

150 mg/ml solution for injection

Each single-use pre-filled pen contains 150 mg alirocumab in 1 ml solution. Each single-use pre-filled syringe contains 150 mg alirocumab in 1 ml solution.

Alirocumab is a human IgG1 monoclonal antibody that targets PCSK9, produced in Chinese Hamster Ovary cells by recombinant DNA technology.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

Sterile, clear, colourless to pale yellow solution for subcutaneous injections with pH of about 6.0, containing no antimicrobial preservatives.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Primary hypercholesterolaemia

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.

Prevention of cardiovascular events

Praluent is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalisation) in adults with established cardiovascular disease, in combination with optimally dosed statins and/or other lipid-lowering therapies (see Section 5.1 Pharmacodynamic properties, CLINICAL TRIALS)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Prior to initiating Praluent secondary causes of hyperlipidaemia or mixed dyslipidaemia (e.g., nephrotic syndrome, hypothyroidism) should be excluded.

The usual starting dose for Praluent is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg once every 2 weeks, or 300 mg once every 4 weeks (monthly), administered subcutaneously.

The dose of Praluent can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels may be measured from 4 to 8 weeks after treatment initiation or titration, to assess the response and dose adjusted accordingly (up-titration or down-titration). If additional LDL-C reduction is needed in patients treated with 75 mg once every 2 weeks or 300 mg once every 4 weeks (monthly), the dosage may be adjusted to the maximum dosage of 150 mg once every 2 weeks.

If a dose is missed, the patient should administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If an every-2-week dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule. If an every-4-week dose is not administered within 7 days, instruct the patient to administer the dose, starting a new schedule based on this date.

No dose adjustments are needed for elderly patients or patients based on weight. No dose adjustments are needed for patients with mild or moderate renal or hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES)

Special populations

Paediatric population

The safety and efficacy of Praluent in children and adolescents less than 18 years of age have not been established. No data are available.

Elderly

No dose adjustment is needed for elderly patients.

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment.

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. Limited data are available in patients with severe renal impairment (see section 5.2).

Body weight

No dose adjustment is needed in patients based on weight.

Method of administration

Praluent is injected as a subcutaneous injection into the thigh, abdomen or upper arm.

To administer the 300 mg dose, give two 150 mg injections consecutively at two different injection sites.

It is recommended to rotate the injection site with each injection.

Praluent should not be injected into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

The patient may either self-inject Praluent, or a caregiver may administer Praluent, after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

Praluent must not be co-administered with other injectable medicinal products at the same injection site.

Praluent is a sterile product and contains no antimicrobial preservatives. Each pre-filled pen or pre-filled syringe is for single use in one patient only.

Before administration, Praluent should be inspected visually for particulate matter and discolouration. If the solution is discoloured or contains particulate matter, the solution should not be used.

Precautions to be taken before handling

To avoid discomfort, Praluent should be allowed to warm to room temperature (up to 25°C) for 30 to 40 minutes prior to use. Do not heat, let it warm up on its own. Praluent should be used as soon as possible after it has warmed up. Time out of refrigeration should not exceed a maximum of 30 days at temperatures below 25°C. (See Section 6.6)

After use, place the Praluent pre-filled pen or pre-filled syringe into a puncture resistant container and discard in accordance with local requirements.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Allergic reactions

General allergic reactions, including pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in clinical studies. Angioedema has been reported in the post-marketing setting (Section 4.8). If signs or symptoms of serious allergic reactions occur, treatment with Praluent must be discontinued and appropriate symptomatic treatment initiated (Section 4.3).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In the ODYSSEY OUTCOMES trial, 5.5% of patients treated with alirocumab 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) detected after initiating treatment compared with 1.6% of patients treated with placebo, most of these were transient responses. Persistent ADA responses were observed in 0.7% of patients treated with alirocumab and 0.4% of patients treated with placebo. Neutralising antibody (NAb) responses were observed in 0.5% of patients treated with alirocumab and in <0.1% of patients treated with placebo in the OUTCOMES trial. Only 1.2% of patients exhibited neutralising antibodies (NAb) in the ten pooled phase 3 studies in the hypercholesterolaemia program, all of them in the alirocumab group.

Anti-drug antibody responses, including NAb, were low titer and did not appear to have a clinically meaningful impact on the efficacy or safety of alirocumab for most patients. Patients

with treatment emergent ADA experienced a higher rate of injection site reactions compared to patients who were ADA negative (7.5% vs 3.6%).

The long-term consequences of continuing alirocumab treatment in the presence of ADA are unknown.

In a pool of ten placebo-controlled and active-controlled trials of patients treated with alirocumab 75 mg and/or 150 mg Q2W as well as in a separate clinical study of patients treated with alirocumab 75 mg Q2W or 300 mg every 4 weeks (including some patients with dose adjustment to 150 mg Q2W), the incidence of detecting ADA and NAb was similar to the results from the ODYSSEY OUTCOMES trial described above.

Immunogenicity data are highly dependent on the sensitivity and specificity of the ADA assay.

Low LDL-C

No adverse consequences of very low LDL-C were observed in clinical and observational trials with Praluent.

Renal impairment

In clinical studies, there was limited representation of patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m^2) (Section 5.2). Praluent should be used with caution in patients with severe renal impairment.

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (Section 5.2). Praluent should be used with caution in patients with severe hepatic impairment.

Elderly

In the phase 3 primary hypercholesterolaemia and mixed dyslipidaemia controlled studies, 1158 patients (34.7%) treated with Praluent were ≥65 years of age and 241 patients (7.2%) treated with Praluent were ≥75 years of age. In the cardiovascular outcomes-controlled study, 2505 patients (26.5%) treated with Praluent were ≥65 years of age and 493 patients (5.2%) treated with Praluent were ≥75 years of age. There were no significant differences observed in safety and efficacy with increasing age.

Paediatric

The safety and efficacy of Praluent in patients below the age of 18 have not been established.

Effects on laboratory tests

No interactions with laboratory tests have been identified.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Effects of alirocumab on other medicinal products

Since alirocumab is a biological medicinal product, no pharmacokinetic effects of alirocumab on other medicinal products and no effect on cytochrome P450 enzymes are anticipated. In clinical studies where alirocumab was administered in combination with atorvastatin or rosuvastatin, no relevant changes in statin concentrations were observed in the presence of repeated administration of alirocumab, indicating that cytochrome P450 enzymes (mainly CYP3A4 and CYP2C9) and transporter proteins such as P-gp and OATP were not affected by alirocumab.

Effects of other medicinal products on alirocumab

Statins and other lipid-modifying therapy are known to increase production of PCSK9, the protein targeted by alirocumab. Because a component of the clearance of alirocumab is target-mediated, an elevation in target could lead to lower alirocumab exposure. However, this effect does not impact the duration of efficacy when alirocumab is administered every two weeks.

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility

There were no adverse effects on surrogate markers of fertility (e.g. oestrous cyclicity, testicular volume, ejaculate volume, sperm motility, sperm concentration and total sperm count per ejaculate) in a 26-week toxicity study in sexually-mature monkeys. The highest dose in this study resulted in a serum AUC that was about 100 times that expected in patients at the maximum recommended dose. In addition, there were no alirocumab-related macroscopic or microscopic findings in reproductive tissues in any rat or monkey toxicity study.

Pregnancy

The use of Praluent is not recommended during pregnancy.

There are no data from the use of Praluent in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity.

When pregnant female animals were exposed to alirocumab, measurable alirocumab concentrations in serum were observed in fetal rats (and also infant monkeys), indicating that alirocumab, like other IgG antibodies, crosses the placenta.

There were no adverse effects on foetal growth or development in the rat embryofoetal development study conducted at doses up to 75 mg/kg/dose administered on gestation days 6 and 12. At this dose, serum AUC was about 20 times the AUC expected in patients at the maximum recommended dose.

There was a slight attenuation of secondary anti-KLH IgG antibody response in infant offspring of cynomolgus monkeys dosed with alirocumab during organogenesis to parturition at maternal exposure of 13-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. Alirocumab given at subcutaneous doses of up to 75 mg/kg/week to pregnant monkeys from gestation day 20 until parturition, had no adverse effects on the growth and development of offspring up to 6 months post-birth. At this dose, serum AUC was about 80 fold the AUC expected in patients at the maximum recommended dose.

Animal studies are not always predictive of human response. Therefore, it is not known whether Praluent can cause foetal harm when administered to a pregnant woman and Praluent should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

For use in combination therapy with a statin

Statins are contraindicated in pregnant women. Please refer to the current respective product information.

Breast-feeding

It is not known whether alirocumab is excreted in human milk. Many drugs and human immunoglobulin G (IgG) are excreted in human milk, in particular in colostrum; the use of Praluent is not recommended in breast-feeding women during this period. A decision should be made whether to discontinue nursing or to discontinue Praluent.

For use in combination therapy with a statin

Statins are contraindicated in breast-feeding women. Please refer to the current respective product information.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Praluent has no or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The safety data are based on pooled results from nine placebo-controlled studies (four phase 2 and five phase 3 studies, all in patients on background statin), and five ezetimibe-controlled phase 3 studies (with three studies in patients on background statin). This reflects exposure to alirocumab in 3340 patients (3451 patient-years of exposure), the majority with high or very high cardiovascular risk, treated with alirocumab at a dose of 75 and/or 150 mg, administered subcutaneously once every 2 weeks, for a treatment duration of up to 18 months (including 2408 patients exposed to alirocumab for at least 52 weeks, and 639 patients exposed to alirocumab for at least 76 weeks).

In ten phase 3 controlled trials, involving patients with primary hypercholesterolaemia and mixed dyslipidaemia, most common adverse reactions were local injection site reactions, upper respiratory tract signs and symptoms, and pruritus. Most common adverse reactions leading to treatment discontinuation in patients treated with Praluent were local injection site reactions.

The safety profile in ODYSSEY OUTCOMES (a long-term cardiovascular outcome trial) was consistent with the overall safety profile described in the phase 3 controlled trials. A total of 9451 patients were exposed to Praluent for a median of 31 months and 9443 patients were exposed to placebo for a median of 32 months.

No difference in the safety profile was observed between the two doses (75 mg and 150 mg) used in the phase 3 program.

Tabulated list of adverse reactions

In controlled studies, 1158 patients (34.7%) treated with Praluent were ≥65 years of age and 241 patients (7.2%) treated with Praluent were ≥75 years of age. There were no significant differences observed in safety and efficacy with increasing age.

Table 1 shows the adverse reactions reported in patients treated with alirocumab in pooled phase 3 controlled studies and the ODYSSEY OUTCOMES trial. Frequencies for all events have been calculated based on their incidence in pooled phase 3 clinical trials.

Adverse reactions are presented by system organ class. Frequency categories are defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 1 - Adverse Reactions reported in patients treated with alirocumab in pooled phase 3 controlled studies and ODYSSEY OUTCOMES

System organ class	*Common*	*Rare*
Immune system disorders		Hypersensitivity, hypersensitivity vasculitis
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract signs and symptoms[a]	
Skin and subcutaneous tissue disorders	Pruritus	Urticaria, eczema nummular
General disorders and administration site conditions	Injection site reactions[b]	

a Including mainly oropharyngeal pain, rhinorrhea, sneezing

b Including erythema/redness, itching, swelling, pain/tenderness

Table 2 shows the adverse events reported in ≥1% of patients treated with alirocumab and more frequently than with placebo in pooled placebo-controlled studies.

Table 2 Adverse events occurring in ≥1% of patients treated with alirocumab and more frequently than with placebo in the pool of placebo-controlled trials

Primary System Organ Class Preferred Term n(%)	Placebo (N=1276)	Alirocumab (N=2476)
Infections and infestations		
Nasopharyngitis	147 (11.5%)	301 (12.2%)
Influenza	63 (4.9%)	147 (5.9%)
Urinary tract infection	65 (5.1%)	129 (5.2%)
Bronchitis	58 (4.5%)	113 (4.6%)
Sinusitis	38 (3.0%)	80 (3.2%)
Pneumonia	18 (1.4%)	37 (1.5%)
Gastroenteritis viral	10 (0.8%)	32 (1.3%)
Pharyngitis	13 (1.0%)	29 (1.2%)
Tooth abscess	13 (1.0%)	26 (1.1%)
Cellulitis	12 (0.9%)	25 (1.0%)
Conjunctivitis	11 (0.9%)	25 (1.0%)
Blood and lymphatic system disorders		
Anaemia	12 (0.9%)	27 (1.1%)
Metabolism and nutrition disorders		
Diabetes mellitus	13 (1.0%)	34 (1.4%)
Gout	13(1.0%)	33 (1.3%)
Nervous system disorders		
Paraesthesia	11 (0.9%)	28 (1.1%)
Cardiac disorders		
Angina unstable	13 (1.0%)	37 (1.5%)
Respiratory, thoracic and mediastinal disorders		
Cough	31 (2.4%)	68 (2.7%)
Oropharyngeal pain	8 (0.6%)	30 (1.2%)

Primary System Organ Class Preferred Term n(%)	Placebo (N=1276)	Alirocumab (N=2476)
Gastrointestinal disorders		
Diarrhoea	61 (4.8%)	128 (5.2%)
Constipation	21 (1.6%)	46 (1.9%)
Abdominal pain	19 (1.5%)	40 (1.6%)
Abdominal pain upper	12 (0.9%)	30 (1.2%)
Skin and subcutaneous tissue disorders		
Rash	16 (1.3%)	34 (1.4%)
Pruritus	5 (0.4%)	31 (1.3%)
Musculoskeletal and connective tissue disorders		
Myalgia	47 (3.7%)	112 (4.5%)
Muscle spasms	39 (3.1%)	82 (3.3%)
Musculoskeletal pain	20 (1.6%)	57 (2.3%)
General disorders and administration site conditions		
Injection site reaction	63 (4.9%)	171 (6.9%)
Oedema peripheral	16 (1.3%)	39 (1.6%)
Investigations		
Alanine aminotransferase increased	12 (0.9%)	29 (1.2%)
Injury, poisoning and procedural complications		
Contusion	17 (1.3%)	57 (2.3%)
Accidental overdose	17 (1.3%)	35 (1.4%)
Laceration	8 (0.6%)	27 (1.1%)

Table 3 shows the adverse events reported in ≥1% of patients treated with alirocumab and more frequently than with ezetimibe in pooled ezetimibe-controlled studies.

Table 3 Adverse events occurring in ≥1% of patients treated with alirocumab and more frequently than with ezetimibe in the pool of ezetimibe-controlled trials

Primary System Organ Class Preferred Term n(%)	Ezetimibe (N=618)	Alirocumab (N=864)
Infections and infestations		
Upper respiratory tract infection	40 (6.5%)	62 (7.2%)
Influenza	23 (3.7%)	37 (4.3%)
Pneumonia	12 (1.9%)	19 (2.2%)
Tooth abscess	3 (0.5%)	9 (1.0%)
Metabolism and nutrition disorders		
Type 2 diabetes mellitus	7 (1.1%)	11 (1.3%)
Psychiatric disorders		
Insomnia	9 (1.5%)	18 (2.1%)
Nervous system disorders		
Headache	24 (3.9%)	43 (5.0%)
Paraesthesia	3 (0.5%)	9 (1.0%)
Eye disorders		
Cataract	7 (1.1%)	11 (1.3%)
Ear and labyrinth disorders		
Vertigo	5 (0.8%)	9 (1.0%)
Cardiac disorders		
Angina pectoris	11 (1.8%)	16 (1.9%)
Acute myocardial infarction	4 (0.6%)	13 (1.5%)
Angina unstable	6 (1.0%)	13 (1.5%)
Atrial fibrillation	8 (1.3%)	13 (1.5%)
Palpitations	6(1.0%)	11(1.3%)

Primary System Organ Class Preferred Term n(%)	Ezetimibe (N=618)	Alirocumab (N=864)
Vascular disorders		
Hypertension	28 (4.5%)	42 (4.9%)
Respiratory, thoracic and mediastinal disorders		
Cough	13 (2.1%)	20 (2.3%)
Chronic obstructive pulmonary disease	2 (0.3%)	11 (1.3%)
Epistaxis	4 (0.6%)	10 (1.2%)
Gastrointestinal disorders		
Diarrhoea	21 (3.4%)	30 (3.5%)
Constipation	11 (1.8%)	20 (2.3%)
Skin and subcutaneous tissue disorders		
Rash	7 (1.1%)	13 (1.5%)
Musculoskeletal and connective tissue disorders		
Arthralgia	26 (4.2%)	42 (4.9%)
Muscle spasms	15 (2.4%)	25 (2.9%)
Osteoarthritis	14 (2.3%)	21 (2.4%)
Musculoskeletal pain	8 (1.3%)	15 (1.7%)
Renal and urinary disorders		
Haematuria	5 (0.8%)	14 (1.6%)
General disorders and administration site conditions		
Fatigue	9 (1.5%)	28 (3.2%)
Injection site reaction	13 (2.1%)	25 (2.9%)
Non-cardiac chest pain	14 (2.3%)	22 (2.5%)
Oedema peripheral	9 (1.5%)	14 (1.6%)
Injury, poisoning and procedural complications		

Primary System Organ Class Preferred Term n(%)	Ezetimibe (N=618)	Alirocumab (N=864)
Accidental overdose	24 (3.9%)	54 (6.3%)
Fall	11 (1.8%)	22 (2.5%)
Contusion	6 (1.0%)	12 (1.4%)

Table 4 shows the adverse events reported in ≥2% of patients treated with alirocumab 300 mg monthly dose as compared to placebo and alirocumab fortnightly dose, irrespective of concomitant statin therapy.

Table 4 Adverse events occurring in ≥2% of patients treated with alirocumab 300 mg monthly as compared to placebo, irrespective of concomitant statin therapy

Primary System Organ Class Preferred Term n(%)	Placebo (N=229)	Alirocumab 75 mg/150 mg Q2W (N=115)	Alirocumab 300 mg Q4W (N=458)
Infections and infestations			
Upper respiratory tract infection	18 (7.9%)	8 (7.0%)	41 (9.0%)
Nasopharyngitis	18 (7.9%)	10 (8.7%)	39 (8.5%)
Sinusitis	11 (4.8%)	4 (3.5%)	28 (6.1%)
Urinary tract infection	10 (4.4%)	7 (6.1%)	28 (6.1%)
Lower respiratory tract infection	2 (0.9%)	3 (2.6%)	13 (2.8%)
Metabolism and nutrition disorders			
Type 2 diabetes mellitus	2 (0.9%)	1 (0.9%)	11 (2.4%)
Nervous system disorders			
Headache	13 (5.7%)	6 (5.2%)	29 (6.3%)
Dizziness	9 (3.9%)	5 (4.3%)	19 (4.1%)
Respiratory, thoracic and mediastinal disorders			
Nasal congestion	5 (2.2%)	4 (3.5%)	11 (2.4%)
Musculoskeletal and connective tissue disorders			
Back pain	14 (6.1%)	4 (3.5%)	29 (6.3%)
Pain in extremity	2 (0.9%)	4 (3.5%)	21 (4.6%)
Osteoarthritis	6 (2.6%)	3 (2.6%)	20 (4.4%)
Myalgia	8 (3.5%)	2 (1.7%)	17 (3.7%)
Musculoskeletal pain	5 (2.2%)	4 (3.5%)	16 (3.5%)

Primary System Organ Class Preferred Term n(%)	Placebo (N=229)	Alirocumab 75 mg/150 mg Q2W (N=115)	Alirocumab 300 mg Q4W (N=458)
General disorders and administration site conditions			
Injection site reaction	16 (7.0%)	10 (8.7%)	74 (16.2%)
Injury, poisoning and procedural complications			
Fall	6 (2.6%)	1 (0.9%)	14 (3.1%)

Adverse Reactions in the Cardiovascular Outcomes Trial

In a double-blind, randomised, placebo-controlled cardiovascular outcomes trial (Study 1: ODYSSEY OUTCOMES, NCT01663402), 18,924 patients received at least one dose of PRALUENT or placebo [see Clinical Studies (14.1)]. The mean age was 58 years (range: 39 to 92 years), 25.2% women, 79.4% Caucasian, 2.5% Black, 13.2% Asian, and 16.6% Hispanic/Latino. Patients were exposed to PRALUENT for a median of 31 months; 87% of patients were exposed for ≥12 months, 78% were exposed for ≥24 months, 33% were exposed for ≥36 months, and 6% were exposed for ≥48 months.

The safety profile of PRALUENT in this trial was consistent with the safety profile described above in the placebo-controlled trials involving patients with primary hyperlipidemia and mixed dyslipidaemia. Serious adverse events occurred in 23.3% of PRALUENT-treated patients and 24.9% of placebo-treated patients. Adverse events led to discontinuation of study treatment in 3.8% of patients treated with PRALUENT and 3.7% treated with placebo. The only adverse reaction reported in at least 2% of PRALUENT-treated patients, and occurring more frequently than in placebo-treated patients, was local injection site reactions (3.8% PRALUENT, 2.1% placebo). General allergic reactions were similar in PRALUENT-treated patients and placebo-treated patients (7.9% PRALUENT, 7.8% placebo). No difference was seen in the incidence of pruritus.

Table 5 shows the adverse events reported in>1% of patients treated with Praluent and more frequently than with placebo in the ODYSSEY OUTCOMES study.

Table 5 Adverse events occurring in > 1% of patients treated with PRALUENT and more frequently than with placebo in the cardiovascular outcomes study (ODYSSEY OUTCOMES)

System Organ Class Preferred Term*	Placebo (N=9443)	Alirocumab (N=9451)
Any class	77.1%	75.8%
Ear and labyrinth disorders		
Vertigo	1.3%	1.4%
Gastrointestinal disorders		

Nausea	1.8%	2.1%
Gastroesophageal reflux disease	1.4%	1.7%
Abdominal pain upper	1.3%	1.4%
General disorders and administration site conditions		
Non-cardiac chest pain	6.8%	7.0%
Injection site reaction	1.4%	2.8%
Infections and infestations		
Nasopharyngitis	5.6%	6.0%
Sinusitis	1.3%	1.5%
Lower respiratory tract infection	1.0%	1.1%
Injury, poisoning and procedural complications		
Contusion	1.7%	1.8%
Musculoskeletal and connective tissue disorders		
Myalgia	5.3%	5.6%
Back pain	4.2%	4.3%
Arthralgia	3.7%	3.9%
Muscle spasms	2.1%	2.3%
Nervous system disorders		
Hypoaesthesia	0.9%	1.0%
Psychiatric disorders		
Insomnia	1.3%	1.5%
Reproductive system and breast disorders		
Benign prostatic hyperplasia	1.2%	1.3%
Erectile dysfunction	0.9%	1.0%
Skin and subcutaneous tissue disorders		
Rash	1.1%	1.2%
Vascular disorders		
Hypotension	1.8%	1.9%

* coded using MedDRA version 20.1

Description of selected adverse reactions

Local injection site reactions

Local injection site reactions, including erythema/redness, itching, swelling, and pain/tenderness, were reported in 6.1% of patients treated with alirocumab versus 4.1% in the control group (receiving placebo injections) with Q2W dosing and in 16.6% of patients treated with alirocumab compared to 7.9% in the placebo arm in the Q4W dose regimen. Patients in the alirocumab 300 mg every 4 weeks treatment group received alternating placebo injections to maintain blinding in regard to injection frequency. Excluding injection site reactions (ISRs) that occurred after these placebo injections, the frequency of ISRs was 11.8% in the alirocumab group. Most injection site reactions were transient and of mild intensity. The discontinuation rate due to local injection site reactions was comparable between the two groups (0.2% in the alirocumab group versus 0.3% in the control group). with the Q2W dose regimen, and 0.7% in the alirocumab group versus 0% in the placebo group with the Q4W dose regimen. In the cardiovascular outcomes study (ODYSSEY OUTCOMES), injection site reactions also occurred more frequently in alirocumab-treated patients than in placebo-treated patients (3.8% alirocumab 2.1% placebo).

General allergic reactions

General allergic reactions were reported more frequently in the alirocumab group than in the control group, mainly due to a difference in the incidence of pruritus. The observed cases of pruritus were typically mild and transient. In addition, rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in controlled clinical studies. (see Section 4.4). In the cardiovascular outcomes study (ODYSSEY OUTCOMES), general allergic reactions were similar in alirocumab-treated patients and placebo-treated patients (7.9% alirocumab 7.8% placebo). No difference was seen in the incidence of pruritus.

Low LDL-C values

LDL-C values <25 mg/dL (<0.65 mmol/L)

In all clinical studies background lipid lowering therapies could not be adjusted by trial design. The percentage of patients who reached LDL-C values <25 mg/dL (<0.65 mmol/L) depended both on the baseline LDL-C and the dose of alirocumab.

In a pool of controlled studies using a 75 mg every 2 week (Q2W) starting dose and in which the dose was increased to 150 mg Q2W if the patient's LDL-C was not <70 mg/dL or < 100 mg/dL (1.81 mmol/L or 2.59 mmol/L), 29.3% of patients with baseline LDL-C <100 mg/dL and 5.0% of patients with baseline LDL-C ≥100 mg/dL treated with alirocumab had two consecutive values of LDL-C <25 mg/dL (<0.65 mmol/L). In the ODYSSEY OUTCOMES study, in which the starting alirocumab dose was 75 mg Q2W and the dose was increased to 150 mg Q2W if the patient's LDL-C was not <50 mg/dL (1.29 mmol/L), 54.8% of patients with baseline LDL-C <100 mg/dL and 24.2% of patients with baseline LDL-C ≥100 mg/dL treated with alirocumab had two consecutive values of LDL-C <25 mg/dL (<0.65 mmol/L).

No adverse consequences of very low LDL-C were observed in clinical and observational trials with Praluent.

Cardiovascular (CV) events

In pre-specified analysis of pooled phase 3 studies the ten pooled phase 3 studies in the hypercholesterolaemia program, treatment-emergent CV events confirmed by adjudication, consisting of coronary heart disease (CHD) death, myocardial infarction, ischemic stroke, unstable angina requiring hospitalisation, congestive heart failure hospitalisation, and revascularisation, were reported in 129 (4.1%) patients in the alirocumab group and 63 (3.5%) patients in the control group (placebo or active control) with Hazard ratios (HR)=1.06 (95% CI, 0.79 to 1.44). MACE confirmed by adjudication were reported in 65 of 3182 (2.0%) patients in the alirocumab group and 39 of 1792 (2.2%) patients in the control group (placebo or active control); HR=0.85 (95% CI, 0.57 to 1.27).

In pre-specified final analyses of the LONG TERM study, treatment-emergent CV events confirmed by adjudication occurred in 72 of 1550 (4.6%) patients in the alirocumab group and in 40 of 788 (5.1%) patients in the placebo group; MACE confirmed by adjudication were reported in 27 of 1550 (1.7%) patients in the alirocumab group and 26 of 788 (3.3%) patients in the placebo group. Hazard ratios were calculated post-hoc; for all CV events, HR=0.91 (95% CI, 0.62 to 1.34); for MACE, HR=0.52 (95% CI, 0.31 to 0.90).

All-cause mortality

All-cause mortality in the ten pooled phase 3 studies in the hypercholesterolaemia program was 0.8% (26 of 3182 patients) in the alirocumab group and 1.1% (20 of 1792 patients) in the control group. The primary cause of death in the majority of these patients was CV events.

Neurocognitive Events

Neurocognitive events were reported in 0.8% of patients treated with alirocumab and 0.7% of patients treated with placebo. Confusion or memory impairment were each reported in 0.2% of patients treated with alirocumab and in <0.1% (for each) in the placebo group patients. The majority of neurocognitive events were non-serious. The causal relationship between these events and alirocumab has not been established.

Post-marketing experience

The following adverse reactions have been reported during post-approval use of Praluent. The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data).

- General disorders and administration site conditions
  - Flu-like illness
- Skin and subcutaneous tissue disorders

- Angioedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

In controlled clinical studies, no safety issues were identified with more frequent dosing than the recommended every 2 week dosing schedule. There is no specific treatment for Praluent overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

For information on the management of overdose, contact the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on overdose management.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other lipid modifying agents, ATC code: C10AX14

Alirocumab inhibits PCSK9 activity in both *in vitro* assays and *in vivo* model systems. Many studies in animals and humans have demonstrated the central role that elevated levels of LDL-C play in the initiation and progression of atherosclerosis.

Mechanism of action

Alirocumab is a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to proprotein 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 primary receptor that clears circulating LDL, 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 LDLR also binds triglyceride-rich VLDL remnant lipoproteins and intermediate-density lipoprotein (IDL). Therefore, alirocumab treatment can produce reductions in these remnant lipoproteins as evidenced by its reductions in apolipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TG). Alirocumab also results in

reductions in lipoprotein (a) [Lp(a)], which is a form of LDL that is bound to apolipoprotein (a). However, the LDLR has been shown to have a low affinity for Lp(a), therefore the exact mechanism by which alirocumab lowers Lp(a) is not fully understood.

In genetic studies in humans, PCSK9 variants with either loss-of-function or gain-of-function mutations have been identified. Individuals with single allele PCSK9 loss-of-function mutation have lower levels of LDL-C, which correlated with a significantly lower incidence of coronary heart disease. A few individuals have been reported, who carry PCSK9 loss-of-function mutations in two alleles and have profoundly low LDL-C levels, with HDL-C and TG levels in the normal range. Conversely, gain-of-function mutations in the PCSK9 gene have been identified in patients with increased LDL-C levels and a clinical diagnosis of familial hypercholesterolaemia.

Observational analyses have demonstrated that the untreated LDL-C levels in patients with gain-of-function mutations in the PCSK9 gene are in a similar range to those observed in patients with the more traditional mutations that cause heterozygous FH (heFH) (such as in the LDLR gene) demonstrating a central role for PCSK9 in LDL-C metabolism and levels. In a multicenter, double-blind, placebo-controlled, 14 week study, 13 patients with heterozygous familial hypercholesterolaemia (heFH) due to gain-of-function mutations in the PCSK9 gene were randomised to receive either alirocumab 150 mg Q2W or placebo. Mean baseline LDL-C was 151.5 mg/dL (3.90 mmol/L). At week 2, the mean reduction from baseline in LDL-C was 62.5% in the alirocumab-treated patients as compared to 8.8% in the placebo patients. At week 8, the mean reduction in LDL-C from baseline with all patients treated with alirocumab was 72.4%.

Pharmacodynamic effects

In *in vitro* assays, alirocumab did not induce Fc-mediated effector function activity (antibody-dependent cell-mediated toxicity and complement-dependent cytotoxicity) either in the presence or absence of PCSK9 and no soluble immune complexes capable of binding complement proteins were observed for alirocumab when bound to PCSK9.

The pharmacodynamic effect of alirocumab in lowering LDL-C is indirect, and mediated through the binding to PCSK9. A concentration-dependent reduction in free PCSK9 and LDL-C is observed until target saturation is achieved. Upon saturation of PCSK9 binding, further increases in alirocumab concentrations do not result in a further LDL-C reduction, however an extended duration of the LDL-C lowering effect is observed.

Clinical efficacy and safety

Summary of the Phase 3 Clinical Trials Program – 75 mg and/or 150 mg every 2 weeks (Q2W) dosing regimen

The efficacy of alirocumab was investigated in ten phase 3 trials (five placebo-controlled and five ezetimibe-controlled studies), involving 5296 randomised patients with hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, with 3188 patients randomised to alirocumab. In the phase 3 studies, 31% of patients had type 2 diabetes mellitus, and 64% of patients had a history of coronary heart disease. Three of the ten studies were conducted

exclusively in patients with heterozygous familial hypercholesterolaemia (heFH). The majority of patients in the phase 3 program were taking background lipid-modifying therapy consisting of a maximally tolerated dose of statin, with or without other lipid-modifying therapies, and were at high or very high cardiovascular (CV) risk. Two studies were conducted in patients who were not concomitantly treated with a statin, including one study in patients with documented statin intolerance. Alirocumab has not been studied in patients with homozygous familial hypercholesterolaemia.

Eight studies were performed with a dose of 75 mg once every 2 weeks, and criteria-based up-titration to 150 mg once every 2 weeks at week 12 in patients who did not achieve their pre-defined target LDL-C based on their level of CV risk at week 8. Two studies (LONG TERM and HIGH FH), involving a total of 2416 patients, were performed with a 150 mg every 2 weeks (Q2W) dose only. Baseline demographic characteristics were well matched between the Praluent and control groups. The age of the patients ranged from 18 to 89 years across studies (mean age 60 years); 38% were women; the majority of patients were Caucasian (90%), 5% were Black, 2% were Asian; the mean body mass index (BMI) was 30 kg/m^2. In the phase 3 studies, 31% of patients had type 2 diabetes mellitus, and 64% of patients had a history of coronary heart disease.

The primary efficacy endpoint in all of the phase 3 studies was the mean percent reduction from baseline in LDL-C at week 24 as compared to placebo or ezetimibe. All of the studies met their primary endpoint.

In general, administration of alirocumab also resulted in a statistically significant greater percent reduction in total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), and lipoprotein (a) [Lp(a)] as compared to placebo/ ezetimibe, whether or not patients were concomitantly being treated with a statin. Alirocumab also reduced triglycerides (TG), and increased high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (Apo A-1) as compared to placebo. For detailed results see Table 7 below. Reduction in LDL-C was seen across age, gender, body mass index (BMI), race, baseline LDL-C levels, patients with heFH and non-heFH, patients with mixed dyslipidaemia, and diabetic patients. Although similar efficacy was observed in patients over 75 years, data are limited in this age group. LDL-C reduction was consistent regardless of concomitantly used statins and doses. A significantly higher proportion of patients achieved an LDL-C of <70 mg/dL (<1.81 mmol/L) in the alirocumab group as compared to placebo or ezetimibe at week 12 and week 24. In studies using the criteria- based up-titration regimen, a majority of patients achieved the pre-defined target LDL-C (based on their level of CV risk) on the 75 mg Q2W dose, and a majority of patients maintained treatment on the 75 mg Q2W dose. The lipid-lowering effect of alirocumab was observed within 15 days after the first dose reaching maximum effect at approximately 4 weeks. With long-term treatment, efficacy was sustained over the duration of the studies (up to 2 years). Following discontinuation of alirocumab, no rebound in LDL-C was observed, and LDL-C levels gradually returned to baseline levels.

In pre-specified analyses before possible up-titration at week 12 in the 8 studies in which patients started with the 75 mg every 2 weeks dosing regimen, mean reductions in LDL-C ranging from 44.5% to 49.2% were achieved. In the 2 studies in which patients were started and maintained on 150 mg every 2 weeks, the achieved mean reduction of LDL-C at week 12 was 62.6%. In analyses of pooled phase 3 studies that allowed up-titration, among the subgroup of patients up-titrated, an

increase from 75 mg Q2W to 150 mg Q2W alirocumab at week 12 resulted in an additional 14% mean reduction in LDL-C in patients on a background statin. In patients not on a background statin, up-titration of alirocumab resulted in an additional 3% mean reduction in LDL-C, with the majority of the effect seen in approximately 25% of patients who achieved at least an additional 10% LDL-C lowering after up-titration. Patients up-titrated to 150 mg Q2W had a higher mean baseline LDL-C.

Table 6 summarises the mean percent change from baseline in LDL-C with Praluent at week 12 (before up-titration) and at week 24 (primary endpoint) based on analyses across pooled phase 3 studies.

Table 6 Mean percent change from baseline in LDL-C with alirocumab at week 12 (before up-titration) and week 24 (primary endpoint) in analyses of pooled phase 3 studies[a]

Week 12	**Placebo controlled studies**		**Ezetimibe controlled studies**			
			Without Background Statin		**With Background Statin**	
Dose	Praluent (additive effect beyond statin)	Placebo (additive effect beyond statin)	Praluent	Ezetimibe	Praluent (additive effect beyond statin)	Ezetimibe (additive effect beyond statin)
75 mg Q2W	-44.5	4.1	-47.0	-15.6	-49.2	-22.3
150 mg Q2W	-62.6	1.1	-	-	-	-
Week 24						
Dose	Praluent (additive effect beyond statin)	Placebo (additive effect beyond statin)	Praluent	Ezetimibe	Praluent (additive effect beyond statin)	Ezetimibe (additive effect beyond statin)
75/150 mg Q2W (up-titration studies)[b]	-48.6	4.2	-45.0	-14.6	-48.9	-19.3
150 mg Q2W	-60.4	0.5	-	-	-	-

[a] Based on ITT analysis - intent-to-treat population, includes all lipid data throughout the duration of the study irrespective of adherence to the study treatment.

[b] Dose was up-titrated to 150 mg once every 2 weeks in 228 (34.5%) patients treated beyond 12 weeks in the placebo-controlled studies and in 180 (22.9%) patients treated beyond 12 weeks in the ezetimibe-controlled studies.

Baseline LDL-C in analyses of pooled up-titration studies (COMBO I, FH I and FH II) was 3.33 mmol/L in the Praluent group and 3.36 mmol/L in the placebo group.

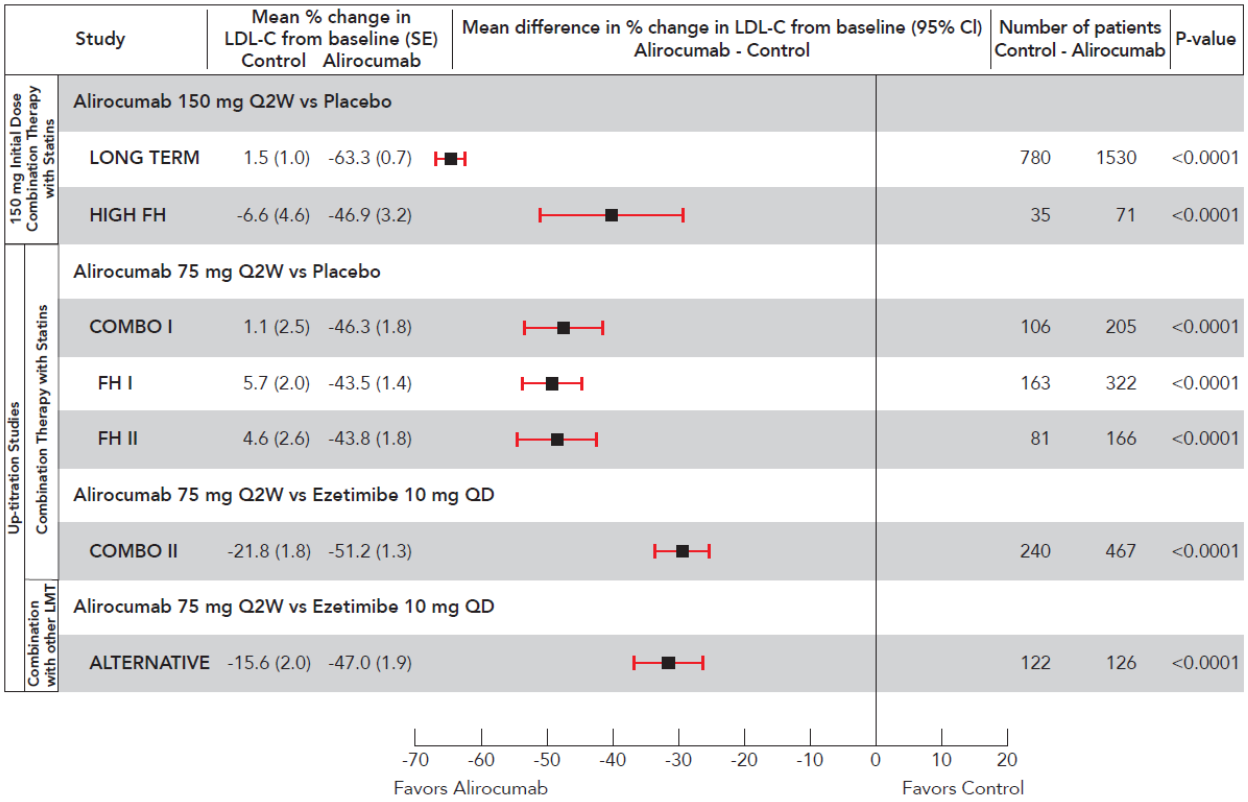
Baseline LDL-C in analyses of pooled studies using the 150 mg once every 2 weeks dose (LONG TERM, HIGH FH) was 3.26 mmol/L in the Praluent group and 3.24 mmol/L in the placebo group.

Baseline LDL-C in analyses of ezetimibe controlled study not on background statin (ALTERNATIVE) was 5.0 mmol/L in the alirocumab group and 5.03 mmol/L in the ezetimibe group.

Baseline LDL-C in analyses of pooled studies on background statin (COMBO II, OPTIONS I and II) was 2.83 mmol/L in the Praluent group and 2.71 mmol/L in the ezetimibe group.

Figure 1 summarises the mean reduction from baseline in LDL-C with Praluent at week 12 (before up-titration) across phase 3 studies. This figure shows the efficacy of the 75 mg once every 2 week and 150 mg once every 2 week doses. Week 24 results are provided in the description of the individual studies.

Figure 1 Summary of mean reduction from baseline in LDL-C with Praluent at week 12 (before up-titration) across phase 3 studies.



Evaluation of Cardiovascular (CV) events

A cardiovascular outcomes trial whose primary endpoint is adjudicated major adverse cardiovascular events (MACE, i.e. CHD death, myocardial infarction, ischemic stroke, and unstable angina requiring hospitalisation) is ongoing.

In pre-specified analyses of pooled phase 3 studies, treatment-emergent CV events confirmed by adjudication, consisting of coronary heart disease (CHD) death, myocardial infarction, ischemic stroke, unstable angina requiring hospitalisation, congestive heart failure hospitalisation, and revascularisation, were reported in 110 (3.5%) patients in the alirocumab group and 53 (3.0%) patients in the control group (placebo or active control) with HR=1.08 (95% CI, 0.78 to 1.50). MACE confirmed by adjudication were reported in 52 of 3182 (1.6%) patients in the alirocumab group and 33 of 1792 (1.8%) patients in the control group (placebo or active control); HR=0.81 (95% CI, 0.52 to 1.25).

In pre-specified final analyses of the LONG TERM study, treatment-emergent CV events confirmed by adjudication occurred in 72 of 1550 (4.6%) patients in the alirocumab group and in 40 of 788 (5.1%) patients in the placebo group; MACE confirmed by adjudication were reported in 27 of 1550 (1.7%) patients in the alirocumab group and 26 of 788 (3.3%) patients in the placebo group. Hazard ratios were calculated post-hoc; for all CV events, HR=0.91 (95% CI, 0.62 to 1.34); for MACE, HR=0.52 (95% CI, 0.31 to 0.90).

All-cause mortality

All-cause mortality in phase 3 studies was 0.6% (20 of 3182 patients) in the alirocumab group and 0.9% (17 of 1792 patients) in the control group. The primary cause of death in the majority of these patients was CV events.

Combination therapy with a statin

Placebo-controlled phase 3 studies (on background statin) in patients with primary hypercholesterolaemia or mixed dyslipidaemia

LONG TERM study

This multicenter, double-blind, placebo-controlled, 18-month study included 2310 patients (1,530 patients in the Praluent group and 780 patients in the placebo group) with primary hypercholesterolaemia at high or very high CV risk and on a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either alirocumab at a dose of 150 mg Q2W or placebo in addition to their existing lipid-modifying therapy. The LONG TERM study included 17.7% heFH patients, 34.6% with type 2 diabetes mellitus, and 68.6% with a history of coronary heart disease. Mean treatment duration was 64.6 weeks, with a majority of patients treated for a minimum of 52 weeks, and 607 patients with 18-month data analysed. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -61.9% (95% CI: -64.3%, -59.4%; p-value: <0.0001). For detailed results see Table 7. At week 12, 82.1% of patients in the alirocumab group reached an LDL-C <70 mg/dL (<1.81 mmol/L)

compared to 7.2% of patients in the placebo group. Difference versus placebo was statistically significant at week 24 for all lipids/ lipoproteins. Reduction in LDL-C was seen across age, gender, body mass index (BMI), race, and baseline LDL-C levels. Efficacy results were consistent in patients with heFH and non-heFH, patients with mixed dyslipidaemia, and diabetic patients. LDL-C reduction was consistent regardless of concomitantly used statins and doses.

COMBO I study

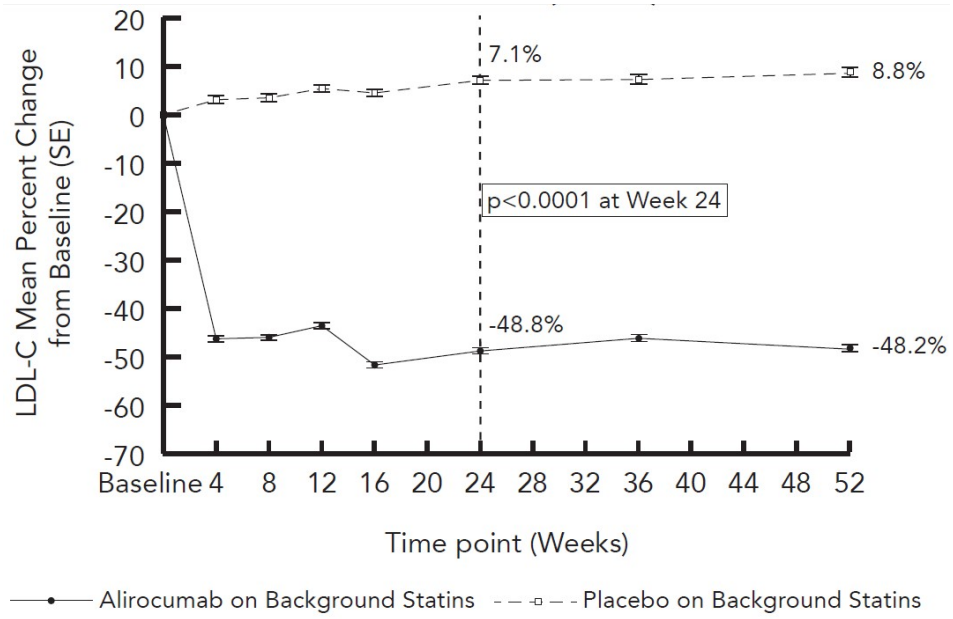
A multicenter, double-blind, placebo-controlled, 52 week study included 311 patients (205 in the Praluent group and 106 in placebo group) categorised as very high CV risk and not at their pre-defined target LDL-C on a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either 75 mg alirocumab Q2W or placebo in addition to their existing lipid-modifying therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -45.9% (95% CI: -52.5%, -39.3%; p-value: <0.0001). For detailed results see Table 7. At week 12 (before up- titration), 76.0% of patients in the alirocumab group reached an LDL-C of <70 mg/dL (< 1.81 mmol/L) as compared to 11.3% in the placebo group. The dose was up-titrated to 150 mg Q2W in 32 (16.8%) patients treated beyond 12 weeks. Among the subgroup of patients up-titrated at week 12, an additional 22.8% mean reduction in LDL-C was achieved at week 24. The difference versus placebo was statistically significant at week 24 for all lipids/ lipoproteins except TG and Apo A-1.

Placebo-controlled phase 3 studies (on background statin) in patients with heterozygous familial hypercholesterolaemia (heFH)

FH I and FH II studies

Two multicenter, placebo-controlled, double-blind 18-month studies included 732 patients with heFH receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either alirocumab 75 mg Q2W or placebo in addition to their existing lipid- modifying therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -55.8% (95% CI: -60.0%, -51.6%; p-value: < 0.0001). For detailed results see Table 7 and Figure 2. At week 12 (before up-titration), 50.2% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 0.6% in the placebo group. Among the subgroup of patients up-titrated at week 12, an additional 15.7% mean reduction in LDL-C was achieved at week 24. Difference versus placebo was statistically significant at week 24 for all lipids/ lipoproteins.

Figure 2 LDL-C over time: Mean percent change from baseline up to 52 weeks – pool of FH studies (FH I and FH II) (ITT analysis)



HIGH FH study

A third multicenter, double-blind, placebo-controlled 18-month study included 106 heFH patients on a maximally tolerated dose of statin, with or without other lipid-modifying therapies, and a baseline LDL-C ≥160 mg/dL (≥4.14 mmol/L). Patients received either alirocumab at a dose of 150 mg Q2W or placebo in addition to their existing lipid-modifying therapy. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -39.1% (95% CI: - 51.1%, -27.1%; p-value: <0.0001). For detailed results see Table 7. Mean changes for all other lipids/ lipoproteins were similar to the FH I and FH II studies, however statistical significance was not reached for TG, HDL-C and Apo A-1.

Ezetimibe-controlled phase 3 study (on background statin) in patients with primary hypercholesterolaemia or mixed dyslipidaemia

COMBO II study

A multicenter, double-blind, ezetimibe-controlled 2 year study included 707 patients categorised as very high CV risk and not at their pre-defined target LDL-C on a maximally tolerated dose of statin. Patients received either alirocumab 75 mg Q2W or ezetimibe 10 mg once daily in addition to their existing statin therapy. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -29.8% (95% CI: -34.4%, -25.3%; p-value: <0.0001). For detailed results see Table 7. At week 12 (before up-titration),

77.2% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 46.2% in the ezetimibe group. Among the subgroup of patients up-titrated at week 12, an additional 10.5% mean reduction in LDL-C was achieved at week 24. Difference versus ezetimibe was statistically significant at week 24 for all lipids/ lipoproteins except for TG, and Apo A-1.

Monotherapy or as add-on to non-statin lipid-modifying therapy

Ezetimibe-controlled phase 3 trials in patients with primary hypercholesterolaemia (without a background statin)

ALTERNATIVE study

A multicenter, double-blind, ezetimibe-controlled, 24 week study included 248 patients with documented statin intolerance due to skeletal muscle-related symptoms. Patients received either alirocumab 75 mg Q2W or ezetimibe 10 mg once daily, or atorvastatin 20 mg once daily (as a re-challenge arm). Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L) or ≥100 mg/dL (≥2.59 mmol/L), depending on their level of CV risk. At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -30.4% (95% CI: -36.6%, -24.2%; p-value: <0.0001). For detailed results see Table 7. At week 12 (before up-titration), 34.9% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 0% in the ezetimibe group. Among the subgroup of patients up- titrated at week 12, an additional 3.6% mean reduction in LDL-C was achieved at week 24. Difference versus ezetimibe was statistically significant at week 24 for LDL-C, Total-C, Non-HDL-C, Apo B, and Lp(a).

This trial evaluated patients who did not tolerate at least two statins (at least one at the lowest approved dose), In these patients, musculo-skeletal adverse events occurred at a lower rate in the alirocumab group (32.5%) as compared to the atorvastatin group (46.0%) (HR= 0.61 [95% CI, 0.38 to 0.99]), and a lower percentage of patients in the alirocumab group (15.9%) discontinued study treatment due to musculo-skeletal adverse events as compared to the atorvastatin group (22.2%). In the five placebo-controlled trials in patients on a maximally tolerated dose of statin (n=3752), the discontinuation rate due to musculo-skeletal adverse events was 0.4% in the alirocumab group and 0.5% in the placebo group.

MONO study

A multicenter, double-blind, ezetimibe-controlled, 24 week study included 103 patients with a moderate CV risk, not taking statins or other lipid-modifying therapies, and a baseline LDL-C between 100 mg/dL (2.59 mmol/L) to 190 mg/dL (4.91 mmol/L). Patients received either alirocumab 75 mg Q2W or ezetimibe 10 mg once daily. Dose up-titration of alirocumab to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L). At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -31.6% (95% CI: -40.2%, -23.0%; p-value: <0.0001). For detailed results see Table 7. At week 12 (before up-titration), 57.7% of patients reached an LDL-C of <70 mg/dL (<1.81 mmol/L) as compared to 0% in the ezetimibe group. The dose was up-titrated to 150 mg Q2W in 14 (30.4%) patients treated beyond 12 weeks. Among the subgroup of patients up-titrated at week 12, an

additional 1.4 % mean reduction in LDL-C was achieved at week 24. The difference versus ezetimibe was statistically significant at week 24 for LDL-C, Total-C, Non-HDL-C and Apo B.

Table 7 - Mean Percent Change from Baseline in LDL-C and Other Lipids/Lipoproteins in Placebo-Controlled and Ezetimibe Controlled Studies – 75 mg and/or 150 mg Q2W Dosing Regimen

Mean Percent Change from Baseline in Placebo-Controlled Studies on Background Statin								
	LONG TERM (N=2310)		FHI and FHII (N=732)		High FH (N=106)		COMBO I (N=311)	
	Placebo	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab
Number of patients	780	1530	244	488	35	71	106	205
Mean Baseline LDL-C in mg/dL (mmol/L)	122.0 (3.16)	122.8 (3.18)	140.9 (3.65)	141.3 (3.66)	201.0 (5.21)	196.3 (5.10)	104.6 (2.71)	100.3 (2.60)
Week 12								
LDL-C (ITT) [a]	1.5	-63.3	5.4	-43.6	-6.6	-46.9	1.1	-46.3
LDL-C (on treatment)[b]	1.4	-64.2	5.3	-44.0	-6.6	-46.9	1.7	-47.6
Week 24								
LDL-C (ITT)[a]	0.8	-61.0[c]	7.1	-48.8[d]	-6.6	-45.7[e]	-2.3	-48.2[f]
LDL-C (on treatment) [b]	0.7	-62.8	6.8	-49.3	-6.6	-45.5	-0.8	-50.7
Non-HDL-C	0.7	-51.6	7.4	-42.8	-6.2	-41.9	-1.6	-39.1
Apo B	1.2	-52.8	1.9	-41.7	-8.7	-39.0	-0.9	-36.7
Total-C	-0.3	-37.8	5.5	-31.2	-4.8	-33.2	-2.9	-27.9
Lp(a)	-3.7	-29.3	-8.5	-26.9	-8.7	-23.5	-5.9	-20.5
TG	1.8	-15.6	4.3	-9.8	-1.9	-10.5	-5.4	-6.0
HDL-C	-0.6	4.0	0.2	7.8	3.9	7.5	-3.8	3.5
Apo A-1	1.2	4.0	-0.4	4.2	2.0	5.6	-2.5	3.3

Mean Percent Change from Baseline in Ezetimibe-Controlled Studies						
	On Background Statin		Without Background Statin			
	COMBO II (N=707)		ALTERNATIVE (N=248)		MONO (N=103)	
	Ezetimibe	Alirocumab	Ezetimibe	Alirocumab	Ezetimibe	Alirocumab
Number of patients	240	467	122	126	51	52
Mean Baseline LDL-C in mg/dL (mmol/L)	104.5 (2.71)	108.3 (2.81)	194.2 (5.03)	191.1 (5.0)	138.3 (3.58)	141.1 (3.65)
Week 12						

LDL-C (ITT) [a]	-21.8	-51.2	-15.6	-47.0	-19.6	-48.1
LDL-C (on treatment) [b]	-22.7	-52.4	-18.0	-51.2	-20.4	-53.2
Week 24						
LDL-C (ITT) [a]	-20.7	-50.6[g]	-14.6	-45.0[h]	-15.6	-47.2[i]
LDL-C (on treatment) [b]	-21.8	-52.4	-17.1	-52.2	-17.2	-54.1
Non-HDL-C	-19.2	-42.1	-14.6	-40.2	-15.1	-40.6
Apo B	-18.3	-40.7	-11.2	-36.3	-11.0	-36.7
Total-C	-14.6	-29.3	-10.9	-31.8	-10.9	-29.6
Lp(a)	-6.1	-27.8	-7.3	-25.9	-12.3	-16.7
TG	-12.8	-13.0	-3.6	-9.3	-10.8	-11.9
HDL-C	0.5	8.6	6.8	7.7	1.6	6.0
Apo A-1	-1.3	5.0	2.9	4.8	-0.6	4.7

a ITT analysis – intent-to-treat population, includes all lipid data throughout the duration of the study irrespective of adherence to the study treatment.

b On-treatment analysis – analysis restricted to the time period that patients actually received treatment.

The % LDL-C reduction at week 24 corresponds to a mean absolute change of:

c -74.2 mg/dL (-1.92 mmol/L);

d -71.1 mg/dL (-1.84 mmol/mL);

e -90.8 mg/dL (-2.35 mmol/L);

f -50.3 mg/dL (-1.30 mmol/L);

g -55.4 mg/dL (1.44 mmol/L);

h -84.2 mg/dL (-2.18 mmol/L);

i -66.9 mg/dL (-1.73 mmol/L)

Every 4 Week (Q4W) Dosing Regimen

CHOICE I study

A multicenter, double-blind, placebo-controlled, 48 week study included 540 patients on a maximally tolerated dose of a statin, with or without other lipid-modifying therapy (308 in the alirocumab 300 mg Q4W group, 76 in the alirocumab 75 mg Q2W group, and 156 in the placebo group), and 252 patients not treated with a statin (144 in the alirocumab 300 mg Q4W group, 37 in the alirocumab 75 mg Q2W group, and 71 in the placebo group). Patients received either alirocumab 300 mg Q4W, alirocumab 75 mg Q2W, or placebo in addition to their existing lipid-modifying therapy (statin, non-statin therapy or diet alone). Patients in the alirocumab 300 mg every 4 weeks treatment group received alternating placebo injections to maintain blinding in regard to injection frequency. Overall, 71.6% of patients were categorized at high or very high CV risk and not at their LDL-C target. Dose adjustment in the alirocumab groups to 150 mg Q2W occurred at week 12 in patients with LDL-C ≥70 mg/dL or ≥100 mg/dL, depending on their level of CV risk, or in patients who did not have at least a 30% reduction of LDL-C from baseline.

In the cohort of patients on background statin, the mean baseline LDL-C was 112.7 mg/dL. At week 12, the mean percent change from baseline with alirocumab 300 mg Q4W in LDL-C (ITT analysis) was -55.3% compared to +1.1% for placebo. At week 12 (before dose adjustment), 77.3% of patients treated with alirocumab 300 mg Q4W reached an LDL-C of <70 mg/dL as compared to 9.3% in the placebo group. At week 24, the mean percent change from baseline with alirocumab 300 mg Q4W/150 mg Q2W in LDL-C (ITT analysis) was -58.8% compared to -0.1% for placebo. At week 24, the mean treatment difference for alirocumab 300 mg Q4W/150 mg Q2W from placebo in LDL-C percent change from baseline was -58.7.% (97.5% CI: -65.0%, -52.4%; p-value:

< 0.0001). In patients treated beyond 12 weeks, the dose was adjusted to 150 mg Q2W in 56 (19.3%) of 290 patients in the alirocumab 300 mg Q4W arm. Among the subgroup of patients dose adjusted to 150 mg Q2W at week 12, an additional 25.4% reduction in LDL-C was achieved at week 24.

In the cohort of patients not treated with a concomitant statin, the mean baseline LDL-C was 142.1 mg/dL. At week 12, the mean percent change from baseline with alirocumab 300 mg Q4W in LDL- C (ITT analysis) was -58.4% compared to +0.3% for placebo. At week 12 (before dose adjustment), 65.2% of patients treated with alirocumab 300 mg Q4W reached an LDL-C of <70 mg/dL as compared to 2.8% in the placebo group. At week 24, the mean percent change from baseline with alirocumab 300 mg Q4W/150 mg Q2W in LDL-C (ITT analysis) was -52.7% compared to -0.3% for placebo. At week 24, the mean treatment difference for alirocumab 300 mg Q4W/150 mg Q2W from placebo in LDL-C percent change from baseline was -52.4% (97.5% CI: -59.8%, -45.0%; p- value: < 0.0001). In patients treated beyond 12 weeks, the dose was adjusted to 150 mg Q2W in 19 (14.7%) of 129 patients in the alirocumab 300 mg Q4W arm. Among the subgroup of patients dose adjusted to 150 mg Q2W at week 12, an additional 7.3% mean reduction in LDL-C was achieved at week 24.

In both cohorts, the difference vs placebo was statistically significant at week 24 for all lipid parameters, except for Apo A-1 in the subgroup of patients on background statin.

CLINICAL EFFICACY AND SAFETY IN PREVENTION OF CARDIOVASCULAR EVENTS

ODYSSEY OUTCOMES study

A multicentre, double-blind, placebo-controlled trial in 18,924 adult patients (9462 alirocumab; 9462 placebo) followed for up to 5 years. Patients had experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomisation and were treated with a lipid-modifying-therapy (LMT) regimen that was statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at maximally tolerated dose of those statins, with or without other LMT. All patients were randomised 1:1 to receive either alirocumab 75 mg once every two weeks (Q2W) or placebo Q2W. At month 2, if additional LDL-C lowering was required based on pre-specified LDL-C criteria (LDL-C ≥50 mg/dL or 1.29 mmol/dL), alirocumab was adjusted to 150 mg Q2W. For patients who had their dose adjusted to 150 mg Q2W and who had two consecutive LDL-C values below 25 mg/dL (0.65 mmol/L), down-titration from 150 mg Q2W to 75 mg Q2W was performed. Patients on 75 mg Q2W who had two consecutive LDL-C values below 15 mg/dL

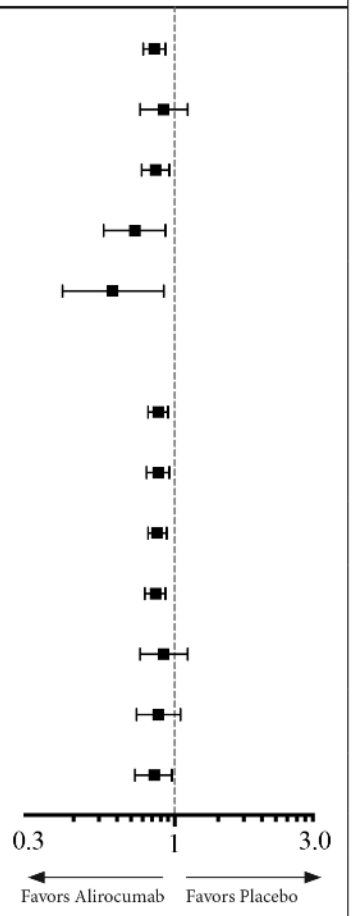
(0.39 mmol/L) were switched to placebo in a blinded fashion. Approximately 2615 (27.7%) of 9451 patients treated with alirocumab required dose adjustment to 150 mg Q2W. Of these 2615 patients, 805 (30.8%) were down-titrated to 75 mg Q2W. Overall, 730 (7.7%) of 9451 patients switched to placebo. A total of 99.5% of patients were followed for survival until the end of the trial. The median follow-up duration was 33 months.

The index ACS event was a myocardial infarction in 83.2% of patients (34.6% STEMI, 48.6% NSTEMI) and an episode of unstable angina in 16.8% of patients. Prior to the index ACS event, 19.2% had a myocardial infarction and 22.7% had coronary revascularisation procedures (CABG/PCI). Most patients (88.8%) were receiving high intensity statin therapy with or without other LMT at randomisation. The mean LDL-C value at baseline was 92.4 mg/dL (2.39 mmo/L).

Alirocumab significantly reduced the risk for the primary composite endpoint of the time to first occurrence of Major Adverse Cardiovascular Events (MACE) consisting of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, or unstable angina (UA) requiring hospitalisation (HR 0.85, 95% CI: 0.78, 0.93; p-value=0.0003). Alirocumab also significantly reduced the following composite endpoints: risk of CHD event; major CHD event; cardiovascular event; and the composite of all-cause mortality, non-fatal MI, and non-fatal ischemic stroke. The results are presented in Table 8. In the subgroup of high risk patients with baseline LDL-C ≥100 mg/dL (2.59 mmol/L), primary and all secondary endpoints were improved with alirocumab treatment including CHD death (HR 0.72, 95% CI: 0.53, 0.98), CV death (HR 0.69, 95% CI:0.52, 0.92) and all-cause mortality (HR 0.71, 95% CI:0.56, 0.90).

Table 8 Efficacy of Alirocumab in ODYSSEY OUTCOMES (Overall Population)

Endpoint	Number of Events		Hazard Ratio (95% CI) p-value
	Alirocumab N=9462 n (%)	Placebo N=9462 n (%)	
Primary endpoint (MACE)	**903 (9.5%)**	**1052 (11.1%)**	**0.85 (0.78, 0.93) 0.0003**
CHD Death	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11) 0.38
Non-fatal MI	626 (6.6%)	722 (7.6%)	0.86 (0.77, 0.96) 0.006[e]
Ischemic Stroke	111 (1.2%)	152 (1.6%)	0.73 (0.57, 0.93) 0.01[e]
Unstable Angina[a]	37 (0.4%)	60 (0.6%)	0.61 (0.41, 0.92) 0.02[e]
Secondary Endpoints			
CHD Event[b]	1199 (12.7%)	1349 (14.3%)	0.88 (0.81, 0.95) 0.0013
Major CHD Event[c]	793 (8.4%)	899 (9.5%)	0.88 (0.80, 0.96) 0.0060
Cardiovascular Event[d]	1301 (13.7%)	1474 (15.6%)	0.87 (0.81, 0.94) 0.0003
All-cause mortality, non-fatal MI, non-fatal ischemic stroke	973 (10.3%)	1126 (11.9%)	0.86 (0.79, 0.93) 0.0003
CHD Death	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11)
CV Death	240 (2.5%)	271 (2.9%)	0.88 (0.74, 1.05)
All-cause Mortality	334 (3.5%)	392 (4.1%)	0.85 (0.73, 0.98)



[a]Unstable angina requiring hospitalisation
[b]CHD event defined as: major CHD event[c], unstable angina requiring hospitalisation, ischaemia-driven coronary revascularisation procedure
[c]Major CHD event defined as: CHD death, non-fatal MI
[d]Cardiovascular event defined as follows: CV death, any non-fatal CHD event, and non-fatal ischemic stroke
[e]Nominal significance

The Kaplan-Meier estimates of the cumulative incidence of the primary endpoint and all-cause mortality endpoint for the overall patient population over time are presented in Figure 3 and Figure 4.

Figure 3 Primary Composite Endpoint Cumulative Incidence Over 4 Years in ODYSSEY OUTCOMES – Overall Population

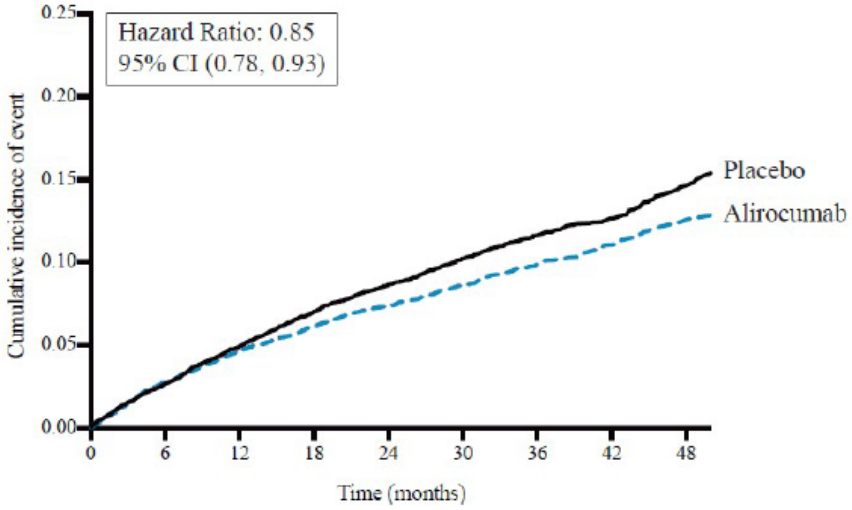
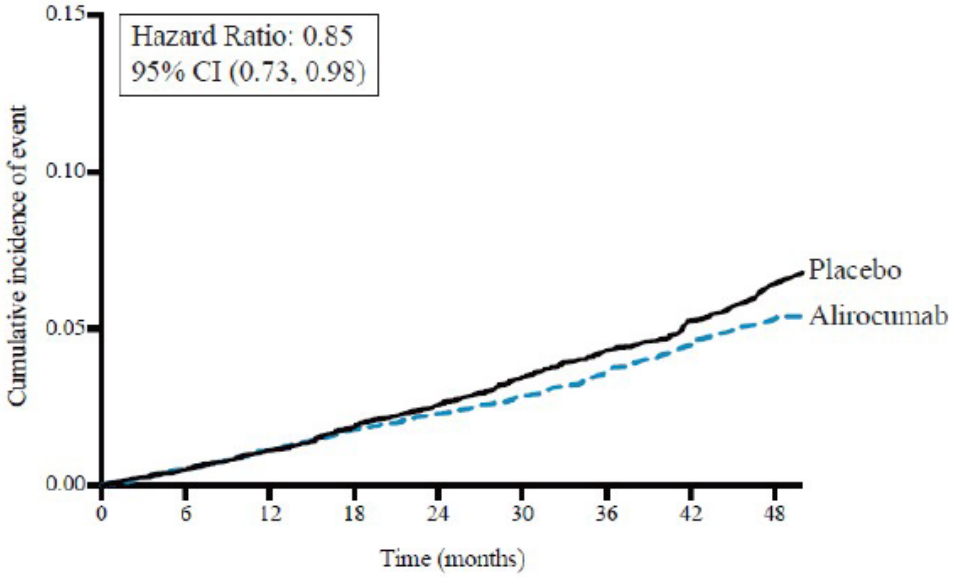


Figure 4 All-cause Mortality Cumulative Incidence Over 4 Years in ODYSSEY OUTCOMES – Overall Population



5.2 PHARMACOKINETIC PROPERTIES

Absorption

After subcutaneous administration of 50 mg to 300 mg alirocumab, median times to maximum serum concentration (t_{max}) were 3-7 days. The pharmacokinetics of alirocumab after single subcutaneous administration of 75 mg into the abdomen, upper arm or thigh were similar. The absolute bioavailability of alirocumab after subcutaneous administration was about 85% as determined by population pharmacokinetic analysis. Steady state was reached after 2 to 3 doses with an accumulation ratio of about 2-fold. Monthly exposure with 300 mg every 4 weeks treatment was similar to that of 150 mg every 2 weeks. The fluctuations between C_{max} and C_{trough} were higher for the every 4 weeks dosage regimen. Steady state was reached after 2 to 3 doses with an accumulation ratio up to a maximum of about 2-fold.

Distribution

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

Biotransformation

Specific metabolism studies were not conducted, because alirocumab is a protein. Alirocumab is expected to degrade to small peptides and individual amino acids.

Elimination

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

Based on a population pharmacokinetic analysis, the median apparent half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab as monotherapy at subcutaneous doses of either 75 mg Q2W or 150 mg Q2W. When co-administered with a statin, the median apparent half-life of alirocumab was 12 days.

Linearity/non-linearity

A slightly greater than dose proportional increase was observed, with a 2.1- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose from 75 mg to 150 mg Q2W.

Special populations

Elderly

In the phase 3 primary hypercholesterolaemia and mixed dyslipidaemia controlled studies, 1158 patients (34.7%) treated with Praluent were ≥ 65 years of age and 241 patients (7.2%) were ≥ 75

years of age. In the cardiovascular outcomes controlled study, 2505 patients (26.5%) treated with Praluent were ≥65 years of age and 493 patients (5.2%) treated with Praluent were ≥75 years of age. Based on a population pharmacokinetic analysis, age was associated with a small difference in alirocumab exposure at steady state, with no impact on efficacy or safety.

Paediatric

The pharmacokinetic effects of alirocumab administration in paediatric patients have not been studied.

Gender

Based on a population pharmacokinetic analysis, gender has no impact on alirocumab pharmacokinetics.

Race

Based on a population pharmacokinetic analysis, race had no impact on alirocumab pharmacokinetics. Following single-dose subcutaneous administration of 100 mg to 300 mg alirocumab, there was no meaningful difference in exposure between Japanese and Caucasian healthy subjects.

Body weight

Based on a population pharmacokinetic analysis, body weight had a small impact on alirocumab exposure, with no effect on efficacy or safety.

Hepatic impairment

In a phase 1 study, after administration of a single 75 mg subcutaneous dose, alirocumab pharmacokinetic profiles in subjects with mild and moderate hepatic impairment were similar as compared to subjects with normal hepatic function. No data are available in patients with severe hepatic impairment.

Renal impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of alirocumab. Population pharmacokinetic analyses showed that alirocumab exposure (AUC0-14d) at steady state at both the 75 and 150 mg Q2W dosing regimen was increased by 22%-35%, and 49%-50% in patients with mild and moderate renal impairment, respectively, compared to patients with normal renal function. The distribution of body weight and age, two covariates impacting alirocumab exposure, were different among renal function categories and most likely explain the observed pharmacokinetic differences. Limited data are available in patients with severe renal impairment (defined as eGFR < 30mL/min/1.73m^2); in these patients the exposure to alirocumab was approximately 2-fold higher compared with subjects with normal renal function.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with alirocumab. As alirocumab is a monoclonal antibody it would not be expected to have genotoxic potential.

Carcinogenicity

Carcinogenicity studies have not been conducted with alirocumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine

Sucrose

Polysorbate 20

Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C to 8°C). Do not freeze. Do not expose to extreme heat.

Can be stored outside the refrigerator (below 25 °C) protected from light for a single period not exceeding 30 days. Must be used within 30 days or discarded after removal from the refrigerator.

Keep the pen or syringe in the outer carton in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

1 mL solution in a siliconised Type 1 clear glass syringe, equipped with a stainless steel staked needle, a styrene-butadiene rubber soft needle shield, and an ethylene tetrafluoroethylene -coated bromobutyl rubber plunger stopper.

Pre-filled pen 75 mg:

The syringe components are assembled into a single-use pre-filled pen with a blue cap and a light green activation button.

Pre-filled pen 150 mg:

The syringe components are assembled into a single-use pre-filled pen with a blue cap and a dark grey activation button.

Pre-filled syringe 75 mg:

The syringe is equipped with a light green polypropylene plunger rod.

Pre-filled syringe 150 mg:

The syringe is equipped with a dark grey polypropylene plunger rod.

Pack size:

1, 2, or 6 pre-filled pens.

1, 2, or 6 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The solution should be clear, colourless to pale yellow. If the solution is discoloured or contains visible particulate matter, the solution should not be used.

After use, place the pre-filled pen/ pre-filled syringe into a puncture resistant container and discard as required by local regulations. Do not recycle the container. Always keep the container out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine.

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

9 March 2017

10 DATE OF REVISION OF THE TEXT

20 June 2022

SUMMARY TABLE OF CHANGES

Section	Change
8	Change of Sponsor