EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/379767/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Praluent

International non-proprietary name: alirocumab

Procedure No. EMEA/H/C/003882/X/0054/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibody
AI	Auto-injector
AUC	Area under curve
BUN	Blood urea nitrogen
CCIT	Container closure integrity
CE-SDS	Capillary electrophoresis-sodium dodecyl sulfate
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum concentration
DP	Drug product
DS	Drug substance
ELISA	Enzyme-linked immunosorbent assay
EMA	European medicines agency
FH	Familiar hypercholesterolemia
HeFH	Heterozygous familiar hypercholesterolemia
HMW	High molecular weight
iCIEF	imaged capillary isoelectric focusing
IG	Immunoglobulin
IMP	Investigational medicinal product
IPC	In-process control
FDS	Formulated drug substance
mITT	Modified intention to treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LMT	Lipid modifying therapy
LMW	Low molecular weight
MEB	Medicines evaluation board
NGHC	Non-glycosylated heavy chain
PCSK9	Proprotein convertase sutililisin/kexin type 9
PD	Pharmacodynamics
PFP	Pre-filled pen
PFS	Pre-filled syringe
Ph. Eur.	European Pharmacopeia
pI	Isoelectric point
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PFS	Pre-filled syringe
PTC	Product Technical complaint
RMP	Risk management plan
SE-HPLC	Size exclusion high-performance liquid chromatography
SC	Subcutaneous
SD	Standard deviation
SHL	Scandinavian health limited
SNS	Soft needle shield
TG	Triglycerides
T_{max}	Time of C_{max}
TOR	Time out of refrigeration
Total-C	Total cholesterol
USP	United States Pharmacopeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The MAH sanofi-aventis groupe submitted on 8 November 2019 a group of variations consisting of an extension of the marketing authorisation and the following variations:

Variation(s) requested		**Type**
B.II.b.3.z	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	IB
B.II.d.2.a	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	IA
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.6.b	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	IA
B.IV.1.c	B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging	II

Grouping of:
• Extension application to introduce a new strength of 300 mg (2 ml (150 mg/ml)) solution for injection in pre-filled pen (in a pack of 1 and 3 pens, EU/1/15/1031/019-20)
• B.II.b.3.z – Change to the manufacturing process of the finished product to introduce a modified pre-filled pen assembly process:
- Introduction of an alternative insertion force for assembly of bulk PFS into the front subassembly (from ≤ 60 N to ≤ 35 N)
- Introduction of an alternative assembly force for assembling the front and rear subassemblies (from ≤ 300 N to ≤ 60 N)
- Introduction of labelling in-line visual/optical control as a new in-process test applied during the manufacture of the modified pre-filled pen. The limit is set to "Each label must be present and variable data must be correct"
- Introduction of packaging in-line visual/optical control as a new in-process test applied during the

manufacture of the modified pre-filled pen. The limit is set to "The printed data must be present and correct"
- Introduction of weight control by in-line check weigher as a new in-process test applied during the manufacture of the modified pre-filled pen. The limit is set to "Each folding box must have the correct weight".
• B.II.d.2.a – Minor changes to the container closure integrity test procedure (CCIT) for the pre-filled pen (PFP) carried out at Sanofi-Aventis Deutschland GmbH, Germany (Frankfurt), to update the system suitability control, positive control preparation and the vacuum pressure applied.
• B.II.e.5.a.1 - To add a new pack-size of 2 pre-filled pens (1 mL) with no activation button for Praluent 75 mg solution for injection (EU/1/15/1031/014)
• B.II.e.5.a.1 - To add a new pack-size of 6 pre-filled pens (1 mL) with no activation button for Praluent 75 mg solution for injection (EU/1/15/1031/015)
• B.II.e.5.a.1 - To add a new pack-size of 1 pre-filled pen (1 mL) with no activation button for Praluent 150 mg solution for injection (EU/1/15/1031/016)
• B.II.e.5.a.1 - To add a new pack-size of 2 pre-filled pens (1 mL) with no activation button for Praluent 150 mg solution for injection (EU/1/15/1031/017)
• B.II.e.5.a.1 - To add a new pack-size of 6 pre-filled pens (1 mL) with no activation button for Praluent 150 mg solution for injection (EU/1/15/1031/018)
• B.II.e.6.b - Change in the elastomeric Soft Needle Shield (SNS) of Praluent 75 and 150 mg/mL solution for injection (EU/1/15/1031/001-017) to introduce a design variant to the needle shield.
• B.IV.1.c - To add a modified pre-filled pen (PFP) with no activation button, which is an integrated part of the primary packaging of the medicinal product for Praluent 75 mg solution for injection 1 pre-filled pen (EU/1/15/1031/013)

Update of sections 1, 2, 4.2, 6.3, 6.5 and 8 of the SmPC; the Labelling and Package Leaflet are updated accordingly.
In addition, the applicant has taken the opportunity to update the contact details of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template (v. 10.1), to remove the black triangle and to introduce editorial changes to modules 3.2.P.3.3, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.5.6, 3.2.P.7, 3.2.P.8.2, 3.2.A.1 and 3.2.R.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, - Extensions of marketing authorisations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice at the CHMP in relation to the changes proposed in this application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

The application was received by the EMA on	8 November 2019
The procedure started on	28 November 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 February 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 March 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	23 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	27 May 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Praluent on	25 June 2020

2. Scientific discussion

2.1. Problem statement

The medicinal product Praluent (EU/1/15/1031) was authorised in the European Union on 23 September 2015.

The purpose of this line extension is to introduce an additional strength of 300 mg (2 ml (150 mg/ml)) in a pre-filled pen without activation button, as well as registering new 1ml (75 mg/ml) and (150 mg/ml) pre-filled pens without activation button grouped with some quality variations.

2.1.1. Disease or condition

The line extension for 300 mg (2 ml (150 mg/ml)) in a pre-filled pen without activation button applies to the following indications:

Primary hypercholesterolaemia and mixed dyslipidaemia

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.

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.

2.1.2. Epidemiology

No new data were submitted in this application.

2.1.3. Management

About the product

Alirocumab is a fully human monoclonal IgG1 (immunoglobulin G1) antibody that binds to Proprotein convertase sutililisin/kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLRs) on the surface of hepatocytes. The LDLR is the major pathway through which cholesterol-rich low-density lipoprotein (LDL) particles are cleared from the circulation and hepatic LDL uptake is a major determinant of circulating low-density lipoprotein cholesterol (LDL-C) levels. When an internalized LDLR is bound to PCSK9, this promotes the degradation of the LDLR, preventing its recycling to the cell surface. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL particles, thereby lowering LDL-C levels.

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

Type of Application and aspects on development

Praluent is currently available in single-use pre-filled syringes and pre-filled pens containing 75 or 150 mg alirocumab in 1 ml solution with activation button.

In order to support the 300 mg Q4W dosing regimen with a single-injection administration, a new 2 mL prefilled pen auto-injector (AI) device (referred to as SYDNEY) has been developed. This submission is based on the results of a clinical program Study MSC14864 designed to assess the usability and

acceptability of the device, as well as the efficacy/pharmacodynamics, safety, and pharmacokinetics (PK) of alirocumab 300 mg Q4W single-injection. The current 1 mL pre-filled pen device was used as a calibrator for the assessments.

The therapeutic indications remain identical to the ones already approved.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 75 mg/mL or 150 mg/mL of alirocumab as active substance. The currently approved presentations are marketed in a 1 mL clear glass prefilled syringe (PFS), containing 75 mg or 150 mg of alirocumab. The PFSs are further assembled in a prefilled pens (PFPs). The currently marketed PFP is the same for both strengths and consists of an autoinjector (AI) device with an activation button.

As summarised in Table 1 below, this grouped application consists of:

- a line extension to introduce a new strength 300 mg (in a 2 mL clear glass syringe containing the same qualitative and quantitative composition of the currently marketed strength 150 mg/mL) in an AI device without an activation button;
- a Type II variation for 75 mg (1 mL of 75 mg/mL) and 150 strength (1 mL of the 150 mg/mL) PFP presentations in which also an AI device without activation button is introduced. The modified device requires a change to the assembly process, in view of the different dimension, these changes are introduced via a Type IB variation.

Table 1: Summary of the product presentations currently marketed and subject of this application

Strengths			**Presentations**		
			PFS	PFP: AI with activation button	PFP: AI without activation button
75 mg	75 mg/mL	1 mL	Marketed	Marketed	Subject of the type II + type Ib
150 mg	150 mg/mL	1 mL	Marketed	Marketed	Subject of the type II + type Ib
300 mg	150 mg/mL	2 mL	N.A.	Not developed	Subject of the line extension (new drug device combination)

2.2.2. Active substance

Alirocumab is a human monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. There are no changes in the active substance part of Module 3.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product, alirocumab, solution for injection is a clear, colourless to pale yellow, aqueous buffered sterile solution, pH 6.0. Other ingredients are: histidine, sucrose, polysorbate 20 and water for injections.

The 300 mg strength is introduced to allow a monthly dosing regimen with administration of a single-injection.

The product is currently available in two strengths, 75 mg (75 mg/mL in 1 mL) and 150 mg (150 mg/mL in 1 mL) of alirocumab as active substance, in a 1 ml siliconised type 1 clear glass prefilled syringe (PFS), equipped with a stainless steel staked needle, a styrene-butadiene rubber soft needle shield, and an ethylene tetrafluoroethylene -coated bromobutyl rubber plunger stopper. The material of the PFS complies with Ph. Eur. and EC requirements. The PFSs are also used as an intermediate in the manufacturing of the marketed prefilled pens (PFPs). The currently marketed PFP consists of an autoinjector (AI) device with an activation button: to deliver the dose, the user depresses the needle cover and pushes the activation button to activate the injection mechanism.

With this application, a PFP consisting of an AI without activation button is proposed for both the marketed strengths and for the new 300 mg strength as a grouped variation. The new AI represents a device improvement in reducing the number of steps needed for the activation of the PFP from 2 to 1: by depressing the PFP itself onto the injection site, the needle cover is depressed, which in turns activate the injection mechanism. Note that although a 2 ml PFS, referred to below, is an intermediate of the new 300mg strength PFP, the 2 ml PFS itself is not an authorised presentation.

There is no change proposed for the 1 mL PFS. For the 2 mL PFS (with a capacity of 2.25 mL), the materials of the primary container closure system and their supplier are the same as those for the 1 mL PFS. The plunger stoppers are sterilised by steam sterilisation instead of gamma-irradiation. During development, no leachables of toxicological concern were observed in the stored samples. Based on these, the new primary container closure system introduced with this application is considered comparable to the approved one. The PFP, with and without activation button, are functionally similar, have similar user interfaces, and have the same design principles and principles of operation.

Since the qualitative and quantitative composition of the 300 mg finished product is the same as the marketed 150 mg, as they both consist of a 150 mg/mL solution of alirocumab and the primary container closure system of the new strength is considered comparable, the main focus of the pharmaceutical development was to adapt the current manufacturing process to support the new PFS size and the assembly of the improved AI.

The assembly process involves the same equipment and process steps for both 1 mL and 2 mL PFPs with modification to accommodate 2.25 mL syringe attribute modifications. To accommodate the different sizes of syringes (1 mL or 2.25 mL) the dimensions of the AI subassembly components have also been adapted.

The minor differences in some of the functional performance specifications are due to the differences in the fill volumes of the respective bulk PFS (e.g. 1 mL or 2 mL alirocumab solution) and set to ensure the full dose is delivered to the patient.

Compliance with the essential requirements of the Medical Device Directive has been discussed. The performance of the modified PFP has been tested according to relevant ISO standards. For the 2 mL PFP, the clinical and commercial PFP comparability has been demonstrated for functional performance,

deliverable volume and principles of operation according to relevant ISO standards; it has been demonstrated that the clinical and commercial version of the PFP are comparable and deliver equivalent doses.

A human factor study was performed with the modified 1 mL and 2 mL PFP in order to evaluate the adequacy of the PFP user interface to support safe and effective use by the intended users. The outcomes of the tests were satisfactory.

Manufacture of the product and process controls

No changes have been introduced to the manufacturer and manufacturing process of the approved 1 mL PFS of either strength (75 mg and 150 mg).

The manufacturer of the 2 mL PFS (300 mg strength) is the same as the currently approved one for the 1 mL PFS.

Product specification

The 1 mL PFP specifications are the same as those for the already approved 75 mg/mL and 150 mg/mL 1 mL PFP presentations, except for the adaptation of the functional performance test specifications. The actuator button activation force test parameter has been removed as the modified AI device is buttonless.

The specification tests for the 300 mg strength (2 mL PFP) finished product are the same as for the 150 mg strength (1 mL PFP)

Batch analysis

Batch analysis data on 3 batches at full commercial scale of the 300 mg (2 mL) finished medicinal product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Stability of the product

For the 300 mg PFP, real time/real condition (2 – 8 °C) stability data of three primary batches of finished product of the 300 mg, 2 mL presentation for 9 months and for up to 6 months under accelerated conditions (25 ºC / 60%) RH, according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Data at stressed conditions study (45°C / 70%) for up to three months for both PFS and PFP is available for one batch. The stability trends between the 1 mL and 2 mL bulk PFS batches are comparable. The applicant commits to continue continuing the stability studies. Based on available stability data and the above justification, the same shelf life as the approved shelf life for the 150 mg PFP is proposed for the 300 mg strength.

A 2-year shelf life, from the date of fill of the bulk PFS, and "Store in a refrigerator (2°C to 8°C). Do not freeze." as stated in the SmPC for the 300 mg strength (2 mL PFP), is acceptable.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

For the 75 mg and 150 mg, supporting real time/real condition (2 – 8°C) stability data of one batch of both the 75 mg and 150 mg strength PFP (1 mL) presentations for 9 months and for up to 3 months under accelerated conditions (25ºC / 60%RH) according to the ICH guidelines were provided. A third batch of the 75 mg strength was stored under the same conditions and tested for appearance of packaged PFP and functional tests. The data provided is comparable with the stability data of the marketed product. The long-term data comply with the acceptance criteria; the data obtained under accelerated conditions are in line with the expected changes in the test parameters. Since the modified auto-injector and changes to the assembly process are not likely to impact the stability of the finished product, the proposed shelf life for the modified AI for the 75 mg and 150 mg strengths is the same as for the already registered 75 mg and 150 mg presentations. A shelf-life of 30 months for the 75 mg strength and 24 months for the 150 mg strength in the 1 mL PFP, calculated from the date of fill of the PFS, when "Store in a refrigerator (2°C to 8°C). Do not freeze." as stated in the SmPC, is acceptable. The applicant commits to complete the stability studies post-approval.

Adventitious agents

Not applicable.

GMO

Not applicable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the new proposed 300 mg strength and presentations of the PFPs (AI without activation button) has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and therefore the product is expected to have a satisfactory and uniform performance in clinical use.

2.2.5. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. The section 3.2.1 on 'Ecotoxicity/environmental risk assessment' (ERA), has been assessed in the current procedure as a new ERA document was submitted.

2.3.2. Ecotoxicity/environmental risk assessment

Alirocumab is a monoclonal antibody derived from biotechnological processes, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, it is not expected to have an adverse effect on the environment.

2.3.3. Discussion on non-clinical aspects

In the current procedure a new ERA document was submitted, in which the Applicant has adequately justified the absence of further studies to assess the environmental risk of alirocumab.

2.3.4. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted for this procedure which is acceptable. There are no objections to an approval of from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 2 Summary of key study information for Study MSC14864

Study Category/Identifier	Summary of key study information	Study duration	Number of patients evaluated for safety
Phase 3 Study MSC14864	Assess the usability of SYDNEY in high or very high CV risk patients with hypercholesterolemia not adequately controlled with their LMT	parallel-arm period with one of the 2 devices (SYDNEY or AI) for the first 4 weeks	67 SYDNEY: 33 (alirocumab 300 mg one single SC injection of 2 mL) AI: 34 (alirocumab 300 mg two consecutive SC injections of 1 mL)
		A single-arm period (with SYDNEY only) for the subsequent	66[a]

Study Category/Identifier	Summary of key study information	Study duration	Number of patients evaluated for safety
		weeks until Week 16	SYDNEY: (alirocumab 300 mg one single SC injection of 2 mL every 4 weeks)

a Two patients (1 in AI group and 1 in SYDNEY group) did not enter the single-arm period due to other reasons including life events. One patient who was not treated in the parallel-arm period due to wrong injection kit entered the single-arm period.

CV: cardiovascular; LMT: lipid modifying therapy; SC: subcutaneous

2.4.2. Pharmacokinetics

A new 2-mL auto-injector device (referred to as SYDNEY) has been developed to deliver 300 mg in a single-injection as an alternative to administering 2 injections of the 150 mg 1-mL auto-injector device (AI). Study MSC14864 aimed to support bridging the data for the alirocumab 300 mg Q4W dosing regimen obtained with the currently marketed 1-mL AI device to the new 2-mL SYDNEY device. The objective of study MSC14864 was to collect real-use (usability) data assessing the robustness and user interaction of SYDNEY and the current 1 mL alirocumab AI device and to assess the PK profile, the PD profile, the safety and the immunogenicity of alirocumab 300 mg Q4W administered using SYDNEY.

Study MSC14864

Study MSC14864 was a phase 3, multicenter, randomized, open-label, parallel-group usability study in high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy. This study consisted of 2 treatment periods, a parallel-arm period (first 4 weeks) with a single alirocumab 300 mg administration with one of the 2 devices (SYDNEY or AI) and a single-arm period with alirocumab 300 mg Q4W administration with SYDNEY device only from Week 4 to Week 16.

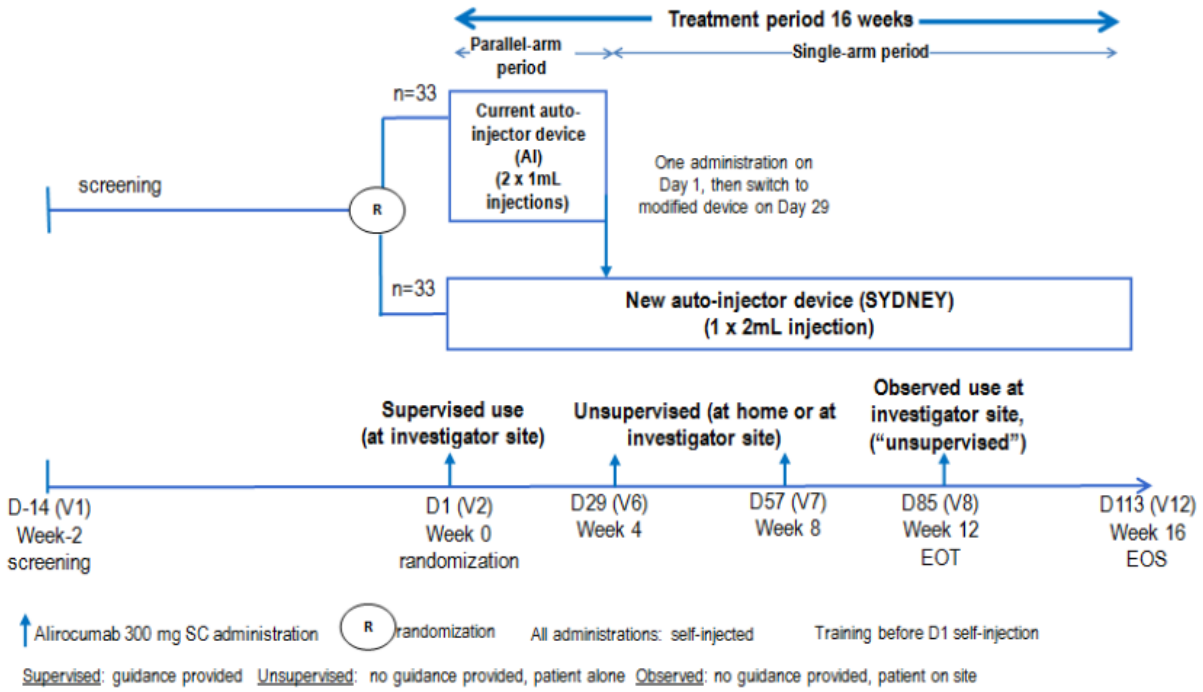

Figure 1: Study design

Route of administration: subcutaneous, administered by self-injection (rotated within an anatomical area [e.g., right thigh then left thigh or right abdomen then left abdomen]) using either the AI device or the SYDNEY device.

On Day 1, prior to the randomization, all patients were trained in self-injection using both devices at clinical site. Randomization occurred when training was completed and considered satisfactory. The first injection after randomization (on Day 1), using either AI or SYDNEY, was done at the investigational site by the patient under direct site staff supervision. Patients were monitored at the investigational site for at least 30 minutes after this first injection.

The 2nd, 3rd, and 4th injections of alirocumab 300 mg, all self-administered via SYDNEY, were done on Week 4 (Day 29), Week 8 (Day 57) and Week 12 (Day 85). The 2nd and 3rd injections were done unsupervised either at home or on site. The 4th injection was done on site under observation by a caregiver (considered unsupervised, with no direction or prompting given); this observation was to assess and record in e-CRF whether the self-injection was performed adequately.

The IMP was ideally to be administered at approximately the same time of the day Q4W; however, it was acceptable to have a window period of ±3 days. The time of the day was based on patient's preference.

Population: The PK population consisted of 67 patients with high or very high cardiovascular risk with hypercholesterolemia in the parallel-arm period (34 in AI group and 33 in SYDNEY group) and 65 in the single-arm period.

Prior to randomization and after a screening period of up to 2 weeks, all patients were trained in self-injection using both devices at clinical site on Week 0 (Day 1).

This study consisted of 2 treatment periods (Study MSC14864):

- A *parallel-arm period* with one of the 2 devices (SYDNEY or AI) for the first 4 weeks:

Eligible patients were randomized to receive alirocumab 300 mg Q4W using either SYDNEY or AI for self-administration on Week 0 (Day 1). The first IMP injection (Week 0) was done on-site under supervision.

- A *single-arm period* (with SYDNEY only) for the subsequent weeks until Week 16:

  All patients received alirocumab 300 mg Q4W using only SYDNEY for subsequent unsupervised self-injections on Week 4, Week 8, and Week 12 respectively. The last self-injection on Week 12 was done on-site under observation only without guidance (considered as unsupervised).

The total study duration (per patient), including the screening period and treatment period, was up to 18 weeks.

Bioanalytical methods

Serum was assayed for total alirocumab, free PCSK9 and total PCSK9 with validated ELISA methods and anti-drug antibodies (ADAs) were assessed by a validated bridging immunoassay. The same bioanalytical methods were used in Study MSC14864 as the ones used in the original dossier for Praluent. The lower limit of quantification was 0.078 µg/mL for total alirocumab concentration, 0.156 µg/mL for total PCSK9 assay, and 0.0312 µg/mL for free PCSK9 assay. Sensitivity of ADA by the validated electrochemiluminescence assay was approximately 5.6 ng/mL.

Pharmacokinetics

Concentrations of total alirocumab and total and free PCSK9 in serum were assessed at Day 1, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12, Week 13, Week 14, Week 15 and Week 16. Total alirocumab concentrations were used to calculate PK parameters. Twenty-four serum alirocumab concentrations were excluded from descriptive statistics as the actual sample collection day deviated by greater than ±15% from the nominal collection day relative to dose administration day.

A non-compartmental analysis, using Phoenix WinNonlin, Certara USA, Inc., Version 6.4, assessed alirocumab maximum concentration (C_{max}), time of C_{max} (t_{max}), area under the serum concentration versus time curve ($AUC_{0\text{-}tau}$) and C_{trough}.

For the parallel-arms period, log-transformed C_{max} and $AUC_{0\text{-}tau}$ estimates and 90% CI for the ratio of geometric means (SYDNEY/AI) were provided using an ANCOVA model with treatment group (SYDNEY, AI) as fixed effect and baseline body weight as covariate.

Absorption

- **Bioavailability**

Not applicable

- **Bioequivalence**

Serum alirocumab concentrations following single dose administration of alirocumab via the AI or SYDNEY device are presented in Figure 1. Alirocumab was absorbed with a median t_{max} of 7 days for both device groups (first time point measured). Pharmacokinetic parameters are summarised in Table 2. The alirocumab exposure in serum after a single SC dose of 300 mg alirocumab via either AI device (2×150 mg) or SYDNEY device (1×300 mg) was comparable; the point estimate of the treatment ratio comparing the SYDNEY device (1×300 mg) versus AI device (2×150 mg) was 1.1 (90% CI: 0.9 to 1.2) for Cmax and 1.1 (90% CI: 1.0 to 1.3) for AUC0-tau, respectively.

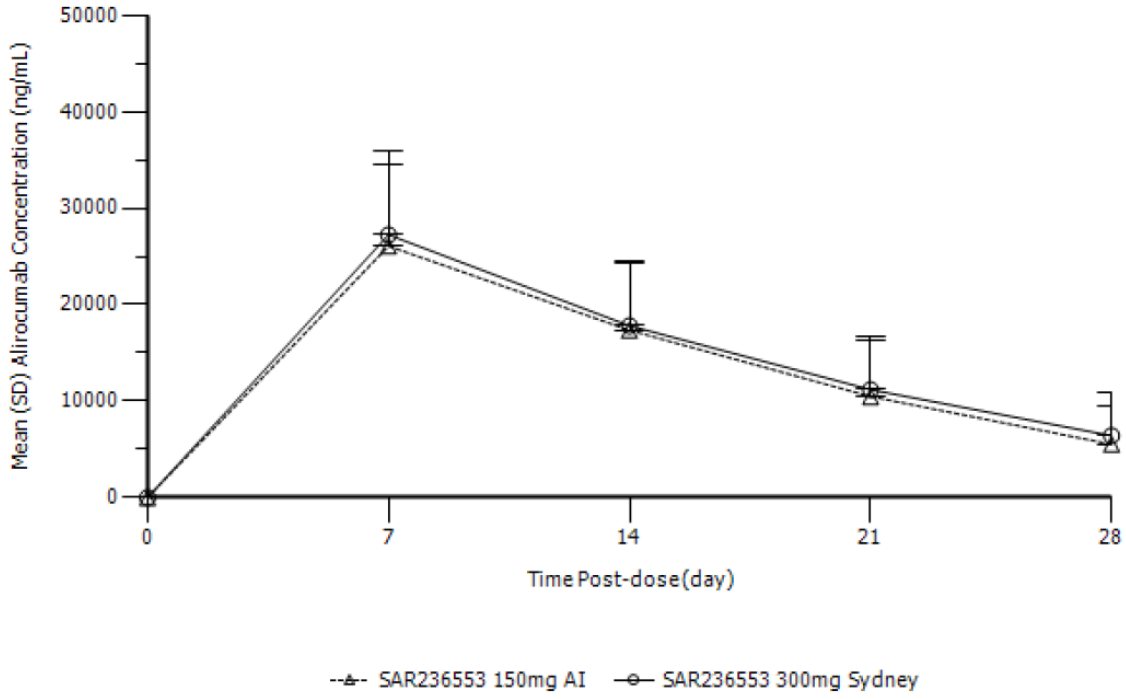

Figure 2 Alirocumab serum concentrations following single dose administration of 300 mg alirocumab via the AI (2x150mg) or SYDNEY (1x300mg) device (arithmetic mean ± SD)

Table 3 Pharmacokinetic parameters of alirocumab following single dose administration of 300 mg alirocumab via the AI (2x150mg) or SYDNEY (1x300mg) device (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**$AUC_{0\text{-}28days}$** **µg/ml/d**	**C_{max}** **µg/ml**	**t_{max}** **day**
SYDNEY (N=31) **(1x300mg)**	414 ± 152	26.8 ± 8.4	7 (6-7)
AI (N=33) **(2x150mg)**	381 ± 147	25.8 ± 8.4	7 (6-14)
***Ratio (90% CI)** **Between subject CV%**	1.1 (1.0 – 1.3) 37% - 39%	1.1 (0.9 – 1.2) 31% - 33%	
$AUC_{0\text{-}t}$ Area under the plasma concentration curve from administration to last observed concentration at time t. C_{max} Maximum plasma concentration t_{max} Time until Cmax is reached			

**ln-transformed values*

Pharmacokinetic parameters of alirocumab following the repeated Q4W SC administration of 300 mg alirocumab via the SYDNEY device on Day 85 (the third Q4W IMP injection in the single-arm period and fourth IMP injection overall), are summarised in Table 3. Graphically, steady state appeared to be reached by Week 4.

Table 4 Pharmacokinetic parameters of alirocumab in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment	$AUC_{0-\tau}$ µg/ml/d	$C_{max,ss}$ µg/ml	$C_{min,ss}$ µg/ml	$t_{max,ss}$ day
SYDNEY (N=64)	509 ± 264	31.9 ± 13.1	7.1 ± 6.6	7 (3-11)
$AUC_{0-\tau}$ Area under the plasma concentration curve during a dosage interval at steady state $C_{max,ss}$ Maximum plasma concentration at steady state $C_{min,ss}$ Minimum plasma concentration at steady state $t_{max,ss}$ Time until Cmax,ss is reached				

**ln-transformed values*

Distribution

Not applicable

Elimination

Not applicable

Dose proportionality and time dependencies

Not applicable

Special populations

Not applicable

Pharmacokinetic interaction studies

Not applicable

Pharmacokinetics using human biomaterials

Not applicable

2.4.3. Pharmacodynamics

Primary pharmacology

PCSK9 total and free concentrations following single dose administration of alirocumab via the AI or SYDNEY device are summarised in Table 4. After a single SC administration of alirocumab 300 mg, free PCSK9 decreased with mean free PCSK9 concentrations initially falling below the LLOQ (ie, 31.2

ng/mL) at Week 1, in both device groups. Detectable concentrations of free PCSK9 were restored at Week 2, with mean concentrations of free PCSK9 remaining close to the limit of quantitation, in AI and SYDNEY groups. At Week 4 following a single SC administration of alirocumab 300 mg, mean free PCSK9 concentrations (± SD) of 78.3 (±103) and 90.1 (±111) ng/mL were observed for the SYDNEY and AI device groups, respectively.

The decrease in free PCSK9 is accompanied by a corresponding increase in total PCSK9 that was comparable in both device groups. At Week 4 following a single SC administration of alirocumab 300 mg, mean total PCSK9 concentrations (± SD) of 3370 (±917) and 3330 (±1148) ng/mL were observed for the SYDNEY and AI device groups, respectively.

Table 5 Total and free PCSK9 concentrations (ng/mL) over time during parallel-arm treatment period

	Free PCSK9 (ng/mL)		**Total PCSK9 (ng/mL)**	
Treatment **Time-point**	**AI (N=34)**	**Sydney (N=33)**	**AI (N=34)**	**Sydney (N=33)**
Baseline	241 ± 82	249 ± 78	721 ± 240	655 ± 199
Week 1	0 ± 0	0 ± 0	3839 ± 980	3510 ± 1136
Week 2	7 ± 25	3 ± 14	4260 ± 996	4013 ± 1101
Week 3	34 ± 65	32 ± 80	3726 ± 1005	3790 ± 993
Week 4	90 ± 111	78 ± 103	3330 ± 1148	3370 ± 917

Secondary pharmacology

Immunogenicity

One patient in the SYDNEY group had pre-existing positive ADA status before the first alirocumab injection. Treatment-emergent positive ADA status was reported in 3 patients during the parallel-arm period: 2 (6.3%) in the AI group and 1 (3.1%) in the SYDNEY group. During the single-arm period, 2 additional patients had a treatment-emergent positive ADA status. The ADAs that were detected in a few subjects were at low titer (≤240) and did not appear to impact the safety of alirocumab. No patient had positive neutralizing ADA status.

2.4.4. Discussion on clinical pharmacology

A new 2-mL auto-injector device (referred to as SYDNEY) has been developed to deliver 300 mg in a single-injection as an alternative to administering 2 injections of the 150 mg 1-mL auto-injector device (AI). The pharmacokinetics of alirocumab and PCSK9 and changes in LDL-C from baseline of alirocumab 300 mg Q4W single-injection using SYDNEY device (1x300 mg) was compared to the current 1-mL AI device (2x150 mg) in Study MSC14864 in high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy. Subsequently all patients were transferred to a single-arm period with alirocumab 300 mg Q4W administration with SYDNEY device only from Week 4 to Week 16 to assess the PK profile, the PD profile, the safety and the immunogenicity of alirocumab 300 mg Q4W administered using SYDNEY.

The alirocumab exposure in serum after a single SC dose of 300 mg alirocumab via either AI device (2×150 mg) or SYDNEY device (1×300 mg) was comparable; the point estimate of the treatment ratio comparing the SYDNEY device (1×300 mg) versus AI device (2×150 mg) was 1.1 (90% CI: 0.9 to 1.2) for Cmax and 1.1 (90% CI: 1.0 to 1.3) for AUC0-tau, respectively.

Ideally, more samples in the absorption phase should have been included to demonstrate comparable pharmacokinetics for the new device and the device used in the clinical studies since Cmax of alirocumab was observed at the first time-point for both devices. Comparative pharmacokinetics were a secondary endpoint together with comparative pharmacodynamics endpoints for the parallel period of the study; additional efficacy and safety data were evaluated in the extension period. In that context, study MSC14864 was sufficiently designed to demonstrate comparable pharmacokinetics and pharmacodynamics following a single dose administration of 300 mg alirocumab for the new device and the device used in the clinical studies.

Following single dose administration free and total PCSK9 concentrations changed similarly over time via both AI and SYDNEY devices.

2.4.5. Conclusions on clinical pharmacology

The alirocumab serum profiles and changes in PCSK9 data from study MSC14864 provide support that there are no meaningful differences in pharmacokinetic or pharmacodynamic profiles between the 2 devices, AI (2x150 mg) and SYDNEY (1x300 mg).

Data on effect on LDL-C are discussed in the efficacy section.

2.5. Clinical efficacy

2.5.1. Main study

Study MSC14864

Methods

Study MSC14864 was a multicenter, randomized, open-label, 16-week study conducted in the US. The study planned to enroll approximately 66 patients randomized 1:1 to the SYDNEY or AI arm for the first 4 weeks (parallel-arm period). Subsequently, all patients switched to the SYDNEY device arm from Week 4 to Week 16 (single-arm period).

The specific design has already been discussed in the clinical pharmacology section 2.1.2.

Study Participants

Key inclusion criteria

Patients with heterozygous familial hypercholesterolemia (HeFH) or patients with high CV risk, and are not adequately controlled with a stable daily dose of atorvastatin (20 mg or 40 mg), or rosuvastatin (10 mg or 20 mg) for at least 4 weeks prior to the screening visit (Week -2), with or without other lipid modifying therapy (LMT).

Patients with heterozygous familial hypercholesterolemia (HeFH) (*by genotyping or by clinical criteria)*, or Non-FH patients with high and very high cardiovascular risk, including patients with coronary heart disease (CHD), non-CHD CVD, and other risk factors which are not adequately controlled with a stable daily dose of atorvastatin (20 mg or 40 mg), or rosuvastatin (10 mg or 20 mg) for at least 4 weeks prior to the screening visit (Week -2), with or without other lipid modifying therapy (LMT).

Key exclusion criteria

Patients with LDL-C <70 mg/dL (<1.81 mmol/L) at screening, taking lipid lowering therapy other than atorvastatin 20 mg or 40 mg, or rosuvastatin 10 mg or 20 mg (such as fibrates, red yeast rice and heterozygous familial hypercholesterolemia within 4 weeks before screening), planned PCI or CABG history of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months, known history of homozygous FH.

Treatments

This study consisted of 2 treatment periods:

- A *parallel-arm period* with one of the 2 devices (SYDNEY or AI) for the first 4 weeks:

  Eligible patients were randomized to receive alirocumab 300 mg Q4W using either SYDNEY or AI for self-administration on Week 0 (Day 1). The first IMP injection (Week 0) was done on-site under supervision.

- A *single-arm period* (with SYDNEY only) for the subsequent weeks until Week 16:

  All patients received alirocumab 300 mg Q4W using only SYDNEY for subsequent unsupervised self-injections on Week 4, Week 8, and Week 12 respectively. The last self-injection on Week 12 was done on-site under observation only without guidance (considered as unsupervised).

The total study duration (per patient), including the screening period and treatment period, was up to 18 weeks.

Objectives

Primary objective

The primary objective of this study was to assess the usability of SYDNEY in patients treated with alirocumab. The study population included patients with either HeFH or non-FH patients at high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their LMT.

Secondary objectives

- Device-related:

To collect real-use (usability) data assessing the robustness and user interaction of SYDNEY and the current 1-mL alirocumab auto-injector device (which is referred to as AI) in supervised settings on Week 0 (Day 1).

- Pharmacokinetics:

To compare alirocumab PK 300 mg Q4W administered using SYDNEY and AI, from baseline until Week 4.

To evaluate alirocumab PK 300 mg Q4W administered using SYDNEY, until Week 16.

- Anti-drug antibodies:

To evaluate the development of anti-drug (alirocumab) antibodies (ADA).

- Efficacy/pharmacodynamics:

To compare the percent and absolute change in LDL-C, from baseline to Week 4 using SYDNEY and AI.

To evaluate the percent and absolute change in LDL-C from baseline to Weeks 8, 12 and 16, using SYDNEY.

- Safety:

To evaluate the safety and tolerability of alirocumab 300 mg Q4W, using both SYDNEY and AI.

Outcomes/endpoints

Primary endpoint

The primary endpoint of this study was to measure the proportion of PTC (product technical complaint) with SYDNEY in unsupervised settings on Weeks 4, 8, and 12.

PTC was defined as any complaint reported on the Patient Complaint Form that triggered an investigation by the Device Department and was categorized as either device-related, patient-related, or undetermined, whether or not associated with an adverse event.

Secondary endpoint

The secondary objectives included the collection of PTC for both devices during the parallel-arm period and measurement of lipid parameters (LDLC, total cholesterol [total-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]).

- Device-related:

To collect real-use (usability) data assessing the robustness and user interaction of SYDNEY and the current 1-mL alirocumab auto-injector device (which is referred to as AI) in supervised settings on Week 0 (Day 1).

- Pharmacokinetics:

To compare alirocumab PK 300 mg Q4W administered using SYDNEY and AI, from baseline until Week 4. (see also section 2.1)

To evaluate alirocumab PK 300 mg Q4W administered using SYDNEY, until Week 16.

- Anti-drug antibodies:

To evaluate the development of anti-drug (alirocumab) antibodies (ADA).

- Efficacy/pharmacodynamics:

To compare the percent and absolute change in LDL-C, from baseline to Week 4 using SYDNEY and AI.

To evaluate the percent and absolute change in LDL-C from baseline to Weeks 8, 12 and 16, using SYDNEY.

Sample size

No formal sample size was calculated, the sample size was based on empirical considerations. Considering a drop-out rate of 10%, it was planned to randomize 66 patients overall (33 in each group) in order to ensure 60 evaluable patients overall (30 in each group) resulting in 180

unsupervised planned injections using SYDNEY. For the main objective of the study, to demonstrate acceptability of the device, it is acceptable that no formal sample size calculation has been performed.

Randomisation

A randomized patient was defined as a patient who was registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file. A patient was not to be randomized more than once in the study. If a treatment was used without contacting the centralized treatment allocation system, the patient was considered as not randomized and withdrawn from the study.

Blinding (masking)

Not applicable, this study was an open-label design.

Statistical methods

No formal sample size was calculated, the sample size was based on empirical considerations. Considering a drop-out rate of 10%, it was planned to randomize 66 patients overall (33 in each group) in order to ensure 60 evaluable patients overall (30 in each group) resulting in 180 unsupervised planned injections using SYDNEY.

The primary endpoint (i.e., number (%) and types of SYDNEY-associated PTCs related to the unsupervised injections will be described on the safety population for the single arm period. The number and % of PTCs will be provided with the 95% CI using Wilson score method. If applicable, the number of PTCs per patient will be described. In addition, the type of PTCs will be described.

All secondary device-related endpoints will be analyzed on the safety population using descriptive statistics. In addition, 95% CI for the number of PTCs, number and % of patients with any PTCs will be provided using Wilson score method.

The primary efficacy analysis population that will be used for the analyses of LDL-C will be the modified intent-to-treat (mITT) population. The mITT population of the parallel arms period will consist of all randomized patients who receive at least 1 dose or part of a dose of IMP visit during this period and who had an evaluable value of LDL-C at baseline and an on-treatment LDL-C value within Week 4 analysis window. The treatment period for the parallel arms period is defined as the time period from the first IMP injection up to 35 days after this injection or up to the day before the second injection, whichever comes first. Patients in this mITT population will be analyzed according to the auto-injector device group allocated by randomization (i.e., as-randomized treatment group). Lipid variables will be summarized (mean, median, standard deviation, minimum, and maximum) in percent and absolute change from baseline. In addition, at Week 4 only, percent change from baseline in LDL-C will be analyzed using an ANCOVA model to determine the estimates and 95% confidence intervals for both SYDNEY and AI.

Data analyzed by timepoint (except PK and PCSK9 variables) were summarized using the analysis windows given in Table 5. These analysis windows are applicable for all analyses, and they were defined to provide more homogeneous data for timepoint-specific analyses. For PK, since measurements were planned every week, e-CRF visits were used instead of analysis windows.

Table 5 - Analysis windows definition

Timepoint	Targeted study day[a]	analysis window in study day
Week 4	29	15 to 42
Week 8	57	43 to 70
Week 12	85	71 to 98
Week 16	113	99 to 126

a Study days are calculated from the day of first IMP injection, the day of first open-label IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

Results

Participant flow

A total of 69 patients were randomized and 67 were treated in the parallel-arm period (34 in the AI group and 33 in the SYDNEY group) and received first investigational medicinal product (IMP) injection on Day 1 via either AI or SYDNEY device. A total of 65 patients out of the 67 patients entered in the subsequent single-arm period (with SYDNEY device). In addition, one patient who received by error the AI training kit at Day 1 during the parallel arm period, entered in the single arm period.

Table 6 - Patient disposition - Parallel-arm period - Randomized population

	AI (N=34)	SYDNEY (N=35)
Randomized but not treated [a]	0	2 (5.7%)
Randomized and treated	34 (100%)	33 (94.3%)
Completed the study treatment period	34 (100%)	33 (94.3%)
Did not complete the study treatment period	0	0
Did not enter the single-arm period	1 (2.9%)	1 (2.9%)
Reason for not entering the single-arm period		
Adverse event	0	0
Death	0	0
Poor compliance to protocol	0	0
Lack of efficacy	0	0
Study terminated by sponsor	0	0
Site terminated by sponsor	0	0
Other reasons	1 (2.9%)	1 (2.9%)
Relocation	0	0
Life events made continuing on the protocol too difficult	0	1 (2.9%)
Related to IMP administration	0	0
Other reasons	1 (2.9%)	0
Patient's decision for not entering the single-arm period	1 (2.9%)	1 (2.9%)

During the single-arm period, 1 patient (1.5%) (who was randomized to SYDNEY group during the parallel-arm period) permanently discontinued study treatment due to an adverse event that occurred near the end of the parallel-arm period.

Table 7 - Patient disposition - Single-arm period - Safety population

	SYDNEY (N=66)
Treated in the single-arm period	66 (100%)
Completed the study treatment period	65 (98.5%)
Did not complete the study treatment period	1 (1.5%)
Reason for treatment discontinuation	
Adverse event	1 (1.5%)
Death	0
Poor compliance to protocol	0
Lack of efficacy	0
Study terminated by sponsor	0
Site terminated by sponsor	0
Other reasons	0
Patient's decision for treatment discontinuation [a]	0
Completed the study period	65 (98.5%)
Did not complete the study period	1 (1.5%)
Reason for study discontinuation	
Adverse event	1 (1.5%)
Progressive disease	0
Lack of efficacy	0
Poor compliance to protocol	0
Other reasons	0

Recruitment

A total of 13 sites in the US participated in this study; each site screened at least one patient and randomized at least 1 patient.

Conduct of the study

In the parallel-arm period, critical or major protocol deviations potentially impacting efficacy/pharmacodynamic analyses occurred in 7 patients (3 [8.8%] in the AI group; 4 [11.4%] in the SYDNEY group), resulting in exclusion of 6 patients (2 [5.9%] in AI group; 4 [11.4%] in SYDNEY group) from the mITT population (Table 8). Missing LDL-C assessment during the parallel-arm period was the main reason for exclusion (in 5 patients).

One patient with critical or major protocol deviations (switched statin therapy from rosuvastatin to atorvastatin during the parallel-arm period) was not excluded from mITT population.

Table 8 - Critical or Major protocol deviations potentially impacting efficacy analyses – Randomized population.

	AI (N=34)	SYDNEY (N=35)	All (N=69)
Any critical or major protocol deviations potentially impacting efficacy analyses	3 (8.8%)	4 (11.4%)	7 (10.1%)
Major deviation resulting in exclusion of the patient from mITT population for Parallel-arm period	2 (5.9%)	4 (11.4%)	6 (8.7%)
Missing LDL-C assessment within Week 4 analysis window	2 (5.9%)	3 (8.6%)	5 (7.2%)
No baseline LDL-C value	0	1 (2.9%)	1 (1.4%)
Patient randomized but not treated	0	1 (2.9%)	1 (1.4%)
Patient randomized but not treated (received training treatment kit at Day 1 by error)	0	1 (2.9%)	1 (1.4%)

Baseline data

The randomized population was mostly Caucasian (79.7%), with a mean age of 65.3 years (range: 45 to 81) and a mean BMI of 32.0 (5.8) kg/m^2 at baseline.

	AI (N=34)	SYDNEY (N=35)	All (N=69)
Age (years)			
Number	34	35	69
Mean (SD)	65.1 (8.6)	65.4 (8.1)	65.3 (8.3)
Median	64.5	67.0	67.0
Min ; Max	45 ; 81	47 ; 79	45 ; 81
Age group (years) [n(%)]			
Number	34	35	69
<65	17 (50.0%)	14 (40.0%)	31 (44.9%)
≥65 to <75	12 (35.3%)	18 (51.4%)	30 (43.5%)
≥75	5 (14.7%)	3 (8.6%)	8 (11.6%)

Sex [n(%)]			
Number	34	35	69
Male	15 (44.1%)	26 (74.3%)	41 (59.4%)
Female	19 (55.9%)	9 (25.7%)	28 (40.6%)
Race [n(%)]			
Number	34	35	69
Caucasian/White	24 (70.6%)	31 (88.6%)	55 (79.7%)
Black or African American	[redacted]	[redacted]	[redacted]
Asian/Oriental	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
Ethnicity [n (%)]			
Number	34	35	69
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Weight (kg)			
Number	34	34	68
Mean (SD)	91.4 (19.2)	93.4 (22.2)	92.4 (20.6)
Median	89.6	91.5	89.8
Min ; Max	53 ; 123	59 ; 165	53 ; 165
Weight group (kg) [n (%)]			
Number	34	34	68
<50	0	0	0
≥50 to <70	5 (14.7%)	5 (14.7%)	10 (14.7%)
≥70 to <100	17 (50.0%)	15 (44.1%)	32 (47.1%)
≥100	12 (35.3%)	14 (41.2%)	26 (38.2%)
BMI (kg/m^2)			
Number	34	34	68
Mean (SD)	32.2 (6.2)	31.9 (5.6)	32.0 (5.8)
Median	31.7	32.0	31.7
Min ; Max	23 ; 46	22 ; 46	22 ; 46
BMI group (kg/m^2) [n (%)]			
Number	34	34	68
<30	13 (38.2%)	12 (35.3%)	25 (36.8%)
≥30	21 (61.8%)	22 (64.7%)	43 (63.2%)

Any cardiovascular history/risk factors	34 (100%)	34 (97.1%)	68 (98.6%)
Coronary heart disease (CHD) [a]	18 (52.9%)	19 (54.3%)	37 (53.6%)
Acute myocardial infarction	4 (11.8%)	9 (25.7%)	13 (18.8%)
Silent myocardial infarction	3 (8.8%)	1 (2.9%)	4 (5.8%)
Unstable angina	1 (2.9%)	3 (8.6%)	4 (5.8%)
Coronary revascularization procedure	15 (44.1%)	16 (45.7%)	31 (44.9%)
Percutaneous coronary intervention (PCI)	9 (26.5%)	13 (37.1%)	22 (31.9%)
Coronary artery bypass graft surgery (CABG)	8 (23.5%)	4 (11.4%)	12 (17.4%)
Stable angina pectoris	4 (11.8%)	3 (8.6%)	7 (10.1%)
Clinically significant asymptomatic coronary heart disease	11 (32.4%)	13 (37.1%)	24 (34.8%)
Non-CHD Cardiovascular disease [a]	10 (29.4%)	9 (25.7%)	19 (27.5%)
Ischemic stroke	2 (5.9%)	5 (14.3%)	7 (10.1%)
Peripheral arterial disease	4 (11.8%)	4 (11.4%)	8 (11.6%)
Abdominal aortic aneurysm	3 (8.8%)	0	3 (4.3%)
Atherosclerotic renal artery stenosis	0	1 (2.9%)	1 (1.4%)
Carotid artery disease	5 (14.7%)	6 (17.1%)	11 (15.9%)
Other risk factors [a]	22 (64.7%)	18 (51.4%)	40 (58.0%)
Moderate chronic kidney disease	3 (8.8%)	1 (2.9%)	4 (5.8%)
Type 1 diabetes mellitus	0	0	0
Type 2 diabetes mellitus	20 (58.8%)	16 (45.7%)	36 (52.2%)
10-year fatal CVD risk SCORE ≥5%	2 (5.9%)	3 (8.6%)	5 (7.2%)

Type of hypercholesterolemia			
Number	34	34	68
Heterozygous Familial Hypercholesterolemia (He-FH)	1 (2.9%)	1 (2.9%)	2 (2.9%)
Non-Familial Hypercholesterolemia (non-FH)	33 (97.1%)	33 (97.1%)	66 (97.1%)
Non-Familial Hypercholesterolemia patients			
Time from hypercholesterolemia diagnosis (years)			
Number	33	33	66
Mean (SD)	11.9 (6.2)	14.7 (11.5)	13.3 (9.3)
Median	11.0	14.0	12.0
Min ; Max	0 ; 24	0 ; 47	0 ; 47
Heterozygous Familial Hypercholesterolemia patients			
Confirmation of diagnosis			
By genotyping	0	0	0
By clinical criteria	1 (2.9%)	1 (2.9%)	2 (2.9%)

LDL-C			
Number	34	34	68
<70 mg/dL / <1.81 mmol/L	3 (8.8%)	1 (2.9%)	4 (5.9%)
≥70 to <100 mg/dL / ≥1.81 to <2.59 mmol/L	16 (47.1%)	25 (73.5%)	41 (60.3%)
≥100 to <130 mg/dL / ≥2.59 to <3.37 mmol/L	11 (32.4%)	7 (20.6%)	18 (26.5%)
≥130 to <160 mg/dL / ≥3.37 to <4.14 mmol/L	4 (11.8%)	1 (2.9%)	5 (7.4%)
≥160 to <190 mg/dL / ≥4.14 to <4.91 mmol/L	0	0	0
≥190 mg/dL / ≥4.91 mmol/L	0	0	0

LDL-C (mg/dL)			
Number	34	34	68
Mean (SD)	98.6 (24.3)	91.0 (15.0)	94.8 (20.4)
Median	98.0	86.5	92.5
Q1 ; Q3	79.0 ; 112.0	81.0 ; 99.0	80.0 ; 106.0
Min ; Max	48 ; 152	66 ; 131	48 ; 152
Total-C (mg/dL)			
Number	34	34	68
Mean (SD)	175.4 (30.3)	167.8 (21.9)	171.6 (26.5)
Median	173.5	165.0	168.5
Q1 ; Q3	153.0 ; 197.0	153.0 ; 178.0	153.0 ; 191.0
Min ; Max	104 ; 236	127 ; 234	104 ; 236
HDL-C (mg/dL)			
Number	34	34	68
Mean (SD)	51.4 (11.0)	48.9 (11.6)	50.1 (11.3)
Median	49.5	47.5	49.0
Q1 ; Q3	42.0 ; 60.0	43.0 ; 54.0	42.5 ; 55.5
Min ; Max	37 ; 75	30 ; 91	30 ; 91
Fasting TG (mg/dL)			
Number	34	34	68
Mean (SD)	126.8 (55.9)	139.5 (67.3)	133.2 (61.8)
Median	108.5	129.0	113.5
Q1 ; Q3	90.0 ; 143.0	87.0 ; 182.0	90.0 ; 162.0
Min ; Max	50 ; 284	57 ; 366	50 ; 366

Background statin uses were comparable between the two treatment groups. Atorvastatin was used by majority of patients (81.2%). During the single-arm period, atorvastatin was used by 55 (83.3%) patients and rosuvastatin by 11 (16.7%) patients.

Numbers analysed

In the parallel-arm period, the mITT population included 63 patients.

Outcomes and estimation

Primary endpoint

The primary endpoint measured by the proportion of PTC (product technical complaint) on SYDNEY device over the 196 unsupervised injections performed in the single-arm period (on Weeks 4, 8, and 12) was 0.5% (1 of 196; 95% CI: 0.0% to 3.2%).

In this single PTC, the patient reported leaking of medication during the injection ('moderate amount of medication leaked from around the yellow needle guard'). Subsequent investigation of the submitted device sample (by device manufacturer) revealed no defect and no root cause to the reported leaking. The complaint was considered to be related to the patient use of the device and categorized as patient-related (by Sanofi Research & Development complaint office). Leaking during self-injection with an auto-injector device could happen in cases when a patient prematurely removes the device before the injection is complete.

Secondary endpoints

For both devices during the parallel-arm period, no PTC regarding injection device was reported at the supervised injections on Day 1 (Week 0) in either treatment group. The vast majority of patients reported that both AI and SYDNEY devices were "very easy" to use, with the mean patient experience scores ≥9.8 (maximum 10 corresponding to "very easy") for both devices in all user experience assessments and overall ease-of-use.

Two complaints (1 in each treatment group) not related to device or patient were reported at the supervised injections on Day 1. These 2 complaints corresponded to a mild injection site reaction in one patient in the SYDNEY group and a one-inch bruise at the injection site (on right lower abdomen) in another patient in the AI group. The event of one-inch bruise was not considered as an injection site reaction by the Investigator. Injection site reactions are known potential adverse events associated with auto-injector administration. Investigation of the device samples associated with the 2 complaints revealed no defects with the devices.

For SYDNEY device only during the single-arm period: no other complaints were received other than the one already described. The SYDNEY device continued to receive high patient experience scores at Week 4, Week 8, and Week 12 injections (mean scores ≥9.7 in all assessments).

The vast majority of patients reported being "very satisfied" with the SYDNEY device (mean patient perspective score ≥9.7 in all assessments) and "very confident" in using the device correctly (mean [SD] patient confidence score 9.9 [0.4]). The SYDNEY device was well accepted by patients in this study with a mean (SD) overall acceptance score of 93.08 (9.94) (out of maximum 100) at Week 12.

A substantial decrease in mean LDL-C value from baseline to Week 4 was observed in both treatment arms during the parallel-arm period, after a single dose of IMP on Day 1 (Week 0). The LS mean (SE) percent change in LDL-C from baseline to Week 4 was -51.2% (4.4) for the AI group and -66.2% (4.4) for the SYDNEY group. The LS mean percent difference of SYDNEY versus AI was -15.0% (95% CI: -27.6% to -2.4%).

Table 10 - Percent change from baseline in LDL-C at Week 4: ANCOVA - On-treatment analysis - Parallel-arm period - mITT population

LDL-C	AI (N=32)	SYDNEY (N=31)
Baseline (mmol/L)		
Number	32	31
Mean (SD)	2.564 (0.635)	2.293 (0.331)
Median	2.538	2.227
Min ; Max	1.24 ; 3.94	1.71 ; 3.16
Baseline (mg/dL)		
Number	32	31
Mean (SD)	99.0 (24.5)	88.5 (12.8)
Median	98.0	86.0
Min ; Max	48 ; 152	66 ; 122
Week 4 percent change from baseline (%)		
LS mean (SE)	-51.2 (4.4)	-66.2 (4.4)
95% CI	(-59.9 to -42.5)	(-75.1 to -57.4)
LS mean difference (SE) vs AI		-15.0 (6.3)
95% CI		(-27.6 to -2.4)

During the single-arm period, the substantial decrease in mean LDL-C value observed during the parallel-arm period was maintained with repeated Q4W IMP injections with the SYDNEY device. The mean (SD) percent change in LDL-C from baseline to Week 8, Week 12, and Week 16 were -53.74% (32.64), -58.61% (25.07), and -56.99% (25.93), respectively.

When the LDL-C values from the entire study (from Day 1 to Week 16) were analyzed according to the treatment group allocated at Day 1 (at randomization) despite the fact that all patients received alirocumab with SYDNEY device from Week 4 to Week 16, the difference in percent LDL-C reduction persisted between the two randomization groups. The mean (SD) percent reduction in LDL-C from baseline was still greater in the "SYDNEY group" than in the "AI" group: -62.4% (21.6) versus -53.1% (29.7) at Week 4, -61.2% (29.5) versus -46.3% (34.4) at Week 8, -63.3% (19.9) versus -54.0% (28.8) at Week 12, and -62.9% (25.1) versus -51.1% (25.8) at Week 16. Therefore, the observed difference between the SYDNEY group and the AI group in LDL-C reduction from baseline to Week 4 was unlikely to be related to the device.

The observed difference appears to be partially attributable to the gender imbalance between the two device groups (55.9% female in the AI group versus 25.7% female in the SYDNEY group), as female patients have been shown to have slightly less LDL-C reduction with alirocumab treatment than male patients in previous alirocumab studies (7). After an adjustment for gender, the difference between device groups was attenuated but still present with a LS mean (SE) percent change in LDL-C from baseline to Week 4 of -53.9% (4.4) for the AI group and -63.5% (4.4) for the SYDNEY group. The LS mean percent difference of SYDNEY versus AI was -9.6% (95% CI: -22.7% to 3.5%).

An improvement of the other lipid parameters (Total-C, HDL-C, and TG) was also observed during the parallel-arm and single-arm periods. The LS mean (SE) percent reduction in Total-C from baseline was also larger in SYDNEY group than in AI group: -36.5% (2.9) versus -27.6% (2.9); LS mean difference of SYDNEY versus AI -8.9% (95% CI: -17.2 to -0.6). The LS mean (SE) percent increase in HDL-C from baseline to Week 4 was similar between the two treatment groups: +6.7% (2.3) for the AI group and +4.5% (2.3) for the SYDNEY group. The adjusted mean (robust regression model) of the percent change from baseline to Week 4 was -1.5% (9.0) in the AI group and +4.7% (9.4) in the SYDNEY group; there was no meaningful difference between the groups. The mean (SD) percent change of Total-C from baseline to Week 8, Week 12, and Week 16 were -29.58% (22.43), -31.55% (17.68), and -31.83% (17.92), respectively. The mean (SD) percent change of HDL-C from baseline to Week 8, Week 12, and Week 16 were +5.53% (13.61), +7.19% (13.67), and +5.98% (14.92), respectively. No marked change in mean fasting triglyceride value from baseline was observed during the single-arm period.

Ancillary analyses

Not applicable.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial MSC14864

Title: A multicenter, randomized, open-label, parallel-group usability study of the commercial 1-mL alirocumab auto-injector device (AI) and the new 2-mL auto injector device (SYDNEY) in high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid-modifying therapy	
Study identifier	**MSC14864**

Design	multicenter, randomized, open-label, parallel-group usability study conducted in the US		
	Duration of main phase:		4 weeks
	Duration of Run-in phase:		Up to 2 weeks
	Duration of Extension phase:		12 weeks
Hypothesis	Exploratory: no power calculation performed		
Treatments groups	Alirocumab 2 x 1 ml 150 mg (existing device IA)		4 weeks randomised
	Alirocumab 1 x 2 ml 300 mg (new SYDNEY device)		4 weeks randomised
	Alirocumab 1 x 2 ml 300 mg (new SYDNEY device)		12 weeks extension single arm
Endpoints and definitions	Primary endpoint	Usability	Proportion of PTC (product technical complaint) with SYDNEY in unsupervised settings on Weeks 4, 8, and 12.
	Secondary endpoint	Usability	Proportion of PTC (product technical complaint) of SYDNEY and the current 1-mL alirocumab auto-injector device in supervised settings (first injection)
	Secondary endpoint	PK	Compare alirocumab PK 300 mg Q4W administered using SYDNEY and AI, from baseline until Week 4.
	Secondary endpoint	PD	Percent and absolute changes in LDL-C, (and total cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), and TG values) from baseline to Week 4, 8, 12 and 16
Database lock	9 Aug 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	SYDNEY	IA	
	Number of subjects	N=33	N=34	
	PE	0.5%	-	

	Usability secondary endpoint	0	0	
	AUC (µg/ml/d)	414 ± 152	381 ± 147	Ratio (90% CI) 1.1 (1.0-1.3)
	Cmax (µg/ml)	26.8 ± 8.4	25.8 ± 8.4	Ratio (90% CI) 1.1 (0.9 - 1.2)
	Total PCSK9 (ng/mL) Week 4	3370 ± 917	3330 ± 1148	
	LDL-C reduction (% (SE))	-66% (4.4)	-51% (4.4)	Difference (95% CI) -15% (-28% to -2.4%)

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive studies

Not applicable

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study MSC14864 was a multicenter, randomized, open-label, 16-week study conducted in the US. The study planned to enrol approximately 66 patients randomized 1:1 to the SYDNEY or AI arm for the first 4 weeks (parallel-arm period). Subsequently, all patients switched to the SYDNEY device arm from Week 4 to Week 16 (single-arm period).

The inclusion and exclusion criteria are appropriate to reflect a population at high risk treated with high intensity statins and appear in line with the current indication.

The primary endpoint of measuring the proportion of PTC (product technical complaint) with SYDNEY in unsupervised settings on Weeks 4, 8, and 12 is important (although this is during the single arm

extension period), however, other aspects including similarity in pharmacodynamics (PK/PD) may be considered more important to demonstrate similarity of the new SYDNEY device with the existing IA device For the primary endpoint no sample size calculation has been performed, which is acceptable. However, for evaluation of PK and PD similarity any sample size calculation would have been preferred to be able to make stronger conclusions.

Efficacy data and additional analyses

The study was only performed in the US but considering the objectives of the trial could be relevant for a European setting as well. During the study, discontinuation was limited to 1 patient each in the parallel period, although this was due to different reasons in each arm. During the single arm period only 1 patient discontinued treatment due to an adverse event. This has overall no major implications for the study findings. The study population reflects a population at high CV risk in accord with the inclusion and exclusion criteria. Baseline data were generally comparable between both arms except for gender (male 74% vs 44%, SYDNEY vs AI, respectively), race and baseline LDL-C levels (91 mg/dL vs 98 mg/dL, (2.3 mmol/L vs 2.6 mmol/L), respectively).

The study showed that any technical complaint with the new device was limited to one incident out of 196 measurements, consisting of leaking of medication during the injection and classified as patient (use) related. No technical issues with the device were noticed, which appears reassuring. In general, during the parallel period patient considered both the new SYDNEY device and the existing IA device easy to use, which is also reassuring. Complaints were limited to an injection site reaction (SYDNEY device) and a one-inch bruise at the injection site (IA device) both on day 1 (supervised period).

Despite the fact that PK evaluation and PCSK9 levels were comparable between both devices and no major issues in quality design were noticed, a greater effect of the SYDNEY device on LDL-C was observed (-66% vs -51%; absolute LDL-C reduction 1.5 mmol/L vs 1.3 mmol/L). This was also supported by a difference in Total-C, while HDL-C and TG were not substantially different during the first 4 weeks. According to the MAH this could partly be explained by gender difference between both groups, but even after adjustment a difference of -64% vs -54% of LDL-C reduction remained. When data were analysed according to this randomisation for the single arm extension period difference in LDL-C effect remained (e.g. -63% vs -51% at week 16), which may suggest that this is not device related. This observation is likely a chance finding as any other reasons to account for this difference could not be identified.

2.5.3. Conclusions on the clinical efficacy

In general, the device appears easy to use. Although there were no major issues in quality design, and a comparable PK and PD (PCSK9 levels) was observed between both devices, an increased effect on LDL-C was demonstrated for the SYDNEY device. However, especially the long-term data provided seem to suggest that this may not be related to the device and is likely to be a chance finding.

2.6. Clinical safety

Patient exposure

During the 4-week parallel-arm period, 67 patients (34 in the AI arm, 33 in the SYDNEY arm) received alirocumab 300 mg on Day 1 via two 1 mL injections using the AI device or one 2 mL injection using the SYDNEY device.

During the single-arm period, 65 patients received one 2 mL injection with SYDNEY at weeks 4, 8, and 12; One patient prematurely discontinued the study after the first injection in the single-arm period (second injection overall) due to an increase in alanine aminotransferase (ALT).

Adverse events

Parallel-arm period

A total of 17 patients (25.0%) experienced TEAEs during the parallel-arm period: 5 (14.7%) in the AI group and 12 (36.4%) in the SYDNEY group.

Table 12 - Overview of adverse event profile: Treatment emergent adverse events - Parallel-arm period - Safety population

	AI (N=34)	SYDNEY (N=33)
Patients with any TEAE	5 (14.7%)	12 (36.4%)
Patients with any treatment emergent SAE	1 (2.9%)	1 (3.0%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	1 (3.0%)

n (%) = number and percentage of patients with at least one TEAE

The TEAE period is defined as the time from the first IMP injection to the second IMP injection for patients entering into the Single-arm period or to 70 days after the first IMP injection, whichever comes first.

PGM=PRODOPS/SAR236553/MSC14864/CSR/REPORT/PGM/ae_overview_s_t.sas OUT=REPORT/OUTPUT/ae_overview_s_t_p_i.rtf (07DEC2018 2:16)

The most frequently reported TEAEs during the parallel-arm period were in the Infections and Infestations SOC (5 patients overall, 1 [2.9%] in the AI group and 4 [12.1%] in the SYDNEY group).

Two patients had TEAEs considered as related to IMP injection by the Investigator: 1 patient in the AI group with blood CK increased and injection site contusion (one-inch bruise on right lower abdomen at the injection site) and 1 patient in the SYDNEY group with mild injection site reaction (swelling). This last event was considered to be related to the IMP injection per the Investigator, but not related to the injection device.

Most TEAEs were of mild or moderate intensity; only 1 patient (in the AI group) had a severe TEAE (acute myocardial infarction).

Single-arm period

In the single-arm period, 23 patients (34.8%) experienced TEAEs.

Table 13 - Overview of adverse event profile: Treatment emergent adverse events - Single-arm period - Safety population

	SYDNEY (N=66)
Patients with any TEAE	23 (34.8%)

	SYDNEY (N=66)
Patients with any treatment emergent SAE	2 (3.0%)
Patients with any TEAE leading to death	0
Patients with any TEAE leading to permanent treatment discontinuation	0

n (%) = number and percentage of patients with at least one TEAE

The TEAE period is defined as the time from the second IMP injection up to the day of last IMP injection + 70 days.

PGM=PRODOPS/SAR236553/MSC14864/CSR/REPORT/PGM/ae_overview_s_t.sas OUT=REPORT/OUTPUT/ae_overview_s_t_s_i.rtf (07DEC2018 2:16)

The most frequently occurring TEAEs during the single-arm period were in the Infections and Infestations SOC (8 patients [12.1%]) and Musculoskeletal and Connective Tissue Disorders SOC (7 patients [10.6%]).

Three patients (4.5%) had TEAEs (4 events total) considered as related to IMP injection by the Investigator (musculoskeletal pain; ALT increased; blood CK increased and contusion [bruising on legs and left bicep]).

Most TEAEs were of mild or moderate intensity; only 1 patient had a severe TEAE (chondritis).

No patient experienced TEAE leading to permanent treatment discontinuation. No local injection site reactions were reported.

Serious adverse event/deaths/other significant events

Serious adverse events

SAEs were experienced by 2 patients during the parallel-arm period (1 [3.0%] in each group) and 2 patients (3.0%) during the single-arm period; none of the SAEs were related to IMP.

Two patients (1 in each group) experienced SAEs (acute myocardial infarction in the AI group and mild ALT increase in the SYDNEY group). In the patient in the SYDNEY group who experienced the SAE of mild ALT increase (>5 ULN from baseline), no relevant or trigger factors were identified for this event. ALT started to decrease prior to alirocumab discontinuation. The event was considered not related to the IMP as per the Investigator. Alirocumab was permanently discontinued due to the event.

Two patients (3.0%) experienced SAEs: one patient experienced worsening of coronary artery disease and one patient experienced worsening of chondritis of auricle.

Deaths

No deaths were reported.

Laboratory findings

CK levels

There was no relevant change over time in mean creatinine kinase (CK) value during the parallel-arm period (from baseline to Week 4, in either treatment group) and during the single-arm period (at Week 8, 12 and 16).

During the single-arm period, 2 patients (3.0%) had PCSA of CK >3 ULN (but <10 ULN) and 25 patients (38.5%) had PCSA of glucose ≥11.1 mmol/L (unfasted) or ≥7 mmol/L (fasted).

One patient presented with an increase in CK to 9.5 ULN. The Investigator did not report this value as an AE. It was reported that the patient had started a new physical work (no additional detail provided) towards the end of study at the time when the peak value of CK occurred, no additional information was provided. The last values of CK at Week 16 (6.38 ULN [1966 U/L; normal range: 39-308]). One patient had a single increased CK value of 3.34 ULN at Week 12 (all other CK values were within normal range).

Liver enzymes

There were no relevant changes over time in mean liver function parameter values (ALT, AST, ALP, total bilirubin, and gamma glutamyl transferase) during the parallel-arm period (in either treatment group); and there were no relevant changes over time in mean liver function parameter values during the single-arm period.

During the parallel-arm period, 1 patient in the SYDNEY group had a post-baseline PCSA of ALT >5 ULN (1.51, 1.37, and 6.46 ULN at screening, Week 0, and Week 4, respectively); there were no other abnormalities.

During the single-arm period, 1 patient had a post-baseline PCSA of ALT >3 ULN and 2 patients had PCSA of AST >3 ULN.

There was no patient with potential Hy's Law cases. No patients had liver function values in or near the range for potential Hy's Law.

Renal parameters

There were no relevant changes over time in mean creatinine, eGFR, and blood urea nitrogen (BUN) values from baseline to Week 16.

Other laboratory values

There were no relevant changes in mean laboratory values from baseline to Week 16 for RBC and platelets and WBCs.

There were no relevant changes in mean laboratory values from baseline to Week 16 for Electrolytes

Safety in special populations

Not applicable

Safety related to drug-drug interactions and other interactions

Not applicable

Immunological events

ADA responses (Positive/Negative, and ADA titer level if positive) were assessed at baseline (Day 1), Week 4, and Week 16 to determine any pre-existing positive ADAs and treatment-emergent positive ADA responses. Samples that were positive in the ADA assay were assessed for neutralizing antibodies. One patient in the SYDNEY group had pre-existing positive ADA status before the first alirocumab injection. Treatment-emergent positive ADA status was reported in 3 patients during the

parallel-arm period: 2 (6.3%) in the AI group and 1 (3.1%) in the SYDNEY group. During the single-arm period, 2 additional patients had a treatment-emergent positive ADA status. The ADAs that were detected in a few subjects were at low titer (≤240) and did not appear to impact the safety of alirocumab. No patient had positive neutralizing ADA status.

Discontinuation due to adverse events

Alirocumab was permanently discontinued due to the event of mild ALT increase (>5 ULN from baseline) in a patient in the SYDNEY group. ALT started to decrease prior to alirocumab discontinuation. The event was considered not related to the IMP as per the Investigator.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

Exposure to alirocumab is too limited with 33 treated with the new SYDNEY device and 34 treated with the existing AI for 4 weeks to allow for any comparison of safety. Further, safety data in the single-arm period (additional 12 weeks) of 65 patients treated with the new SYDNEY device is also too limited to draw any meaningful conclusions.

Despite these limitations, it was noticed that more adverse events were reported with the SYDNEY device (12 (36%)) than for the AI device (5 (15%)), however, in the SYDNEY group only one event of a mild injection site reaction was considered treatment related. Of the 23 (35%) of AEs reported during the single-arm period, only for 3 patient events were considered treatment related (musculoskeletal pain; ALT increased; blood CK increased and contusion).

Frequency of serious adverse events was limited, and none were considered related to study treatment, which appears reassuring. Although one patient in the SYDNEY group had a ALT >5 ULN (1.51, 1.37, and 6.46 ULN at screening, Week 0, and Week 4, respectively) during the parallel period, which was identified as a serious event and led to treatment discontinuation, this was not considered treatment related.

Several laboratory abnormalities were observed during alirocumab treatment including 2 patients (3.0%) with CK >3 ULN, and 25 patients with glucose ≥11.1 mmol/L (unfasted) or ≥7 mmol/L (fasted) during the single-arm period. Furthermore, beside the ALT >5 ULN case, 1 patient had ALT >3 ULN and 2 patients had AST >3 ULN during the single-arm period were observed. These findings are generally in line with the known safety profile of alirocumab. Due to the limited data no specific conclusions can be drawn on these laboratory observations.

The ADAs that were detected in a few subjects were at low titer (≤240) and did not appear to impact the safety of alirocumab. No patient was positive for neutralizing activity. This appears reassuring.

Discontinuation due to AEs was limited to the one patient with ALT > 5 ULN, and not considered related to study medication, which is reassuring.

2.6.2. Conclusions on the clinical safety

The safety database derived from this study is very limited and does not allow for meaningful conclusions on any safety comparison between the new SYDNEY device and the AI device, and is also

too limited for any specific safety evaluation for the new SYDNEY device. However, since exposure is not different between both devices, it is not expected that safety will be different. Further, based on this very limited database no unexpected safety findings have been observed, which is reassuring.

2.7. Risk Management Plan

There is no RMP update required for a line extension to introduce the new presentation.

2.8. Pharmacovigilance

Pharmacovigilance system

No changes to the pharmacovigilance system are made within this procedure.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

As a consequence of the line extension and the grouped variations, sections 1, 2, 4.2, 6.5, 8 of the SmPC have been updated. The Package Leaflet and the Labelling have been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to include some editorial changes and to align the PI with the latest QRD template (version 10.1) and to update the contact details of local representatives in the Package Leaflet.

2.9.1. User consultation

A Focus test of the instructions for use new to the pre-filled pen without activation button is carried out with the Package Leaflet of Praluent 150 mg. Information was found and understood by more than 90% of participants. The user test is considered sufficient. Bridging reports were provided for the Package Leaflets of the 75 mg and 300 mg strengths, which is acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Praluent (alirocumab) was removed from the additional monitoring list as a new active substance and new biological following five years of authorisation (renewal procedure R/0055).

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, was removed from the summary of product characteristics and the package leaflet within the present procedure.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The therapeutic indication for Praluent is not changed with this line extension procedure.

3.1.2. Available therapies and unmet medical need

There are 3 categories of lipid-lowering drugs that are registered for the prevention of CV risk including statins (HMG CoA reductase inhibitors), ezetimibe (inhibitor of the intestinal absorption of cholesterol and related plant sterols), and evolocumab (a PCSK9 inhibitor).

Statins are among the most studied drugs in CVD prevention and considered as the gold-standard for CV risk prevention in clinical guidelines. Although clinical guidelines clearly support the use of statins as treatment initiation with a LDL-C target <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 mmol/L and 3.5 mmol/L (70 mg/dL and 135 mg/dL) in patients at very high-risk, a need exists for additional therapies for LDL-C lowering and CVD prevention, because some patients who are already receiving a maximum tolerated dose of a statin still have a residual CVD risk due to high baseline LDL-C or limitations in statin tolerability. It is well known that some patients suffer from statin side effects (e.g., myalgia) that limit their ability to take a statin or a high enough dose of statin to reach their LDL-C goal. Statin-intolerant patients are at higher risk of not achieving target LDL-C levels appropriate to their level of CV risk given that non-statin therapies, other than PCSK9 inhibitors, typically provide only about a 15-20% reduction in LDL-C.

Ezetimibe is also registered in several countries to reduce the risk of CV events in adult patients with CHD and a history of ACS when added to ongoing statin therapy or initiated concomitantly with a statin. In clinical guidelines ezetimibe is recommended to be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients intolerant to statins or with contraindications to these drugs, although the absolute benefit from adding ezetimibe may be limited.

For the reduction of CV risk, evolocumab is indicated to reduce the cardiovascular risk in patients with "established atherosclerotic cardiovascular disease (myocardial infarction, stroke, or peripheral arterial disease) . . .". This indication is based on the results of the CV outcomes trial conducted with evolocumab, the FOURIER study. This study was a double-blind, randomized (1:1 ratio), placebo-controlled, event-driven study involving 27564 patients with established cardiovascular disease and with LDL-C ≥70 mg/dL and/or non-HDL-C ≥100 mg/dL despite high-or moderate-intensity statin therapy, with a median follow-up duration of 26 months. Established cardiovascular events were defined as a history of myocardial infarction, non-haemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional CV risk factors, which appears somewhat wider than the patients included in the ODYSSEY OUTCOME study. Evolocumab significantly reduced the risk for the primary composite endpoint (time to first occurrence of CV death, MI, stroke, hospitalization for UA, or coronary revascularization; HR 0.85; 95%CI: 0.79 to 0.92; p<0.001), with an absolute risk reduction of approximately 2% within this time frame.

3.1.3. Main clinical studies

Study MSC14864 was a multicenter, randomized, open-label, parallel-group 16-week usability study conducted in the US. The study planned to enrol approximately 66 patients randomized 1:1 to the SYDNEY (single 2 mL injection using new device) or AI arm (two 1 mL injections existing device) for the first 4 weeks (parallel-arm period). Subsequently, all patients switched to the new SYDNEY device arm from Week 4 to Week 16 (single-arm period).

3.2. Favourable effects

Use of the new device was generally experienced to be acceptable with limited technical complaints. The primary endpoint measured by the proportion of PTC (product technical complaint) on SYDNEY device over the 196 unsupervised injections performed in the single-arm period (on Weeks 4, 8, and 12) was 0.5% (1 of 196; 95% CI: 0.0% to 3.2%). This included one report of leaking of medication during the injection, but no defect and no root cause were reported with this leaking, and the complaint was considered to be related to the patient use of the device.

The alirocumab exposure in serum after a single SC dose of 300 mg alirocumab via either AI device (2×150 mg) or SYDNEY device (1×300 mg) was comparable; the point estimate of the treatment ratio comparing the SYDNEY device (1×300 mg) versus AI device (2×150 mg) was 1.1 (90% CI: 0.9 to 1.2) for C_{max} and 1.1 (90% CI: 1.0 to 1.3) for $AUC_{0\text{-}tau}$, respectively.

Comparable mean total PCSK9 concentrations (± SD) of 3370 (±917) and 3330 (±1148) ng/mL were observed for the SYDNEY and AI device groups at Week 4.

The quality design of the new device was assessed as acceptable, with no major issues identified.

3.3. Uncertainties and limitations about favourable effects

No formal sample size calculation has been performed for any of the endpoints including the secondary endpoints of comparability for PK parameters and PD parameters (e.g. LDL-C reduction).

A greater effect of the SYDNEY device on LDL-C was observed (-66% vs -51%; absolute LDL-C reduction 1.5 mmol/L vs 1.3 mmol/L; (95% CI) -15% (-28% to -2.4%)) at Week 4. This was also supported by a difference in Total-C, while HDL-C and TG were not substantially different during the first 4 weeks. According to the MAH this could partly be explained by gender difference between both groups, but even after adjustment a difference of -64% vs -54% of LDL-C reduction remained. When data were analysed according to this randomisation for the single arm extension period, difference in LDL-C effect remained (e.g. -63% vs -51% at week 16), which may suggest that this is not device related.

For both devices during the parallel-arm period, no PTC regarding injection device was reported at the supervised injections on Day 1 (Week 0) in either treatment group. The vast majority of patients reported that both AI and SYDNEY devices were "very easy" to use, with the mean patient experience scores ≥9.8 (maximum 10 corresponding to "very easy") for both devices in all user experience assessments and overall ease-of-use. However, any comparison of both devices in a home setting has not been undertaken.

The PK parameter Cmax of alirocumab was observed already at the first time-point for both devices, so ideally, more samples in the absorption phase should have been included in order to exactly determine the Cmax.

3.4. Unfavourable effects

More adverse events were reported with the SYDNEY device (12 (36%)) than for the AI device (5 (15%)), however, in the SYDNEY group only one event of a mild injection site reaction was considered treatment related. Of the 23 (35%) of AEs reported during the single-arm period, only for 3 patient events were considered treatment related (musculoskeletal pain; ALT increased; blood CK increased and contusion).

Frequency of serious adverse events was limited, and none were considered related to study treatment. Although one patient in the SYDNEY group had a ALT >5 ULN (1.51, 1.37, and 6.46 ULN at screening, Week 0, and Week 4, respectively) during the parallel period, which was identified as a serious event and led to treatment discontinuation, this was not considered treatment related. This was the only patient who discontinued due to an AE.

Several laboratory abnormalities were observed during alirocumab treatment including 2 patients (3.0%) with CK >3 ULN, and 25 patients with glucose ≥11.1 mmol/L (unfasted) or ≥7 mmol/L (fasted) during the single-arm period. Furthermore, beside the ALT >5 ULN case, 1 patient had ALT >3 ULN and 2 patients had AST >3 ULN during the single-arm period were observed. These findings are generally in line with the known safety profile of alirocumab.

The ADAs that were detected in a few subjects were at low titer (≤240) and did not appear to impact the safety of alirocumab. No patient was positive for neutralizing activity.

3.5. Uncertainties and limitations about unfavourable effects

Exposure to alirocumab is very limited with 33 patients treated with the new SYDNEY device and 34 treated with the existing IA for 4 weeks. Further, safety data in the single-arm period (additional 12 weeks) of 65 patients treated with the new SYDNEY device is also limited.

3.6. Effects Table

Table 14: Effects Table for Praluent line extension (data cut-off: 17 February 2019)

Effect	Short Description	Unit	Treatment (SYDNEY)	Control (IA)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Usability (unsupervised)	Proportion of PTC (product technical complaint) with SYDNEY in unsupervised settings on Weeks 4, 8, and 12	n/N (%)	1/33 (0.5%)	-	Unc: Not compared against IA control group. No formal powered comparison for any endpoint (exploratory)	
Usability (supervised)	Proportion of PTC (product technical complaint) of SYDNEY and the current 1-mL alirocumab auto-injector device in supervised settings (first injection).	n/N (%)	0/33 (0%)	0/34 (0%)	Unc: Only first injection in a supervised setting – no reflection of real world setting.	
PK	PK, from baseline until Week 4				No formal powered comparison	
	AUC	µg/ml/d	414 ± 152	381 ± 147	Unc: Ratio (90% CI) 1.1 (1.0-1.3)	
	Cmax	µg/ml	26.8 ± 8.4	25.8 ± 8.4	SoE: Ratio (90% CI) 1.1 (0.9 - 1.2)	
PD					No formal powered comparison	
	Total PCSK9 at Week 4	ng/mL	3370 ± 917	3330 ± 1148	Unc: No formal ratio comparison	

Effect	Short Description	Unit	Treatment (SYDNEY)	Control (IA)	Uncertainties/ Strength of evidence	References
	LDL-C reduction at Week 4	(% (SE)	-66% (4.4)	-51% (4.4)	Unc: Also difference in Total-C; no difference in HDL-C and TG Unc: Analysed according to these randomisation - difference in LDL-C effect remained at Week 16 (single arm extension period)	
Unfavourable Effects						
Adverse events	Overall	N (%)	12/33 (36%)	5/34 (15%)	Unc: only 4 weeks parallel observation, limited number of patients SoE: only 2 treatment related; 1 patient in SYDNEY group with mild injection site reaction, 1 patient in the AI group with blood CK increased and injection site contusion SoE: During the single arm period, only 3 (4.5%) of the 23 (35%) AEs were treatment related (musculoskeletal pain; ALT increased; blood CK increased and contusion)	
	Serious adverse events	N (%)	1 (3.0%)	1 (3.0%)	SoE: Not treatment related (mild ALT increase in the SYDNEY group and acute MI in AI group)	
Anti-alirocumab antibodies		N (%)	2 (6.3%)	1 (3.1%)	2 additional ADAs during single arm period	
Patients discontinued due to AE		N (%)	1 (3.0%)	0	SoE: Increase in ALT, not considered treatment related. No discontinuations during single arm period	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

It is considered of importance that comparability in exposure and effect can be demonstrated for the new device in comparison to the existing device. In this respect, the study design is not considered ideal (parallel, no formal power calculation for PK and/or effect comparison). Nevertheless, the new device (SYDNEY) showed comparability to the existing IA device in terms of exposure based on PK evaluation of AUC and Cmax. This was supported by a comparable effect on PCSK9 levels. Further, no major issues in quality design of the new device are noticed. Although some difference in effect in LDL-C during the parallel phase of the study were noticed, this is unlikely to be device related as this difference in effect remained during the single phase when analysed according to the randomised groups.

Evaluation of usability of the device is also acceptable, although no major issues were expected considering the simplicity in use of the device. Nevertheless, as expected, patients experienced the automated pen to be easy to use.

Safety data were limited which limits the possibility to draw any meaningful conclusion on the safety aspects of the use of the new device. However, since no new substance is used, and exposure is comparable to the existing device, no new safety issues are to be expected.

3.7.2. Balance of benefits and risks

The benefit risk of the new SYDNEY device is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The B/R of Praluent 300 mg (2 ml (150 mg/ml)) solution is positive.

The variations for the existing presentations are acceptable.

The overall B/R of Praluent remains positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Praluent 300mg is favourable in the following indications:

Primary hypercholesterolaemia and mixed dyslipidaemia

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.

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.

The CHMP therefore recommends the extension of the marketing authorisation for Praluent subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning

the following change(s):

Variations requested		Type	Annexes affected
B.II.d.2.a	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	Type IA	None
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.b.3.z	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	Type IB	None
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, II, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.6.b	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	Type IA	None
B.IV.1.c	B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging	Type II	I, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A

Precise scope:

Grouping of:
• Extension application to introduce a new strength of 300 mg (2 ml (150 mg/ml)) solution for injection in pre-filled pen (in a pack of 1 and 3 pens, EU/1/15/1031/019-20)
• B.II.b.3.z – Change to the manufacturing process of the finished product to introduce a modified pre-filled pen assembly process:
- Introduction of an alternative insertion force for assembly of bulk PFS into the front subassembly

(from ≤ 60 N to ≤ 35 N)
- Introduction of an alternative assembly force for assembling the front and rear subassemblies (from ≤ 300 N to ≤ 60 N)
- Introduction of labelling in-line visual/optical control as a new in-process test applied during the manufacture of the modified pre-filled pen. The limit is set to "Each label must be present and variable data must be correct"
- Introduction of packaging in-line visual/optical control as a new in-process test applied during the manufacture of the modified pre-filled pen. The limit is set to "The printed data must be present and correct"
- Introduction of weight control by in-line check weigher as a new in-process test applied during the manufacture of the modified pre-filled pen. The limit is set to "Each folding box must have the correct weight".
• B.II.d.2.a – Minor changes to the container closure integrity test procedure (CCIT) for the pre-filled pen (PFP) carried out at Sanofi-Aventis Deutschland GmbH, Germany (Frankfurt), to update the system suitability control, positive control preparation and the vacuum pressure applied.
• B.II.e.5.a.1 - To add a new pack-size of 2 pre-filled pens (1 mL) with no activation button for Praluent 75 mg solution for injection (EU/1/15/1031/014)
• B.II.e.5.a.1 - To add a new pack-size of 6 pre-filled pens (1 mL) with no activation button for Praluent 75 mg solution for injection (EU/1/15/1031/015)
• B.II.e.5.a.1 - To add a new pack-size of 1 pre-filled pen (1 mL) with no activation button for Praluent 150 mg solution for injection (EU/1/15/1031/016)
• B.II.e.5.a.1 - To add a new pack-size of 2 pre-filled pens (1 mL) with no activation button for Praluent 150 mg solution for injection (EU/1/15/1031/017)
• B.II.e.5.a.1 - To add a new pack-size of 6 pre-filled pens (1 mL) with no activation button for Praluent 150 mg solution for injection (EU/1/15/1031/018)
• B.II.e.6.b - Change in the elastomeric Soft Needle Shield (SNS) of Praluent 75 and 150 mg/mL solution for injection (EU/1/15/1031/001-017) to introduce a design variant to the needle shield.
• B.IV.1.c - To add a modified pre-filled pen (PFP) with no activation button, which is an integrated part of the primary packaging of the medicinal product for Praluent 75 mg solution for injection 1 pre-filled pen (EU/1/15/1031/013)

Update of sections 1, 2, 4.2, 6.3, 6.5 and 8 of the SmPC; the Labelling and Package Leaflet are updated accordingly.
In addition, the applicant has taken the opportunity to update the contact details of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template (v. 10.1), to remove the black triangle and to introduce editorial changes to modules 3.2.P.3.3, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.5.6, 3.2.P.7, 3.2.P.8.2, 3.2.A.1 and 3.2.R.

Appendix

Product Information (changes highlighted) as adopted by the CHMP on 25 June 2020.