Praluent®

SANOFI

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. see- *Undesirable effects* for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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 produced in Chinese Hamster Ovary cells by recombinant DNA technology.

For the full list of excipients, see- *List of excipients*.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

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

4.2 Posology and method of administration

Posology

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 administered subcutaneously once every 2 weeks.

The dose of Praluent can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dose adjusted accordingly (up-titration or down-titration). Patients should be treated with the lowest dose necessary to achieve the desired LDL-C reduction.

If a dose is missed, the patient should administer the injection as soon as possible and thereafter resume treatment two weeks from the day of the missed dose.

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- *Pharmacokinetic properties*).

Body weight

No dose adjustment is needed in patients based on weight.

Method of administration

Subcutaneous use.

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

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.

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

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.

Precautions to be taken before handling

Praluent should be allowed to warm to room temperature prior to use. Praluent should be used as soon as possible after it has warmed up. (see- *Special precautions for storage*)

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in (see- *List of excipients)*.

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 (see- *Undesirable effects*). If signs or symptoms of serious allergic reactions occur, treatment with Praluent must be discontinued and appropriate symptomatic treatment initiated (see- *Contraindications*).

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- *Pharmacokinetic properties*). 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 (see- *Pharmacokinetic properties*). Praluent 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- *Preclinical safety data*). Animal studies do not indicate direct or indirect harmful effects with respect to maintenance of pregnancy or embryo-fetal 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- *Preclinical safety data*). 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- *Preclinical safety data*). 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

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.

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

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

The following adverse reactions were reported in patients treated with alirocumab in pooled controlled studies:

Table 1 – Adverse Reactions reported in patients treated with alirocumab in pooled controlled studies

System organ class	*Common*	*Rare*
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
General disorders and administration site conditions	Injection site reactions**	

* 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).

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- *Special warning and precautions for use*)

Special populations

Elderly

Although no safety issues were observed in patients over 75 years of age, data are limited in this age group. 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.

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

In pooled controlled studies, 796 of 3340 patients (23.8%) treated with Praluent had two consecutive values of LDL-C <25 mg/dL (<0.65 mmol/L), including 288 patients (8.6%) with two consecutive values <15 mg/dL (<0.39 mmol/L). These mostly occurred when patients were initiated and maintained on 150 mg Q2W of Praluent regardless of the baseline LDL-C value or the response to treatment. No adverse reaction was identified related to these LDL-C values.

Immunogenicity/ Anti-drug-antibodies (ADA)

In phase 3 studies, 4.8% of alirocumab-treated patients had a treatment-emergent ADA response as compared to 0.6% in the control group (placebo or ezetimibe). The majority of those patients exhibited transient low-titer ADA responses with no neutralising activity. Compared to patients who were ADA negative, patients with an ADA positive status did not exhibit any difference in alirocumab exposure, efficacy, or safety, except for a higher rate of injection site reactions. Only 1.2% of patients exhibited neutralising antibodies (NAb), all of them in the alirocumab group. Most of these patients had only one positive neutralising sample. Only 10 patients (0.3%) had two or more NAb positive samples. The data do not suggest a correlation between the presence of NAb and LDL-C lowering efficacy or safety. Immunogenicity data are highly dependent on the sensitivity and specificity of the ADA assay.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned 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 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.

Clinical efficacy and safety

Summary of the Phase 3 Clinical Trials Program

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 lipidmodifying 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 2416 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 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 4 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 criteriabased 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 78 weeks in the LONG TERM study). 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.

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 posthoc; 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 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 <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.

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 ≥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 2. 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 $\geq$70 mg/dL ($\geq$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 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.

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 $\geq$160 mg/dL ($\geq$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 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 $\geq$70 mg/dL ($\geq$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 2. 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.

<u>Monotherapy or as add-on to non-statin lipid-modifying therapy</u>

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%; pvalue: <0.0001). For detailed results see Table 2. 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 2. 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 2: Mean Percent Change from Baseline in LDL-C and Other Lipids/ Lipoproteins in Placebo-Controlled and Ezetimibe-Controlled Studies

	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
Week24						
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)

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Praluent in one or more subsets of the paediatric population in the treatment of elevated cholesterol (see- *Posology and method of administration* for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with Praluent in all subsets of the paediatric population in the treatment of mixed dyslipidaemia (see – *Posology and method of administration for information on paediatric use*).

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.

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 (AUC_{0-14d}) 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.

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 evaluations 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 fetal 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

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.

Time out of refrigeration should not exceed a maximum of 24 hours at temperatures below 25°C.

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. MARKETING AUTHORISATION HOLDER

Sanofi-aventis (Thailand) Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Alirocumab CCDS v.2 (23 Oct 2015)