1. NAME OF THE MEDICINAL PRODUCT

Praluent 75 mg/ml
Praluent 150 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml single-use pre-filled pen/syringe contains 75 mg or 150 mg alirocumab*.
Each 2 ml single-use pre-filled pen contains 300 mg alirocumab*.
*Alirocumab is a human IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colorless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, and in paediatric patients 8 years of age and older with heterozygous familial hypercholesterolaemia (HeFH) 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.

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

4.2 Posology and method of administration

Posology

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

The usual starting dose for alirocumab 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 alirocumab can be individualized based on patient characteristics such as baseline LDL-C level, goal of therapy and response. Lipid levels can be assessed 4 to 8 weeks after treatment initiation or titration, 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.

HeFH in paediatric patients 8 years of age and older

Body weight of patients	Recommended dose	Recommended dose if additional LDL-C reduction is needed*
Less than 50 kg	150 mg once every 4 weeks	75 mg once every 2 weeks
50 kg or more	300 mg once every 4 weeks	150 mg once every 2 weeks

* Lipid levels can be assessed 8 weeks after treatment initiation or titration and dose adjusted accordingly.

Missed dose
If a dose is missed, the dose should be administered as soon as possible and thereafter, dosing should be resumed on the original schedule.

Special populations
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 (see section 5.2).

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.

Paediatric population

Praluent is not indicated for children under 8 years old.
The safety and efficacy of Praluent in children less than 8 years of age have not been established. No data are available.

Method of administration

Subcutaneous use.

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

Each pre-filled pen or pre-filled syringe is for single use only.

To administer the 300 mg dose, either one 300 mg injection or two 150 mg injections should be given consecutively at two different injection sites.

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

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

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

Precautions to be taken before handling or administering the medicinal product
The solution should be allowed to warm to room temperature prior to use (see section 6.6).

Paediatric patients 8 years of age and older
In adolescents 12 years of age and older, it is recommended that Praluent be administered by or under the supervision of an adult.
In children less than 12 years of age, Praluent must be given by a caregiver.

Adults
Adult patients may either self-inject alirocumab, or a caregiver may administer alirocumab, after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 postmarketing setting (see section 4.8). If signs or symptoms of serious allergic reactions occur, treatment with alirocumab must be discontinued and appropriate symptomatic treatment initiated (see section 4.3).

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) (see section 5.2). Alirocumab 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 (see section 5.2). Alirocumab should be used with caution in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products 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.

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. This leads to the increased target-mediated clearance and reduced systemic exposure of alirocumab. Compared to alirocumab monotherapy, the exposure to alirocumab is about 40%, 15%, and 35% lower when used concomitantly with statins, ezetimibe and fenofibrate, respectively. However, reduction of LDL-C is maintained during the dosing interval when alirocumab is administered every two weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Praluent in pregnant women. Alirocumab is a recombinant IgG1 antibody, therefore it is expected to cross the placental barrier (see section 5.3). Animal studies do not indicate direct or indirect harmful effects with respect to maintenance of pregnancy or embryo-foetal development; maternal toxicity was noted in rats, but not in monkeys at doses in excess of the human dose, and a weaker secondary immune response to antigen challenge was observed in the offspring of monkeys (see section 5.3).
The use of Praluent is not recommended during pregnancy unless the clinical condition of the woman requires treatment with alirocumab.

Breast-feeding
It is not known whether alirocumab is excreted in human milk. Human immunoglobulin G (IgG) is excreted in human milk, in particular in colostrum; the use of Praluent is not recommended in breast-feeding women during this period. For the remaining duration of breast-feeding, exposure is expected to be low. Since the effects of alirocumab on the breast-fed infant are unknown, a decision should be made whether to discontinue nursing or to discontinue Praluent during this period.

Fertility
In animal studies, there were no adverse effects on surrogate markers of fertility (see section 5.3). There are no data on adverse effects on fertility in humans.

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 most common adverse reactions, at recommended doses, are local injection site reactions (6.1%), upper respiratory tract signs and symptoms (2.0%), and pruritus (1.1%). Most common adverse reactions leading to treatment discontinuation in patients treated with alirocumab were local injection site reactions.

The safety profile in ODYSSEY OUTCOMES was consistent with the overall safety profile described in the Phase 3 controlled trials.

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
The following adverse reactions were reported in patients treated with alirocumab in pooled controlled studies and/or post-marketing use (see Table 1).

Frequencies for all adverse reactions identified from clinical trials 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).

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse reactions is qualified as "not known".

Table 1 – Adverse reactions

System organ class	***Common***	***Rare***	***Not known***
Immune system disorders		Hypersensitivity, hypersensitivity vasculitis	
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract signs and symptoms*		
Skin and subcutaneous tissue disorders	Pruritus	Urticaria, eczema nummular	Angioedema
General disorders and administration site conditions	Injection site reactions**		Flu-like illness

* including mainly oropharyngeal pain, rhinorrhea, sneezing
**including erythema/redness, itching, swelling, pain/tenderness

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). 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). 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 versus 2.1% placebo).

General allergic reactions

General allergic reactions were reported more frequently in the alirocumab group (8.1% of patients) than in the control group (7.0% of patients), 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.

Special populations

Elderly

Although no safety issues were observed in patients over 75 years of age, data are limited in this age group. In the Phase 3 primary hypercholesterolemia and mixed dyslipidaemia controlled studies, 1,158 patients (34.7%) treated with alirocumab were ≥65 years of age and 241 patients (7.2%) treated with alirocumab were ≥75 years of age. In the cardiovascular outcomes controlled study, 2,505 patients (26.5%) treated with alirocumab were ≥65 years of age and 493 patients (5.2%) treated with alirocumab were ≥75 years of age. There were no significant differences observed in safety and efficacy with increasing age.

Paediatric population

The safety and efficacy of Praluent have been established in children and adolescents with heterozygous familial hypercholesterolaemia (HeFH). A clinical study to evaluate the effects of Praluent was conducted in 153 patients, 8 to 17 years of age with HeFH. No new safety findings were identified and the safety data in this population were consistent with the known safety profile of the product in adults with HeFH.

The experience of alirocumab in paediatric patients with homozygous familial hypercholesterolaemia (HoFH) is limited to 18 patients aged 8 to 17 years. No new safety finding was observed compared to the known adult safety profile.

Every 4 week dosing study

The safety profile in patients treated with a 300 mg once every 4 week (monthly) dosing regimen, was similar to the safety profile as described for the clinical studies program using a 2 week dosing regimen, except for a higher rate of local injection site reactions. Local injection site reactions were reported overall at a frequency of 16.6% in the 300 mg once every 4 weeks treatment group and 7.9% in the placebo group. 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%. The discontinuation rate due to injection site reactions was 0.7% in the 300 mg once every 4 weeks treatment group and 0% in the placebo group.

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

In all clinical studies background lipid lowering therapies could not be adjusted by trial design. The percentage of patients who reached LDL-C values <0.65 mmol/L (<25 mg/dL) 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 <1.81 mmol/L or < 2.59 mmol/L (<70 mg/dL or <100 mg/dL), 29.3% of patients with baseline LDL-C <2.59 mmol/L (<100 mg/dL) and 5.0% of patients with baseline LDL-C ≥2.59 mmol/L (≥100 mg/dL) treated with alirocumab had two consecutive values of LDL-C <0.65 mmol/L (<25 mg/dL).
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 <1.29 mmol/L (<50 mg/dL), 54.8% of patients with baseline LDL-C <2.59 mmol/L (<100 mg/dL) and 24.2% of patients with baseline LDL-C ≥ 2.59 mmol/L (≥100 mg/dL) treated with alirocumab had two consecutive values of LDL-C <0.65 mmol/L (<25 mg/dL).

Although adverse consequences of very low LDL-C were not identified in alirocumab trials, the long-term effects of sustained very low levels of LDL-C are unknown.

Immunogenicity/Anti-drug-antibodies (ADA)

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.

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, except for a higher rate of injection site reactions in patients with treatment emergent ADA 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
/https://sideeffects.health.gov.il

4.9 Overdose

There is no specific treatment for alirocumab overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents, ATC code: C10AX14.

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.

In a multicentre, 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 3.90 mmol/L (151.5 mg/dL). 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.

Clinical efficacy and safety in primary hypercholesterolaemia and mixed dyslipidaemia

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 Phase3 trials (five placebo-controlled and five ezetimibe-controlled studies), involving 5,296 randomized patients with hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, with 3,188 patients randomized to alirocumab. In the Phase3 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 Phase3 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.

Two studies (*LONG TERM* and HIGH FH), involving a total of 2,416 patients, were performed with a 150 mg every 2 weeks (Q2W) dose only. Eight studies were performed with a dose of 75 mg Q2W, and criteria-based up-titration to 150 mg Q2W 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.

The primary efficacy endpoint in all of the Phase3 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 2 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 <1.81 mmol/L (<70 mg/dL) 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 Phase3 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.

Evaluation of cardiovascular (CV) events

In pre-specified analyses of pooled Phase3 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). Major adverse cardiovascular events ("MACE- plus", i.e.: CHD death, myocardial infarction, ischemic stroke, and unstable angina requiring hospitalisation) confirmed by adjudication were reported in 52 of 3,182 (1.6%) patients in the alirocumab group and 33 of 1,792 (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 1,550 (4.6%) patients in the alirocumab group and in 40 of 788 (5.1%) patients in the placebo group; MACE-plus confirmed by adjudication were reported in 27 of 1,550 (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-plus, HR=0.52 (95% CI, 0.31 to 0.90).

All-cause mortality

All-cause mortality in Phase3 studies was 0.6% (20 of 3,182 patients) in the alirocumab group and 0.9% (17 of 1,792 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 2,310 patients 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. 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 2. At week 12, 82.1% of patients in the alirocumab group reached an LDL-C <1.81 mmol/L (<70 mg/dL) compared to 7.2% of patients in the placebo group. Difference versus placebo was statistically significant at week 24 for all lipids/ lipoproteins.

COMBO I study

A multicenter, double-blind, placebo-controlled, 52 week study included 311 patients 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 ≥1.81 mmol/L (≥70 mg/dL)). 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 2. At week 12 (before up-titration), 76.0% of patients in the alirocumab group reached an LDL-C of < 1.81 mmol/L <70 mg/dL) 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 ≥1.81 mmol/L (≥70 mg/dL). 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 2. At week 12 (before up-titration), 50.2% of patients reached an LDL-C of <1.81 mmol/L (<70 mg/dL) 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.

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 ≥4.14 mmol/L (≥160 mg/dL). 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 2. 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 ≥1.81 mmol/L (≥70 mg/dL). 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 2. At week 12 (before up-titration), 77.2% of patients reached an LDL-C of <1.81 mmol/L (<70 mg/dL) 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 multicentre, 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 ≥1.81 mmol/L (≥70 mg/dL) or ≥2.59 mmol/L (≥100 mg/dL), 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 2. At week 12 (before up-titration), 34.9% of patients reached an LDL-C of <1.81 mmol/L (<70 mg/dL) 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, musculoskeletal 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 musculoskeletal 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 musculoskeletal 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 2.59 mmol/L (100 mg/dL) to 4.91 mmol/L (190 mg/dL). 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 ≥1.81 mmol/L (≥70 mg/dL). 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 2. At week 12 (before up-titration), 57.7% of patients reached an LDL-C of <1.81 mmol/L (<70 mg/dL) 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 2: 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 mmol/L (mg/dL)	3.16 (122.0)	3.18 (122.8)	3.65 (140.9)	3.66 (141.3)	5.21 (201.0)	5.10 (196.3)	2.71 (104.6)	2.60 (100.3)
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 mmol/L (mg/dL)	2.71 (104.5)	2.81 (108.3)	5.03 (194.2)	5.0 (191.1)	3.58 (138.3)	3.65 (141.1)
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] -1.92 mmol/L (-74.2 mg/dL); [d] -1.84 mmol/L (-71.1 mg/dL); [e] -2.35 mmol/L (-90.8 mg/dL); [f] -1.30 mmol/L (-50.3 mg/dL); [g] -1.44 mmol/L (-55.4 mg/dL) ;[h] -2.18 mmol/L (-84.2 mg/dL); [i] -1.73 mmol/L (-66.9 mg/dL)

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 ≥1.81 mmol/L (≥70 mg/dL) or ≥2.59 mmol/L (≥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 2.91 mmol/L (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 <1.81 mmol/L (<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 3.67 mmol/L (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 <1.81 mmol/L (<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

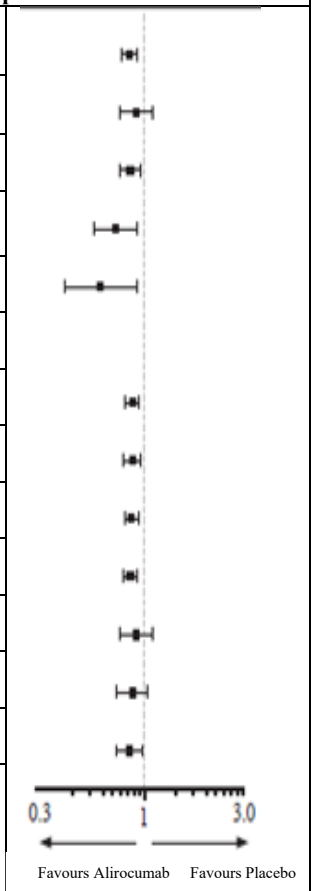
A multicentre, double-blind, placebo-controlled trial included 18,924 adult patients (9,462 alirocumab; 9,462 placebo) followed for up to 5 years. Patients had experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and were treated with a lipid-modifying-therapy (LMT) 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. Patients were randomized 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 ≥ 1.29 mmol/L or ≥50 mg/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 0.65 mmol/L (25 mg/dL), 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 0.39 mmol/L (15 mg/dL) were switched to placebo in a blinded fashion. Approximately 2,615 (27.7%) of 9,451 patients treated with alirocumab required dose adjustment to 150 mg Q2W. Of these 2,615 patients, 805 (30.8%) were down-titrated to 75 mg Q2W. Overall, 730 (7.7%) of 9,451 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. Most patients (88.8%) were receiving high intensity statin therapy with or without other LMT at randomization. The mean LDL-C value at baseline was 2.39 mmol/L (92.4 mg/dL).

Alirocumab significantly reduced the risk for the primary composite endpoint of the time to first occurrence of Major Adverse Cardiovascular Events (MACE-plus) consisting of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, or unstable angina (UA) requiring hospitalization (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. A reduction of all-cause mortality was also observed, with only nominal statistical significance by hierarchical testing (HR 0.85, 95% CI: 0.73, 0.98). The results are presented in Table 3.

Table 3: Efficacy of alirocumab in ODYSSEY OUTCOMES (overall population)

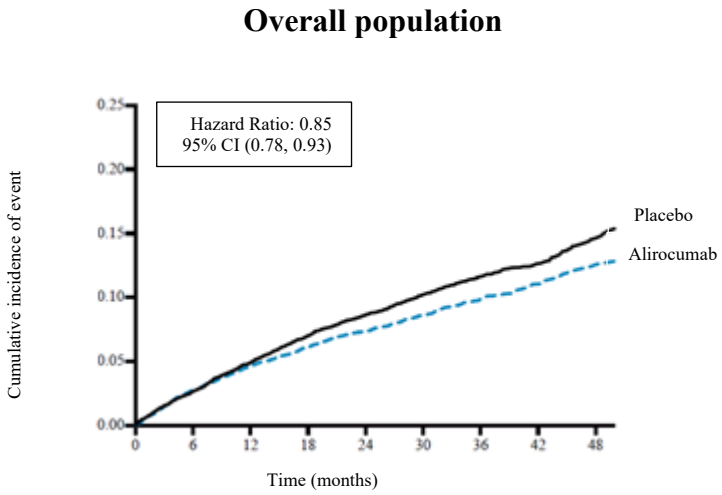
Endpoint	Number of events		Hazard ratio (95% CI) p-value
	Alirocumab N=9,462 n (%)	Placebo N=9,462 n (%)	
Primary endpoint (MACE-plus[a])	903 (9.5%)	1052 (11.1%)	0.85 (0.78, 0.93) 0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92 (0.76, 1.11) 0.38
Non-fatal MI	626 (6.6%)	722 (7.6%)	0.86 (0.77, 0.96) 0.006[f]
Ischemic stroke	111 (1.2%)	152 (1.6%)	0.73 (0.57, 0.93) 0.01[f]
Unstable angina[b]	37 (0.4%)	60 (0.6%)	0.61 (0.41, 0.92) 0.02[f]
Secondary endpoints			
CHD event[c]	1199 (12.7%)	1349 (14.3%)	0.88 (0.81, 0.95) 0.0013
Major CHD event[d]	793 (8.4%)	899 (9.5%)	0.88 (0.80, 0.96) 0.0060
Cardiovascular event[e]	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) 0.3824
CV death	240 (2.5%)	271 (2.9%)	0.88 (0.74, 1.05) 0.1528
All-cause mortality	334 (3.5%)	392 (4.1%)	0.85 (0.73, 0.98) 0.0261[f]



[a] MACE-plus defined as a composite of: coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, or unstable angina (UA) requiring hospitalization
[b] Unstable angina requiring hospitalization
[c] CHD event defined as: major CHD event[d], unstable angina requiring hospitalization, ischemia-driven coronary revascularization procedure
[d] Major CHD event defined as: CHD death, non-fatal MI
[e] Cardiovascular event defined as follows: CV death, any non-fatal CHD event, and non-fatal ischemic stroke
[f] Nominal significance

The Kaplan-Meier estimates of the cumulative incidence of the primary endpoint for the overall patient population over time are presented in Figure 1.

Figure 1 Primary composite endpoint cumulative incidence over 4 years in ODYSSEY OUTCOMES



Neurocognitive function

A 96 week, randomized, double-blinded, placebo-controlled trial evaluated the effect of alirocumab on neurocognitive function after 96 weeks of treatment (~2 years) in patients with heterozygous familial hypercholesterolemia (HeFH) or non-familial hypercholesterolemia at high or very high cardiovascular risk.

Neurocognitive function was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). A total of 2171 patients were randomized; 1087 patients were treated with alirocumab 75 mg and/or 150 mg every 2 weeks and 1084 patients were treated with placebo. A majority (>80%) of patients in each group completed the 96-week, double-blind treatment period.

Over the 96 weeks of treatment, alirocumab showed no effect on neurocognitive function. The percentage of patients who experienced neurocognitive disorders was low in the alirocumab (1.3%) treatment groups and comparable to placebo (1.7%). No safety concerns related to neurocognitive function were observed in patients treated with alirocumab who experienced either 2 consecutive LDL-C values <0.65 mmol/L (<25 mg/dL) or <0.39 mmol/L (<15 mg/dL) during the treatment period.

Paediatric population

Treatment of homozygous familial hypercholesterolaemia (HoFH) in paediatric patients

A 48-week, open-label study was conducted to evaluate the efficacy and safety of alirocumab 75 mg Q2W (if body weight (BW) < 50 kg) or 150 mg Q2W (if BW ≥ 50 kg) in 18 paediatric patients (8 to 17 years of age) with HoFH on top of background treatments. Patients received alirocumab 75 or 150 mg

Q2W without dose adjustment up to week 12.

The mean baseline LDL-C was 9.6 mmol/L (373 mg/dL). The mean percent change from baseline in LDL-C to week 12 was -4.1% (95% CI: -23.1% to 14.9%) in the ITT population (N=18) and was associated with a high variability in the response with regard to the decrease in LDL-C. Responders achieving ≥15% reduction from baseline at weeks 12, 24, and 48 were 50%, 50% and 39% respectively.

Treatment of heterozygous familial hypercholesterolaemia (HeFH) in paediatric patients

The efficacy and safety of alirocumab was evaluated in 153 patients 8 - ≤17 years of age with HeFH in a Phase-3 multicentre study. This study consisted of a 24-week randomized, double blind (DB) treatment where patients received placebo or alirocumab. This was followed by an 80-week open-label (OL) treatment with alirocumab. Patients had to be on a low-fat diet and receiving background lipid-lowering therapy. Enrolled patients were randomised in a 2:1 ratio to receive alirocumab Q2W or Q4W regimen and placebo. In the Q4W dosing regimen, 79 patients received a dose of 150 mg for body weight (BW) <50 kg or 300 mg for BW ≥50 kg. Dose up-titration of alirocumab to 75 mg Q2W for BW <50 kg or 150 mg Q2W for BW ≥50 kg occurred at week 12 in patients with LDL-C ≥2.84 mmol/L (≥110 mg/dL).

Double-blind treatment period:
The primary efficacy endpoint in this study was the percent change from baseline to week 24 in LDL-C. Data is further detailed in Table 4. Mean absolute LDL-C values at week 24 were 2.847 mmol/L (110.09 mg/dL) in the alirocumab group and 4.177 mmol/L (161.52 mg/dL)in the placebo group in the Q4W cohort. Reductions in LDL-C were observed through the first post-baseline assessment at week 8 and maintained throughout the 24 weeks of DB treatment period.

Table 4: Treatment effects of alirocumab and placebo in paediatric patients with HeFH

Mean percent change from baseline at week 24 (in %)		
Q4W Dose Regimen		
	Placebo	**Alirocumab**
Number of patients	N= 27	N= 52
LDL-C	-4.4	-38.2
Non-HDL-C	-3.7	-35.6
TC	-3.6	-34.6
Apo B	-3.6	-34.3

LDL-= low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TC = total cholesterol; ApoB = apolipoprotein B. All adjusted p-values <0.0001.

Open-label treatment period:
A total of 74 patients from the Q4W cohort participated in an 80-week open-label single arm study. The initial dose was the alirocumab dose selected for the DB period, according to body weight and dosing regimen. Dose could be up- and down-titrated by the investigators based on their medical assessment. The mean (SE) percent change in LDL-C from baseline (randomisation in DB period) was -23.4% (4.7) at week 104. The mean (SE) percent change from baseline to week 104 in other lipid endpoints were: -21.5% (26.2) non-HDL-C, -17.8% (21.7) ApoB, -17.4% (19.9) TC.

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. 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

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.

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

Body weight was identified as one significant covariate in the final population PK model impacting alirocumab pharmacokinetics. Alirocumab exposure (AUC0-14d) at steady state at both the 75 and 150 mg Q2W dosing regimen was decreased by 29% and 36% in patients weighing more than 100 kg as compared to patients weighing between 50 kg and 100 kg. This did not translate into a clinically meaningful difference in LDL-C lowering.

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; in these patients the exposure to alirocumab was approximately 2-fold higher compared with subjects with normal renal function.

Paediatric population

The pharmacokinetics of Praluent were evaluated in 140 paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia (HeFH). The steady state mean C_{trough} was reached at or before Week 8 (first PK sampling during repeated dosing) with the recommended dosing regimen (see Section 4.2).

Limited pharmacokinetic data are available in 18 paediatric patients (8 to 17 years of age) with HoFH. The steady-state mean C_{trough} alirocumab concentrations was reached at or before Week 12 in both

alirocumab 75 mg Q2W and 150 mg Q2W groups. No studies with alirocumab have been performed in paediatric patients less than 8 years of age (see section 5.1).

Pharmacokinetic/pharmacodynamic relationship(s)

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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, and repeated dose toxicity.

Reproductive toxicology studies in rats and monkeys indicated that alirocumab, like other IgG antibodies, crosses the placental barrier.

There were no adverse effects on surrogate markers of fertility (e.g. estrous cyclicity, testicular volume, ejaculate volume, sperm motility, or total sperm count per ejaculate) in monkeys, and no alirocumab-related anatomic pathology or histopathology findings in reproductive tissues in any rat or monkey toxicology study.

There were no adverse effects on foetal growth or development in rats or monkeys. Maternal toxicity was not evident in pregnant monkeys at systemic exposures that were 81 times the human exposure at the 150 mg Q2W dose. However, maternal toxicity was noted in pregnant rats at systemic exposures estimated to be approximately 5.3 times greater than the human exposure at the 150 mg Q2W dose (based on exposure measured in non-pregnant rats during a 5-week toxicology study).

The offspring of monkeys that received high doses of alirocumab weekly throughout pregnancy had a weaker secondary immune response to antigen challenge than did the offspring of control animals. There was no other evidence of alirocumab-related immune dysfunction in the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Sucrose
L-Histidine/L-Histidine monohydrochloride monohydrate
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:

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.
Praluent can be stored outside the refrigerator (below 25 °C) protected from light for a single period not exceeding 30 days. After removal from the refrigerator, the medicinal product must be used within 30 days or discarded.

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

6.5 Nature and contents of container

1 ml or 2 ml solution in a siliconised Type 1 clear glass syringe, equipped with a stainless steel staked needle, a styrene-butadiene rubber needle shield, and an ethylene tetrafluoroethylene -coated bromobutyl rubber plunger stopper.

Pre-filled pen 75 mg/ml

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

Pack size:
1, 2 or 6 pre-filled pens.

Pre-filled pen 150 mg/ml

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

Pack size:
1, 2 or 6 pre-filled pens.

Pre-filled pen 300 mg/2 ml

The syringe components are assembled into a single-use pre-filled pen with a blue cap and without activation button.

Pack size:
1 or 3 pre-filled pens.

Pre-filled syringe 75 mg/ml

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

Pack size:
1, 2 or 6 pre-filled syringes.

Pre-filled syringe 150 mg/ml

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

Pack size:
1, 2 or 6 pre-filled syringes.

Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After use, the pre-filled pen/ pre-filled syringe should be placed into a puncture resistant container. The container should not be recycled.

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

7. LICENSE NUMBER

Praluent 150 mg/ml: 156-09-34568
Praluent 75 mg/ml: 156-08-34583

8. REGISTRATION HOLDER

Sanofi Israel ltd. Greenwork Park, P.O box 47, Yakum.

Revised in January 2026.